Recurrent Glomerulonephritis after Renal Transplantation: An Unsolved Problem

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Background and objectives: Despite advances in prevention of acute rejection and improved short- and long-term kidney graft survival, recurrent glomerulonephritis remains problematic and poorly characterized. This study analyzed prevalence and outcome of recurrent glomerulonephritis from various registries.

Design, setting, participants, & measurements: Definition, classification, and limitations in evaluating epidemiology of native and recurrent glomerulonephritis are discussed. Epidemiology of native glomerulonephritis as the cause of end-stage renal failure and subsequent recurrence of individual glomerulonephritis was evaluated using data from various registries, and pathogenesis of individual glomerulonephritis is discussed.

Results: Analysis of data from transplant registries revealed that glomerulonephritis is an important cause of end-stage renal disease in white and pediatric recipients; however, glomerulonephritis as the cause of end-stage renal disease is not characterized well in black recipients, and many of them are perhaps labeled to have hypertensive nephrosclerosis as the cause of renal disease without renal biopsy. A systematic approach toward urinalysis after transplantation and utility of immunofluorescence and electron microscopic examination of renal biopsy tissues will identify the true prevalence of recurrent glomerulonephritis. Data on recurrent glomerulonephritis should be compiled by either using registry analysis or pooling data from multiple centers. This will provide true data on prevalence and outcome and could potentially initiate translational research studies.

Conclusions: The understanding of the pathogenesis of recurrent glomerulonephritis is critical to optimize prevention as well as to treat individual recurrent glomerulonephritis, which can enhance long-term graft survival.

Clin J Am Soc Nephrol 3: 800–807, 2008. doi: 10.2215/CJN.04050907

Recurrence of glomerulonephritis (GN) and the occurrence of new GN (*de novo* GN) in the transplanted kidney are not uncommon and have been reported since the early days of transplantation (1–3). There have been improvements in short- and long-term graft survival after renal transplantation in the past two decades (4). Development of new immunosuppressive medications has been targeted toward controlling acute and chronic rejections but has not influenced the occurrence and outcome of recurrent and *de novo* GN after renal transplantation (5). It is estimated that approximately 10 to 20% of patients with GN develop recurrence in the allograft and 50% of them lose their graft on long-term follow-up, thus having a negative impact on long-term graft survival (5–7).

Diagnosis and management of recurrence of native GN is critical to optimize and improve long-term kidney transplant graft survival and also provides a unique opportunity to explore the pathogenesis of native kidney disease (8). The goal for the 21st century should be to understand the pathogenesis of

recurrent GN and to implement protocols for the prevention and treatment of recurrent GN, thus optimizing renal transplant outcome. This article illustrates clinical and histologic classifications of recurrent GN and analyzes the problems related to diagnosis of recurrent GN. In addition, epidemiology of native GN in patients with ESRD and recurrent GN after renal transplantation are discussed. This article includes a section on individual GN but does not address metabolic diseases such as diabetic nephropathy.

Definition and Classification of Recurrent Disease

Recurrent and *de novo* glomerular diseases can be classified according to clinical or histologic criteria and are shown in Table 1. GN that occurs in the transplanted kidney can be caused by either recurrent or *de novo* disease. In clinical practice, transplant GN sometimes occurs in patients for whom the native kidney disease was not determined. In these cases, the disease ideally could be either true recurrence or *de novo* disease; however, a true distinction cannot be made. To circumvent this common problem, we have introduced a third category: Transplant glomerulopathy with unknown primary disease:

1. True recurrence: Native kidney disease and transplant kidney disease are the same as confirmed by kidney biopsies.

Table 1. Classification of recurrent glomerular diseases[a]

Clinical classification
1. True recurrence: Native and recurrent disease are the same confirmed by histology
2. Transplant glomerulopathy with unknown primary disease: Transplant renal biopsy confirming disease without histologic confirmation of native kidney disease.
3. *De novo* disease: Occurrence of new disease in the transplant kidney.

Histologic classification
1. Recurrence of primary glomerulonephritides (recurrent FSGS, MPGN, IgAN, MN)
2. Recurrence of secondary glomerulonephritides (SLE, Henoch-Schönlein purpura, HUS/TTP, crescentic GN, anti-GBM disease)
3. Recurrence of metabolic or systemic disease (diabetic nephropathy, oxalosis, amyloidosis, Fabry disease, scleroderma, cystinosis, fibrillary GN)
4. *De novo* diseases (anti-GBM disease in Alport syndrome, MN in patients with polycystic kidney disease)

[a]GBM, glomerular basement membrane; GN, glomerulonephritis; HUS-TTP, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus.

2. Transplant glomerulopathy with unknown primary disease: Biopsy-proven transplant kidney disease is possibly the same disease as the native kidney disease; however, the native kidney diagnosis was never documented by renal biopsy.
3. *De novo*: Biopsy-proven kidney disease that occurs in the transplant kidney is different from the native kidney disease. The transplant kidney disease is a *de novo* disease.

Histologic classification can be divided into four types, according to the type of disease:

1. Recurrence of primary GN: Recurrent FSGS, membranoproliferative GN (MPGN), IgA nephropathy (IgAN), Henoch-Schönlein purpura, membranous nephropathy (MN)
2. Recurrence of secondary GN: Systemic lupus erythematosus (SLE), hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS-TTP), rapidly progressive-crescentic GN, anti–glomerular basement membrane (anti-GBM) disease
3. Recurrence of metabolic or systemic disease: Diabetic nephropathy, oxalosis, amyloidosis, Fabry disease, scleroderma, cystinosis, fibrillary GN
4. *De novo* diseases: Anti-GBM disease in patients with Alport syndrome, MN, FSGS

Limitations in Evaluating the Epidemiology of Native and Recurrent GN

The challenges in diagnosis of recurrent GN are numerous and include (*1*) misdiagnosis or mislabeling of native kidney disease, (*2*) lack of a unified approach in using diagnostic tools for the diagnosis of recurrent GN, and (*3*) difficulties in differentiating GN from drug toxicity and alloantigen-dependant chronic immunologic damage to the transplant kidney (4,9). These points are illustrated in Table 2.

Diagnosis of Native Kidney GN

The diagnosis of native kidney disease remains unknown for some patients who reach ESRD and undergo renal transplantation. Although this was a far greater problem in the past, before widespread use of native renal biopsies, it still remains a major problem for many patients and especially those with lack of adequate access to medical care. As patients approach ESRD, kidneys develop substantial scarring and become small and contracted. Renal biopsy in such patients is associated with a higher complication rate, including bleeding, and a lower

Table 2. Limitations in the diagnosis of recurrent glomerulonephritides[a]

Native kidney disease
  unknown in many patients with ESRD
  black patients are often labeled to have hypertensive nephrosclerosis
  difficulties in determining the cause of native kidney disease when presenting at a late stage
  difficulties in differentiating primary *versus* secondary FSGS
Indication for posttransplantation renal biopsy
  lack of unified approach in diagnosing patients with posttransplantation proteinuria, hematuria, and renal dysfunction
  non-uniform indications for biopsy: protocol *versus* clinical renal disease
  immunofluorescence and electron microscopic examinations not routinely performed on all transplant biopsies
Diagnosis of posttransplantation GN
  lack of histologic features of FSGS in early stage of recurrence
  difficulties in differentiating primary *versus* secondary FSGS
  difficulties in differentiating MPGN *versus* AG
  difficulties in differentiating primary *versus* secondary IgAN
  difficulties in differentiating the cause of HUS/TTP: primary *versus* drug toxicity *versus* humoral rejection

[a]AG, allograft glomerulopathy.

chance of therapy's influencing outcome. Most important, renal histology is often unable to characterize the cause of renal disease as a result of advanced scarring of renal tissue. Lack of native kidney diagnosis is more likely to happen in black patients, and many of them are labeled as having hypertensive nephrosclerosis, although some of them may have underlying GN. The diagnosis of GN as the cause of native kidney disease remains problematic, and this influences the true prevalence of GN as the cause of ESRD and subsequent recurrent GN after transplantation (9,10).

Diagnosis of GN after Renal Transplantation

Proteinuria and hematuria remain the hallmark findings suggesting recurrence of GN. Many transplant centers do not include a urinalysis for detecting proteinuria and hematuria as part of their routine transplant surveillance or even for some patients with worsening renal function before transplant renal biopsy. In a majority of renal transplant patients who undergo renal biopsy, tissue is not routinely submitted for immunofluorescence (IF) and for electron microscopy (EM), which is essential for the diagnosis of some forms of GN. Patients with early or mild recurrence of IgAN, MN, and lupus nephritis thus easily receive a misdiagnosis. There is no unified approach for evaluating renal transplant patients for the diagnosis of recurrent GN after renal transplantation (4,9).

Differential Diagnosis of Posttransplantation GN

Differential diagnosis of posttransplantation GN remains problematic. For example, renal histologic changes are subtle and less specific early in the course of recurrent FSGS. Clinically, recurrence usually presents as an early posttransplantation nephrotic syndrome. Histologically, podocyte fusion is the only finding, without typical segmental lesions of FSGS. In addition, histologic features of FSGS are seen in other conditions, including allograft glomerulopathy (AG) and late stages of other kidney failure. Despite difficulties with interpreting the renal biopsy in cases of suspected recurrent FSGS, it remains valuable because it can differentiate FSGS from other diseases, and suggestive findings such as podocyte fusion can support a clinical diagnosis of FSGS. The diagnosis of recurrent FSGS can be made with the aforementioned histologic findings and clinical criteria such as the timing of recurrence, recipient age, and lack of other findings such as acute rejection and calcineurin toxicity.

It is often difficult even for an experienced pathologist to differentiate recurrent MPGN from AG because histologic findings can be similar. True differentiation lies in careful histologic evaluation, including IF and EM examination. In addition, AG may have C4d positivity, as opposed to lack of antibody-mediated rejection, in patients with recurrent MPGN. Transplant renal biopsy findings of IgA deposits are commonly seen in patients with primary IgAN as well as with SLE. IgA deposits can be detected without overt renal dysfunction, proteinuria, and/or hematuria. Subclinical IgA deposits may represent only histologic recurrence and may not affect kidney graft function or survival (11,12). Occurrence of HUS-TTP in renal transplant recipients could either be recurrent or *de novo* disease. *De novo* disease could result from systemic infections, calcineurin inhibitor nephrotoxicity, or acute humoral rejection. Immunosuppressive agents such as cyclosporine, tacrolimus, and sirolimus have been associated with occurrence of posttransplantation HUS-TTP (13). Histologic findings of HUS-TTP can also be seen in patients with acute and chronic humoral rejection with C4d deposits in the peritubular capillaries. Histologic features of HUS-TTP can represent true recurrence or be secondary to immunosuppressive toxicity or humoral rejection, posing difficulty in differentiating from recurrent GN (9).

Despite these difficulties, transplant renal biopsy remains the gold standard, and clinicians rely on renal histologic findings to diagnose and to prognosticate recurrent GN. Early diagnosis of FSGS, recurrent IgAN, and other diseases helps clinicians to consider interventional therapy to optimize long-term graft outcome.

Epidemiology of Native and Recurrent GN

An understanding of the epidemiology of native kidney disease secondary to GN is critical to characterizing the epidemiology of recurrent GN. For this review, epidemiology of native kidney disease was analyzed using the data from various registries, as shown in Tables 3 and 4. These registries include North American Pediatric Renal Transplant Collaborative Study (NAPRTCS), US Renal Data System (USRDS), Australia New Zealand Dialysis Transplant Data System (ANZDATA), and Renal Allograft Disease Registry (RADR). Data from the collaborative transplant registry do not have information about native and recurrent GN; therefore, it is not included in this

Table 3. Epidemiology of native glomerulonephritides reported through various registries[a]

Registry	Prevalence of GN as the Cause of ESRD (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/TTP (%)
NAPRTCS 2006	25.9	11.7	1.3	2.7	0.5	1.6	2.7
USRDS 2000 to 2004	10.3	2.0	0.7	0.3	0.4	1.0	0.1
ANZDATA 2005	25.0[b]	4.0	22.0	4.0	5.0	4.0	–
RADR 1998 to 2001	14.0	4.0	4.0	2.0	0.6	0.2	0.3

[a]ANZDATA, Australia New Zealand Dialysis Transplant Data System; NAPRTCS, North American Pediatric Renal Transplant Collaborative Study; RADR, Renal Allograft Disease Registry; USRDS, US Renal Data System
[b]Data for 2002 through 2005; all other ANZDATA refers to year 2005 only.

Table 4. Epidemiology of recurrent glomerulonephritis reported through various registries

Registry	Prevalence of Recurrent GN after Transplantation (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/TTP (%)
NAPRTCS 2006	12.0	5.5	–	0.8	–	–	1.1
ANZDATA 1996 to 2005	4.0	–	–	–	–	–	–
RADR 1998 to 2001	2.9	1.0	0.1	0.1	0.1	0.1	0.2

section (Gerald Opelz, MD, Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Heidelberg, Germany, personal communication, July 2006, American Society of Transplantation Annual Meeting, Boston, MA). The analyses of registries revealed that the prevalence of native GN varies according to the population studied and depends on racial distribution as well as recipient age. The duration of follow-up of the population and whether analysis includes both those with loss of the allograft to recurrence and those with recurrence in a functioning allograft will also influence the statistics of recurrence.

Registry Analysis

The NAPRTCS registry has registered 2333 (26.3%) patients with GN as the cause of ESRD from a total of 8990 patients through September 2006 (14). USRDS has registered GN as the cause of ESRD in 51,124 (10.3%) of 497,934 recipients from December 2000 through December 2004 (15). The ANZDATA shows GN as the cause of ESRD in 2492 (25%) of 9871 patients with ESRD from 2002 through 2005 (16). Although the total number of GN cases registered through USRDS is much higher than that for NAPRTCS and ANZDATA, the percentage of GN cases is far less in this population (Tables 3 and 4). The RADR was initiated to understand better the problem of recurrent disease in transplantation. Prospective analysis through this registry revealed that approximately 25% of registrants with ESRD had a native kidney biopsy, and most of them received a diagnosis of GN as the cause of ESRD. These are pooled data from 11 renal transplant centers in the United States (5,9). The aforementioned data are compiled in Tables 3 and 4, which compare the most current data from each registry, showing both primary and recurrent disease when available.

The prevalence of GN as the cause of ESRD varies between 10 and 25%, with higher prevalence in children and white patients. The variability of prevalence of GN in children is related to lower prevalence of diabetes as the cause of ESRD in this population as opposed to adults. Predominance of white patients in ANZDATA may explain a difference in the type of native kidney disease compared with a large cohort of black patients in the USRDS population. Lower prevalence of reported GN in black patients is possibly related to paucity of information on renal biopsy in this population as well as higher prevalence of hypertensive nephrosclerosis and diabetic nephropathy in this population.

Recurrent GN with Functioning Graft

The true prevalence of recurrent GN also depends on counting both patients who have lost their allograft as a result of recur-

rence and those who have recurrence with a functioning graft. A retrospective analysis of the ANZDATA database revealed that 8.4% of patients lost their grafts as a result of recurrent GN by 10 yr after transplantation (7); however, this analysis did not include those with a functioning graft. A more recent analysis of the ANZDATA database from 2001 though 2004, including those with a functioning graft, revealed recurrence in 93 (4.2%) of 3502 renal transplant recipients. The lower prevalence in the cohort of patients from 2001 through 2004 is possibly related to shorter duration of follow-up (16). An analysis by NAPRTCS in 2006 revealed recurrent GN in 174 (12.1%) of 1427 patients (14). An analysis by RADR revealed that 95 (2.9%) of 3216 had recurrent GN, with limited follow-up for 1 yr after transplantation (17). Table 4 compares the reported incidence of recurrent GN among the available registries, broken down by specific diagnosis. Note that recurrent GN epidemiology generally mirrors that of native disease.

From various registry analyses, the prevalence of recurrent GN varies from 2.9 to 12.1% and is inversely proportional to recipient age and directly proportional to the duration of follow-up. Prevalence of recurrent GN is higher when patients with recurrence in a functioning graft with GN are included in the analysis. The prevalence rates of native kidney disease GN and recurrent GN are higher in children and in the white population, and the true prevalence in black patients needs further evaluation.

Individual GN

FSGS

Overall, FSGS recurs after transplantation in approximately 20 to 30% of cases. FSGS can be further stratified into primary, familial, and secondary forms, each incurring a different rate of recurrence. *De novo* FSGS has also recently been related to sirolimus therapy in some transplant patients (18). Unfortunately, these distinctions are not always possible clinically, leading to mixed data.

If one includes only series with primary FSGS and those weighted for pediatric patients and young adults who are more likely to have primary FSGS, the incidence is as high as 50% (19–27). Familial FSGS has been linked to genes encoding various podocyte-related proteins, including podocin, α-actinin 4, and nephrin (28). Familial forms of FSGS do not recur after transplantation, an observation that is consistent with the theory that the defect is intrinsic and specific to the kidney and can be treated effectively by successful renal transplantation (29).

Typically, recurrence of primary FSGS occurs early in the posttransplantation period with heavy proteinuria and pro-

gressive renal insufficiency and graft failure. Current animal and human data suggest that primary FSGS is likely to be initiated by podocyte injury; however, Savin *et al.* (30) described a circulating plasma factor and its association with many cases of primary and recurrent FSGS. The rapid nature of recurrent FSGS after transplantation is consistent with the theory that one or more circulating factors may be playing a major role in the pathogenesis of recurrence. This factor has been suggested as a risk factor for recurrence; however, there is conflicting evidence regarding the utility of testing for the glomerular permeability factor in treating patients with native and recurrent FSGS (30–32). The ability to assay for the presence of this permeability factor will hopefully lead basic science closer to the specific pathophysiology of this disease; however, this test has not been adopted in clinical practice because of its high sensitivity with low specificity, poor reproducibility, lack of test availability at many centers, and paucity of prospective data from clinical studies in patients with FSGS. Other risk factors proposed for recurrent FSGS are younger age, rapid progression to ESRD from the onset of proteinuria, collapsing variant of FSGS, and previous transplant failure as a result of recurrent FSGS (33,34). In a recent single-center analysis of 1140 transplants from 1997 through 2006, 8% of the patients had FSGS as a diagnosis: 72% were primary FSGS, and 22% had biopsy-proven recurrence. Black patients tended to have fewer recurrences. Those with shorter time to ESRD had higher recurrence rates, but there was no increase in the risk for recurrence with collapsing FSGS (22%) (35). The recurrence rate for repeat transplant after failure of the first graft as a result of recurrent FSGS can be as high as 80% (27). The rationale for therapy of recurrent FSGS has largely been based on the theory of clearance of the proposed circulating factor and remission of proteinuria. Plasma exchange, immunoadsorption, and high-dosage cyclosporine have been attempted to treat recurrent FSGS with varying success (36–39). These therapies have been reported to induce partial or transient remission in certain cases but have not been studied in a prospective, controlled manner. Thus, the pathogenesis and treatment of recurrent FSGS need further methodical evaluation.

IgAN
Morphologic recurrence of IgAN after transplantation is seen in from 20 to 60% of patients in retrospective analyses (7,40–47). Diagnosis of *de novo* IgAN is complicated by the fact that IgA deposition can be present in the donated kidney (48). Progression of IgAN in the transplanted kidney is generally slow, but graft failure certainly can occur on long-term follow-up. The incidence of recurrence and allograft loss is clearly influenced by the nature of the glomerular lesions—for example, those with slowly progressive mesangial lesions with sclerosis as opposed to those with severe crescentic GN. Allograft loss as a result of recurrence varies from 45 to 70% of patients with documented recurrence followed long term. Incidence of recurrence has been thought to be lower with the use of mycophenolate mofetil for immunosuppression as opposed to azathioprine-based therapy; however, it could not be verified in a

small retrospective study and has not been tested in a prospective study (49).

MN
MN recurs in from 10 to 30% of renal allografts (50). Although the numbers are variable, in one large study, recurrent MN led to graft loss at 10 yr in 12.5% of 81 allografts in patients with MN as their native disease (7,19,45,51,52). Patients with recurrence early after transplantation and those with massive proteinuria progress rapidly toward graft failure. Hepatitis B and C and autoimmune diseases such as SLE may be the causative factor for recurrent MN in a small proportion of patients, although the largest group of recurrent MN are those with primary MN (53).

MPGN
The recurrence rate of MPGN depends on the pattern, the surveillance, and the analysis of the data (19,45,51,54–57). MPGN type I recurs in from 20 to 30% of allografts. MPGN type II (dense-deposit disease) recurs in 50 to 100% of allografts and is even more likely to lead to graft loss; however, the rate of graft loss is not consistent in various reports, and one recent study provided strong data that it is the age of the patient and presence of crescents and not the pattern of MPGN that influences recurrence (58).

HUS/TTP
Recent findings have elucidated the pathophysiology of some forms of HUS/TTP, whereas others are still unexplained. On the basis of an improved understanding, Besbas *et al.* (59) proposed a classification scheme based on etiology of this disease. Broadly, using the proposed classification, cases are divided into two groups: (*1*) HUS/TTP with specific etiology and (*2*) HUS/TTP with unclear etiology, including those associated with calcineurin inhibitor therapy. The former group includes infection-induced disorders of complement regulation and disorders of von Willebrand proteinase (ADAMTS13) deficiency, among others. Infection-induced cases include those caused by Shiga-like toxin–producing bacteria. These cases have historically been described as postdiarrheal HUS, although they can occur without diarrhea. The risk for recurrence is different depending on cause in many cases of HUS/TTP. Bresin *et al.* (60) performed a literature review of transplant outcomes in patients with non–infection-related HUS and found a 60% recurrence rate, with graft failure in >90% of those with recurrence. In 36 patients with HUS/TTP and factor H mutations, recurrence rate was high at 73.7% with significant irreversible graft failure. All three patients with factor I gene mutations also experienced recurrence and irreversible graft failure. In contrast, four patients with membrane cofactor protein (MCP) mutations had no recurrence on long-term follow-up. The proposed rationale for lack of recurrence in patients with MCP mutations is that MCP is expressed in glomerular epithelial cells and is replaced by the new transplanted kidney (59). A review on recurrence rates of HUS/TTP illustrates high rates of recurrence in patients with factor H mutations as opposed to a lower rate (0.8%) in those with postdiarrheal HUS (61). Both

transient acquired and constitutional deficiencies of AD-AMTS13 can result in HUS/TTP. Data on risk for recurrence in these patients remain sparse, although in the case of constitutional deficiencies, fresh frozen plasma infusions to replace the factor may be protective (62).

Systemic Diseases

Recurrence rates of various systemic diseases differ on the basis of the specific disease. Recurrent lupus nephritis can be seen in 2 to 10% of allografts (63–67). While the incidence may be low due to the use of various immunosuppresive agents after renal transplantation at least one recent report documents a much higher incidence of recurrence (65). Although there is limited experience on transplantation in Wegener's granulomatosis, a pooled analysis suggested a recurrence rate of 17% (68). In that report, ANCA positivity at the time of transplantation was not a risk factor for recurrence. Anti-GBM disease may also recur after transplantation, although morphologic detection of linear GBM staining is much more common than allograft dysfunction (51). *De novo* anti-GBM disease after transplantation can occur in those with Alport syndrome as a result of development of anti-GBM antibody in patients with genetic deficiency of type IV collagen proteins in their native kidneys (69).

Conclusions and Recommendations

Despite the overall progress in renal transplant research with improved short- and long-term outcome and more effective immunosuppressive regimens, there has been limited advance in the area of recurrent GN. As newer and more judicious use of immunosuppression prolongs allograft survival, the impact of recurrent GN will become an even greater threat to graft longevity. Moreover, recurrent GN after transplantation provides a unique opportunity to study individual GN in the presence of ongoing immunosuppressive regimens and thus can provide unique and crucial insights into the pathogenesis of native GN.

On the basis of this analysis, we offer several recommendations regarding risk for recurrence in specific diagnostic categories. In the case of HUS/TTP secondary to infection, renal transplantation is safe. Similarly, transplantation is safe in patients with complement disorders related to MCP deficiency; however, living donors with similar deficiency should be avoided. In cases of other disorders, such as factor H and I abnormalities, increased risk for recurrence and high graft failure rates should be discussed before transplantation. Repeat transplantation from a living donor should be discouraged in these patients if they lose their first graft as a result of recurrence. In the case of familial FSGS, the risk for recurrence is extremely low, and transplantation should be the preferred treatment. In nonfamilial FSGS, the risk for recurrence depends on the underlying disease. In all cases of primary FSGS, transplantation should be offered as a preferred choice of therapy; however, risk for recurrence has to be discussed with all recipients before transplantation. Rates of recurrence in repeat transplantation can be as high as 80% after the loss of first graft as a result of recurrence; therefore, living-donor transplantation should be discouraged after loss of primary transplant as a result of recurrence. It is instinctive to recommend that trans-

plantation not be performed in patients with active anti-GBM antibody disease, SLE, or ANCA-associated vasculitis; however, there are no data to support this recommendation. Several other recommendations can be made to advance our understanding of recurrent disease. First, when not contraindicated, obtaining native kidney biopsies should help to clarify the true incidence of recurrent disease. Extra efforts may be necessary in certain populations, such as black patients, indigent patients, and those without adequate access to health care to avoid labeling bias with the far less helpful diagnoses of "chronic renal failure or ESRD of unknown etiology." Second, urinalysis or a simple dipstick check of the urine for protein and blood should be performed on all transplant patients at every visit. This simple intervention will lead to increased and earlier diagnosis of recurrent GN. There is already evidence in some recurrent diseases (*e.g.*, FSGS) that earlier diagnosis and intervention will lead to remissions of recurrent GN and improved allograft survival. Third, the finding of urinary changes should lead to a transplant biopsy. In all patients with GN as their diagnosis in their native kidneys, full evaluation of the biopsy including IF and EM is warranted. Fourth, data should be collected *via* single centers or, better still, registry groups to establish populations who will benefit the most from new and innovative interventions to prevent or ameliorate recurrent disease. These data should include studies of genetic variants of the disease (*e.g.*, podocin and α-actinin defects in FSGS), morphologic patterns (*e.g.*, collapsing FSGS, crescentic IgA), and links to basic science (analysis of undergalactosylated IgA) whenever possible. Finally, therapeutic interventions should be studied in a collaborative manner for each disease entity to provide more than just anecdotal information on therapy of recurrent disease. The future study of recurrent GN in the allograft can provide a huge amount of information both to help individual patients directly and to extend our knowledge of glomerular diseases.

Disclosures
None.

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