EDUCATIONAL REVIEW

Management of proteinuria in the transplanted patient

Tomáš Seeman

Abstract Proteinuria is a relatively frequent complication in children after renal transplantation (40–80 %). It is usually mild and non-nephrotic in nature and predominantly tubular in origin. The major causes of post-transplant proteinuria are recurrence of primary glomerulonephritis [mostly focal segmental glomerulosclerosis (FSGS)], rejection (acute and chronic), mTOR inhibitors or hypertension. Proteinuria is a risk factor for graft loss and patient death in adults, and even a mild proteinuria (0.1–0.2 g/day) is associated with impaired graft and patient survival. In children, proteinuria seems to be associated with graft but not patient survival. Proteinuria (protein/creatinine ratio) should be assessed regularly in all children. In children with prior chronic kidney disease due to idiopathic FSGS, proteinuria should be assessed daily during the first month after transplantation to enable early diagnosis of recurrence. The cause of proteinuria should be identified, and graft biopsy should be considered in children with unexplained proteinuria, especially with new onset proteinuria or deterioration of previously mild proteinuria. Treatment must be primarily targeted at the cause of proteinuria, and in normotensive children symptomatic antiproteinuric therapy with angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists should also be initiated. Other antihypertensive drugs should be used to achieve target blood pressure of<75th percentile. Target proteinuria should be<20 mg/mmol creatinine.

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Introduction

Proteinuria is a common complication in most chronic kidney diseases (CKD) and together with hypertension is the most important risk factor for progression of native kidney diseases [1–3]. In recent years there has been an increasing interest in the role of proteinuria also in patients after renal transplantation, as it has been demonstrated that it is an important and potentially treatable risk factor for graft loss and patient mortality [4].

The aim of this review is to summarize the management of proteinuria in patients after renal transplantation.

Prevalence of post-transplant proteinuria and methods for its measurement

Proteinuria is a common complication in patients after renal transplantation (RTx). The prevalence of proteinuria reported in different studies on adult and pediatric populations varies considerable, from 11 to 82 % [4–13]. The main reason for this wide variation in prevalence of proteinuria is the different threshold used in these studies to define proteinuria. In studies involving adult populations which used a very liberal threshold of 2–3 g/day, prevalence was only 10—15 % [5, 7]. In contrast, studies that used a threshold similar to that used for non-transplanted patients (0.15–0.25 g/day) revealed proteinuria in 31–45 % of patients [4, 11].

In children, proteinuria has been investigated in only a limited number of studies [14–17]. In one of these studies proteinuria was detected in 100 % of children 1 week after

transplantation when the threshold was 200 mg/g creatinine [16]. In two other studies proteinuria was detected in 47–82 % of patients at least 6 months after RTx using the threshold of 0.096 g/m^2/day or 22 mg/mmol creatinine [15, 17]. This prevalence is higher than that found in adult studies; however, when a threshold of 0.960 g/m^2/day was used, which corresponds with a threshold of about 2 g/day, the prevalence was only 12 % and corresponds with the prevalence in adults at this threshold [15]. The prevalence of post-transplant proteinuria according to different thresholds in different studies is summarized in Fig. 1.

The currently recommended method to assess total proteinuria in children with CKD is to determine the protein/creatinine ratio in a random urine sample, with a threshold of 20 mg/mmol creatinine, i.e. 200 mg/g creatinine [18, 19]. The threshold in 24-h urine collection is 96 mg/m^2/day for children and 150 mg/day for adults. The currently recommended method to assess the glomerular type of proteinuria (albuminuria) is determination of the albumin/creatinine ratio, with a threshold of 3 mg/mmol creatinine, i.e. 30 mg/g creatinine [18, 19]. The tubular type of proteinuria is usually assessed by measuring the urinary excretion of microglobulins, such as alpha-1-microglobulin or beta-2-microglobulin, with a threshold of 0.55 and 0.04 mg/mmol creatinine for alpha-1-microglobulinuria and beta-2-microglobulin, respectively. These same methods and thresholds should also be used in transplanted children. The methods and thresholds for proteinuria are summarized in Table 1.

Types of post-transplant proteinuria

Proteinuria can be classified according to the time of onset, persistency, quality (glomerular or tubular origin), quantity (degree) and cause.

Early proteinuria is very common in transplanted patients. In a pediatric study by Chua et al., 100 % of children had proteinuria at 1 week after RTx; however, it disappeared in 70 % of patients at 8–9 weeks post-transplant [16]. Such transient proteinuria does not have negative impact on long-term graft survival [6–8, 20]. To the contrary, later onset proteinuria (>2–3 months post-transplant) or persistent proteinuria (duration >3 months) does have a negative impact on long-term graft survival (see below section Clinical consequences).

The origin of proteinuria (i.e. glomerular or tubular) has been investigated in several studies [17, 21–23]. Most of these have demonstrated that the predominant type of proteinuria in transplanted patients is tubular in origin, occurring in up to 79 and 80 % of adult and pediatric transplant patients, respectively. There is an inverse relationship between total proteinuria and tubular proteinuria, with the lower the total proteinuria, the higher the percentage of tubular proteinuria, and vice versa [23]. On the other hand, glomerular proteinuria with increased albuminuria can signal primary glomerular injury, such as recurrence of de novo glomerular disease, transplant glomerulopathy, hypertension-induced glomerulopathy (hypertensive nephropathy of the graft) or chronic allograft nephropathy.
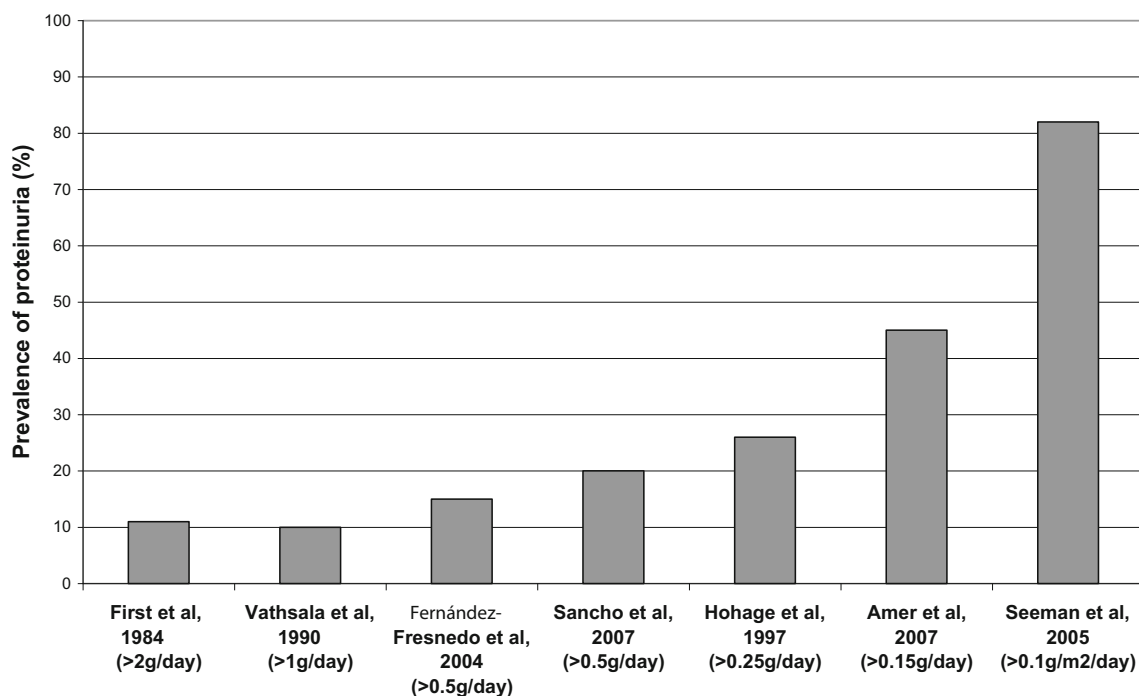

Fig. 1 Prevalence of post-transplant proteinuria according the threshold used for definition of proteinuria

Table 1 Methods and thresholds for the assessment of proteinuria[a]

Parameter	Collection method	Threshold for pathological finding
Proteinuria (total)	Spot urine	>20 mg/mmol creatinine, i.e. >200 mg/g creatinine Nephrotic range: >220 mg/mmol creatinine, i.e. >2,200 mg/g creatinine
	24-h urine collection (children)	>96 mg/m^2/day Nephrotic range: >960 mg/m^2/day
	24-h urine collection (adults)	>150 mg/day Nephrotic range: >2,200 mg/day
Albuminuria	Spot urine	>3 mg/mmol creatinine; i.e. >30 mg/g creatinine
Alpha-1-microglobulinuria; beta-2-microglobulinuria	Spot urine	>0.55 mg/mmol creatinine
	Spot urine	>0.04 mg/mmol creatinine

[a] According to Kidney Disease Improving Global Outcome (KDIGO) guidelines

In the only pediatric study conducted to date on profiling proteinuria, we demonstrated that tubular proteinuria also prevails (79 %) in transplanted children [17]. However, also in our study the presence of glomerular proteinuria signaled in most cases the presence of chronic allograft nephropathy or uncontrolled hypertension.

Tubular as well as glomerular proteinuria is associated with impaired graft survival [22, 23]. Furthermore, both glomerular and tubular proteinuria have the potential to be biomarkers of signal acute rejection as in one study increased albuminuria was detected in patients with clinically relevant acute rejection presenting with decreased glomerular filtration rate (GFR) [24] and alpha-1-microglobulinuria as early as 1–4 days before clinically relevant acute rejection was apparent [25]. However, in one small pediatric study, urinary proteins (albumin or low-molecular-weight proteins) had no predictive value in the detection of acute rejection before clinical symptoms of acute rejection appeared [14]. Therefore, the value of increased proteinuria in predicting acute rejection remains controversial.

In view of the predominance of tubular proteinuria in transplant recipients, proteinuria should be measured in transplanted patients as total proteinuria or both tubular (alpha-1-microglobulin, beta-2-microglobulin) and glomerular (albumin) proteinuria—and not as albuminuria only.

The quantity of proteinuria is usually mild and non-nephrotic. The mean proteinuria in two pediatric studies was only 256 mg/m^2/day and 20 mg/mmol creatinine [15, 17]. In another German pediatric study the mean proteinuria was about 200 mg/m^2/day [14]. In adult studies, the degree (quantity) of proteinuria has been found to be associated with allograft glomerular pathology, as biopsy-proven glomerular disease (e.g. transplant glomerulopathy) has been found to be more prevalent in patients with nephrotic-range proteinuria (66–80 %) than in those with non-nephrotic proteinuria (only 12 % glomerular lesions) [7, 11, 23, 26]. The association between the degree of proteinuria and histological pathology is depicted in Fig. 2. Therefore, not only the quality (glomerular, tubular) but also the quantity (degree) of proteinuria is an important marker of the specific type of graft injury.

Fig. 2 Association between the degree of post-transplant proteinuria and histological pathology of the graft
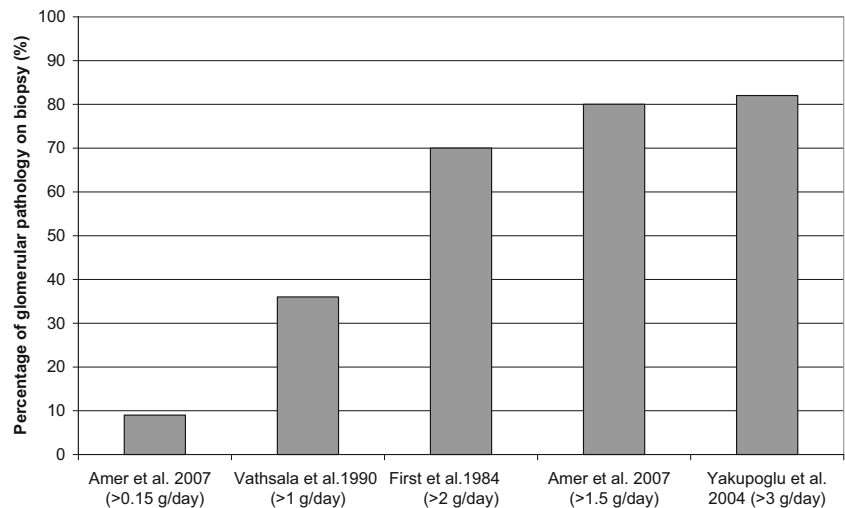
Proteinuria in a patient after RTx may result not only from the graft but also from the residual urine output from the native kidneys. It is of paramount importance to differentiate graft versus native kidney causes of proteinuria, especially in patients with CKD due to idiopathic focal segmental glomerulosclerosis (FSGS) who are at a high risk of recurrence of proteinuria after transplant. Few studies have investigated the early post-transplant evolution of proteinuria. In the largest study on pre-transplant patients with proteinuria conducted to date, Myslak et al. demonstrated that pre-transplant proteinuria strikingly decreases as early as 3 weeks after RTx, from severe nephrotic-range proteinuria (3.6 g/day) to 0.5 g/day [20]. The only patient in this study with nephrotic-range proteinuria at 3 weeks post-transplant had a recurrence of FSGS. Similar results were obtained in a smaller study by D'Cunha et al., who showed normalization of native kidney proteinuria in 100 % of patients in an average time of 4.5 weeks after RTx [27]. Therefore, persistence of nephrotic-range proteinuria 3–4 weeks post-RTx in a patient with primary native kidney disease FSGS (without bilateral nephrectomy before transplantation) must raise the suspicion of recurrence of the primary renal disease in the graft.

Causes and risk factors for post-transplant proteinuria

Post-transplant proteinuria can be caused by many factors (Fig. 3), the most common of which are recurrent FSGS, rejection, hypertension and mTOR inhibitors. Determining the cause of proteinuria may be difficult, but is of great importance for the patient because the causal treatment of proteinuria could significantly affect the prognosis of the graft. Therefore, this might be an area in need of further research. In clinical practice the most common cause of post-transplant proteinuria (mainly glomerular type) in a child with idiopathic FSGS is recurrence of FSGS; in a child with acute onset (mainly glomerular type) proteinuria and decreased graft function, it is acute rejection; in a child with mild proteinuria and uncontrolled hypertension, it is the deleterious effect of high blood pressure.

Recurrent or de novo glomerular disease

Recurrence of FSGS is the most common cause of early and acute onset nephrotic-range proteinuria in patients after RTx [28]. It occurs in 30–40 % of patients with idiopathic FSGS, but is absent in patients with genetically determined FSGS [29]. Proteinuria recurrence occurs usually very early (as early as the first post-transplant day) and is usually of nephrotic range. The detailed management of recurrence of FSGS is

beyond the scope of this review and is adequately covered by recent reviews elsewhere [28, 30].

Recurrence of other glomerular diseases (immunoglobulin A nephropathy, membranoproliferative glomerulonephritis) and de novo glomerular diseases in children after transplant are a rare cause of post-transplant proteinuria.

Rejection

Acute as well chronic rejection [or in older studies chronic allograft nephropathy (CAN)] can cause proteinuria [14, 31, 32]. Many adult studies have shown that a history of previous acute rejection, current acute rejection and chronic rejection are risk factors for post-transplant proteinuria [10, 11, 32]. Also two pediatric studies have shown that children with a history of acute rejection have significantly higher mean proteinuria than children who have never had an episode of rejection (mean proteinuria 416 vs.107 and 376 vs. 165 mg/m^2/day, respectively) [14, 15] (Fig. 4). Moreover, in one of these studies, proteinuria increased to nearly nephrotic range (960 mg/m^2/day) 1–2 days after biopsy-proven acute rejection [14].

Chronic rejection (formerly referred to as CAN) has been also shown to be a risk factor in most adult studies [5–7, 9]. However, one study based on biopsy findings showed a similar proportion of CAN in proteinuric and non-proteinuric adult patients [11]. In two studies conducted by our group in children, CAN was common in those with mainly glomerular proteinuria [17], however total mean proteinuria was not significantly higher in children with biopsy-proven chronic rejection than in those without chronic rejection (147 vs. 263 mg/m^2/day, respectively) [15]. In the former study [17] pathological total proteinuria was also not significantly higher in children with CAN (28 %) than in children without CAN (21 %). However, the patients with CAN had higher albuminuria and had glomerular proteinuria more frequently than children without CAN, showing that CAN manifests predominantly by glomerular proteinuria. Proteinuria was shown to be a significant risk factor for the development of chronic allograft dysfunction in a Polish study on nearly 200 children [33].

Chronic antibody-mediated rejection (CAMR) is an additional risk factor for proteinuria. In a pediatric study by Billing et al. [34], all 20 children with CAMR had proteinuria and 35 % of them had nephrotic-range proteinuria. Based on the results of these studies, transplant glomerulopathy would appear to be a negative prognostic factor for both proteinuria and graft loss.

mTOR inhibitors

mTOR inhibitors (sirolimus, everolimus) are well-known risk factors for proteinuria [35–37], and therefore all patients after conversion to mTOR inhibitors should have regular
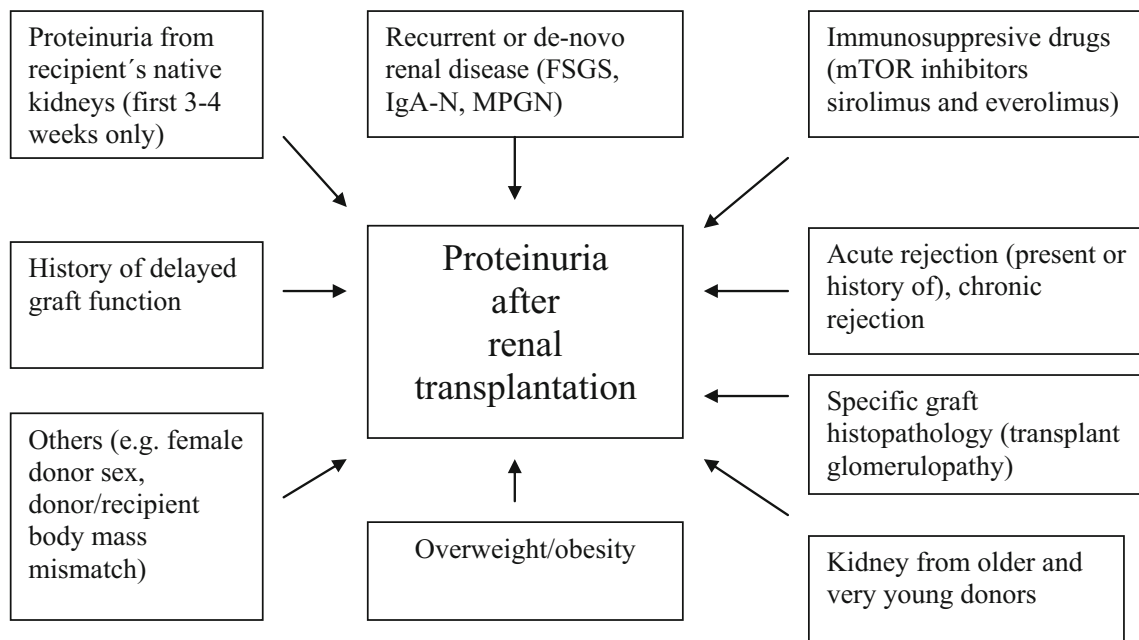
FSGS = focal segmental glomerulosclerosis

IgA-N = IgA nephropathy

MPGN = membranoproliferative glomerulonephritis

Fig. 3 Causes of proteinuria in patients after renal transplantation

proteinuria assessment. Children receiving low-dose everolimus combined with low-dose calcineurin inhibitors have a lower incidence of drug-related proteinuria than patients receiving full-dose sirolimus exposure without calcineurin inhibitors. Proteinuria before conversion to mTOR inhibitors also serves as a predictor of success in conversion from
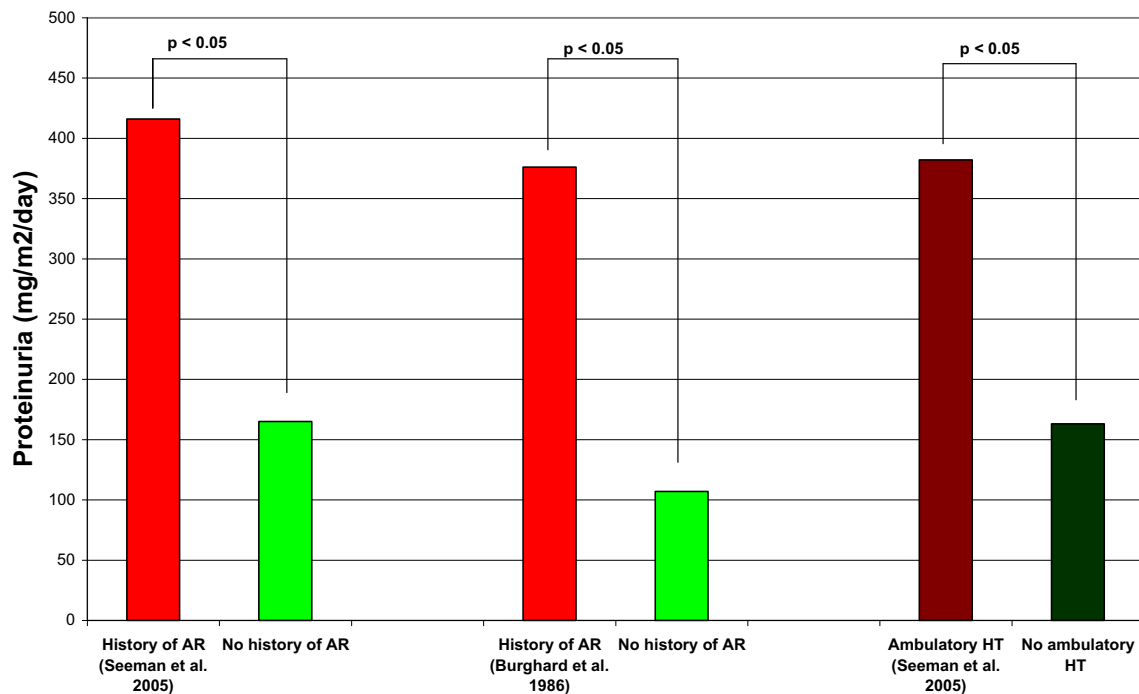

Fig. 4 Proteinuria in transplanted children with/without history of acute rejection (*AR*) or hypertension (*HT*)

calcineurin inhibitor to sirolimus. Diekmann et al. [38] examined the predictors of success in adult patients with chronic allograft dysfunction upon conversion from calcineurin inhibitor to sirolimus and found that those with pre-conversion proteinuria of >0.8 g/day had less of a benefit from the conversion than patients with proteinuria of <0.8 g/day and that proteinuria of <0.8 g/day at conversion was the only independent predictor of positive outcome in conversion.

The mechanism for mTOR inhibitor-induced proteinuria is still under discussion, and various mechanisms have been hypothesized, including antiproliferative and proapoptotic effects on tubular cells or reduction of the expression of nephrin, podocin and other slit diaphragm proteins, leading to reduced podocyte adhesion [37]. No specific histopathology has been observed on graft biopsies in patients with sirolimus-associated proteinuria [11, 39].

Hypertension and obesity

One of the most important and treatable causes of post-transplant proteinuria is hypertension similar to the deleterious effects of hypertension on native CKD [40]. It has been demonstrated in many adult studies that hypertension, or increased blood pressure (BP), is associated with post-transplant proteinuria [11, 15, 41]. Amer et al. found that both systolic and diastolic BP are significantly associated with increasing levels of proteinuria [11].

Hypertension also seems to be a risk factor for proteinuria in the pediatric patient population. Our group found that children with ambulatory hypertension [confirmed by 24-h ambulatory blood pressure monitoring (ABPM)] had significantly higher proteinuria than normotensive children (382 vs. 163 mg/m^2/day, respectively) [15] (Fig. 4). We also reported that children with uncontrolled ambulatory hypertension had twofold higher proteinuria than children with spontaneous normotension or controlled hypertension. Moreover, improved control of ambulatory hypertension with decreased prevalence of uncontrolled hypertension has led to a significant decrease of proteinuria in our 2-year interventional trial [42]. In contrast, children with hypertension defined by office BP only did not have pathological proteinuria more frequently than normotensive children [17]. These results underscore the importance of ABPM in transplanted children.

In adults, obesity and increased body mass index have been shown to be associated with post-transplant proteinuria [12, 43]. In one pediatric study proteinuria was similar in obese and non-obese children after RTx [44].

Donor factors

Older and very young donor age (>50–60 years and <6 years) and delayed graft function seem to be risk factors for proteinuria [10–12, 43, 45]. To the contrary, the donor source (cadaver vs. living) does not affect the presence of post-transplant proteinuria [43]. No studies to date have tested possible associations between donor factors and proteinuria in transplanted children.

Histopathological findings in transplanted patients with proteinuria

Many studies have investigated the histopathological characteristics in patients with proteinuria after RTx [5, 7, 9, 11, 21, 26]. Transplant glomerulopathy with glomerulonephritis (recurrent or de novo) and chronic vascular rejection are the most common histological findings. The different histological findings in adult proteinuric patients are summarized in Table 2. The results show that the higher the amount of proteinuria or albuminuria, the higher the prevalence of glomerular pathology of the graft (Table 2, Fig. 2).

In children, no study has performed biopsies primarily due to proteinuria. In our pediatric study on profiling proteinuria, three of five children with glomerular proteinuria had biopsy-proven CAN [17].

Clinical consequences of proteinuria in transplant recipients

Consequences to renal allograft

In adults proteinuria is a strong and independent risk factor for decreased graft survival and a predictor of graft loss. Transplant patients with proteinuria show shorter graft survival than those without proteinuria [4, 6–12] (Table 3; Fig. 5). The most robust evidence comes from the results of the large nationwide Spanish study on 3,365 patients [10], which showed that proteinuria at 1-year after RTx is an excellent marker of poor long-term allograft prognosis.

The association between proteinuria and graft survival is linear, i.e. the higher the amount of proteinuria, the lower the graft survival. Adults with proteinuria of >3 g/day have a 2.5-fold higher risk of graft loss than patients with proteinuria of 0.5–1.5 g/day, fivefold higher risk than patients with proteinuria of 0.150–0.5 g/day and 19-fold higher risk than patients with proteinuria of <0.150 g/day [39]. Furthermore, the association between proteinuria and graft survival is independent of the glomerular pathological state found on graft biopsy and baseline GFR [9, 11]. The inverse relationship between proteinuria and graft survival is obvious even in patients with low proteinuria levels, such as 0.150–0.2 g/day [11, 13]. This relationship is evident not only 1-year post-transplant [4, 10, 11, 13], but also as early as 3 months after RTx [46, 47]

Table 2 Histopathology findings in kidney transplant recipients with proteinuria

Study	Proteinuria at the time of graft biopsy	Number of patients with graft biopsy	Chronic allograft nephropathy/ chronic rejection/IFTA (%)	Transplant glomerulopathy (%)	Glomerulonephritis (recurrent/de-novo) (%)	Acute rejection (%)
First et al. 1984 [5]	>2 g/day	44	27	39	29	0
Bear et al. 1988 [6]	>3 g/day	61	41	21	25	8
Vathsala et al. 1990 [7]	>1 g/day	71	49	24	12	15
Peddi et al. 1997 [9]	>2 g/day	98	45 (together with TG)	45 (together with chronic rejection)	33	0
Amer et al. 2007 [11]	>0.15 g/day	276 (protocol biopsies)	45	8	11	31

IFTA, Interstitial fibrosis and tubular atrophy; TG, transplant glomerulopathy

(Table 3). Therefore, persistent proteinuria due to pathological causes at any level, starting with 0.150 g/day, and at any time post-transplant, starting 3 months after RTx, is clearly associated with decreased graft survival in adults.

Despite these findings of a clear association between proteinuria and graft survival, it is still a matter of debate whether post-transplant proteinuria is a real cause of graft loss or only the result of the primary pathology (e.g. recurrence of FSGS, acute and chronic rejection, hypertension, etc.), or both [18, 48–50]. The mechanisms by which proteinuria may induce renal injury include: (1) the release of fibrosis-promoting factors from renal cells activated by the proteinuria, resulting in interstitial fibrosis; (2) the uptake of urinary proteins from proximal tubular cells, triggering an increased production of angiotensin II, endothelin, cytokines, chemoattractants and transcriptional factors that promote lymphocyte and monocyte recruitment with transdifferentiation of tubular epithelial cells into fibroblasts, leading to scarring [18, 43, 48–53]. Moreover, many studies using multivariate analysis have shown that proteinuria is an independent risk factor for graft loss after adjustment for other possible causes, such as rejection or hypertension [4, 10, 46].

In children with chronic nephropathies of native kidneys, proteinuria is, together with hypertension, a well-established risk factor for progression [1, 2, 54]. Moreover, reduction of proteinuria with angiotensin–converting enzyme inhibitors (ACEIs) is associated with slower progression of chronic renal insufficiency [54].

In transplanted children, no study has been published dealing with the association between proteinuria and graft survival, and the data from pediatric studies dealing with the recurrence of proteinuria in patients with idiopathic FSGS and its impact on graft survival are conflicting. Some studies showed an impaired graft survival in FSGS patients [29, 55], whereas others did not find any differences in graft survival between recurrent FSGS patients and non-FSGS children [56, 57]. Unpublished data from a retrospective study conducted in our transplantation center show that children (without recurrent FSGS) with pathological proteinuria at 1-year post-transplant have significantly worse long-term graft survival than those with normal proteinuria at 1-year post transplant. Therefore, it seems that proteinuria is associated with worse graft survival not only in adults but also in children.

Consequences to the patients

Similar to the general adult population, proteinuria is also, together with hypertension, associated with increased patient mortality in the population of transplanted patients [4, 10]. Adult proteinuric patients have a lower patient survival than

Table 3 Proteinuria and clinical and allograft characteristics in kidney transplant recipients

Study	Number of investigated patients	Definition of proteinuria	Time after transplantation	Prevalence of proteinuria (%)	Causes/risk factors	Graft/patient survival
First et al. 1984 [5]	44	>2 g/day	Different	11	TG, allograft nephropathy, chronic rejection	Only 23 % prolonged graft function, majority of grafts losed within 1 year
Bear et al. 1988 [6]	61	>3 g/day	≥3 months	29	Chronic vascular rejection, TG	Impaired 5-year graft survival (62 vs. 82 % in non-proteinuric patients)
Vathsala et al. 1990 [7]	71	>1 g/day	≥1 month	10	Chronic rejection, TG	Impaired 5-year graft survival (69 vs. 93 % in non-proteinuric patients)
Peddi et al. 1997 [9]	98	>2 g/day	Different	22	Chronic vascular rejection, TG, recurrent glomerulonephritis	Impaired graft survival (half-life 5 vs. 16 years in non-proteinuric patients) independent of the cause of proteinuria
Hohage et al. 1997 [8]	357	>0.25 g/day	1–6 months	26	Increased serum creatinine	Impaired 5-year graft survival (59 vs. 86 % in non-proteinuric patients)
Roodnat et al. 2001 [4]	722	>0.2 g/l	1 year	33	Primary renal diseases (GN, hypertension, systemic diseases)	Impaired graft and patient survival
Fernández-Fresnedo et al. 2004 [10]	3,365	>0.5 g/day	1 year	15	Chronic rejection, primary renal disease, older donor age, DGF, acute rejection	Impaired graft and patient survival
Seeman et al. 2005 [15]	33 (children)	>0.1 g/m^2/day	Different (mean 25 months)	82	Ambulatory hypertension, history of acute rejection	Not determined
Sancho et al. 2007 [12]	68	>0.5 g/day	Different (mean 53 months)	20	Increased serum creatinine, increased BP, DGF, BMI	Impaired 5-year graft survival (69 vs. 93 % in non-proteinuric patients)
Amer et al. 2007 [11]	276 (protocol biopsies)	>0.15 g/day	1 year	45	Increased serum creatinine, increased BP,	Impaired graft survival independent of other risk factors

GN, Glomerulonephritis; DGF, delayed graft function; BP, blood pressure; BMI, body mass index; ND, Not determined; TG, transplant glomerulopathy
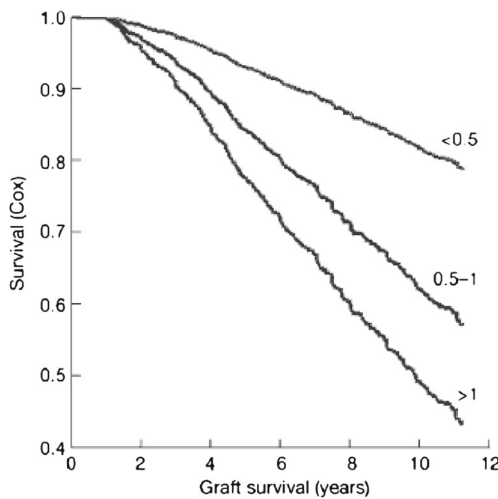
Fig. 5 Graft survival according to 1-year proteinuria in adult kidney transplant recipients (from Fernández-Fresnedo et al. 2004 [10], reproduced with permission)

non-proteinuric patients. Similar studies in children are lacking, and this area could be of interest for further research.

Diagnostics of post-transplant proteinuria

How should proteinuria be measured in transplanted children?

Both total proteinuria and albuminuria should be measured in transplanted patients to determine the total amount and glomerular type of proteinuria. To assess the tubular type of proteinuria, i.e. the predominant type of proteinuria in transplanted patients, either tubular proteins (e.g. alpha-1-microglobulin, beta-2-microglobulin) should be measured simultaneously or the non-albumin proteinuria (i.e. tubular, non-glomerular) should be calculated from total proteinuria and albuminuria (non-albumin proteinuria = total proteinuria minus albuminuria) [23].

Proteinuria and albuminuria should be preferably measured as the protein (albumin)/creatinine ratio. The same thresholds suggested by the Kidney Disease Improving Global Outcomes (KDIGO) for the definition of pathological proteinuria as for non-transplant patients should be used in transplanted children (Table 1).

How frequently should proteinuria be measured?

The current 2009 KDIGO clinical practice guideline on the care of adult transplant recipients [58] suggests measuring proteinuria at least once within the first month after RTx, at least every 3 months between months 1 and 12, and at least annually ≥1 year post transplant. A similar minimal frequency should also be used for screening proteinuria measurements in

transplanted children. Patients with proteinuria should be measured more frequently (every 1–3 months) to monitor the changes in proteinuria.

The most recent 2012 KDIGO clinical practice guideline for the evaluation and management of CKD newly includes proteinuria (as part of the cause), GFR and albuminuria (proteinuria) criteria for the purpose of CKD risk stratification/staging [19]. The consensus stated that the cause of disease is included because of the fundamental importance in predicting the outcome of CKD and choice of cause-specific treatments. This new staging system is fully applicable to pediatric patients. However, in these guidelines there are many gaps in the assessment, timing and quality for various pediatric-specific proteinuria measures, not to mention pediatric transplant-specific recommendations. There is a need for future research to provide evidence for appropriate evidence-based thresholds for transplant proteinuria, especially in pediatric patients.

Special care must be taken in patients with idiopathic (non-genetic) FSGS who have a 30–40 % risk of recurrence of proteinuria/FSGS. In these patients proteinuria should be measured daily in the first 2–3 weeks post-RTx to detect and treat possible recurrence as early as possible. Thereafter, proteinuria should be measured at every outpatient visit during the first year post-RTx as the recurrence can also occur later.

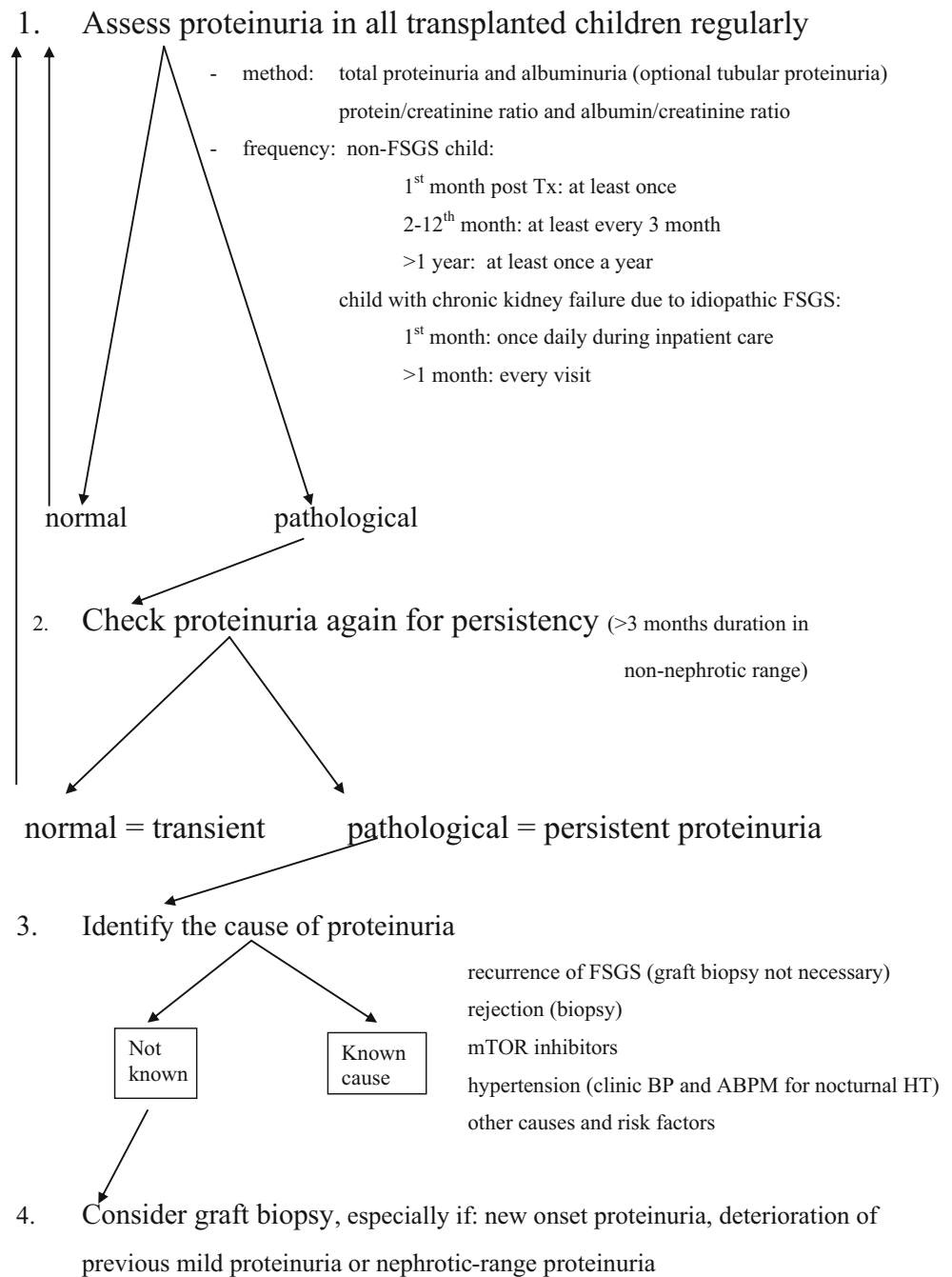What is the cause of proteinuria?

All efforts must be made to reveal the cause of post-transplant proteinuria (e.g. recurrence, rejection, hypertension). Renal graft biopsy is not necessary to diagnose recurrence of disease in a child with idiopathic FSGS who has acute onset nephrotic-range proteinuria. On the contrary, biopsy should be performed in unexplained persistent proteinuria (duration >3 months), especially in new-onset proteinuria, acute deterioration of proteinuria or unexplained nephrotic-range proteinuria, as these patients always show graft-specific pathological findings, such as de novo glomerulonephritis, transplant glomerulopathy or chronic rejection [20].

The diagnostic algorithm for proteinuria in transplanted children is given in Fig. 6.

Treatment of post-transplant proteinuria

The treatment of post-transplant proteinuria should be started early after its diagnosis, should be especially focused on persistent proteinuria (duration >3 months) of any pathological range (even low levels of >0.150 g/day) and on unexplained nephrotic-range proteinuria of any duration. The

Fig. 6 Diagnostic algorithm for a transplanted child with proteinuria. *BP* Blood pressure, *ABPM* ambulatory blood pressure monitoring, *HT* hypertension, *Tx* transplantation, *FSGS* focal segmental glomerulosclerosis

1. Assess proteinuria in all transplanted children regularly

- method: total proteinuria and albuminuria (optional tubular proteinuria)

protein/creatinine ratio and albumin/creatinine ratio

- frequency: non-FSGS child:

1st month post Tx: at least once

2-12th month: at least every 3 month

>1 year: at least once a year

child with chronic kidney failure due to idiopathic FSGS:

1st month: once daily during inpatient care

>1 month: every visit

normal   pathological

2. Check proteinuria again for persistency (>3 months duration in

non-nephrotic range)

normal = transient   pathological = persistent proteinuria

3. Identify the cause of proteinuria

recurrence of FSGS (graft biopsy not necessary)

rejection (biopsy)

Not known   Known cause   mTOR inhibitors

hypertension (clinic BP and ABPM for nocturnal HT)

other causes and risk factors

4. Consider graft biopsy, especially if: new onset proteinuria, deterioration of

previous mild proteinuria or nephrotic-range proteinuria

treatment should be causal whenever possible and symptomatic if the precise cause could not be identified.

Causal treatment

The primary cause must be treated if it has been identified (e.g. recurrence, rejection, hypertension). The precise recommendations for the treatment of these causes of proteinuria are beyond the scope of this review article and are covered comprehensively elsewhere [28, 56, 57, 59].

Symptomatic non–specific antiproteinuric treatment with ACEIs/ARBs

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can decrease proteinuria not only in adults but also in pediatric renal transplant recipients [60, 61]. Ramipril reduces proteinuria in nearly all proteinuric children even without influencing the BP [61]. Therefore, ACEIs/ARBs should also be used in normotensive patients with proteinuria. These drugs are also

recommended by the recent KDIGO guidelines on hypertension in CKD [62].

The recommended doses should be similar to those administered to non-transplanted children (Table 4). Combination ACEI/ARB therapy was found to further reduce proteinuria by 30–40 % in non-transplanted children already on maximal doses of ACEIs [63]. This combination is also possible in transplanted patients [17], but caution must then be taken due to the increased risk of hyperkalemia or acute deterioration of the GFR, especially if the child is dehydrated. The mechanisms of the antiproteinuric effects of ACEI/ARB therapy are various, with the main ones being long-term reduction of systemic and intraglomerular pressure (hemodynamic mechanisms) and antiproliferative and antifibrotic effects or preservation of the podocyte slit diaphragm structure (non-hemodynamic mechanisms) [64].

BP-lowering therapy by non-ACEI/non-ARB antihypertensive drugs and vitamin D analogs

In children with persistent proteinuria despite ACEI/ARB therapy, other antihypertensive drugs that are allowed in children (calcium channel blockers, especially non-dihydropyridine, beta-blockers, diuretics) should be added to achieve the recommended target BP of<75th percentile. This recommendation is based on current KDIGO guidelines for adult transplant patients [58], expert opinion [39] and on the European Society for Hypertension guidelines for non-transplanted CKD children [65]. However, it should be noted that no study in adult or children has ever shown a benefit of these BP targets in transplanted patients.

Antiproteinuric effects of non-ACEI/ARB antihypertensive drugs have also been demonstrated in pediatric transplant patients with proteinuria, in whom proteinuria decreased after a reduction of BP using only non-ACEI/ARB drugs [66].

Several studies have showed that vitamin D analogs may further reduce proteinuria in CKD patients, including renal transplant recipients with residual proteinuria, in addition to current treatment regimens with ACEI/ARB/other antihypertensive drugs [67]. However, as no studies in pediatric transplant patients have been published to date, no recommendation can be given for transplanted children.

What is the target proteinuria in transplanted children?

There are no published recommended targets for transplanted patients. However, taking into account the evidence that even low levels of proteinuria (0.150–0.2 g/day) is a risk factor for graft loss in adults [13, 39], that pediatric patients with proteinuria of>30 mg/mmol creatinine have worse graft survival than children without this level of proteinuria and that the threshold for normal proteinuria according the recent KDIGO guidelines is<20 mg/mmol creatinine, adoption of the latter target would seem logical.

The treatment algorithm for proteinuria in transplanted children is given in Fig. 7.

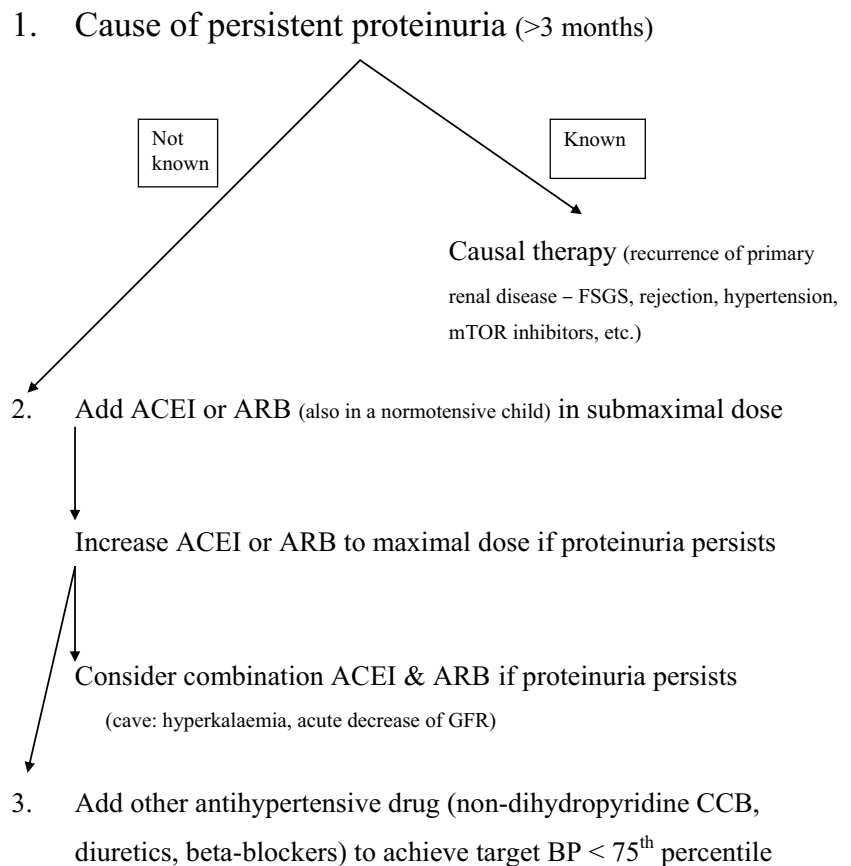#### Can decreased proteinuria improve graft survival?

There is no prospective interventional study showing that antiproteinuric therapy results in improved graft survival. However, three indices speak for a renoprotective effect of antiproteinuric treatment in transplanted patients. The first is an independent association between proteinuria and graft survival from observational studies (Table 3); the second is a retrospective adult study by Halimi et al., which showed that treatment-induced reduction of proteinuria is associated with decreased long-term graft loss independently of initial proteinuria [46]. Lastly, the pediatric ESCAPE trial showed that a decrease in proteinuria is a significant independent predictor of delayed progression of native CKD [54].

Table 4 Recommended doses for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in children

Class of drugs	Generic name	Recommended daily dose (mg/kg/day, if not indicated otherwise)	Number of daily doses
Angiotensin-converting enzyme inhibitors	Enalapril[a]	0.08–0.6	2×
	Ramipril[a]	1.5–6 (mg/m^2/day)	1×
	Fosinopril	0.1–0.6	1×
	Lisinopril	0.08–0.6	1×
Angiotensin receptor blockers	Losartan[a]	0.7–1.4	1×
	Irbesartan[a]	6–12 years of age: 75–150 mg/day;≥13 years of age: 150–300 mg/day	1×
	Valsartan	1–2	1×
	Candesartan[a]	0.16–0.5	1×

[a] Drugs used in the clinical setting in children after renal transplantation, based on published studies

Fig. 7 Treatment algorithm for a transplanted child with persistent proteinuria. *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blockers, *CCB* calcium channel blockers, *GFR* glomerular filtration rate, *FSGS* focal segmental glomerulosclerosis

1. Cause of persistent proteinuria (>3 months)

> Not known   Known

Causal therapy (recurrence of primary renal disease – FSGS, rejection, hypertension, mTOR inhibitors, etc.)

2. Add ACEI or ARB (also in a normotensive child) in submaximal dose

Increase ACEI or ARB to maximal dose if proteinuria persists

Consider combination ACEI & ARB if proteinuria persists
(cave: hyperkalaemia, acute decrease of GFR)

3. Add other antihypertensive drug (non-dihydropyridine CCB, diuretics, beta-blockers) to achieve target BP < 75th percentile

Consider active vitamin D therapy in a vitamin D deficient child

Target (total) proteinuria should be ≤20 mg/mmol creatinine

Conclusions

Proteinuria is a frequent complication in children after RTx, with a prevalence ranging from 40 to 80 %. It is usually mild and of predominantly tubular in origin; however, the glomerular type of proteinuria prevails in patients with higher amounts of proteinuria. The most common etiologies and risk factors are recurrent FSGS, rejection, mTOR inhibitors and hypertension. Post-transplant proteinuria is, independently of its cause, associated with worse graft survival. Therefore, it is a useful prognostic marker for graft survival beyond that provided by graft histopathology, graft function or BP. Proteinuria should be measured routinely in all transplanted children to diagnose it early and enable appropriate treatment.

Treatment of post-transplant proteinuria should be focused primarily on the cause. Symptomatic antiproteinuric therapy consists of ACEI/ARBs, but other antihypertensive drugs should be added to the therapeutic regimen to reach the target BP of <75th percentile. Target proteinuria should be as normal as possible with a suggested threshold of <20 mg/mmol creatinine.

Further prospective interventional studies are needed to answer the open question of whether antiproteinuric therapy can delay the progression of chronic allograft dysfunction, thereby improving the long-term graft survival in kidney transplant recipients.

Key summary points

1. Proteinuria is common in children after RTx (40–80 %).
2. The main causes and risk factors for post-transplant proteinuria are recurrent FSGS, rejection, hypertension and mTOR inhibitors.

3. Proteinuria has a deleterious effect on graft survival in adults and probably also in pediatric patients after renal transplantation.
4. Proteinuria should be regularly measured in all transplanted patients.
5. Treatment of post-transplant proteinuria should be focused on the cause—if unknown, non-specific antiproteinuric ACEI/ARB therapy should be initiated and BP targeted to<75th percentile.

Multiple choice questions (only one correct answer-answers are provided following the Reference list)

1. How frequent is proteinuria in children after renal transplantation:

    a. 5–10 %
    b. 10–20 %
    c. 20–40 %
    d. 40–80 %

2. What is the recommended method for assessment of proteinuria in transplanted children?

    a. Albuminuria alone
    b. Total proteinuria and alpha-1-microglobulinuria
    c. Alpha-1-microglobulinuria alone
    d. Total proteinuria and albuminuria

3. The main causes of persistent post-transplant proteinuria are:

    a. Proteinuria from the diseased native kidneys
    b. mTOR inhibitors and calcineurin inhibitors
    c. Recurrence of FSGS, hypertension and rejection
    d. Older donor age and delayed graft function

4. The consequences of proteinuria after transplantation are:

    a. Hyperfiltration
    b. Impaired graft function and survival
    c. Edema and hypertension
    d. Hypotension

5. Angiotensin receptor blockers can further decrease proteinuria in children already treated with angiotensin-converting enzyme inhibitors by:

    a. 10–20 %
    b. 20–30 %
    c. 30–40 %
    d. 40–60 %

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Answers to questions

1. d
2. d
3. c
4. b
5. c