Recurrent glomerulonephritis after renal transplantation

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Purpose of review
The current understanding of the incidence, predisposing factors, pathophysiology and effective treatment of recurrent glomerulonephritis (RGN) in renal transplants remains at best patchy and at worst, completely lacking. Current reports have been limited by inconsistencies in study design, sample populations and lengths of follow-up. Making sense of the available evidence will provide the tools to support transplant nephrologists in their management of allograft donors and recipients.

Recent findings
With better survival of renal allografts, RGN has become a dominant factor influencing allograft survival. Evidently, the risk of recurrence is proportional to the incremental time posttransplantation. The proposed risk factors for RGN include but are not limited to the severity of primary glomerulonephritis (PGN), younger recipient age, live-related donor allograft, minimal HLA mismatch, steroid avoidance and nonuse of induction therapy. Unfortunately, these findings are derived from retrospective cohort and registry studies; hence, true causality for RGN is hard to prove.

Summary
The management of RGN is improving, as we gain greater understanding of its pathophysiology, including the genetic, alloimmune and autoimmune contributions to recurrence. With better pretransplant risk stratification, posttransplant surveillance, novel biomarkers and new treatment strategies, we hope the transplant community will eventually have the tools to predict risk, prevent recurrence and personalise treatment of RGN.

Keywords
allograft failure, biomarkers, recurrent glomerulonephritis, renal transplantation

INTRODUCTION

Glomerulonephritis remains one of the leading causes of end-stage renal disease (ESRD) worldwide [1,2▪] It represents the cause of ESRD in 23, 32, 42 and 48% of the renal transplant population of the UK, USA, Australia and China, respectively [3–6]. Kidney transplantation is associated with both superior quality of life and a survival advantage over dialysis [2▪]. Unfortunately, the lifespan of renal allografts is finite, and so are the associated lifesaving benefits. The management of renal allografts is therefore aimed at achieving optimum graft function for the longest possible time by preventing and/or mitigating the factors that cause graft loss [7].

In recent decades, improvements in the pre, peri and postoperative management of transplants, immunosuppressive therapy and cardiovascular disease prevention have led to better short to medium-term survival of renal allografts [8]. Unfortunately, these improvements have not translated into appreciable improvements in long-term allograft survival [9–11]. Whereas the frequency of acute rejection has undoubtedly reduced, recurrence of primary renal disease, once thought to be a minor player in allograft outcomes, is now the third most common cause of allograft loss after immunologic rejection and death with functioning transplant [2▪,12]. More cases of RGN are being diagnosed as renal allografts survive beyond the first few years of transplantation. Transplant physicians need to acknowledge and understand the potential impact of RGN on allograft outcomes in order to provide

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KEY POINTS

- With the increasing prevalence of recurrent primary renal disease, the need to understand the risks and impact of RGN on allograft outcomes has become necessary.
- Primary glomerulonephritis such as MPGN, FSGS, membranous nephropathy and IgAN are more likely than secondary glomerulonephritis, to recur in allografts with FSGS and MPGN associated with earlier recurrence and poorer graft outcomes.
- 'There are wide variations in the reported incidence and predictors of RGN, which are likely due to differences in biopsy practices, length of follow up, histologic diagnostic approach and widely differing sample populations.
- Several potential biomarkers that can predict the onset and progression of RGN have been identified, but they still require further population-wide validation to assess their accuracy and reliability.
- To date, there is no consensus on the best and effective treatments for the different forms of recurrent PGN, although the anti-CD20 antibody, rituximab, has shown great promise in cases of FSGS, membranous nephropathy and MPGN.

adequate risk assessments and counselling of potential kidney transplant recipients (KTRs) and their donors [13▪▪]. Certainly, information regarding the epidemiology, pathophysiology and prognosis of RGN has increased and has led to improved risk stratification, better surveillance, earlier diagnosis and better treatment [12]. Nevertheless, significant knowledge gaps still exist in predicting which patients are at-risk, identifying disease biomarkers, judging of severity and prognostication. Understanding these factors is essential for better planning and prioritization of interventional strategies before irreversible damage has occurred in the allografts [14].

This review summarizes current evidence on the epidemiology, biomarkers, treatment and outcomes of RGN in transplant recipients with the commonest PGN: Immunoglobin A nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and membranous nephropathy. It highlights areas that may benefit from further research.

REVIEW METHODOLOGY

A literature search was carried out in February 2020 that included the published literature since June 2018 on the recurrence of glomerulonephritis in renal allografts. Information was retrieved from Medline through the NICE healthcare data base advanced search (NICE HDAS) using the keywords 'Renal transplant', 'Allograft', 'Recurrent glomerulonephritis', 'IgA nephropathy', 'Membranous nephropathy', 'Focal segmental glomerulosclerosis', 'Membranoproliferative glomerulonephritis' in the title/abstract. A total of 275 articles were identified of which 58 were considered relevant to the topic. Other manuscripts were located through the reference list of relevant articles. These articles were evaluated based on the following criteria: how current the article was, if the article addressed research questions on the prevalence, predictors, outcomes, treatment or biomarkers of one or more of the recurrent PGNs in adults. Some articles were included that were published before 2018, as they had established important concepts and knowledge, which is currently relevant.

EPIDEMIOLOGY OF RECURRENT GLOMERULONEPHRITIS

The reported incidence of RGN has varied from 3 to 20% [13▪▪,15–24], the variations thought to be the result of differences in biopsy practices, lack of histological diagnoses in late presentations of ESRD and variable lengths of follow up. Also, variations in clinical presentations have resulted in failure to diagnose clinically asymptomatic cases [13▪▪,25,26]. Furthermore, biopsy specimens are not always subjected to precise and complete histological analysis. Hence, some RGNs have been misrepresented as other causes of late allograft dysfunction [13▪▪,27]. A recent study reported a recurrence rate of 11% and a median time to recurrence of 15 months amongst 862 KTR whose primary disease was biopsy-proven glomerulonephritis [28]. Another study reported an incidence of 19.7% amongst 183 KTR followed for a mean period of 8.5 years and resulted in the loss of up to 55.6% of the affected allografts [23]. A large registry study by Jiang *et al.* [2▪] included 7236 KTR of which 4025 had biopsy-proven PGN, followed up for a median period of 6.1 years; glomerulonephritis was identified in 7% (511) of allografts (both primary and secondary native glomerulonephritis) and 10.5% (424 out of 4025) of patients with PGN. Table 1 summarizes the incidences, time to recurrence and outcomes of the individual primary glomerulonephritis.

RISK FACTORS FOR RECURRENT GLOMERULONEPHRITIS

The ability to predict which KTR will develop RGN would be invaluable in pretransplant counselling, enabling the physician to personalise preventive and surveillance strategies and to initiate timely

Table 1. Summary of recent studies showing prevalence and outcomes of each of the four primary glomerulonephritis

GN type	Study details (Ref. and study period)	Study population	Mean/ median Follow-up period	Incidence of RGN	Time to recurrence	Outcome
Focal segmental glomerulosclerosis	Uffing *et al.* [37▪▪] International multicentre study (2005–2015)	176 (primary idiopathic FSGS)	5.0 years	32% (57/176)	1.5 months	GL RGN vs. non-RGN = 39 vs. 15% HR = 4.8
	Singh *et al.* [28] WisARD (1994–2013)	298	6.3 years	13% (39/298)	3.7 months	–
	Jiang *et al.* [2▪] ANZDATA (1985–2013)	975	6.1 years	10.4% (101/975)	6.7 months	5 years DCGS = 55.6 vs. 86.6% HR-1.83
	Park *et al.* [23] Korea (1982–2017)	47 (first KT)	8.5 years	25.5% (12/47)	–	–
	Francis *et al.* [39]	736. (first KT)	5.0 years	10.3% (76/736)	–	5 years GS = 52 vs. 83%
	Allen *et al.* [22] ANZDATA (1985–2014)	1043	7.7 years	10% (144/1403)	–	5 years GS = 57%
Total		3275		429/3275, 13%		
IgA nephropathy	Singh *et al.* [28] WisARD (1994–2013)	306	6.3 years	8.8% (27/306)	33.7 months	–
	Garnier *et al.* [81] France (2003–2014)	67	6.0 years	20.8% (14/67)	–	GL 21.4 vs. 10.4%
	Jiang *et al.* [2▪] ANZDATA (1985–2013)	2393	6.1 years	9.7% (231/2392)	4.63 years	5 years DCGS = 88.3 vs. 90.2% HR = 4.49
	Park *et al.* [23] Korea (1982–2017)	95	8.5 years	20% (19/95)	–	–
	Allen *et al.* [22] ANZDATA (1985–2014)	2501	7.7 years	9% (225/2501)	–	5-year GS-58%
Total		5362		516/5362, 9.6%		
Membranoproliferative glomerulonephritis/ mesangial-capillary glomerulonephritis	Jiang *et al.* [2▪] ANZDATA (1985–2013)	348	6.1 years	15.5% (54/348)	1.87 years	5-year DCGS- = 44.6 vs. 79.5% HR-3.14
	Wilson *et al.* [57] ANZDATA (1996–2016)	190	2.74 years	18% (34/190)	–	GL from disease recurrence- MPGN vs. all other GNs = 32 vs. 5%
	Park *et al.* [23] Korea (1982–2017)	14	8.5 years	21.4% (3/14)	–	–
	Allen *et al.* [22] ANZDATA (1985–2014)	376	7.7 years	16% (61/376)		5-year GS = 30%
Total		928		152/928, 16.4%		
membranous nephropathy	Singh *et al.* [28] WisARD (1994–2013)	81	6.3 years	16% (13/81)	11.7 months	–
	Yang *et al.* [82] ANZDATA (1998–2010)	167	5.6 years	11.4%(19/16)	3.6 years	47% graft loss. Hazard ratio for GL- MN vs. non-MN = 1.55
	Jiang *et al.* [2▪] ANZDATA (1985–2013)	309	6.1 years	12.3% (38/309)	3.93 years	5-year DCGS- RGN vs. non-RGN = 70 vs. 88.3% HR = 2.20
	Park *et al.* [23] Korea (1982–2017)	9	8.5 years	22.2% (2/9)	–	–
	Allen *et al.* [22] ANZDATA (1985–2015)	357	7.7 years	13.7% (49/357)	–	5-year GS = 59%
Total		923		121/923, 13.1%		

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CR, complete remission; DCGS, death-censored graft survival; FSGS, focal segmental glomerulosclerosis; FU, follow-up; GL, graft loss; GN, glomerulonephritis; GS, graft survival; HR, hazard ratio; IgAN, IgA nephropathy; MCGN, mesangiocapillary glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; PR, partial remission; PY, patient-years; RGN, recurrent glomerulonephritis; WisARD, Wisconsin allograft recipient database.

treatment. Unfortunately, inconsistencies in the reported predictors of RGN has made generalizability and establishing causal relationships challenging [13▪▪,29]. Several risk factors for RGN have been reported (Table 2). Some of the reported predictors include younger age at transplantation [2▪,19,22,23,30], male sex [2▪,19], shorter duration of primary renal disease history [23], low/zero HLA mismatch [22], steroid avoidance/early steroid withdrawal [22,31], shorter total ischemic time [22], live-related donor transplantation [16,19,32,33], nonuse of lymphocyte-depleting

Table 2. Summary of prevalence, risks, biomarkers, available and potential future treatments of recurrent glomerulonephritis

	FSGS	IgAN	MPGN	MN
Recurrence rates[a] %	10–35	8.8–20	15–21	11–22
Median time to recurrence	1.5–12 months	2–5 years	4 months–24 years	1–4 years
Graft loss at 5 years with recurrence %	20–40	2–16	30–70	30–40
Risk predictors	Younger age (inconsistent) Aggressive course of original disease Previous failed transplant LRT	Zero HLA mismatch Younger age Crescents in native disease LRT Absence of Steroid use at baseline (inconsistent)	LRT Low Complement level Presence of monoclonal proteins Preemptive transplantation	Severity of pretransplant proteinuria. Pretransplant Anti-PLA2R antibody level LRT
Screening	Proteinuria	Proteinuria Serum Creatinine	Complement levels Proteinuria, Serum Creatinine	Pretransplant Anti-PLA2R Proteinuria Serum creatinine
Potential Biomarkers	Apolipoprotein A-Ib Serum/urine SuPAR Cardiolipin like cytokine factor 1 CLCF1 Anti-CD40 antibody Anti-ATIR antibody	GD-IgA1 IgA1-IgG specific autoantibody CD89 Complexes	Complement factors C3, C9, C3 nephritic factor, Complement regulatory proteins eg Clusterin & Vitronectin. Apolipoprotein E	Anti-PLA2R Anti-THSD7A CD19, CD20, CD138, CD34 Auto antibodies to podocyte antigens AR, SOD2, αENO [13▪▪]
Best available treatment	Plasmapheresis with rituximab	Corticosteroids improved proteinuria but higher risk of infections MPA- mixed results Alkylating agents for crescentic IgAN	Rituximab for Ig-mediated MPGN Eculizumab (mixed results) for Complement mediated MPGN. Other complement inhibitors undergoing trials Antivirals for HCV Treat monoclonal gammopathy	Anti CD20 MAB-Rituximab Alkylating agents (Cyclophosphamide) in combination with corticosteroids
Possible future therapies	Anti-CD40 antibody Lucatumumab [50▪]	Tyrosine kinase inhibitor Fostamatinib [49], MBL pathway inhibitor OMS721, B-cell activating factor inhibitor Atacicept [50▪] Insulin like growth factor 1 inhibitor octreotide [80]	Proteasome inhibitor (Bortezomib) for monoclonal gamopathy associated MPGN [66]	Proteasome inhibitor (Bortezomib [83]) Anti-CD38 MABs (Daratumumab and Isatuximab) [84] New anti-CD20 MABs (Ofatumumab and Obinutuzumab [84]

AR, aldose reductase; ATIR, angiotensin receptor II type 1; αENO, alpha enolase; GD-IgA1, galactose-deficient immunoglobulin A1; HCV, hepatitis C virus; HLA, human leucocyte antigen; LRT, live related donor; MAB, monoclonal antibody; MBL, mannose-binding lecithin complement pathway.
[a]Data from studies within the last 5 years.

induction agents [33] and shorter duration of pretransplant dialysis [22,33]. There is an evident lack of consensus on the majority of the proposed risk factors. Jiang *et al.* [2▪] identified live donor transplantation and male sex as risk factors for RGN, while Allen *et al.* [22] and An *et al.* [24] found no link between RGN and one or both of these factors. The increased risk of recurrence in live related donor kidneys may suggest a genetic contribution to some RGN. Also, certain HLA haplotypes have been linked to RGN [34,35]. Early steroid withdrawal as a predictor of RGN has been reported by some studies [22] but not corroborated by others [36]. Amongst glomerulonephritis subtypes, the majority of studies have reported MPGN and FSGS as the most commonly recurring forms of RGN [2▪,20,22,32,33]. However, studies of Southeast Asian populations reported IgAN as the commonest RGN [21,24].

IMPACT OF RECURRENT GLOMERULONEPHRITIS ON GRAFT OUTCOMES

There is clear evidence of significant detrimental effects of RGN on allograft survival, but variations exist amongst studies. Graft losses of 8–50% have been reported at 5 years posttransplantation [19,21,23]. In one study, KTRs with RGN were three times as likely to lose their grafts as those without RGN [2▪]. Favi *et al.* [27] evaluated the long-term graft survival of 426 KTR of which 99 (23%) had PGN, comparing the effects on graft survival of RGN, acute rejection and chronic allograft nephropathy (CAN). Respectively, KTRs with RGN had a 10-year graft loss of 42% compared with 30% for acute rejection and 23% for CAN [27]. Jiang *et al.* [2▪] reported a higher allograft loss with recurrent MPGN and FSGS than with recurrent IgAN. Similar outcomes were observed by Singh *et al.* [28] and Canas *et al.* [32] but not by Yu *et al.* [21] who noted a poorer outcome amongst Taiwanese KTRs with recurrent IgAN [21], suggesting that both epidemiology and outcomes of glomerulonephritis may be influenced by ethnic differences.

PATHOPHYSIOLOGY, BIOMARKERS AND TREATMENT OF SUBTYPES OF RECURRENT PRIMARY GLOMERULONEPHRITIS

Table 2 summarizes the prevalence rates, potential diagnostic biomarkers, current and potential future treatment strategies of RGNs.

FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

The reported incidence of recurrent FSGS varies widely amongst studies ranging from as low as 9% in some studies to as high as 55% in orders. Smaller studies tend to report higher incidence (17–55%), while registry studies have reported lower incidence (9–15%) [37▪▪]. More recent studies report incidents of between 10 and 35% [2▪,22,23,37▪▪,38,39]. The wide variations are likely due to differences in patient selection and grouping within the different studies. Firstly, FSGS is not a specific disease entity but rather a histologic pattern of injury. Resulting from a range of glomerular insults, which could be idiopathic (but immune-mediated), infective, genetic, toxic or a secondary maladaptive response to nephron loss [40,41]. Secondly, some of these underlying aetiologies reoccur at varying rates in kidney allografts. Although idiopathic FSGS has a high recurrence rate, due to the suspected but still elusive circulating permeability factor [42], genetic and secondary FSGS have a much lower risk of recurrence [43,44]. Therefore, aggregating all cases of FSGS, with widely varying underlying kidney insults, into one cohort could conceivably confound the analysis of FSGS recurrence. Furthermore, the FSGS lesions in the native and transplant kidneys of a patient may sometimes have different causes (e.g. a genetic cause in the native kidney and a maladaptive cause in the allograft). Consequently, without identifying and grouping patients on the basis of their underlying cause (such as with genetic testing), statements regarding reoccurrence rates should be viewed with some degree of scepticism. Recurrent FSGS is associated with a five-fold increase in graft loss when compared to KTRs with primary FSGS but nonrecurrence [37▪▪]. Most recurrences occur early with a median time of 1.5–12 months in primary FSGS [37▪▪,45]. The early and high recurrence rates of primary FSGS has been attributed to the presence of a circulating permeability factor in the sera of KTRs, the identity of which has been the subject of ongoing research [42,46]. Savin *et al.* [47] first demonstrated that rats exposed to sera of patients with recurrent FSGS developed albuminuria, while Gallon *et al.* [48] later described a case of rapidly recurrent FSGS in a living donor recipient in which there was a reversal of the histopathologic and clinical features of FSGS in the same allograft after it was explanted and retransplanted into a different recipient without native FSGS. The most studied candidate circulating factor is the soluble urokinase plasminogen activating receptor (SuPAR). High pretransplantation levels of SuPAR have been linked to increased risk of FSGS

recurrence posttransplantation [13▪▪]. SuPAR is believed to cause podocyte foot process effacement and proteinuria by activating podocyte β3 integrin [42,49]. Other circulating factors under investigation include anti-CD40 auto-antibody, Apolipoprotein A-lb (ApoA-lb) and cardiotrophin-like cytokine factor-1 (CLCF1) [42]. Podocyte foot processes are believed to be the main sites of injury in most forms of primary FSGS [42]. Lucatumumab, an anti-CD40 antibody, is currently in development for the treatment of FSGS [13▪▪]. Corticosteroids, calcineurin inhibitors (CNIs), plasmapheresis, immunoadsorption, rituximab, cyclophosphamide and Abatacept/belatacept have all been used, in varying combinations and with varying degrees of success, for the treatment of FSGS [37▪▪]. A recent study by Uffing *et al.* [43] found that plasmapheresis with rituximab was the only remission inducing treatment amongst 75 KTR with recurrent FSGS. Compared with idiopathic FSGS, most genetic forms FSGS are less likely to reoccur. Genetic FSGS have defective podocyte components, such as in podocin and nephrin; therefore, their risk of recurrence in allografts is low, as these allografts are less likely to have same podocyte defects [50▪].

IgA NEPHROPATHY

The reported incidence of IgA nephropathy (IgAN) varies in the literature because of the reasons already mentioned. Centres that performed protocol biopsies have reported a higher rate of recurrence (30–50%) [51]. However, as expected, registry reports suggest lower incidence, 5.4 and 10.8% at 5 and 10 years, respectively [52]. Aberrantly glycosylated IgA1 has been identified as an important element in the pathogenesis of IgAN resulting in the production of galactose deficient IgA1 (Gd-IgA1) [53]. In one study involving 60 KTR with biopsy-proven IgAN followed up for a median period of 8.6 years, the pretransplant levels Gd-IgA1, serum IgA, IgG glycan specific autoantibodies and CD89 complexes were found to be significantly higher in the recurrence group than the nonrecurrence and healthy control groups, and predicted IgAN recurrence, disease progression and allograft failure [54,55]. Suzuki *et al.* [52] characterized and validated a mAb, KM55 that can detect serum as well as glomerular Gd-IgA1 deposits with high specificity using a novel lectin-independent Gd-IgA1 ELISA. This assay can also distinguish between Gd-IgA1 deposits in IgAN from non Gd-IgA1-IgA deposits that occur in lupus nephritis, membranous nephropathy, hepatitis C infection and liver failure [53,56▪▪]. KM55, when fully developed, could revolutionize the diagnosis of IgAN and provide a tool for risk assessment and surveillance for recurrent IgAN [55,56▪▪]. Immunosuppressive agents in recurrent IgAN have had little impact on eGFR decline, but they have been associated with significant adverse events. Steroids improve proteinuria, but at the expense of increased adverse events [54,56▪▪]. MMF has had mixed results, while rituximab and tacrolimus provided no benefit [56▪▪]. Current trials are investigating the value of the tyrosine kinase inhibitor Fostamatinib, OMS721 a mAb that inhibits the mannose-binding lecithin complement pathway, and a B-cell activating factor blocker, Atacicept in primary IgAN [57,58].

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is characterized by mesangial proliferation and expansion, endocapillary proliferation, diffuse basement membrane thickening and reduplication caused by immune complex deposition [20,22,33]. The old classification of MPGN (types I, II and III) was based on the location and appearance of immune deposits in the glomerulus, but this provided very little information about the underlying pathogenesis [57]. The latest classification is based on the mechanism of injury and broadly divides MPGN into immune complex-mediated (IC-MPGN) (presence of immune complexes and complement in biopsy) and complement-mediated MPGN (C-MPGN) (presence of complement without immune complexes) [59]. Most studies on recurrent MPGN were based on the old system of classification and have reported recurrence rates ranging from 18 to 65% [60]. Compared with other RGN, MPGN is associated with a poorer 5-year allograft survival and a shorter time to graft loss [61]. Complement factors C3 to C9, and complement regulatory proteins vitronectin and clusterin, have been suggested as potential biomarkers of complement-mediated MPGN [58]. The persistence or recurrence of hypocomplementemia and or monoclonal proteins posttransplantation have also been shown to predict MPGN recurrence [57].

There are suggestions that C3 glomerulopathy may be responsible for most cases of MPGN recurrence [62]. However, this has been difficult to prove, as most studies were based on the old classification system [63–67]. In 2016, Alasfer *et al.* [68] undertook a single-centre retrospective study of recurrent MPGN amongst KTRs transplanted over a 20-year period and assessed the incidence and outcomes of recurrent MPGN using the new classification system. Out of a total of 34 patients who received 40 allografts, 88% of the pretransplant MPGN was classified as IC-MPGN, while 12% was classified as C-MPGN. Recurrence

occurred in 18 out of 40 allografts (45%) of which 16 were IC-MPGN, and two were C-MPGN. Living related allografts, preemptive transplantations, low complement level and presence of monoclonal gammopathy were factors associated with a higher rate of IC-MPGN recurrence. Due to the very small number of recurrent C-MPGN in the cohort, predictors for C-MPGN were not assessed. Half of the patients with recurrence lost their allografts. Allograft survival was not statistically different, although there was a trend towards worse survival in the group with recurrence [66].

Treatment outcomes of recurrent MPGN have not been encouraging. In addition to antiproteinuric treatment, MMF with or without steroids has shown varying degrees of success in native kidney MPGN [69,70] but not so much in transplant MPGN. Long-term use of alkylating agents has been limited by the increased risk of malignancy and infections [71]. Rituximab with or without plasmapheresis has shown inconsistent results [13▪▪,69] as has eculizumab [72▪,73], Perhaps the new classification system will make it possible to tailor the right treatment to the right underlying disease, such as using plasmapheresis and rituximab for immune complex MPGN [74–76], whilst anticomplement therapy could be useful in complement-mediated disease. Complement inhibitors that are currently available for such treatment include eculizumab (anti-C5 complement antibody), Compostin (CP40, a soluble peptide C3 complement inhibitor), soluble CR1 (a recombinant cell surface glycoprotein that regulates C3 convertase) as well as monoclonal antibodies against C3, factor B and properdin [77–79]. Most of these therapies are still undergoing clinical trial evaluation, but some have shown great promise in C-MPGN.

MEMBRANOUS NEPHROPATHY

Primary membranous nephropathy is characterized by subepithelial deposits comprising immunoglobulin (usually IgG4), antigen and complement components. The recurrence rate posttransplantation is between 7 and 50% [75]. In a study of 63 KTR with biopsy-proven membranous nephropathy followed up with protocol biopsy for a median period of 77 months, a 48% histologic recurrence rate was observed [73]. The discovery of autoantibodies against the podocyte PLA2R, and more recently the antithrombospondin type-1 domain-containing 7A (THSD7A), has provided a better understanding of the pathophysiology and made the diagnosis of idiopathic membranous nephropathy much easier [74]. In cases of anti-PLA2R MN, recurrence is related to the same antibody that caused the original disease [76], and the level of circulating autoantibody at transplantation has been shown to correlate with the risk and severity of recurrence and the likelihood of remission following treatment of recurrence [75]. In one study of 26 KTR with membranous nephropathy, a positive anti-PLAR2 pretransplantation predicted recurrence with a positive predictive value of 83% [74]. Gupta *et al.* [74] have now shown that an anti-PLA2R level more than 29 RU/ml (normal <14 RU/ml) pretransplantation is a strong predictor of RGN with 85% sensitivity and 92% specificity. In contrast, Seitz-Polski *et al.* [56▪▪] found no correlation between the pretransplantation anti-PLA2R level and the risk of recurrence but instead noted a relationship between the 6-month posttransplantation anti-PLA2R level and recurrent membranous nephropathy. Regular monitoring of patients using anti-PLA2R assays and proteinuria quantification as well as prompt kidney biopsy when clinically indicated will help identify asymptomatic/early recurrence [72▪,80]. The evidence for appropriate treatment of recurrent membranous nephropathy is limited and mainly extrapolated from the treatment of native kidney membranous nephropathy [73]. As with Native kidney MN, treatment is dependent on the degree of proteinuria (>1 g/day), the trajectory of GFR, the severity of histological changes and the autoantibody level [50▪]. There is no evidence that modifying the posttransplant immunosuppression alters the risk of recurrence [50▪]. Alkylating agents in combination with corticosteroids (modified Ponticelli regime) have been the mainstay of treatment until recently [13▪▪]. However, the use of rituximab has gained popularity in recent years [81]. One small study of 17 KTR treated with rituximab found that 82% achieved complete or partial remission [81]. Randomized control trials to determine the most effective treatment of recurrent membranous nephropathy are lacking.

CONCLUSION

The effects of posttransplant immunosuppression, the immunogenic burden of both the donor and recipient, as well as the altered autoimmune and alloimmune milieu of allografts, significantly impacts the pathophysiology of posttransplant glomerulonephritis, their progression and their response to treatment. Despite the progress made in understanding the epidemiology and pathophysiology of these conditions, significant gaps still exist in our knowledge of the risks, outcomes and efficacy of current treatment strategies. It is therefore crucial that we gain a better understanding of these diseases to enable active risk stratification, better monitoring and prompt effective treatment. Achieving this will

require international, collaborative, multicentre prospective research studies with an emphasis on identifying and validating predictive biomarkers as well as providing evidence-based effective treatments. Encouragingly, there are several under development.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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