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Abstract

Recurrent glomerulonephritis (GN) is an important cause of kidney allograft failure. Approximately 15% of death-censored graft failures are due to recurrent GN. In this review we will focus specifically on the most common forms of primary GN, including IgA Nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis. New understanding of the pathogenesis of these diseases has had direct clinical implications for transplantation, allowing better identification of candidates at high risk of recurrence and an earlier diagnosis. More than ever, it is essential to fully characterize GN before transplantation as this information will direct our management post transplantation.

Keywords: Renal transplantation; GN recurrence; Allograft loss; Primary glomerulonephritis

Abbreviations: ESRD: End Stage Renal Disease; GN: Glomerulonephritis; MN: Membranous Nephropathy; FSGS: Focal Segmental Glomerulo Sclerosis; MPGN: Membrano Proliferative Glomerulonephritis

Introduction

Glomerulonephritis (GN) are the underlying cause of end-stage renal disease (ESRD) in 30-50% of kidney transplant recipients [1]. These patients are at risk of the recurrence of the disease after renal transplantation. Previously, recurrent GN was considered to be a minor contributor to graft loss. With the prolongation of graft survival, recurrent diseases are assuming a greater importance on graft survival. Studies on recurrence are difficult as not all patients have undergone a native kidney biopsy and the true occurrence may be under estimate. Additionally, is often difficult to differentiate between de novo and recurrent disease. The contribution to graft dysfunction by recurrent disease is also difficult because of the concomitant histological lesions on the transplanted kidney from chronic allograft dysfunction and from chronic lesions due to calcineurin inhibitors. Despite all these difficulties, accumulating evidences highlight the recurrent GN as an important cause of graft loss [2,3]. According to registry study, the risk of graft loss from recurrence increases since the time of transplantation from 0.6% at first year to 8.4% at 10 years. However, the reported allograft loss rates ascribed to disease recurrence vary between 7% and 55% internationally, largely influenced by differing follow-up and the era of transplantation [4-7]. Recurrent GN is the fourth most common cause of allograft loss after acute rejection, chronic rejection and death with a functioning graft.

Additionally, also the incidence of GN recurrence may vary internationally from 2.6% to 50% [8-10]. This fact may be ascribed to different follow-up times, incomplete biopsy data, different population characteristics, inconsistent reporting. Several factors including male gender, younger recipient age [10], living related donors [10] and closer HLA matching [11] have been reported as associated with a higher GN recurrence rate, but not all have been reconfirmed. The primary GN recurrent after transplantation are: IgA nephropathy (IgAN), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and membranoproliferative glomerulonephritis (MPGN) recently divided in two different diseases (MPGN immune complex related and C3GN related to complement abnormalities).

Epidemiology, Risk Factors, Graft Loss

A recent report from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) on the recurrence of GN after kidney transplantation examined 17549 patients who received their first kidney transplant between 1985 and 2014. Primary GN was the cause of ESRD in 6597 biopsy proven patients. In the following study we first report the epidemiology and characteristics of all patients together independently from the recurrent GN, second, we will treat separately all the recurrent primary GN.

a) Incidence of Recurrent GN: In the cited study [12] 479 patients had recurrence. At 10 years after transplantation the recurrence rate was higher for membranous nephropathy (16.6%), followed by MPGN (15.6%), IgAN (10.3%) and FSGS (9.6%).

b) Risk Factor for Recurrence: Age at transplantation was identified as an independent risk factor. For every year increase in age at transplantation, there was a 2% reduction of risk for recurrence. Other significant and independent risk factors have been steroid use at baseline (HR: 0.54; p<0.001) and ischemia time (HR: 0.97; p< 0.001) (Table 1).

Table 1: Risk factors for disease recurrence in recipients with IgA nephropathy, membranous GN, FSGS, and MPGN as primary cause of ESRD.

Characteristics	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age (per year increase)	0.97 (0.96-0.98)	<0.001	0.96 (0.95-0.97)	<0.001
Prednisone at baseline	0.66 (0.48-0.89)	0.007	0.54 (0.37-0.76)	<0.001
Total ischemic time (per hour increase)	0.98 (0.96-0.99)	0.005	0.97 (0.96-0.99)	<0.001

GN: Glomerulonephritis; FSGS: Focal Segmental Glomerulo Sclerosis; MPGN: Membrano Proliferative Glomerulo Nephritis; ESRD: End Stage Renal Disease

c) Disease Recurrence and Graft Loss: Overall GN recurrence was associated with an increased risk of graft loss. The adjusted HRs for death censored and overall allograft loss for those patients who experienced recurrent GN compared with those who did not were 3.19 and 2.04, respectively.

d) Graft survival after disease recurrence: The 5-year graft survival rate for all GN types after disease recurrence was 55% with MPGN exhibiting the lower survival rate (30%). After examining these complete and recent data cumulative for all the recurrent GN as reported in the recent study of ANZDATA, we will now describe the international data for each type of recurrent GN taken separately.

IgA Nephropathy

Recurrent IgA deposition in the allograft is common and may cause hematuria, proteinuria or progressive graft dysfunction. In some patients IgA deposits are observed on biopsy, but do not seem to cause clinically significant disease [13].

a) Epidemiology: The reported frequency of significant recurrence of IgAN varies in literature [14,15]. In retrospective analyses of allograft biopsies performed for graft dysfunction the IgAN recurrence ranged from 21% to 58% [16,17].

b) Risk factors for IgAN recurrence: Possible risk factors for IgAN recurrence are the following:

i. Use of living-related donor kidney: Conflicting data exist concerning a possible increased risk for IgAN recurrence in recipients of living, related allograft. Several retrospective analyses have found no increased risk of recurrence in recipients of living, related allograft [18,19]. By comparison other studies have reported an increased risk of recurrence in recipients of living, related allograft [20-22].

ii. Good match between donor and recipient: A registry study from ANZDATA showed that zero HLA mismatched living donor recipients were more likely to develop recurrence (17%) [22]. Conversely a Korean study found no association with full HLA match and the risk of recurrence [23].

iii. Serum IgA concentration: An increased serum IgA concentration may be a risk factor for recurrence as suggested by a retrospective study.

c) Clinical Manifestations: Patients with recurrent IgAN generally present with persisted microscopic hematuria, new or worsening proteinuria or/and an increase in the serum creatinine. Occasionally, patients may develop early graft failure associated with crescentic IgAN [24,25].

d) Diagnosis: Recurrent IgAN should be suspected in patients who have a history of IgAN in the native kidney and who present with hematuria, new or worsening proteinuria or an increased creatinine. The diagnosis should always be confirmed by a renal biopsy.

e) Treatment: Treatment with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) may delay progression for recurrent disease in allograft [26,27]. A retrospective study on 75 patients with recurrent IgAN documented a higher 5 and 10-years graft survival in patients treated by ACEI or ARB [27]. Immunosuppressive treatment may be attempted in patients with rapid increase of serum creatinine or with a nephritic range proteinuria. High dose prednisone may be given for a short period of time, followed by tapering to return to the dosage already given as antirejection therapy. In the case of a steroid resistance, oral or intravenous cyclophosphamide may be attempted on the basis of studies on patients affected by native IgAN. When cyclophosphamide is given all other antimetabolite drugs must be interrupted. Pre-transplant tonsillectomy does not affect IgAN recurrence [28].

f) Prognosis: In one study allograft in IgAN recipients exhibited a similar 10-year survival rate as allograft in recipients with either non IgAN or non glomerular disease. More recently one group reported that the allograft survival beyond 12 years was lower for patients with IgAN [29]. Another study reported that the 15 years outcome was lower for patients with recurrent IgAN compared with controls [30].

g) Markers for progression: as with all GN, increased urinary protein excretion and increased sclerosis and fibrosis on renal biopsy in patients affected by IgAN are associated with an enhanced risk of progressive disease. Persistent microscopic hematuria that is an early marker of recurrent IgAN, does not predict a poor outcome.

Membranous Nephropathy

Membranous nephropathy (MN) may occur in the transplanted kidney, either as recurrent disease in patients who had MN as the cause of ESRD in the native kidneys or as de novo in patients who had another cause of ESRD.

a) Epidemiology: The reported incidence of recurrent MN ranges between 10 and 45% [31,32]. The reason for the wide variability is that the diagnosis is made only by biopsy and the indication for biopsy varies between the transplant centers [33]. The best data are from one study of 19 patients with MN who underwent surveillance biopsies after transplantation, of which recurrent MN was detected in 8 (42%). Initial reports suggested that patients with living, related transplants are at higher risk for recurrence [34,35]. More recent studies were unable to confirm a higher risk associated with living, related transplantation [36].

b) Pathogenesis: The occasionally rapid recurrence of MN following transplantation suggests the presence of a circulating factor that may be present at the time of transplantation [36]. This factor could be an autoantibody to the M-type phospholipids A2 receptor (PLA2R), which has been implicated in the MN pathogenesis [37]. Several studies have identified circulating anti PLA2R antibodies at or after the time of kidney transplantation as a risk factor for the development of recurrent MN. A positive test and high titers of anti PLA2R antibodies at the time of transplantation are associated with a positive predictive value greater than 80% [38-41]. Thus, testing for anti PLA2R antibodies at the time of kidney transplantation and serial monitoring of the antibody levels after transplantation might help the clinician to identify

patients who need further interventation with either increasing maintenance immunosuppression or other immunosuppressant's (Figure 1).

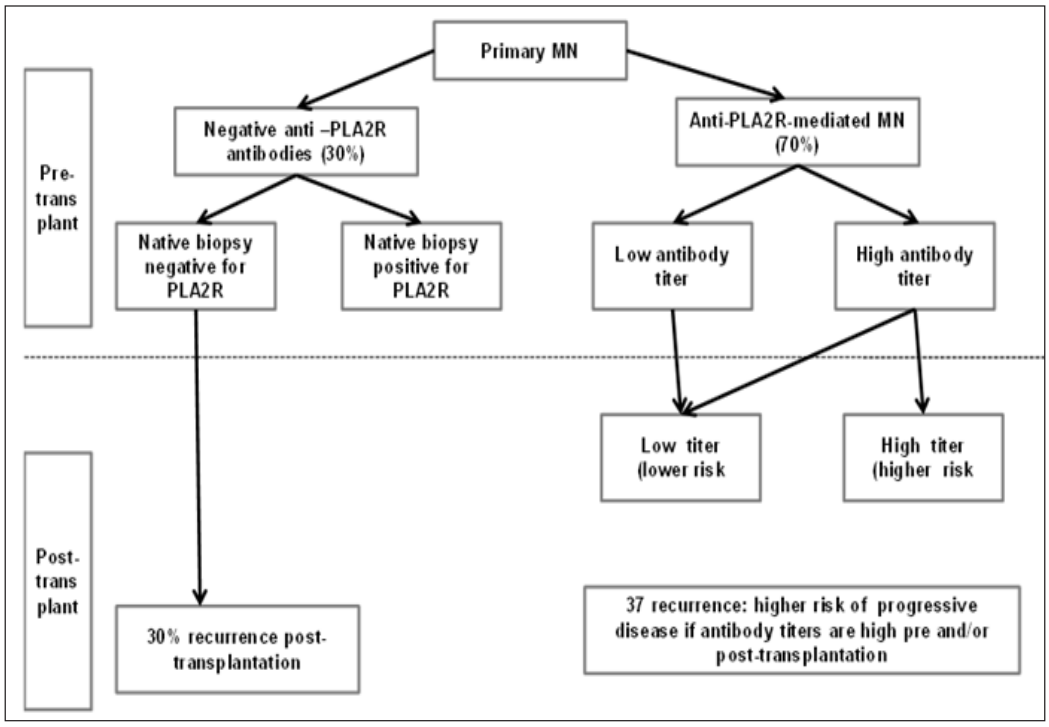

Figure 1: Assessment of risk of MN recurrence and progression post transplant based on laboratory parameters obtained before and after transplantation.

c) Clinical presentation: Recurrent MN is typically observed 13 to 15 months after transplantation, although may also be observed within weeks. The most common clinical manifestation is proteinuria, the degree of which may vary on presentation. Progression of proteinuria is common even among patients with mild or no proteinuria at presentation. In one study, among 29 patients, the median proteinuria increased from 331 mg/day at diagnosis to 1409 mg/day during a mean of 19 months of follow-up [42]. Glomerular filtration rate (GFR) is often normal, but often falls with the progression of the disease.

d) Diagnosis: Recurrent MN is suspected in the transplant patient who develops new and progressive proteinuria. The diagnosis of recurrent MN is made by classic findings of MN on renal biopsy. The association of the PLA2R antigen/autoantibody system in the majority of primary MN cases also holds true in recurrent MN. In one study, 50% of recurrent MN cases were seropositive for anti PLA2R and stained positively for the PLA2R antigen within immune deposits on biopsy of the allograft [43].

e) Prognosis: Recurrent MN can lead to loss of the allograft [1,44]. Among 81 renal transplant recipients with MN on biopsy of their native kidney, the incidence of graft loss at 10-year due to recurrent MN was 12.5%. In another study, among 28 kidney transplant patients, recurrent disease was associated with a 10% risk of death-censored graft loss over 50 months of follow-up.

f) Treatment: Treatment for recurrent MN includes non immunosuppressive and/or immunosuppressive therapies. Patients with no or minimal protein excretion, stable GFR, and only histological evidence of recurrent MN are treated with non immunosuppressive therapy alone as ACEI or intensive blood pressure control. Patients with protein excretion > 1 g/day and/or decreasing GFR are treated with both immunosuppressive and non immunosuppressive therapy. Many authors prefer to add rituximab (RTX) to the already existing immunosuppressive regimen. Other immunosuppressive agents have not been shown to be effective. Standard dose of cyclosporine, tacrolimus and mycophenolate mofetil (MMF) do not seem to protect against the recurrent GN [45].

The best data in favor of RTX come from two series. In one series, 8 patients with recurrent MN and nephrotic proteinuria were given RTX. By 24 months, 6 patients had remission and showed at least partial resolution of histological changes.RTX stabilized or reduced proteinuria and stabilized GFR in four patients with recurrent MN [36]. Depletion of B cells was documented in all patients. Among transplanted patients who do not respond to RTX, cytotoxic agents as cyclophosphamide may be used. The doses are based upon data derived from non transplanted patients with idiopathic MN. Patients who are started on cyclophosphamide should discontinue any antimetabolites assumed as anti rejection therapy.

Focal segmental glomerulosclerosis

FSGS recurrent in the allograft may be primary idiopathic or related to known causes as infections, toxin exposure, genetic mutations or hyper filtration.

a) Epidemiology: Approximately 30% of cases of primary FSGS will recur after transplantation. Late recurrence is difficult to diagnose because FSGS is relatively common late post transplant probably because reduced renal mass, hyper filtration and the effect of drugs [46]. Secondary FSGS are less common to recur. Indeed, genetic forms of FSGS, including those related to apolipoprotein L1 (APOL1) genotype, have a very low risk of recurrence [47]. Additionally, one study suggests that podocyn mutations (NPHS2) are not associated with a reduced risk of recurrence [48]. Among patients with idiopathic FSGS as a cause of ESRD, allograft loss due to the recurrent disease is almost frequent. In one study from ANZDATA, the incidence of graft loss at 10 years due to recurrent disease was 12.7 % [1]. Another analysis conducted by the United States Renal Data System (USRDS) reported a graft loss at 3 years of only 2.6%, but many patients were lost at follow-up [49]. 5 histological patterns of idiopathic FSGS have been recognized [50]. In one study 81% had recurrence of the same histological subtype [51] (Table 2). In a later study the histological subtype in the native kidney did not predict the histological type of recurrent disease [52].

Table 2: Histological variants of FSGS

Type I	Tip lesion variant	Segmental sclerosis at the origin of proximal tubule
Type II	Cellular variant	Endocapillary hypercellularity
Type III	Collapsing variant	Epithelial cell hypertrophy, hyperplasia and collapsed glomerular tuft
Type IV	Perihilar variant	Segmental sclerosis near the hilum
Type V	FSGS NOS	No characteristic feature

FSGS NOS: Focal Segmental Glomerulo Sclerosis Not Otherwise Specified

b) Risk factors for recurrence: Recurrence is higher in younger patients, in patients rapidly progressive to ESRD and in patients with high level proteinuria pretransplantation [53]. Initial sensitivity to steroids may predict recurrence as documented by a study on 125 pediatric transplant recipients [54]. Overall, the most reliable risk factor for recurrence is the recurrence in a previous allograft [55].

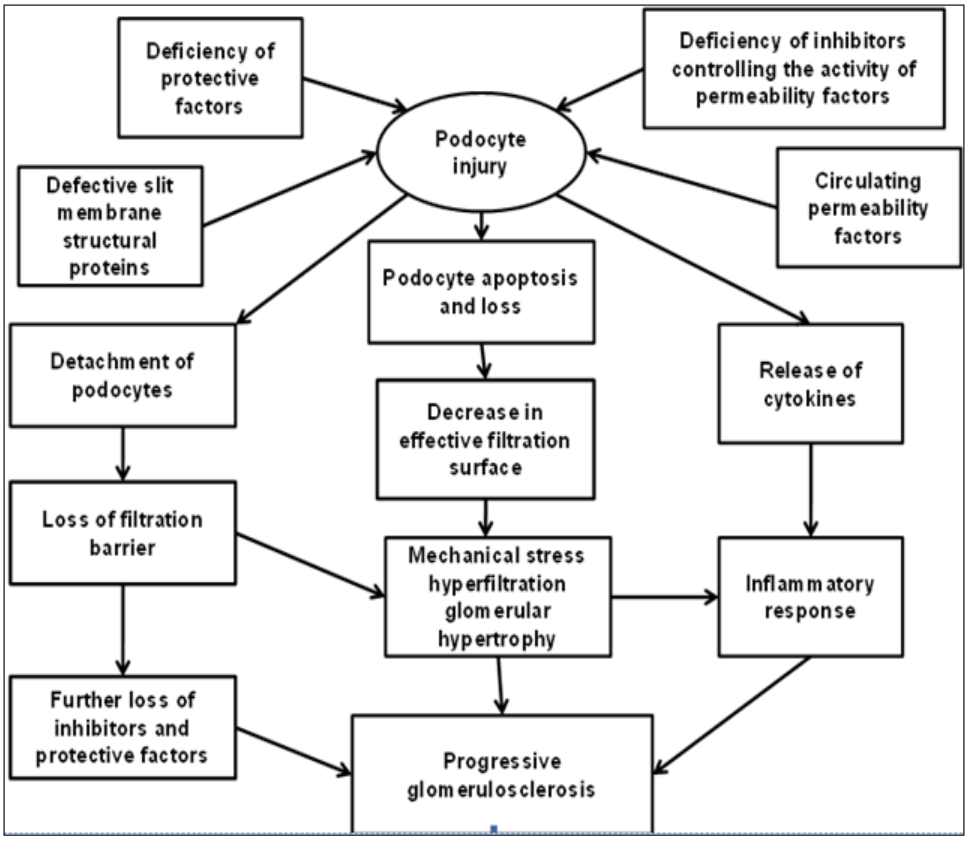

Figure 2: Putative pathogenesis of recurrent FSGS post renal transplantation.

c) Pathogenesis: Recurrent primary idiopathic FSGS is likely due to a circulating factor or to the absence of a normally present factor in plasma [56,57]. This factor could target glomerular podocytes, causing diffuse podocyte foot process fusion and proteinuria [55] (Figure 2). Recent reports suggest a role for soluble urokinase plasminogen activator receptors (su PARs) [58]. One study suggests the role of B7-1 pathway [59]. In some cases of recurrent FSGS, tumor necrosis factor (TNF) alpha pathway could be activated [60,61].

d) Clinical manifestations: Patients with recurrent primary FSGS present with proteinuria, often in the nephrotic range. This may be observed in the early post-transplant period. To detect early recurrence post-transplantation, at risk patients should be screened for proteinuria the day of hospital discharge, weekly for weeks and then monthly for one year after transplantation [62]. A renal biopsy should be performed if post-transplant proteinuria exceeds 1g/day. No interventions have been conclusively shown to prevent recurrent primary FSGS in the transplanted kidney. Two studies had suggested that prophylactic RTX administration may prevent recurrence. In one study RTX treatment was associated with lower incidence of proteinuria [63]. In another study RTX prevented FSGS recurrence in patients who had already lost a previous graft for recurrent disease [64].

e) Treatment: Recurrent FSGS may resolve after RTX administration [65]. This fact could be due to the action of RTX on B lymphocytes or to be the effect of RTX directly on glomerular sphingomyelin phosphodiesterase acid like 3 (SMPDL-3b) protein of the cytoskeleton [64]. However, the effect of RTX refers to case studies and small series of patients. Additionally, the interpretation of RTX effect is complicated by the fact that many patients are receiving simultaneously plasmapheresis (PP) in the attempt of removing the circulating factor [66]. In these patients the therapeutic effect of PP and RTX may be additive [66]. A previous study described a small group of patients with recurrent FSGS responsive, but dependent on PP who were able to discontinue PP after RTX administration. Prolonged beneficial results have also been reported in children treated with PP on cyclophosphamide [67,68]. A definitive conclusion concerning the use of cyclophosphamide requires further studies.

f) MembranoProliferative Glomerulonephritis: MPGN is classified into subtypes, including immune complex-mediated MPGN and C3 glomerulopathy. Immune complex-mediated MPGN is characterized by both immunoglobulin and complement protein deposition in the kidney, C3 glomerulopathy is characterized by complement deposition in the absence of immunoglobulin deposition. MPGN immune complex-mediated is divided according the immunoglobulin deposition in polyclonal and monoclonal. Complement mediated MPGN is divided into C3GN and dense deposit disease (DDD). The different characteristics of MPGN have effect on their recurrence rate that may be extremely variable [55] (Table 3). MPGN with polyclonal Ig deposits has a relatively low risk of recurrence and its progression is slow [69]. Patients with low complement levels have a higher risk of recurrence [69].

Table 3: Incidence of different pathogenic subtypes of primary MPGN in adult kidney transplant candidates.

Glomerular deposits by immunofluorescence	Subtype	No (%) 62	Recurrence risk %	Graft failure if recurrence
Igs	Polyclonal	24 (38.7)	30-35	10%
	Monoclonal	24 (38.7)	66	50%
Complement (C3)	C3GN	12 (19.3)	70	50%
	DDD	2 (3.2)	80-90	25%

C3GN: C3 Glomerulopathy; DDD: Dense Deposit Disease; MPGN: Membrano Proliferative Glomerulonephritis

MPGN with monoclonal deposits recurs often, early post-transplantation with an aggressive course [70]. 30% of patients with MPGN and monoclonal Ig deposits have serum monoclonal proteins. This group of patients fits into the category of diseases now called monoclonal gammopathies of renal significance [71,72]. The risk of recurrence may be very high in these patients [73]. MPGN immune complex-mediated presents with proteinuria, hematuria, hypertension and declining GFR. Hypocomplementemia is commonly observed [74]. Transplant glomerulopathy may be difficult to distinguish from recurrent MPGN since clinical presentation and histological features may be similar [75]. However, findings on electron microscope may be useful in the distinction [76]. There is no proven treatment for recurrent idiopathic MPGN. In uncontrolled studies, anti CD20 antibodies have been reported to be effective in the treatment of MPGN with monoclonal deposits in the allograft [77].

Low complement levels and living-related kidney transplantation are associated with an increased risk of recurrence [80]. The diagnosis is done with renal biopsy in suspected patients. An evaluation of the alternative complement pathway is often performed since the identification of an abnormality in the alternative complement pathway informs the immunosuppressive therapy. There are several reports on the use of monoclonal antibodies that inhibit the activation of C5 in patients with C3GN [81-83]. Given the highly variable behavior of MPGN subtypes, it is essential to clarify these diseases before transplantation. Table 4 summarizes pre-transplantation information helpful in this classification.

Table 4: Pre-transplantation characteristics helpful in classifying primary MPGN and predicting risks of recurrence and progression post-transplantation.

Pre-transplantation studies	Lower risk of recurrence and progression	Higher risk of recurrence and progression
Native kidney biopsy a) Immunofluorescence b) Electron microscopy	Polyclonal Ig deposits	Monoclonal Ig deposits C3GN DDD
Serum studies c) Complement levels (C3,C4) d) Monoclonal proteins	Normal Absent	Low C3 and/or C4 Present
Additional complement studies e) Alternative patway activation ? f) Classic/lectin pathway activation? g) Terminal pathway activation? h) C3Nef, C4Nef? i) Other autoantibodies? j) Genetic mutations?	Classic/lectin pathway activation (positive glomerular C4d) is associated with MPGN with polyclonal Ig deposits	Overactivation of alternative and/or terminal pathway

C3GN: C3 Glomerulopathy; C3NeF: C3 Nephritic Factor; DD: Dense Deposit Disease; MPGN: Membranoproliferative Glomerulonephritis

Conclusion

The risk of graft failure due to graft GN and in particular recurrent GN is high, almost certainly higher that estimated in previous studies. Furthermore, the risk associated with recurrent GN expands the entire transplant course. Randomized studies on the prevention and treatment of allograft GN are essential to further improve graft survival. To date has been documented the possibility to prevent the GN recurrence or, thank to new drugs to control their impact on graft survival.

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