TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Recurrence from primary and secondary glomerulopathy after renal transplant

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Keywords
renal transplantation, glomerulopathy, recurrence, risk factors, outcome, therapeutic management.

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Conflicts of Interest
The authors disclose no conflicts of interest.

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Received: 12 January 2012
Revision requested: 9 February 2012
Accepted: 16 March 2012
Published online: 16 April 2012

doi:10.1111/j.1432-2277.2012.01483.x

Summary

Glomerulonephritis is the primary cause of end-stage renal failure in 30–50% of kidney transplant recipients and recurrence of the initial disease is an important determinant of long-term graft outcome after transplantation. Although renal transplantation remains the best treatment option for patients with end stage renal diseases in most cases, diagnosis and management of recurrences of glomerulopathies are critical for the optimization and improvement of long-term kidney transplant graft survival and provide a unique opportunity to explore the pathogenesis of native kidney disease. This review aims to update knowledge for a large panel of recurrent primary and secondary glomerulonephritis after kidney transplantation, excluding diabetic nephropathy including primary focal and segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, lupus, vasculitis but also less usual secondary nephropathy related to sarcoidosis, AA and AL amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary glomerulonephritis.

Introduction

Glomerulonephritis is the primary cause of end-stage renal failure in 30–50% of kidney transplant recipients [1]. Recurrence occurs in up to 20% of renal allograft recipients [2] and is now considered as an important determinant of graft survival, after a recent registry study revealed that biopsy-confirmed recurrence was the third most frequent cause of graft loss 10 years after transplantation [1].

The diagnosis and management of recurrences of glomerulopathies are critical for the optimization and improvement of long-term kidney transplant graft survival and provide a unique opportunity to explore the pathogenesis of active kidney disease.

This review aims to update knowledge for a large panel of recurrent primary and secondary glomerulonephritis after kidney transplantation, excluding diabetic nephropathy. We will focus on recent findings obtained with new immunosuppressive regimens and new approaches to the treatment of recurrences, but will also consider recent analyses of transplant outcome in patients with less classical forms of glomerular disease including amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary glomerulonephritis.

Primary glomerulonephritis

Primary focal and segmental glomerulosclerosis

Primary focal and segmental glomerulosclerosis (FSGS) is the most frequently acquired condition leading to end-stage renal disease (ESRD) in children (NAPRTCS 2004, annual report) [3–8]. FSGS frequently recurs after kidney transplantation (20–40%) and such recurrences are associated with poor graft survival [9–12]. The pathophysiology of primary FSGS remains unclear, but the secretion of a circulating factor is thought to play a key role in excessive glomerular permeability. The pathophysiology of this disease has yet to be fully elucidated, but is thought to involve at least three types of cells (T cells, B cells and podocytes) and a circulating factor [13]. Knowledge of the pathogenesis of this disease has improved in recent years, but the introduction of new treatments has not decreased recurrence rates. A T-cell disorder is thought to be involved, based on the considerable evidence for Th2 cytokine bias in idiopathic nephrotic syndrome (INS). Sahali *et al.* were the first to report that T cells from INS patients develop a Th2 phenotype [14]. These findings were supported by the observation of higher levels of cytoplasmic IL-13 mRNA in T cells from patients with relapsing INS than in those from patients in remission and control patients [15]. Levels of the soluble ST2 protein (sST2), a marker of Th2 cells predicted to be regulated by c-maf, have been recently investigated in a population of patients with FSGS recurrence after transplantation [16]. However, despite the evidence for T-cell dysfunction in INS, treatments targeting T cells (calcineurin inhibitors, anti-CD3, or anti-CD52 antibodies) are not completely effective for the prevention or treatment of recurrent FSGS. Evidence of B-cell participation has also been recently provided, in the form of remission following treatment with rituximab (anti-CD20) [17]. The presence of a circulating vascular permeability factor involved in the physiopathology of this disease is highlighted by (i) the early recurrence of nephrotic syndrome after transplantation [18], (ii) the ability of serum from patients with recurrent FSGS to induce albuminuria in rats [19], (iii) the occurrence of a transient nephrotic syndrome in newborn infants born to women with FSGS, [20] and (iv) the efficacy with which plasma exchange and/or immunoadsorption induces remission [21]. However, the biochemical characteristics of this factor remain unknown. Its molecular weight is thought to be between 30 and 100 kDa, and Dantal *et al.* have suggested that it may form a complex with immunoglobulins [22]. Savin *et al.* recently reported that this circulating factor had a high affinity for galactose and that its activity was entirely eliminated by passage through galactose affinity columns [23]. The third player in this complex disease is the podocyte. It has been suggested that the circulating factor and/or immune cells interact directly with podocytes, inducing a redistribution of slit diaphragm proteins, a loss of nephrin and/or podocin and effacement of the foot processes, a hallmark of podocyte injury [24]. The soluble urokinase-activating receptor (suPAR) has been recently identified as a potential cause of FSGS [25]. The authors of this study previously reported that mice lacking urokinase receptor ($PLAUR^{-/-}$) were protected against LPS-induced albuminuria [26]. They reported that concentrations of suPAR in the blood were higher in patients with primary FSGS and, particularly, in patients with recurrence after transplantation.

Some studies have identified risk factors for recurrent FSGS in children, including rapid progression to ESRD, early onset of FSGS and, of course, loss of a previous graft from recurrent disease, but none of these studies was able to identify clearly those patients that would or would not subsequently present with recurrence.

Despite the introduction of new immunosuppressive regimens, the discovery of cyclosporine and the use of induction therapies, the incidence of FSGS recurrence has remained unchanged [27–29]. Treatment for recurrence is not standardized and the results obtained are variable [21,27,30–37]. Cyclosporine (CsA) has been found to be effective, to a certain extent, in children. Indeed, intravenous CsA treatment of FSGS recurrence has been shown to be associated with a large decrease in proteinuria in 82% of patients, although plasmapheresis (PE) was also required in some resistant cases [35]. The use of tacrolimus to prevent or to treat recurrence has been investigated in several studies, but with inconsistent results [38,39]. Owing to the presence of a circulating permeability factor, most transplant teams evaluate the efficacy of PE, in which the plasma of the patient is replaced with plasma from healthy pooled donors, albumin or colloidal substance. This treatment usually decreases proteinuria and, in some cases, may lead to complete remission. It is often difficult to determine when to begin PE, the frequency with which this procedure should be carried out, its duration and the optimal time at which to stop such treatment. Most cases of remission are PE-dependent. Other supportive approaches have also been used, including anti-human immunoglobulin affinity immunoadsorption and tryptophan immunoadsorption [22,40].

We recently conducted a nonrandomized pilot trial of intensive and prolonged multiple treatments of FSGS recurrence in adult kidney transplant recipients [41]. As this complex disease involves systemic immune dysregulation targeting podocytes, we used a strategy of concomitant high-dose steroids and intravenous CsA, not only for their immunosuppressive properties but also to stabilize the podocyte cytoskeleton, combined with PE sessions.

The glucocorticoid receptors present on podocytes have anti-apoptotic properties *in vitro* and are able to stabilize the actin cytoskeleton [42,43]. CsA acts directly on podocytes, by blocking the calcineurin-mediated dephosphorylation of synaptopodin and stabilizing the actin cytoskeleton [44]. We decided to include PE sessions in the treatment, based on the presence of the circulating factor. Details of our therapeutic strategy consisted of high dose of oral steroids (1 mg/kg/day) for the first 4 weeks followed by tapering according to the following sequence: 0.75 mg/kg/day for 2 weeks, 0.5 mg/kg/day for 2 weeks, 0.25 mg/kg/day for 2 weeks, and 0.2 mg/kg/day or a maximal daily dose of 10 mg thereafter. We used 14 days of intravenous CsA (2 mg/kg, targeting a blood level between 200 and 400 ng/mL) followed by oral treatment, targeting C2 levels between 1200 and 1400 ng/mL. Complete proteinuria remission was achieved in all patients, a mean of 22.9 ± 6.6 days after diagnosis. All patients were still in complete remission 3 months after diagnosis (mean proteinuria 0.16 ± 0.09 g/day) and all but one patient remained in remission at 1 year (mean proteinuria 0.19 ± 0.29 g/day). In the nine patients with complete remission, PE treatment was gradually tapered until month 9 and was then stopped. During early and long-term follow-up (mean 15.8 ± 3.3 months), none of these nine patients suffered a relapse and no serious adverse event was reported.

Other treatments are available [13]. Indeed, pre-emptive PE has been reported in few studies, but with inconsistent results concerning efficacy and no control group [45].

Rituximab has also been tested in this setting since 2006, but, again, the results obtained have been inconsistent [17,46–49]. Rituximab seems to induce remission in about 50% of cases, but certain questions remain unanswered. It remains unclear, for example, when the infusion should begin: as an induction therapy or at the time of recurrence? It is also unclear how many infusions should be administered, given that the depletion of circulating B cells is not always correlated with lymphoid organ depletion. The long-term side effects of this treatment also remain unknown. No consensus has yet emerged, and double-blind studies are required to determine the therapeutic potential of Rituximab. It has been recently suggested that Rituximab may act directly on podocytes [50].

The B7.1 costimulation molecule is normally expressed on antigen-presenting cells and B cells. Reiser *et al.* recently reported the expression of B7.1 on podocytes and its possible upregulation in many proteinuric states [51]. The significance of the presence of this molecule is not clearly understood and remains a matter for speculation. No published study has ever evaluated the blockade of this costimulation pathway for the treatment of FSGS recurrence. TNFα mRNA upregulation in macrophages has been reported to precede the development of nephrotic syndrome in Buffalo/Mna rats [52]. Furthermore, high TNFα mRNA levels have been found in mononuclear cells from patients with FSGS [53]. Anti-TNFα treatment was recently tested in a child with resistant recurrent FSGS; it induced transient complete remission, but every relapse was sensitive to anti-TNFα infusion [54]. In agreement with Savin's findings [23], both this and another group reported a significant decrease in proteinuria following the administration of galactose in conjunction with other treatments [55]. A clinical trial (NCT00098020) is currently recruiting patients for evaluations of the treatment of primary FSGS in native kidneys with galactose. Galactose has an excellent safety profile and is thus a potentially interesting candidate treatment.

Membranous nephropathy

Idiopathic membranous nephropathy (MN) leads to an end-stage renal disease in almost 40% of patients [56]. The frequency of recurrence after transplantation is variable. Indeed, recurrence has been reported to occur in 7–44% of patients and most studies have found that recurrence was associated with a reduced allograft survival rate [1,57–59]. This high degree of variability in reported recurrence rates can be accounted for principally by the use of biopsies for surveillance. Indeed, Dabade and coworkers reported histologically, documented recurrence in up to 42% of patients attending a center at which protocol biopsies were carried out after transplantation [60]. They observed that histologic MN recurrence was not systematically associated with the presence of proteinuria, highlighting the importance of these biopsies for the detection of recurrence. The occurrence of *de novo* MN in a transplanted kidney that is indistinguishable from idiopathic MN represents a particular case. However, *de novo* MN tends to occur after a longer time interval than the recurrence of idiopathic MN [61]. Recent findings concerning the pathophysiology of MN have improved our understanding of this disease. There is now evidence to suggest that MN is triggered by antibodies directed against podocyte proteins. The first antigen identified, the neutral endopeptidase (NEP), was discovered a few years ago [62]. This particular alloantigen has been implicated in neonatal cases of MN in infants born to NEP-deficient mothers. The second antigen to be identified was the M-type phospholipase A_2 receptor (PLA_2R1), which is normally expressed in podocytes and was the first antigen responsible for idiopathic MN to be identified in adults [63]. Antibodies directed against this receptor have been observed in 70% of patients with idiopathic MN.

Serum anti-PLA_2R1 antibody levels have been linked to disease activity in native kidneys. Beck and coworkers observed that changes in antibody levels because of Rituximab treatment preceded changes in proteinuria [64]. The situation is somewhat more complex after transplantation. A first clinical observation reported a correlation between autoantibody levels and proteinuria, suggesting that the titer of anti-PLA_2R1 antibodies might be predictive of recurrence [65]. However, a larger study performed by Debiec and coworkers showed marked heterogeneity in antibody kinetics and titers, resulting in a low predictive value for recurrence [61]. This discrepancy between the development of MN in native and transplanted kidneys may result from conformational epitopes exposed or genetically determined in the donor. Many treatments for recurrent MN have been tested, with various results. The recent confirmation of an autoimmune process mediated by B cells has led to the use of Rituximab in this setting, for the treatment of both native and transplanted kidneys. This drug has been tested in several studies and has been shown to be associated with a high rate of remission [66,67]. However, although Rituximab therapy resulted in a gradual decrease in proteinuria, the histologic changes did not become detectable until several months after treatment [66].

IgA nephropathy

IgA nephropathy (IgAN) was first described in the 1960s, by Berger *et al.*, and has since been recognized as the most frequent primary glomerulonephritis, leading to ESRD in up to 50% of patients [68]. IgAN accounts for 10–20% of the patients in renal transplant programs [69]. The pathophysiology of this condition remains poorly understood, but its recurrence after transplantation has provided evidence for a systemic disease. Moreover, kidneys from donors with IgA deposition but no IgAN events are cleared of IgA deposits shortly after transplantation into recipients with diseases other than IgAN, providing evidence for both a systemic process and a local process in the kidney. The pathophysiology of IgAN involves the synthesis of an aberrantly glycosylated IgA1, the formation of immune complexes with IgG antibodies directed against this abnormally glycosylated IgA1 and the binding of these complexes to mesangial cells, leading to the recruitment of molecular pathways [70]. A recent genome-wide association study (GWAS) identified five susceptibility loci for IgAN [71]. Patient and allograft survival rates for IgAN patients undergoing transplantation are much better than those for transplant recipients with diseases other than IgAN [1]. Recurrence is frequent, occurring in 20–60% of patients [72,73]. This variation in reported recurrence rates may be accounted for by the biopsy policy of the center, with the asymptomatic recurrence of IgAN in the transplant frequently being detected in protocol biopsies. It may also be accounted for the duration of follow-up and racial disparities in the distribution of IgAN. No factors predictive of recurrence have yet been described. It has been recently suggested that induction regimen with antithymoglobulin may modify recurrence rates [74]. Furthermore, maintenance of steroids regimen may reduce the risk of recurrence [75].

Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) refers to a specific histologic pattern of glomerular injury characterized by glomerular mesangial expansion because of an expansion of the matrix and an increase in cellularity. Mesangial and subendothelial immune deposits are observed, with various degrees of cellular interposition, in the capillary wall, and new basement membrane synthesis results in the duplication or splitting of glomerular basement membranes. There are three principal types of MPGN. Type I is characterized by subendothelial deposits of IgG and C3 or isolated C3 deposits; type II, also called dense deposit disease (DDD), is characterized by electron-dense deposits within the lamina densa of the glomerular basement membrane; type III, which is very rare, is characterized by subendothelial, mesangial, and subepithelial IgG and C3 deposits.

MPGN type I may be idiopathic or secondary to various diseases, including autoimmune diseases and hepatitis C. MPGN recurrence rates after transplantation are highly variable (27–65%), probably because of the small number of patients concerned, the presence of different disease subtypes, and the diagnosis of recurrence on clinical grounds rather than through surveillance biopsies [76–78]. Moreover, recurrence may occur at any time from 1 week to several years after transplantation [76–78]. Recurrence is associated with poor allograft survival rates [1,78].

MPGN type II often results from uncontrolled alternative complement pathway activation, frequently leading to ESRD. Recurrence rates after transplantation are close to 100%, and recurrence is associated with a lower rate of allograft survival [79]. In this particular setting, eculizumab may represent a potential therapeutic drug [80].

Secondary glomerulonephritis

Systemic lupus erythematosus

The reported incidence of SLE recurrence after renal transplantation ranges between less than 5% and 54% [81–86]. In a large retrospective study based on the UNOS database, Contreras *et al.* showed that 167 of 6850 (2.44%) recipients with SLE suffered a recurrence after renal transplantation [82].

However, Norby *et al.* reported that 54% of patients had biopsy-proven recurrence, in a study based on protocol biopsies. In this study, most patients with recurrence had no marked clinical or biological signs and the renal lesions identified on renal biopsy examination were of class I or II according to the standard classification [86]. A wide spectrum of glomerular lesions has been described in renal allografts from patients with SLE, suggesting that different mechanisms of glomerular injury may be involved in SLE recurrence [87]. In a recent pathological study of 220 lupus nephritis patients undergoing kidney transplantation, recurrent disease was demonstrated in 11% of patients and mesangial lesions constituted the predominant pattern of renal injury in the engrafted kidney [81]. Renal signs of SLE recurrence generally include mild proteinuria, associated with microscopic hematuria and acute renal impairment in some patients. Extrarenal signs related to the clinical activity of SLE may be associated with renal symptoms. The risk factors for recurrence identified in the study by Contreras included being black, but nonhispanic, female under the age of 33 years [82]. Patient receiving kidneys from living donors seem to have a higher risk of recurrence [86].

The effect of SLE on graft outcome remains a matter of debate. In the study by Grimbert, none of the patients presented a loss of the kidney graft directly because of recurrent disease and actuarial graft and patient survival rates in SLE patients were not significantly different from those in the matched control group [84]. Long-term (15-year) death-censored graft survival did not differ significantly between the SLE and control groups in the study by Moroni [85]. The recurrence of lupus nephritis has been described as relatively benign, with no effect on graft function [81], and Contreras *et al.* found that only 7% of graft losses were directly related to SLE recurrence [82]. Conflicting results were reported for a large multicenter study in which 1-year graft survival was significantly poorer in SLE patients undergoing transplantation than in the control group [88]. Chelamcharla *et al.* reported similar results for graft survival, with a mean follow-up period of 4.7 years (±2.4 years) [89].

Most studies have shown patient survival to be similar to that for kidney allograft recipients with other underlying diseases [82,84,85]. However, one study reported that patient survival was significantly lower in SLE patients undergoing transplantation than in patients undergoing transplantation for diabetic nephropathy [89]. Another study reported excess cardiovascular mortality in patients with SLE undergoing transplantation [86].

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of a heterogeneous group of antiphospholipid antibodies (APA), thromboembolic complications of the venous, arterial or capillary vasculature and/or fetal loss during pregnancy [90]. The correlation between APA detection and clinical events is inconsistent, depending on clinical events. Anti-phosphatidylserine/prothrombin antibodies, anti-β_2-glycoprotein I antibodies (anti-β_2GPI antibodies) and lupus anticoagulant antibodies are the best indicators of an increase in the risk of thrombosis, whereas aCL antibodies are less reliable for predicting clinical events [91,92].

APS is the most common cause of acquired thrombophilia and may be primary or secondary to another autoimmune disorder, such as SLE in particular. Whether primary and secondary, APS is associated with specific intrarenal vascular changes characterized by fibrous intimal hyperplasia, focal cortical atrophy, and thrombotic microangiopathy [93,94]. This APS nephropathy impairs kidney function and may ultimately lead to ESRD. However, isolated APA, principally because of low titers of aCL antibodies, have been found in 1–5% of asymptomatic individuals, and its prevalence may be even higher in several chronic diseases, such as infections, cancers or ESRD for which there is no clear evidence of an increase in susceptibility to thrombosis [95–97]. For instance, aCL antibodies have been found in up to one-third of hemodialysis patients [98].

Only a few studies of cohorts limited by the number of available patients have explored the early post-transplant outcome of recipients with genuine APS. These studies have shown that APS patients are prone to arterial and venous thrombosis, which may affect large allograft vessels. In addition to graft-vessel thrombosis and perioperative bleeding, APS patients are faced with two major threats after renal transplantation: surgery-triggered catastrophic antiphospholipid syndrome and the recurrence of APS nephropathy. Moreover, the post-transplantation consequences of APA in patients with no symptoms before transplantation remain unclear. This led us to perform a single-center retrospective nested case–control study, to assess the long-term clinical effects of APS and the histologic changes in the allograft observed in protocol biopsies carried out on candidates for renal transplantation with either confirmed APS or the presence of APAs, principally LA [99]. At the time of transplantation, APAs were found in 37 patients (2.7% of the total population), 12 of whom satisfied the criteria for primary ($n = 3$) or secondary ($n = 9$) APS before transplantation. Allograft survival and post-transplant survival rates were significantly lower in patients with APA than in a matched control group. This high mortality rates recorded resulted from a high frequency of thrombotic or hemorrhagic complications or catastrophic antiphospholipid syndrome-related multiple organ failure. The overall

thrombotic complication rate after transplantation was higher in APA+ patients than in controls. We also found that the presence of LA was associated with a faster progression of chronic vascular changes during the first year after transplantation. These early-onset vascular lesions probably contributed to the significantly faster decline of measured glomerular filtration rate (mGFR), recorded at 3 and 12 months, in LA+ patients than in controls.

ANCA-associated vasculitis

Crescentic glomerulonephritis related to the presence of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a major cause of end-stage renal failure. A pooled analysis of published data reported a relapse rate of 17.3% in 127 patients undergoing kidney transplantation for ANCA vasculitis [100]. The average time to relapse was 30.9 months (range 4–89 months). Recurrent disease occurred in 21 patients and was demonstrated by renal biopsy in 12 cases; by contrast, vasculitis relapse was exclusively extrarenal in 10 patients [100]. In a more recent study, in the era of modern immunosuppression, Gera *et al.* reported an incidence of relapse (without renal injury) of 9%, with no apparent negative effect on allograft function [101]. A higher incidence of relapse (36.8%), after a mean of 45 months, was reported in a single-center study of 19 patients [102]. In a retrospective multicenter study, the relapse rate was estimated at 0.02 per patient-year in 85 patients undergoing renal transplantation for ANCA vasculitis [103]. No clear risk factors for vasculitis recurrence have emerged from these previous studies. Nachman *et al.* found that the incidence of relapse was similar in patients with Wegener granulomatosis and in those with microscopic polyangiitis (20.4% vs. 15.7%, $P = 0.62$) and did not depend on ANCA pattern (recurrence rates of 20% in the cANCA subgroup and 17.2% in the pANCA subgroup, $P = 0.99$). Moreover, the presence of circulating ANCA at the time of kidney transplantation seemed to have no effect on the risk of recurrence [100], although severe, early recurrence has been reported in patients with high ANCA titers before kidney transplantation [104,105]. In the study by Geetha *et al.*, no association with recurrence was found for ANCA subtype, disease category, and duration of remission before transplantation [103]. Most previous studies found that graft and patient survival rates were not significantly lower in recipients with ANCA vasculitis than in control groups [102,103]. Thus, actuarial 10-year patient survival was reported to be 87% and death-censored graft survival was reported to be 84% in the study by Moroni [102]. In the study by Briganti *et al.*, graft loss directly related to relapse of ANCA vasculitis had occurred in only 7.7% of patients at 10 years [1]. Little *et al.* reported an overall graft survival of 70% at 10 years, for 107 patients with ANCA vasculitis undergoing kidney transplantation [106]. In this recent study, the presence of circulating ANCA at the time of kidney transplantation was significantly associated with vascular lesions, but not with graft loss. Multivariate analysis demonstrated frequently higher frequency of death in transplant recipients with less than 1 year of postvasculitis remission [106]. These results strongly suggest that it is advisable to wait for a full year after the achievement of complete remission of vasculitis before carrying out kidney transplantation. Patients with relapses in the renal allograft generally present acute or subacute allograft dysfunction associated with crescentic necrotizing glomerulonephritis detection on a biopsy specimen from the graft [104,105]. The optimal therapeutic management of vasculitis recurrence should probably include a combination of cyclosphosphamide and steroids. Additional PE may also be advisable in cases of severe renal dysfunction [104,105,107]. Geetha *et al.* recently reported a favorable outcome for two patients with ANCA-associated vasculitis relapse treated with Rituximab [108].

Anti-glomerular basement membrane (GBM) disease

Recurrent anti-GBM disease in the renal allograft seems to be a very rare in kidney transplant patients whose anti-GBM antibody levels have been below the detection threshold for at least 12 months [109]. None of the 10 patients undergoing transplantation for anti-GBM disease displayed recurrence in the graft within a mean follow-up period of 62 months [110]. According to previous case reports, the mean time interval from transplantation to recurrence is 5 months to 12 years [111]. Renal biopsy specimens typically show crescentic glomerulonephritis on histologic analysis. The treatment protocol for recurrent GMB disease should include PE, steroid pulses, and cyclophosphamide, as usually proposed for anti-GBM disease in native kidneys. Improvements in the function of kidney grafts have been reported with this protocol [111], whereas graft loss occurred in one patient treated with steroids alone [112]. Recurrent anti-GBM disease should be distinguished from *de novo* anti-GBM disease, which has been reported to occur in some patients with Alport syndrome. In this situation, the formation and linear deposition of anti-GBM antibodies results from exposure to neoantigens in the kidney graft [113,114].

Henoch-Schonlein purpura nephropathy

Henoch-Schonlein nephritis (HSN) is a small-vessel vasculitis characterized by granular deposits of immunoglobulin A in the mesangium, leading to end-stage renal

disease in some patients. In 1994, Meulders *et al.* estimated that the risk of HSN recurrence at 5 years was 35% [115]. In this study, graft loss resulting directly from recurrence occurred in 11% of cases. Recent studies have extensively evaluated the outcome of HSN after renal transplantation with current immunosuppressive protocols. The overall rate of HSN recurrence at 10 years was found to be 15.4% in 20 Korean patients [116]. Han *et al.* reviewed published cohort studies relating to kidney transplantation in HSN patients and calculated the overall incidence of recurrence at 29.4%, although the length of the follow-up period was not accurately stated in most studies [116]. Kanaan *et al.* showed that the actuarial risk of clinical recurrence was 11.5% at 10 years and the actuarial risk of graft loss directly related to recurrence was 7.5% at 10 years, in 43 patients undergoing transplantation for HSN [117]. Thervet *et al.* showed that the recurrence of histologic features of HSN, identified on protocol biopsies, was common (61% of grafts after a mean of 24 months) [118]. They also found that mean GFR was similar in patients with and without biopsy-proven HSN recurrence. In a matched retrospective cohort study based on the analysis of 339 HSN recipients from the UNOS database, the frequency of graft loss related to HSN recurrence was estimated at 13.6% [119]. In this study, renal graft survival at 10 years did not differ significantly between the HSN group and patients undergoing transplantation for IgA nephropathy (58.4% and 59.3%, respectively). The risk factors for recurrence have been little studied. The time interval between the achievement of complete remission and transplantation, the time from disease onset to the occurrence of ESRD, immunosuppressive regimen and type of donor seem to have no influence on the risk of recurrence [115–117].

AA amyloidosis

Kidney transplantation is probably the best treatment option in patients with ESRD because of AA amyloidosis. Conflicting results for graft and patient survival have been published for patients with this disease. In a retrospective study, Sherif *et al.* found that graft and patient survival were similar in 23 recipients of kidneys from live donors and a control group [120]. By contrast, patients with AA amyloidosis were found to have significantly lower graft and patient survival than the control group in another study [121]. We recently performed a multicentrer retrospective study to determine both graft and patient outcome in 59 patients with AA amyloidosis undergoing transplantation [122]. We found that AA amyloidosis was significantly associated with a 10-year decrease in patient survival (61.7% vs. 83.4%, $P = 0.013$), whereas 10-year death-censored graft survival did not significantly differ between the AA amyloidosis group and the matched control group (77.5% vs. 71.3%). The incidence of AA amyloidosis recurrence in the graft was found to be 14%. Multivariate analysis demonstrated a significant association of the risk of death with AA amyloidosis recurrence in the graft and with older age of the recipient. One study has suggested that colchicine treatment may prevent the recurrence of AA amyloidosis in the graft, in patients with familial Mediterranean fever [123]. Further studies are required for definitive determination of the incidence of recurrence through protocol biopsies and to investigate the potential value of serum amyloid A concentration screening for predicting recurrence, as demonstrated for native kidneys [124].

AL amyloidosis

AL amyloidosis is a multisystemic disease characterized by the deposition, in some tissues, of immunoglobulin light chain as insoluble fibrils, leading to progressive multiple organ dysfunction. In past decades, patients with ESRD related to AL amyloidosis have not been considered for kidney transplantation because of the shortage of organs, the lack of curative treatment to prevent extrarenal progression of the disease and the high rates of recurrence of AL amyloidosis in the graft. However, recent advances in the therapeutic management of AL amyloidosis have greatly increased patient survival, raising questions about the possible benefits of kidney transplantation in these patients [125,126]. In 2005, Leung *et al.* demonstrated the feasibility of sequential living-donor kidney transplantation and autologous stem cell transplantation (ASCT) in carefully selected patients with chronic renal failure related to AL amylodosis [126]. These findings, subsequently confirmed in other studies, suggest that the eligibility criteria for organ transplantation in patients with severe cardiac and/or kidney involvement should be reconsidered. We recently demonstrated the feasibility of combined heart and kidney transplantation in a patient with severe heart and kidney involvement because of AL amyloid deposits [127]. In a recent UK survey, Sattianayagam *et al.* reported 1-year and 5-year patient survival rates of 95% and 67%, respectively, in 22 patients undergoing kidney transplantation for AL amyloidosis [128]. Nineteen of these patients underwent chemotherapy or ASCT before kidney transplantation, resulting in a significant clonal response in 14 of the 15 evaluable patients. No graft loss because of AL amyloidosis was observed in any of the patients, after a median follow-up of 4.8 years. In another study, three groups of patients ($n = 19$) were defined on the basis of specific treatments for AL amyloidosis (ASCT after (group 1) or before (group 2) kidney transplantation and kidney transplanta-

tion performed after the achievement of complete remission within nonmyeloablative therapy (group 3)) [129]. Overall patient survival was similar in the three groups, and 79% of the patients studied were still alive after a median follow-up of 41.4 months. The causes of death in the other patients included infectious complications and cardiovascular events. Protocol biopsies led to the diagnosis of a recurrence of amyloidosis in one patient from group 2 and one patient from group 3. These studies highlight the feasibility of renal transplantation in selected AL amyloidosis patients with sustained complete remission of the hematological disorder [130].

Monoclonal immunoglobulin deposition disease (MIDD)

MIDD is a rare plasma cell dyscrasia characterized by the deposition of immunoglobulin chains (mostly light chains), leading to a gradual change in organ function. Renal involvement, leading to ESRD, is a frequent complication of MIDD and has a poor prognosis [131].

Kidney transplantation has been performed in rare selected cases of ESRD related to MIDD.

The recurrence of light chain deposition disease (LCDD) seems to be frequent after kidney transplantation and is frequently associated with graft failure [132–134]. In the largest study carried out to date, five of seven kidney graft recipients (71%) displayed a recurrence of light chain deposition disease in the graft after a mean of 33.3 months (range 2–45 months) [133]. Four of the patients with recurrent disease had died by the end of the follow-up period and overall graft survival in the seven patients was estimated at 37.3 months.

No standard treatment for the prevention or treatment of recurrence in the graft is currently available. Kidney transplantation should therefore probably be reserved for patients considered to be in sustained remission, with light chain production controlled by drugs and/or ASCT [135,136]. Rituximab treatment has been reported to be beneficial, preventing or delaying LCCD recurrence in grafts [137]. Bortezomib, a reversible proteasome inhibitor widely used in the curative treatment of plasma cell dyscrasia, including LCDD, may be a promising treatment for LCDD recurrence [138].

Fibrillary glomerulonephritis

Fibrillary glomerulonephritis (FGN) is a rare glomerular disease characterized by the deposition of fibrillary structures in the glomeruli, leading to a nephrotic syndrome and chronic renal impairment, which is rarely observed in the context of the underlying malignancies and plasma cell dyscrasia [139]. A few case reports have described the recurrence of FGN after renal transplantation [140,141]. In the study by Samaniego *et al.*, FGN recurrence was observed in 43% of cases, in patients with relatively stable renal allograft function [142]. In a more recent survey including protocol biopsy, Czarnecki *et al.* showed that recurrence was more frequent in patients with FGN associated with monoclonal gammopathy (five cases), occurring between 3 and 87 months after transplantation [143]. As reported for recipients with LCDD [133], graft and patient survival were poor in patients with FGN related to plasma cell dyscrasia [143]. Thus, as previously described for patients with AL amyloidoisis and LCDD, kidney transplantation should be offered to patients with FGN after complete remission of the hematological disorder has been achieved.

Conclusion

Improvements in long-term allograft survival have resulted in an increase in the importance of recurrence as a significant contributor to late graft loss. Large amounts of data are now available for the spectrum of primary and secondary glomerulopathies, for incidence, risk factor and the effect of recurrence on graft outcome, but there is still a lack of prospective studies of the treatment of recurrent glomerulonephritis. Such studies will probably require a cooperative multicenter approach. Recent reports of beneficial effects of Rituximab in cases of recurrent FSGS highlight the value of the ''transplant model'' for improving our understanding of the pathological or immunological mechanisms involved in primary disease.

References

1. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002; **347**: 103.
2. Hariharan S, Adams MB, Brennan DC, *et al.* Recurrent and de novo glomerular disease after renal transplantation: a report from Renal Allograft Disease Registry (RADR). *Transplantation* 1999; **68**: 635.
3. Habib R, Levy M, Gubler MC. Clinicopathologic correlations in the nephrotic syndrome. *Paediatrician* 1979; **8**: 325.
4. Cameron JS. The enigma of focal segmental glomerulosclerosis. *Kidney Int* 1996; **57**: S119.
5. Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA Jr, Germain MJ. Changing incidence of glomerular diseases in adults. *Am J Kidney Dis* 2000; **35**: 878.
6. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976–1979 and 1995–1997. *Am J Kidney Dis* 1997; **30**: 621.

7. Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. *Am J Kidney Dis* 2004; **44**: 815.
8. Filler G, Young E, Geier P, Carpenter B, Drukker A, Feber J. Is there really an increase in non-minimal change nephrotic syndrome in children? *Am J Kidney Dis* 2003; **42**: 1107.
9. Cameron JS, Senguttuvan P, Hartley B, *et al.* Focal segmental glomerulosclerosis in fifty-nine renal allografts from a single centre; analysis of risk factors for recurrence. *Transplantation Proc* 1989; **21**: 2117.
10. Dantal J, Baatard R, Hourmant M, Cantarovich D, Buzelin F, Soulillou JP. Recurrent nephrotic syndrome following renal transplantation in patients with focal glomerulosclerosis. A one-center study of plasma exchange effects. *Transplantation* 1991; **52**: 827.
11. Dantal J, Soulillou JP. Relapse of focal segmental glomerulosclerosis after kidney transplantation. *Adv Nephrol Necker Hosp* 1996; **25**: 91.
12. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis posttransplantation in 42 allografts in children–a single-center experience. *Transplantation* 1991; **51**: 401.
13. Canaud G, Martinez F, Noel LH, Mamzer MF, Niaudet P, Legendre C. Therapeutic approach to focal and segmental glomerulosclerosis recurrence in kidney transplant recipients. *Transplant Rev* 2010; **24**: 121.
14. Sahali D, Pawlak A, Valanciute A, *et al.* A novel approach to investigation of the pathogenesis of active minimal-change nephrotic syndrome using subtracted cDNA library screening. *J Am Soc Nephrol* 2002; **13**: 1238.
15. Yap HK, Cheung W, Murugasu B, Sim SK, Seah CC, Jordan SC. Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 1999; **10**: 529.
16. Bruneau S, Le Berre L, Herve C, *et al.* Potential role of soluble ST2 protein in idiopathic nephrotic syndrome recurrence following kidney transplantation. *Am J Kidney Dis* 2009; **54**: 522.
17. Pescovitz MD, Book BK, Sidner RA. Resolution of recurrent focal segmental glomerulosclerosis proteinuria after rituximab treatment. *N Engl J Med* 2006; **354**: 1961.
18. Hoyer JR, Vernier RL, Najarian JS, Raij L, Simmons RL, Michael AF. Recurrence of idiopathic nephrotic syndrome after renal transplantation. *Lancet* 1972; **2**: 343.
19. Zimmerman SW. Increased urinary protein excretion in the rat produced by serum from a patient with recurrent focal glomerular sclerosis after renal transplantation. *Clin Nephrol* 1984; **22**: 32.
20. Lagrue G, Branellec A, Niaudet P, Heslan JM, Guillot F, Lang P. [Transmission of nephrotic syndrome to two neonates. Spontaneous regression]. *Presse Med* 1991; **20**: 255.
21. Dantal J, Bigot E, Bogers W, *et al.* Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *N Engl J Med* 1994; **330**: 7.
22. Dantal J, Godfrin Y, Koll R, *et al.* Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. *J Am Soc Nephrol* 1998; **9**: 1709.
23. Savin VJ, McCarthy ET, Sharma R, Charba D, Sharma M. Galactose binds to focal segmental glomerulosclerosis permeability factor and inhibits its activity. *Transl Res* 2008; **151**: 288.
24. Kim BK, Hong HK, Kim JH, Lee HS. Differential expression of nephrin in acquired human proteinuric diseases. *Am J Kidney Dis* 2002; **40**: 964.
25. Wei C, El Hindi S, Li J, *et al.* Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011; **17**: 952.
26. Wei C, Moller CC, Altintas MM, *et al.* Modification of kidney barrier function by the urokinase receptor. *Nat Med* 2008; **14**: 55.
27. Raafat RH, Kalia A, Travis LB, Diven SC. High-dose oral cyclosporin therapy for recurrent focal segmental glomerulosclerosis in children. *Am J Kidney Dis* 2004; **44**: 50.
28. Gagnadoux MF. Ask the expert. Does antibody induction therapy with daclizumab or basiliximab increase the risk of recurrence of post-transplant focal segmental glomerulosclerosis? *Pediatr Nephrol (Berlin, Germany)* 2002; **17**: 305.
29. Hubsch H, Montane B, Abitbol C, *et al.* Recurrent focal glomerulosclerosis in pediatric renal allografts: the Miami experience. *Pediatr Nephrol (Berlin, Germany)* 2005; **20**: 210.
30. Laufer J, Ettenger RB, Ho WG, Cohen AH, Marik JL, Fine RN. Plasma exchange for recurrent nephrotic syndrome following renal transplantation. *Transplantation* 1988; **46**: 540.
31. Ingulli E, Tejani A, Butt KM, *et al.* High-dose cyclosporine therapy in recurrent nephrotic syndrome following renal transplantation. *Transplantation* 1990; **49**: 219.
32. Cochat P, Kassir A, Colon S, *et al.* Recurrent nephrotic syndrome after transplantation: early treatment with plasmaphaeresis and cyclophosphamide. *Pediatr Nephrol (Berlin, Germany)* 1993; **7**: 50.
33. Dall'Amico R, Ghiggeri G, Carraro M, *et al.* Prediction and treatment of recurrent focal segmental glomerulosclerosis after renal transplantation in children. *Am J Kidney Dis* 1999; **34**: 1048.
34. Cheong HI, Han HW, Park HW, *et al.* Early recurrent nephrotic syndrome after renal transplantation in children with focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2000; **15**: 78.
35. Salomon R, Gagnadoux MF, Niaudet P. Intravenous cyclosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. *Transplantation* 2003; **75**: 810.

36. Deegens JK, Andresdottir MB, Croockewit S, Wetzels JF. Plasma exchange improves graft survival in patients with recurrent focal glomerulosclerosis after renal transplant. *Transpl Int* 2004; **17**: 151.
37. Valdivia P, Gonzalez Roncero F, Gentil MA, *et al.* Plasmapheresis for the prophylaxis and treatment of recurrent focal segmental glomerulosclerosis following renal transplant. *Transplant Proc* 2005; **37**: 1473.
38. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE. Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome. *Nephrol Dial Transplant* 1993; **8**: 1286.
39. Kessler M, Champigneulles J, Hestin D, Frimat L, Renoult E. A renal allograft recipient with late recurrence of focal and segmental glomerulosclerosis after switching from cyclosporine to tacrolimus. *Transplantation* 1999; **67**: 641.
40. Bussemaker E, Passauer J, Franz T, Gross P. Tryptophan immunoadsorption strongly reduces proteinuria in recurrent nephrotic syndrome. *Nephrol Dial Transplant* 2001; **16**: 1270.
41. Canaud G, Zuber J, Sberro R, *et al.* Intensive and prolonged treatment of focal and segmental glomerulosclerosis recurrence in adult kidney transplant recipients: a pilot study. *Am J Transplant* 2009; **9**: 1081.
42. Wada T, Pippin JW, Marshall CB, Griffin SV, Shankland SJ. Dexamethasone prevents podocyte apoptosis induced by puromycin aminonucleoside: role of p53 and Bcl-2-related family proteins. *J Am Soc Nephrol* 2005; **16**: 2615.
43. Ransom RF, Lam NG, Hallett MA, Atkinson SJ, Smoyer WE. Glucocorticoids protect and enhance recovery of cultured murine podocytes via actin filament stabilization. *Kidney Int* 2005; **68**: 2473.
44. Faul C, Donnelly M, Merscher-Gomez S, *et al.* The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; **14**: 931.
45. Gohh RY, Yango AF, Morrissey PE, *et al.* Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. *Am J Transplant* 2005; **5**: 2907.
46. Gossmann J, Scheuermann EH, Porubsky S, Kachel HG, Geiger H, Hauser IA. Abrogation of nephrotic proteinuria by rituximab treatment in a renal transplant patient with relapsed focal segmental glomerulosclerosis. *Transpl Int* 2007; **20**: 558.
47. Hristea D, Hadaya K, Marangon N, *et al.* Successful treatment of recurrent focal segmental glomerulosclerosis after kidney transplantation by plasmapheresis and rituximab. *Transpl Int* 2007; **20**: 102.
48. Kamar N, Faguer S, Esposito L, *et al.* Treatment of focal segmental glomerular sclerosis with rituximab: 2 case reports. *Clin Nephrol* 2007; **67**: 250.
49. Yabu JM, Ho B, Scandling JD, Vincenti F. Rituximab failed to improve nephrotic syndrome in renal transplant patients with recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2008; **8**: 222.
50. Fornoni A, Sageshima J, Wei C, *et al.* Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011; **3**: 85ra46.
51. Reiser J, von Gersdorff G, Loos M, *et al.* Induction of B7-1 in podocytes is associated with nephrotic syndrome. *J Clin Invest* 2004; **113**: 1390.
52. Le Berre L, Herve C, Buzelin F, Usal C, Soulillou JP, Dantal J. Renal macrophage activation and Th2 polarization precedes the development of nephrotic syndrome in Buffalo/Mna rats. *Kidney Int* 2005; **68**: 2079.
53. Bakr A, Shokeir M, El-Chenawi F, El-Husseni F, Abdel-Rahman A, El-Ashry R. Tumor necrosis factor-alpha production from mononuclear cells in nephrotic syndrome. *Pediatr Nephrol (Berlin, Germany)* 2003; **18**: 516.
54. Leroy S, Guigonis V, Bruckner D, *et al.* Successful anti-TNF-alpha treatment in a child with posttransplant recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2009; **9**: 858.
55. De Smet E, Rioux JP, Ammann H, Deziel C, Querin S. FSGS permeability factor-associated nephrotic syndrome: remission after oral galactose therapy. *Nephrol Dial Transplant* 2009; **24**: 2938.
56. Maisonneuve P, Agodoa L, Gellert R, *et al.* Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study. *Am J Kidney Dis* 2000; **35**: 157.
57. Monga G, Mazzucco G, Basolo B, *et al.* Membranous glomerulonephritis (MGN) in transplanted kidneys: morphologic investigation on 256 renal allografts. *Mod Pathol* 1993; **6**: 249.
58. Cosyns JP, Couchoud C, Pouteil-Noble C, Squifflet JP, Pirson Y. Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. *Clin Nephrol* 1998; **50**: 144.
59. Poduval RD, Josephson MA, Javaid B. Treatment of de novo and recurrent membranous nephropathy in renal transplant patients. *Semin Nephrol* 2003; **23**: 392.
60. Dabade TS, Grande JP, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy after kidney transplantation: a surveillance biopsy study. *Am J Transplant* 2008; **8**: 1318.
61. Debiec H, Martin L, Jouanneau C, *et al.* Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. *Am J Transplant* 2011; **11**: 2144.
62. Debiec H, Guigonis V, Mougenot B, *et al.* Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med* 2002; **346**: 2053.
63. Beck LH Jr, Bonegio RG, Lambeau G, *et al.* M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361**: 11.
64. Beck LH Jr, Fervenza FC, Beck DM, *et al.* Rituximab-induced depletion of anti-PLA2R autoantibodies predicts

response in membranous nephropathy. *J Am Soc Nephrol* 2011; **22**: 1543.
65. Stahl R, Hoxha E, Fechner K. PLA2R autoantibodies and recurrent membranous nephropathy after transplantation. *N Engl J Med* 2010; **363**: 496.
66. El-Zoghby ZM, Grande JP, Fraile MG, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy: early diagnosis by protocol biopsies and treatment with anti-CD20 monoclonal antibodies. *Am J Transplant* 2009; **9**: 2800.
67. Sprangers B, Lefkowitz GI, Cohen SD, *et al.* Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. *Clin J Am Soc Nephrol* 2010; **5**: 790.
68. Berger J, Hinglais N. [Intercapillary deposits of IgA-IgG]. *JUrol Nephrol* 1968; **74**: 694.
69. Ponticelli C, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. *Clin J Am Soc Nephrol* 2010; **5**: 2363.
70. Suzuki H, Kiryluk K, Novak J, *et al.* The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; **22**: 1795.
71. Gharavi AG, Kiryluk K, Choi M, *et al.* Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 2011; **43**: 321.
72. Ponticelli C, Traversi L, Banfi G. Renal transplantation in patients with IgA mesangial glomerulonephritis. *Pediatr Transplant* 2004; **8**: 334.
73. Ponticelli C, Traversi L, Feliciani A, Cesana BM, Banfi G, Tarantino A. Kidney transplantation in patients with IgA mesangial glomerulonephritis. *Kidney Int* 2001; **60**: 1948.
74. Berthoux F, El Deeb S, Mariat C, Diconne E, Laurent B, Thibaudin L. Antithymocyte globulin (ATG) induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy. *Transplantation* 2008; **85**: 1505.
75. Clayton P, McDonald S, Chadban S. Steroids and recurrent IgA nephropathy after kidney transplantation. *Am J Transplant* 2011; **11**: 1645.
76. Lien YH, Scott K. Long-term cyclophosphamide treatment for recurrent type I membranoproliferative glomerulonephritis after transplantation. *Am J Kidney Dis* 2000; **35**: 539.
77. Lorenz EC, Sethi S, Leung N, Dispenzieri A, Fervenza FC, Cosio FG. Recurrent membranoproliferative glomerulonephritis after kidney transplantation. *Kidney Int* 2010; **77**: 721.
78. Licht C, Fremeaux-Bacchi V. Hereditary and acquired complement dysregulation in membranoproliferative glomerulonephritis. *Thromb Haemost* 2009; **101**: 271.
79. Cochat P, Fargue S, Mestrallet G, *et al.* Disease recurrence in paediatric renal transplantation. *Pediatr Nephrol (Berlin, Germany)* 2009; **24**: 2097.
80. Pickering M, Cook HT. Complement and glomerular disease: new insights. *Curr Opin Nephrol Hypertens* 2011; **20**: 271.
81. Burgos PI, Perkins EL, Pons-Estel GJ, *et al.* Risk factors and impact of recurrent lupus nephritis in patients with systemic lupus erythematosus undergoing renal transplantation: data from a single US institution. *Arthritis Rheum* 2009; **60**: 2757.
82. Contreras G, Mattiazzi A, Guerra G, *et al.* Recurrence of lupus nephritis after kidney transplantation. *J Am Soc Nephrol* 2010; **21**: 1200.
83. Goral S, Ynares C, Shappell SB, *et al.* Recurrent lupus nephritis in renal transplant recipients revisited: it is not rare. *Transplantation* 2003; **75**: 651.
84. Grimbert P, Frappier J, Bedrossian J, *et al.* Long-term outcome of kidney transplantation in patients with systemic lupus erythematosus: a multicenter study. Groupe Cooperatif de Transplantation d'ile de France. *Transplantation* 1998; **66**: 1000.
85. Moroni G, Tantardini F, Gallelli B, *et al.* The long-term prognosis of renal transplantation in patients with lupus nephritis. *Am J Kidney Dis* 2005; **45**: 903.
86. Norby GE, Strom EH, Midtvedt K, *et al.* Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study. *Ann Rheum Dis* 2010; **69**: 1484.
87. Meehan SM, Chang A, Khurana A, Baliga R, Kadambi PV, Javaid B. Pauci-immune and immune glomerular lesions in kidney transplants for systemic lupus erythematosus. *Clin J Am Soc Nephrol* 2008; **3**: 1469.
88. Stone JH, Amend WJ, Criswell LA. Outcome of renal transplantation in systemic lupus erythematosus. *Semin Arthritis Rheum* 1997; **27**: 17.
89. Chelamcharla M, Javaid B, Baird BC, Goldfarb-Rumyantzev AS. The outcome of renal transplantation among systemic lupus erythematosus patients. *Nephrol Dial Transplant* 2007; **22**: 3623.
90. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002; **346**: 752.
91. Galli M, Barbui T. Antiphospholipid syndrome: clinical and diagnostic utility of laboratory tests. *Semin Thromb Hemost* 2005; **31**: 17.
92. Nojima J, Iwatani Y, Suehisa E, Kuratsune H, Kanakura Y. The presence of anti-phosphatidylserine/prothrombin antibodies as risk factor for both arterial and venous thrombosis in patients with systemic lupus erythematosus. *Haematologica* 2006; **91**: 699.
93. Nochy D, Daugas E, Droz D, *et al.* The intrarenal vascular lesions associated with primary antiphospholipid syndrome. *J Am Soc Nephrol* 1999; **10**: 507.
94. Daugas E, Nochy D, Huong DL, *et al.* Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. *J Am Soc Nephrol* 2002; **13**: 42.
95. Harada M, Fujisawa Y, Sakisaka S, *et al.* High prevalence of anticardiolipin antibodies in hepatitis C virus infection:

lack of effects on thrombocytopenia and thrombotic complications. *J Gastroenterol* 2000; **35**: 272.
96. Dalekos GN, Zachou K, Liaskos C. The antiphospholipid syndrome and infection. *Curr Rheumatol Rep* 2001; **3**: 277.
97. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun* 2000; **15**: 145.
98. Ducloux D, Pellet E, Fournier V, *et al.* Prevalence and clinical significance of antiphospholipid antibodies in renal transplant recipients. *Transplantation* 1999; **67**: 90.
99. Canaud G, Bienaime F, Noel LH, *et al.* Severe vascular lesions and poor functional outcome in kidney transplant recipients with lupus anticoagulant antibodies. *Am J Transplant* 2010; **10**: 2051.
100. Nachman PH, Segelmark M, Westman K, *et al.* Recurrent ANCA-associated small vessel vasculitis after transplantation: a pooled analysis. *Kidney Int* 1999; **56**: 1544.
101. Gera M, Griffin MD, Specks U, Leung N, Stegall MD, Fervenza FC. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression. *Kidney Int* 2007; **71**: 1296.
102. Moroni G, Torri A, Gallelli B, *et al.* The long-term prognosis of renal transplant in patients with systemic vasculitis. *Am J Transplant* 2007; **7**: 2133.
103. Geetha D, Eirin A, True K, *et al.* Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation* 2011; **91**: 1370.
104. Lobbedez T, Comoz F, Renaudineau E, Pujo M, Ryckelynck JP, Hurault de Ligny B. Recurrence of ANCA-positive glomerulonephritis immediately after renal transplantation. *Am J Kidney Dis* 2003; **42**: E2.
105. Rostaing L, Modesto A, Oksman F, Cisterne JM, Le Mao G, Durand D. Outcome of patients with antineutrophil cytoplasmic autoantibody-associated vasculitis following cadaveric kidney transplantation. *Am J Kidney Dis* 1997; **29**: 96.
106. Little MA, Hassan B, Jacques S, *et al.* Renal transplantation in systemic vasculitis: when is it safe? *Nephrol Dial Transplant* 2009; **24**: 3219.
107. Nyberg G, Akesson P, Norden G, Wieslander J. Systemic vasculitis in a kidney transplant population. *Transplantation* 1997; **63**: 1273.
108. Geetha D, Seo P, Specks U, Fervenza FC. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post-kidney transplant: report of two cases. *Am J Transplant* 2007; **7**: 2821.
109. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. *Nephrol Dial Transplant* 2003; **18**: 1260.
110. Deegens JK, Artz MA, Hoitsma AJ, Wetzels JF. Outcome of renal transplantation in patients with pauci-immune small vessel vasculitis or anti-GBM disease. *Clin Nephrol* 2003; **59**: 1.
111. Khandelwal M, McCormick BB, Lajoie G, Sweet J, Cole E, Cattran DC. Recurrence of anti-GBM disease 8 years after renal transplantation. *Nephrol Dial Transplant* 2004; **19**: 491.
112. Fonck C, Loute G, Cosyns JP, Pirson Y. Recurrent fulminant anti-glomerular basement membrane nephritis at a 7-year interval. *Am J Kidney Dis* 1998; **32**: 323.
113. Kalluri R, Torre A, Shield CF 3rd, *et al.* Identification of alpha3, alpha4, and alpha5 chains of type IV collagen as alloantigens for Alport posttransplant anti-glomerular basement membrane antibodies. *Transplantation* 2000; **69**: 679.
114. Milliner DS, Pierides AM, Holley KE. Renal transplantation in Alport's syndrome: anti-glomerular basement membrane glomerulonephritis in the allograft. *Mayo Clin Proc* 1982; **57**: 35.
115. Meulders Q, Pirson Y, Cosyns JP, Squifflet JP, van Ypersele de Strihou C. Course of Henoch-Schonlein nephritis after renal transplantation. Report on ten patients and review of the literature. *Transplantation* 1994; **58**: 1179.
116. Han SS, Sun HK, Lee JP, Ha JW, Kim SJ, Kim YS. Outcome of renal allograft in patients with Henoch-Schonlein nephritis: single-center experience and systematic review. *Transplantation* 2010; **89**: 721.
117. Kanaan N, Mourad G, Thervet E, *et al.* Recurrence and graft loss after kidney transplantation for henoch-schonlein purpura nephritis: a multicenter analysis. *Clin J Am Soc Nephrol* 2011; **6**: 1768.
118. Thervet E, Aouizerate J, Noel LH, *et al.* Histologic recurrence of Henoch-Schonlein Purpura nephropathy after renal transplantation on routine allograft biopsy. *Transplantation* 2011; **92**: 907.
119. Samuel JP, Bell CS, Molony DA, Braun MC. Long-term outcome of renal transplantation patients with Henoch-Schonlein purpura. *Clin J Am Soc Nephrol* 2011; **6**: 2034.
120. Sherif AM, Refaie AF, Sobh MA, Mohamed NA, Sheashaa HA, Ghoneim MA. Long-term outcome of live donor kidney transplantation for renal amyloidosis. *Am J Kidney Dis* 2003; **42**: 370.
121. Heering P, Hetzel R, Grabensee B, Opelz G. Renal transplantation in secondary systemic amyloidosis. *Clin Transplant* 1998; **12**: 159.
122. Kofman T, Grimbert P, Canoui-Poitrine F, *et al.* Renal transplantation in patients with AA amyloidosis nephropathy: results from a French multicenter study. *Am J Transplant* 2011; **11**: 2423.
123. Livneh A, Zemer D, Siegal B, Laor A, Sohar E, Pras M. Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever. *Nephron* 1992; **60**: 418.
124. Lachmann HJ, Goodman HJ, Gilbertson JA, *et al.* Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356**: 2361.
125. Jaccard A, Moreau P, Leblond V, *et al.* High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357**: 1083.
126. Leung N, Griffin MD, Dispenzieri A, *et al.* Living donor kidney and autologous stem cell transplantation for

primary systemic amyloidosis (AL) with predominant renal involvement. *Am J Transplant* 2005; **5**: 1660.
127. Audard V, Matignon M, Weiss L, *et al.* Successful long-term outcome of the first combined heart and kidney transplant in a patient with systemic Al amyloidosis. *Am J Transplant* 2009; **9**: 236.
128. Sattianayagam PT, Gibbs SD, Pinney JH, *et al.* Solid organ transplantation in AL amyloidosis. *Am J Transplant* 2010; **10**: 2124.
129. Herrmann SM, Gertz MA, Stegall MD, *et al.* Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. *Nephrol Dial Transplant* 2011; **26**: 2032.
130. Bridoux F, Ronco P, Gillmore J, Fermand JP. Renal transplantation in light chain amyloidosis: coming out of the cupboard. *Nephrol Dial Transplant* 2011; **26**: 1766.
131. Ronco P, Plaisier E, Aucouturier P. Ig-related renal disease in lymphoplasmacytic disorders: an update. *Semin Nephrol* 2010; **30**: 557.
132. Larsen T, Hammer A, Jorgensen KA. Recurrence of light-chain deposition disease after renal transplantation. *Scand J Urol Nephrol* 2008; **42**: 187.
133. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis* 2004; **43**: 147.
134. Short AK, O'Donoghue DJ, Riad HN, Short CD, Roberts IS. Recurrence of light chain nephropathy in a renal allograft. A case report and review of the literature. *Am J Nephrol* 2001; **21**: 237.
135. Lorenz EC, Gertz MA, Fervenza FC, *et al.* Long-term outcome of autologous stem cell transplantation in light chain deposition disease. *Nephrol Dial Transplant* 2008; **23**: 2052.
136. Royer B, Arnulf B, Martinez F, *et al.* High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int* 2004; **65**: 642.
137. Kuypers DR, Lerut E, Claes K, Evenepoel P, Vanrenterghem Y. Recurrence of light chain deposit disease after renal allograft transplantation: potential role of rituximab? *Transpl Int* 2007; **20**: 381.
138. Kaposztas Z, Kahan BD, Katz SM, Van Buren CT, Cherem L. Bortezomib successfully reverses early recurrence of light-chain deposition disease in a renal allograft: a case report. *Transplant Proc* 2009; **41**: 4407.
139. Nasr SH, Valeri AM, Cornell LD, *et al.* Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol* 2011; **6**: 775.
140. Alpers CE, Rennke HG, Hopper J Jr, Biava CG. Fibrillary glomerulonephritis: an entity with unusual immunofluorescence features. *Kidney Int* 1987; **31**: 781.
141. Calls Ginesta J, Torras A, Ricart MJ, *et al.* Fibrillary glomerulonephritis and pulmonary hemorrhage in a patient with renal transplantation. *Clin Nephrol* 1995; **43**: 180.
142. Samaniego M, Nadasdy GM, Laszik Z, Nadasdy T. Outcome of renal transplantation in fibrillary glomerulonephritis. *Clin Nephrol* 2001; **55**: 159.
143. Czarnecki PG, Lager DJ, Leung N, Dispenzieri A, Cosio FG, Fervenza FC. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. *Kidney Int* 2009; **75**: 420.