Recurrent Glomerular Disease after Kidney Transplantation
Diagnostic and Management Dilemmas

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Abstract

Recurrent glomerular disease after kidney transplant remains an important cause of allograft failure. Many of the different entities post-transplant still suffer from incomplete knowledge on pathophysiology, and therefore lack targeted and effective therapies. In this review, we focus on specific clinical dilemmas encountered by physicians in managing recurrent glomerular disease by highlighting new insights into the understanding and treatment of post-transplant focal segmental glomerulosclerosis, membranous nephropathy, atypical hemolytic uremic syndrome, C3 glomerulopathy, amyloid light-chain (AL) amyloidosis, and IgA nephropathy.

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Introduction

Glomerular disease is one of the leading causes of kidney failure, representing the third most common reason for kidney transplantation in the United States (1). After kidney transplantation, glomerular disease has been identified as an important contributor to allograft failure in registry studies worldwide (2–4). Glomerular disease after transplantation includes a variety of disease entities and has already been subjected to many high-quality reviews. This review will address specific dilemmas that clinicians face in the management of post-transplant glomerular disease and highlight emerging evidence that may help guide management.

FSGS

Recurrence of primary FSGS after kidney transplant is immensely challenging. Recurrence rates after transplant vary from 30%–60% between studies (5), due to variability in study size, study design, and the criteria used for the selection of patients with presumed primary FSGS, including methods used for exclusion of secondary and genetic FSGS, and the definition of recurrent FSGS. The pathogenesis of recurrent FSGS is still largely unknown, although the presence of a circulating factor toxic to podocytes is highly suggestive (6). Despite the use of multiple treatment approaches, resistant disease and graft loss remain common.

Dilemma: How Do the Clinic-Pathologic Features of Native FSGS Inform the Risk of Recurrence after Transplant? FSGS describes a histologic pattern found on kidney biopsy caused by a heterogeneous group of etiologies that lead to podocyte injury. Identifying the different causes of FSGS is pivotal in counseling patients because there is a high risk of recurrence in

patients with primary FSGS, but negligible risk in patients with secondary (7) and genetic forms.

One important clinical clue about the risk of recurrence is the presence or absence of nephrotic syndrome in the patient's presentation of native FSGS. Patients without nephrotic syndrome at disease manifestation seem to have a very low risk of recurrence after kidney transplantation (8). This was endorsed by our own data from the Post-Transplant Glomerular Disease (TANGO) cohort in which 22 patients with biopsy-proven FSGS without clinicopathological signs of secondary FSGS, and no nephrotic syndrome at manifestation, did not experience a recurrence after kidney transplantation (5). FSGS histologic variants (collapsing, tip lesion, cellular, perihilar lesion, not otherwise specified) have no effect on the risk of recurrence (9), and there is no literature supporting an association between the degree of podocyte foot process effacement on electron microscopy and risk of recurrence after transplant.

Many studies have attempted to identify clinical factors that are associated with higher or lower risk of recurrence, resulting in associations between recurrence and older age, White race, faster time to kidney failure, living (related) donation, and nephrectomy of native kidneys. However, most studies relied on univariable analysis and did not mention methods to exclude genetic and secondary FSGS. Because a distinction between primary and secondary FSGS is difficult, and greatly influences recurrence risk, the found associations are likely confounded by misclassification of secondary FSGS and lack of genetic testing, including APOL-1 high-risk variants in recipients and donors. Overall, specific histologic changes on native biopsy are not associated with FSGS recurrence, and the absence of nephrotic syndrome at disease presentation is associated with nonrecurrence.

Dilemma: Should Patients with Primary FSGS Undergo Genetic Testing before Kidney Transplantation? More than 50 genes have been associated with FSGS. Children with FSGS have a higher prevalence of monogenic or familial genetic FSGS (approximately 30%) versus adults, and most pathogenic variants are podocyte specific (kidney intrinsic) (10). Studies of FSGS recurrence in patients with monogenic or familial FSGS have revealed a low recurrence rate, as low as 0% in a large pediatric cohort (11). One exception is a specific *NPHS1* mutation (Fin-major/Fin-major type) that has a recurrence rate of 25%–34%, but this mutation is rare outside Finland (12,13). Given the availability of comprehensive and low-cost genetic testing panels for FSGS (14), and the increasing number of identified genes associated with adult-onset FSGS, such as the COL4A genes, we believe genetic testing should be considered an important tool for the risk stratification of FSGS recurrence.

APOL1 high-risk variants found among individuals with sub-Saharan ancestry have been associated with augmented risk of several kidney diseases, including FSGS (15). Our understanding suggests that *APOL1*-related FSGS should not recur after transplant because kidney-specific expression of *APOL1* high-risk variants is a crucial driver of podocyte injury (16). Indeed, 5-year graft survival of recipients with *APOL1* high-risk alleles was similar to patients without risk alleles (17), whereas *donor APOL1* status been associated with higher risk of graft failure (18). The important question of how donor *APOL1* status should influence organ allocation is beyond the scope of this review and is being explored by the APOL1 Long-term Kidney Transplantation Outcomes Network (19).

Dilemma: Should Patients with Primary FSGS Undergo Prophylactic Treatment around Kidney Transplantation? Prophylactic plasmapheresis in patients with a presumed high risk of FSGS recurrence was first reported over 20 years ago; although to date, no study has found a significant effect of prophylactic plasmapheresis on recurrent FSGS (Table 1). All published studies suffered from small sample sizes and thus low power, retrospective design, and a lack randomization of treatment. In addition, the choice for prophylaxis was chosen by the practicing clinician depending on presumed risk, which makes it difficult to interpret outcomes. For prophylactic rituximab or LDL-apheresis, studies are even more limited. Because of the low level of evidence, it is recommended to avoid pretransplant treatment to prevent recurrent FSGS. Instead, thorough surveillance after kidney transplantation with initial daily proteinuria measurements is advised on the basis of its usual early recurrence post-transplant. Ongoing trials are assessing the preemptive use of rituximab, bleselumab, or adrenocorticotropic hormone on recurrent FSGS (NCT03763643, NCT02921789, and NCT02683889, respectively).

Dilemma: Should Patients with Primary FSGS Undergo Native Nephrectomies before Transplant? Recurrent FSGS has a peak incidence in the first weeks after kidney transplantation, and strict monitoring of post-transplant proteinuria is required. In case a patient still has significant diuresis pre-transplantation with severe proteinuria, nephrectomy of native kidneys has been considered in the past to facilitate monitoring for disease recurrence. In children, native nephrectomies have been performed due to refractory hypo-albuminemia and continuous requirement for intravenous albumin administration (20). However, in adults, native nephrectomies have been associated with higher risk of FSGS recurrence and have been abandoned by most centers (5,21). There is no evidence that placing a patient on dialysis before transplant will reduce the risk of recurrence, and preemptive transplantation should be offered to these patients. In sum, native nephrectomies are generally not recommended before transplant in adults. Patients with risk of recurrence should be monitored with daily measurements of proteinuria in the first 1–2 weeks after kidney transplantation, after which the frequency of measurements can be slowly tapered. Late-onset recurrent FSGS does occur, but is rare, and in these patients, other etiologies such as transplant glomerulopathy or donor high-risk APOL-1–related disease should be ruled out to guide further management.

Dilemma: What Is the Best Treatment Strategy for Patients with Recurrent FSGS after Kidney Transplantation? The treatment of recurrent FSGS remains empirical because no randomized controlled trials have ever been performed. Although various agents have been described to treat recurrent FSGS (Table 2), international cohorts and surveys reveal most patients receive treatment with plasmapheresis, in many patients combined with rituximab (5,22). Plasmapheresis is used with the goal of removing the elusive circulating factor, whereas rituximab may act by a direct effect on podocytes or by its depletion effect on immune B cells (23). The remission rates in studies with plasmapheresis, rituximab, and/or other treatments for recurrent FSGS vary widely (listed in Table 2), likely due to varying treatment regimens, definition of partial and complete remission, and the possibility of publication bias. In some centers, especially in France, intravenous cyclosporine is part of the standard care after recurrence of FSGS because it has been reported to have a function in stabilization of the podocyte cytoskeleton (24). However, this treatment is not widely used, possibly due to the concern for nephrotoxicity and logistical challenges with continuous intravenous infusion, and the available alternative treatments.

In a minority of centers, plasmapheresis has been replaced by immunoadsorption, an apheresis method that enables more selective removal of immunoglobulin, with the advantage that no substitution fluid is needed and no coagulation factors are lost. The efficacy of the more expensive and less available immunoadsorption method compared with plasmapheresis has never been assessed in a trial, although average remission rates between both treatment modalities seem similar (25–27). The crucial limitation is that it is unclear what circulating factor that drives the podocyte injury is being removed with either therapy. In patients without response to pheresis/rituximab, other treatments have been proposed, such as LDL apheresis, abatacept, adrenocorticotropic hormone gel, and adalimumab, mainly in case reports. The published studies since 2010 with >10 participants on these treatments are listed in Table 2, but the evidence for these therapies being useful in recurrent FSGS is low. Other than a single-armed trial to LDL-apheresis (NCT04065438), no actively recruiting trials are registered to investigate new treatments for recurrent FSGS.

Table 1. Selected studies of prophylactic treatment before kidney transplantation in patients with primary FSGS

Treatment	Study	Population	Design	Total (n)	Genetic Testing	Dosage	Recurrence Rate Per Group Recurrence/No Remission (%)	Comments
Plasmapheresis	Ohta et al. 2001 (75)	Children	Retrospective PPP versus none	21	No info	2–3 sessions PP pre-transplant	PPP: 5 out of 15 (33%) None: 4 out of 6 (67%)	No information on exclusion of genetic FSGS Multiple allografts per patient
	Gohh et al. 2005 (76)	Adults + 1 child	Retrospective Single group (PPP)	10	No info	8 sessions PP peri-Tx	PPP: 3 out of 10 (30%)	No control group Large differences in time point PP was started
	Hickson et al. 2009 (77)	Adults + children	Retrospective PPP versus none	30	Not performed Familial FSGS excluded	1 or more sessions PP pre-Tx	PPP: 6 out of 7 (86%) None: 7 out of 23 (30%)	Study was designed to define patients with high-risk for FSGS recurrence, not to assess effects of PPP
	Gonzalez et al. 2011 (78)	Children	Retrospective PPP versus none	34	NPHS2 tested in 10 patients	1–10 sessions PP pre-Tx	PPP: 9 out of 17 (53%) None: 10/17 (59%)	1 patient had a heterozygous NPHS2 mutation
	Verghese et al. 2018 (79)	Children	Retrospective PPP versus none (historical cohort)	51	NPHS2 tested in PPP group	1–3 sessions PP pre-Tx, 5 sessions post-Tx	PPP: 7 out of 26 (27%) None: 8 out of 31 (26%)	Historical control group, significant differences between groups No genetic testing in control group
Plasmapheresis + rituximab	Alasfar et al. 2018 (80)	Adults	Prospective PPP+PRTX and PRTX versus none	66	Genetic FSGS excluded, no info on number of patients tested	3–10 sessions PP peri-Tx 1–2 doses RTX	PRTX and PPP+PRTX: 23 out of 37 (62%) None: 14 out of 27 (52%)	Prophylactic treatment on the basis of high/low risk No differentiation between PRTX only and combined PRTX+PPP
Rituximab	Fornoni et al. 2011 (23)	Children	Retrospective PRTX versus none (historical cohort)	41	No info	1 dose RTX (375 mg/m^2)	PRTX: 8 out of 27 (30%)[a] None: 10 out of 14 (71%)	Study was designed to investigate mechanisms of rituximab, therefore limited clinical data and significant differences between groups
LDL-apheresis + rituximab	Sannomiya et al. 2018 (81)	Adults	Retrospective Single group (RTX + LDL-apheresis)	5	No info	1 dose RTX (100 mg) and 2 sessions LPL-apheresis pre-Tx	PRTX+LDL: 0 out of 5 (0%)	No control group Exclusion of secondary FSGS not mentioned

PPP, prophylactic plasmapheresis; PP, plasmapheresis; Tx, transplant; PRTX, prophylactic rituximab.
[a]No clear definition of FSGS recurrence; numbers are on the basis of treatment with plasmapheresis within 1 month after transplant.

Table 2. Selected studies of treatment of recurrent FSGS after kidney transplantation (published after 2010 with more than 10 participants)

Treatment	Study	Population	Design	Total (n)	Dosage	Response Rate Complete Remission + Partial Remission [a] /No Remission (%)	Comments
Plasmapheresis	Ponticelli et al. 2010 (82)	Children and adults	Review of case series and case reports	144	Variable	98 out of 144 (68%)	Review of case reports, therefore publication bias
	Gonzalez et al. 2011 (78)	Children	Retrospective, single center	17	Unknown	15 out of 17 (88%)	Treatment of recurrent FSGS not described in methods
	Schachter et al. 2010 (83)	Children and adults	Retrospective, single center	12	PP: 4–48 sessions	8 out of 12 (75%)	
	Mansur et al. 2019 (84)	Children and adults	Retrospective, single center	61	PP: median 20 sessions	22 out of 61 (36%)	Patients also received high dose steroids (70%)
	Francis et al. 2018 (85)	Children	Retrospective, multicenter	20	PP: 10–92 sessions	15 out of 20 (75%)	Some patients also received RTX (16%) Many other treatments used: iv CsA, CP, RTX, high dose steroids, ABT, galactose
Plasmapheresis + rituximab	Alasfar et al. 2018 (80)	Adults	Prospective single center	40	PP: >10 sessions RTX: 1–2 doses (375 mg/ m²)	35 out of 40 (87%)	Not all participants received RTX (50%) No definition of recurrent FSGS
	Uffing et al. 2020 (5)	Adults	Retrospective, multicenter	61	Variable	35 out of 61 (57%)	Large differences between treatment regimen between patients Not all patients received RTX (57%)
	Garrouste et al. 2017 (86)	Adults	Retrospective, multicenter	19	PP: unknown RTX: 1–4 doses (375 mg/m²)	12 out of 19 (63%)	Some patients also received iv CsA (26%)
	Alachkar et al. 2013 (87)	Adults	Retrospective, single center	24	PP: median 15 sessions RTX: 1–2 doses (375 mg/m²)	19 out of 24 (79%)	Not all patients received RTX (54%)
	Staeck et al. 2015 (88)	Adults	Retrospective, single center	12	PP: median 11 sessions RTX: unknown	11 out of 12 (92%)	Not all patients received RTX (50%) Other treatments used: iv CsA, high dose steroids
Immunoadsorption	Allard et al. 2018 (25)	Children	Retrospective, multicenter	12	IA: median 129 sessions	10 out of 12 (83%)	Many other treatments used: PP, iv CsA, RTX, ABT, BTZ, CP, saquinavir, galactose
Plasmapheresis + iv cyclosporine	Canaud et al. 2010 (89)	Children and adults	Prospective, single center	10	PP: 25–39 sessions CsA iv: 14 days (target level 200–400)	10 out of 10 (100%)	All patients also received high dose oral steroids
Oral cyclosporine	Shishido et al. 2013 (90)	Children	Prospective, single center	10	CsA oral: target level 4500–5500 ng^{a}h/ml	9 out of 10 (90%)	All patients also received high dose iv steroids
ACTH gel	Grafals et al. 2019 (91)	Adults	Retrospective, two centers	14	ACTH: 80 units twice a week	5 out of 14 (36%)	Many other treatments used: PP, high-dose steroids, ABT, Bela, RTX ACTH used as "last resort." In patients without PP, ACTH did not result in response Study sponsored by pharmaceutical company
	Alhamad et al. 2019 (92)	Adults	Retrospective, two centers	20	ACTH: 40–80 units twice a week	10 out of 20 (50%)	ACTH used as "last resort" if PP and RTX did not work. Divergent definition of CR and PR Researcher funded by pharmaceutical company

PP, plasmapheresis; RTX, rituximab; CsA, cyclosporine; CP, cyclophosphamide; ABT, abatacept; iv, intravenous; BTZ, bortezomib; ACTH, adrenocorticotropic hormone; Bela, belatacept; IA, immunoadsorption; CR, complete remission; PR, partial remission.
[a]CR and PR were differently defined in different studies.

Dilemma: Should Patients with Previous Graft Loss Due to FSGS Recurrence Be Considered for Another Kidney Transplant? In patients with a previous graft loss due to recurrent FSGS, the risk of recurrence increases up to 80% in a second, to almost certain recurrence in a third allograft. Whether these patients should have the opportunity to obtain another kidney transplant has been a matter of debate. In the view of organ shortage and living donation, "wasting" an organ to almost certain recurrent disease can be considered unethical. In contrast, many patients with FSGS are young, and precluding them from organ transplantation sentences them to greater mortality risk and decreased quality of life linked to dialysis requirement. In the TANGO cohort, some patients with one previous graft loss due to recurrent FSGS did not have a second recurrence, or were able to obtain partial or complete remission after recurrence in a subsequent transplant (5). This would be an argument for transplanting patients a second time, although these decisions have to be made on an individual level, taking into account personal factors, previous course after kidney transplantation, and risks of treatments of recurrent FSGS.

For patients with two previous transplant losses due to recurrent FSGS, especially when both graft losses were soon after kidney transplantation with no signs of response to extensive treatment, the perspective is more limited, and living donors should be avoided. For these patients, progress in research of the etiology of primary FSGS and new therapies are desperately needed for the hope of attempting another kidney transplant.

Membranous Nephropathy

Testing for serum antibodies against the podocyte M type phospholipase A2 receptor (PLA2R Ab) has revolutionized the understanding and management of membranous nephropathy. PLA2R-associated membranous nephropathy accounts for 70%–80% of patients with primary membranous nephropathy (28). Trends in PLA2R Ab titers correlate with proteinuria, changes in antibody levels precede changes in proteinuria by weeks to months (29), and the presence of PLA2R Ab is associated with developing native membranous nephropathy months to years before clinical disease (30). Additionally, PLA2R Ab testing with combined indirect immunofluorescence and ELISA assays is a highly specific (98%–100%) diagnostic biomarker and may obviate the need for kidney biopsy in most patients with native membranous nephropathy (31). PLA2R-associated membranous nephropathy can also be diagnosed by kidney biopsy staining for the PLA2R antigen, which makes a retrospective diagnosis of PLA2R on a prior biopsy possible (32). Other autoantibody-antigen systems associated with membranous nephropathy include thrombospondin type-1 domain-containing 7A, neural epidermal growth factor-like 1 protein, exostosin-1/2, protocadherin 7, and semaphorin 3B (33).

Dilemma: How Can PLA2R Testing Be Used to Improve the Management of Patients with Membranous Nephropathy in the Transplant Setting? In the largest cohort to date ($n=63$), Grupper *et al.* showed that detectable PLA2R Ab before transplantation was significantly associated with recurrent membranous nephropathy by protocol or clinically-indicated kidney biopsies (hazard ratio, 3.76; 95% confidence interval, 1.64 to 8.65) (34). Other studies have supported that positivity of PLA2R Ab testing shortly before or at the time of transplant is associated with recurrent disease (35,36). However, some studies have not found this association (37). Studies on monitoring PLA2R Ab post-transplant are limited but support that persistent or reemerging PLA2R Ab is associated with an increase of proteinuria and, in some patients, resistant disease (35,37).

In the study by Grupper *et al.*, one third of patients with negative pretransplant PLA2R Ab experienced recurrent disease (34), and a study by Kattah *et al.* found the negative predictive value of pretransplant PLA2R Ab was only 42% (35). Quintana *et al.* found a much higher negative predictive value of 92% when using a lower cutoff value of 45 RU/ml on ELISA, highlighting that the pretransplant PLA2R Ab titer may be important (36). Nonetheless, as other autoantibodies have emerged as potential culprits in membranous nephropathy, more research will be needed to assess their individual predictive value at time of transplant.

There is important clinical heterogeneity in these data that precludes a "one-size-fits-all" approach to care. Moreover, most research available so far came from a single center (34). Replication by other centers would give greater validity to these results. We advocate for trending serum PLA2R Ab levels using indirect immunofluorescence and ELISA at the time of initial transplant evaluation, and at the time of transplant, in all patients with membranous nephropathy to establish baseline values.

In patients with stable PLA2R-associated membranous nephropathy post-transplant, following PLA2R Ab levels every 3–6 months is likely to detect trends to guide further monitoring. Additionally, PLA2R staining of previous native and/or allograft biopsies can help guide the use of PLA2R Ab testing for patients with a prior diagnosis of membranous nephropathy with unknown PLA2R status (evidence grade for above recommendations: expert opinion/not graded) (32). Furthermore, the use of PLA2R Ab as a diagnostic biomarker (*i.e.*, to replace kidney biopsy) in the transplant setting requires study.

Recent discoveries in the genetics of membranous nephropathy also require mention. Risk alleles in HLA and *PLA2R1* have been linked to disease. Berchtold *et al.* investigated 105 kidney transplant recipients with membranous nephropathy and donor pairs, finding that donor single-nucleotide polymorphisms in between *HLA-DRB1* and *HLA-DQA1,* and three single nucleotide polymorphisms in *PLA2R1,* were associated with post-transplant membranous nephropathy (38). Although this deserves further study, it is likely that combining biopsy, serologic, and genetic testing will improve the understanding, prediction, and management of post-transplant membranous nephropathy.

Dilemma: What Is Best Practice for Treating Post-Transplant Membranous Nephropathy? There is a lack of evidence for risk stratifying patients with post-transplant membranous nephropathy. Studies conducted in the pre-PLA2R/rituximab era showed the burden of post-transplant membranous nephropathy on graft survival (39–41). However, when an effective therapy is administered, disease recurrence does not appear to correlate with worse graft survival (34). It seems clear that renin-angiotensin-aldosterone blockade should be prescribed for all patients with post-transplant membranous nephropathy,

and additional immunosuppression prescribed in the setting of worsening kidney function, overt nephrotic syndrome, and/or thromboembolic complications of nephrotic syndrome, unless contraindicated. However, data are lacking for other clinical phenotypes. The study by Grupper *et al.* used a threshold of 1000 mg of proteinuria, despite the use of angiotensin-converting enzyme inhibitors and/or aldosterone receptor blockers to qualify for rituximab treatment (34), a cutoff some experts have advocated for (42).

In patients with post-transplant membranous nephropathy who require immunosuppression, rituximab is the drug of choice because patients are usually already taking calcineurin inhibitors, and it is desirable to avoid alkylating agents due to risk of malignancy. Rituximab leads to complete or partial remission in most patients with recurrent membranous nephropathy (Table 3). The optimal dosing for rituximab in recurrent membranous nephropathy is not established, but it is reasonable to prescribe two doses of 1000 mg separated by 2 weeks, as used in the Rituximab or Cyclosporine for the Treatment of Membranous Nephropathy (MENTOR) study (43). After rituximab therapy, we advocate for routine laboratory monitoring including CD19 counts and PLA2R antibody levels (in PLA2R-associated membranous nephropathy). Repeated rituximab dosing may be required, particularly in patients who have not achieved immunologic remission (*i.e.*, PLA2R Abs still detectable) (all above recommendations: expert opinion/ not graded). Additional therapies such as bortezomib targeting plasma cells and other anti-CD20 antibodies (obinutuzumab and ofatumumab) have been described in case reports for resistant membranous nephropathy pre- and post-transplant, and deserve further study in treatment of post-transplant membranous nephropathy (44–46).

Pretransplant antibody depletion strategies (*i.e.,* anti–B cell therapy, plasmapheresis) are likely not necessary for most patients with membranous nephropathy because recurrent membranous nephropathy is often slowly progressive and responds well to therapy. Preemptive antibody depletion deserves further study in patients who previously lost their allograft due to recurrent membranous nephropathy who have persistently positive PLA2R antibody titers (47).

Atypical Hemolytic Uremic Syndrome

Dilemmas: Should Patients with Atypical Hemolytic Uremic Syndrome Who Are Planning for Kidney Transplant Receive Eculizumab Prophylactically, and How Does Complement Testing Inform Management of These Patients? Recurrence of atypical hemolytic uremic syndrome (aHUS) occurs in 20%–100% of patients, strongly influenced by genetic background. Patients with mutations in complement factor genes have a three-fold risk of recurrence compared with patients without mutations (48), with the highest risk in patients with mutations in genes encoding complement regulatory proteins (such as *CFH, CFI, C3,* and *CFB*). Risk haplotypes for aHUS have been identified in the *CFH* and *MCP* genes with varying recurrence rates, whereas the recurrence of anti-FH associated aHUS has been shown to depend on the antibody titer (49).

The 2015 Kidney Disease Improving Global Outcomes Controversies Conference for aHUS and C3 glomerulopathy summarized a risk stratification for prescribing prophylactic eculizumab, on the basis of clinical phenotype and specific complement testing (49) (Table 4). The Global aHUS Registry found the highest mean eGFR at 6 months, and lowest risk of dialysis for patients treated prophylactic eculizumab ($n=88$) versus no prophylaxis in patients with ($n=52$) or without ($n=48$) a previous diagnosis of aHUS (50). A recent systematic review and meta-analysis comprising 380 adult kidney transplant recipients who received eculizumab for prevention or treatment of aHUS revealed a pooled estimated rate of allograft loss of 6% in the prophylaxis group compared with 23% in those treated after disease recurrence (51). In the French atypical hemolytic uremic syndrome cohort (52), no patient who received eculizumab prophylaxis developed recurrent disease ($n=52$, 75% high risk and 25% moderate risk for recurrence) versus a clinical recurrence of 41% in the nonprophylactic group ($n=74$, 47% high risk, 41% moderate risk, 12% low risk). Furthermore, death-censored graft loss was significantly more common in the nonprophylaxis group (38% versus 4%, $P<0.001$). The Kidney Disease Improving Global Outcomes Controversies Conference recommends starting prophylactic eculizumab at the time of transplant, but noted there were no studies comparing prophylactic or pretransplant strategies of treatment or monitoring (49).

Conversely, a smaller case series from The Netherlands demonstrated good allograft outcomes in 17 patients who were high risk and underwent living donor kidney transplantation without prophylactic eculizumab (53). With a mean follow-up of 25 months, only one patient experienced disease recurrence that was successfully treated with eculizumab. The authors hypothesized that these impressive outcomes in a high-risk group could be related to living donation and the use of lower dose calcineurin inhibitor regimens compared with previously published studies. The same group also found that kidney transplantation with use of eculizumab upon recurrence of aHUS (as opposed to prophylactically) was more cost effective, and that use of prophylactic eculizumab did not result in more quality-adjusted life years (54).

Taken together, these data support that genetic complement testing should be performed in all patients with aHUS who are undergoing kidney transplant evaluation, and large registry studies indicate that graft survival may be improved by using prophylactic eculizumab, particularly in patients who are high and moderate risk. However, further study is required to understand additional donor and recipient characteristics, and aspects of post-transplant management, to further optimize patient outcomes. More data are also required to help guide decisions around stopping eculizumab treatment in patients with aHUS after kidney transplant.

C3 Glomerulopathy

Dilemma: How Should Patients with C3 Glomerulopathy Be Managed before Transplant and after Disease Recurrence? Does Complement Testing Inform Management of Patients with C3 Glomerulopathy Undergoing Evaluation for Kidney Transplantation? Recurrent C3 glomerulopathy after kidney transplant is common. The two largest case series exploring C3 glomerulopathy and transplantation are from the Mayo Clinic ($n=21$) and Columbia

Table 3. Case series and retrospective cohort studies on rituximab for recurrent membranous nephropathy

Study	Design	Total n	Recurrence Treatment	Dose of Rituximab	Clinical Condition At Last Follow-up	Follow-up (Months)	Adverse Effects
El-Zoghby et al. 2009 (93)	Retrospective, single center	8	RTX	2 doses of 1000 mg 2 weeks apart	PR/CR: 6 out of 8 (75%) Relapse[a]: 1 (13%) For 1 patient, no long-term data were available	Mean 37 (SD ± 31)	2 patients required hospitalization for infection 9 and 12 months after treatment
Sprangers et al. 2010 (94)	Case series	4	RTX + steroids	4 weekly doses of 375 mg/m² or 2 doses of 1000 mg 2 weeks apart	Proteinuria decreased from 4 g/24 h to 1.8 g/24 h	Mean 81 (SD ± 41)	No
Spinner et al. 2015 (95)	Part of retrospective cohort study	3	RTX	Single dose of either 200 mg or 500 mg	CR: 3 out of 3 patients (100%)	Median 25 (IQR 12–43)	N/A
Makhdoomi et al. 2015 (96)	Case report	2	RTX	4 doses of either 600 mg or 900 mg every 2 weeks	CR: 2 out of 2 patients (100%)	36, 18	No
Kattah et al. 2015 (35)	Case series	11	RTX	Not stated	CR: 5 out of 11 (45%) PR: 2 out of 11 (18%) NR: 4 out of 11 (36%)	Median 88 (IQR 64–122)	N/A
Quintana et al. 2015 (36)	Case series	6	RTX (n=3) RTX + PP (n=3)	RTX: 4 weekly doses of 375 mg/m² PP: 7 exchanges over the course of 14 days	CR: 1 out of 6 (17%) PR: 3/6 (50%) NR: 1 out of 6 (17%) For 1 patient, no long-term data were available	Median 141	No
Gupta et al. 2016 (97)	Case series	6	RTX	1–2 doses of 375 mg/m² 2 weeks apart	PR: 5 out of 6 (83%) For 1 patient, no long-term data were available	Median 70 (IQR 12–108)	No
Grupper et al. 2016 (34)	Retrospective cohort study	17	RTX + steroids	2 doses of 1000 mg 2 weeks apart	CR: 9 out of 17 (53%) PR: 5 out of 17 (29%) NR: 3 out of 17 (18%)	Median 87.5 (IQR 42.7–139)	5 patients required hospitalization due to infection within 2 years after treatment

RTX, rituximab; CR, complete remission (defined as proteinuria ≤0.3 g/24 h with a stable kidney function); PR, partial remission (defined as reduction of 50% in baseline proteinuria <3.5 g/24 h with a stable kidney function); SD, standard deviation; IQR, interquartile range; N/A, not available; NR, no remission; PP, plasma exchange.
[a]Relapse was defined as proteinuria ≥3.5 g/24 h after a period of CR or PR.

Table 4. Risk stratification and recommendations for prophylactic treatment in patients with atypical hemolytic uremic syndrome undergoing kidney transplant evaluation

Risk Category	Criteria	Recommendation
High risk (50%–100%)	Previous early recurrence of aHUS Pathogenic mutation in aHUS gene Gain-of-function mutation	Prophylactic eculizumab recommended
Moderate risk	No mutation identified Isolated mutation in *CFI* Variant of unknown significance in complement gene Persistent low titer anti-FH antibody	Prophylactic eculizumab or plasma exchange recommended
Low risk (<10%)	Isolated *MCP* mutation Persistently negative anti-FH antibodies	No prophylaxis recommended

aHUS, atypical hemolytic uremic syndrome. Adapted from ref. 49, with permission.

Table 5. Considerations for transplantation in patients with C3 glomerulopathy

Risk stratification
  Avoid transplantation during acute period of kidney loss and acute inflammation, as limited data suggest that rapid progression to kidney failure in the native kidneys is associated with a higher risk for recurrence
  No data exist to support whether serum complement abnormalities predict risk of recurrent disease after transplant
  Monoclonal gammopathy-associated C3G has a high rate of recurrence
Treatment of recurrent C3G
  There are no known strategies to reduce the recurrence risk of C3G
  The use of anticomplement therapy is on the basis of small open-label trial and case reports with unknown effect of publication bias

C3G, C3 glomerulopathy. Adapted from ref. 49, with permission.

University (*n*=19) and observed recurrent disease in 67%–84% patients, with a median time to recurrence of 14–28 months (55,56). In the Mayo Clinic series, half of the patients with recurrent disease developed allograft failure at a median of 18 months after diagnosing recurrent C3 glomerulopathy. No data exist to support an association between complement testing and recurrent disease after transplantation (49) (Table 5).

A recent systematic review of the literature on the treatment of C3 glomerulopathy after kidney transplant included 12 studies comprising 122 patients (57), half of whom did not receive treatment due to stable kidney function or clinical discretion. For treated patients, the pooled rate of allograft loss was 33% with eculizumab, 42% with therapeutic plasma exchange, and 81% with rituximab. When stratified by disease subgroup, eculizumab was associated with lower rates of graft loss in C3 glomerulonephritis (22% versus 56% for TPE and 70% for rituximab), with limited data in dense deposit disease (53% rate of allograft loss with eculizumab). The pooled risk of allograft loss for those who did not receive treatment was 32%. Data on the soluble membrane attack complex (sMAC) were available for only seven patients. In total, 80% of those with elevated sMAC levels responded to eculizumab, and all responders normalized sMAC levels after treatment. These data must be interpreted with caution due to publication bias.

With these data in mind, we advocate performing genetic and functional complement testing before transplant in all patients with C3 glomerulopathy from kidney failure in the clinical research setting, but these results should not guide decisions on transplantation status or peritransplant management. Ideally, longitudinal complement testing (such as sMAC levels) should be followed to observe trends that may inform associations with clinical phenotype and disease management. The use of eculizumab for posttransplant C3 glomerulopathy remains controversial, but in the absence of other treatment options, can be considered for patients at high risk of graft loss, such as those with worsening or high-grade proteinuria and/or progressive decline in kidney function.

AL Amyloidosis
Dilemma: Should Patients with Kidney Failure Due to AL Amyloidosis Undergo Kidney Transplant? Management of amyloid light-chain (AL) amyloidosis relies on diagnosing the underlying clonal cell disorder followed by treatment with clone-directed therapy to achieve hematologic response (*i.e.,* reduction or normalization of paraprotein levels in the blood and urine), which is associated with improved kidney outcomes, morbidity, and mortality. Autologous stem cell transplant and/or antiplasma cell therapies, including bortezomib and daratumumab, have led to tremendous improvements in hematologic response, organ response, and survival for patients with AL amyloidosis.

Two of the largest amyloidosis programs have published data supporting kidney transplant in selected patients with AL amyloidosis. In a study by Angel-Korman *et al.* comprising 49 patients at Boston University, graft survival at 1, 3, and 5 years was 94%, 89%, and 81%, respectively (58). Achieving a complete or very good partial hematologic response before kidney transplant was associated with improved patient and graft survival, and resulted in lower

rates of clinical or pathologic indicators of disease recurrence in the allograft (15% versus 69% in patients with partial or no remission). Heybeli *et al.* described 60 patients with AL amyloidosis treated at the Mayo Clinic, of whom 51 had undergone treatment before kidney transplant (59). The estimated median overall survival for the group was >10 years, with best survival occurring in patients with complete or very good partial hematologic response and in those who were treatment naïve at the time of kidney transplant, but who were treated after kidney transplantation. Sawinski *et al.* also used United Network of Organ Sharing data to show that patients with amyloidosis (all types) who underwent kidney transplant had similar overall and graft survival compared with patients with diabetes-associated kidney failure and patients over age 65 who underwent transplant (60).

There is limited experience describing the use of anti-plasma cell agents after solid organ transplant for relapsed AL amyloidosis or maintenance of hematologic response. Case reports of patients who developed acute cellular rejection during treatment with lenalidomide may give pause to using this agent in the post-transplant setting (61,62). Bortezomib has been studied for the treatment of antibody-mediated rejection and does not require dose adjustment for kidney function. There are limited descriptions for the use of bortezomib for multiple myeloma and AL amyloidosis after kidney transplant (63,64). The anti-CD38 antibody daratumumab has shown efficacy as an add-on therapy for AL amyloidosis (65). One recent case series described the use of daratumumab as part of salvage therapy in five patients with plasma cell neoplasms after solid organ transplant, four of whom had AL amyloidosis, and three of whom experienced infectious complications (66).

In aggregate, these data suggest patients with kidney failure and AL amyloidosis who do not have cardiac involvement and who otherwise meet criteria for transplantation should be considered for kidney transplantation, particularly those who have achieved complete or very good partial hematologic responses. Multidisciplinary collaboration with hematology and cardiology is essential for appropriate evaluation, risk stratification, and management of these patients.

IgA Nephropathy

The incidence of recurrent IgA nephropathy increases with time after transplant (67). Its manifestation is variable, and recurrence rates vary from 10% to 30% in studies with for-cause biopsies, and 25%–53% in studies with protocol biopsies (68). Recurrence of IgA nephropathy seems to have no effect on short-term graft survival, although in studies with longer follow-up, graft outcomes seem to be worse compared with patients without recurrence.

Dilemma: Should Early Steroid Withdrawal Be Avoided in Patients Who Have Been Transplanted and Have Kidney Failure Due to IgA Nephropathy? The early removal of steroids after transplant is performed in about 30% transplants in the United States. In patients with IgA nephropathy, a commonly accepted view is to avoid early steroid withdrawal because few studies comment on the possible association between early steroid withdrawal and recurrence of IgA nephropathy. However, when reviewing these studies thoroughly, significant limitations emerge.

An important concern with registry studies that investigate IgA recurrence is misclassification of graft loss due to a lack of kidney biopsy. In the setting of graft dysfunction, patients receiving a steroid-free regimen may be more likely to receive a kidney biopsy than patients on steroids, and thus more likely to receive a diagnosis of recurrent IgA. Supporting this concern, two registry studies (United Network of Organ Sharing/Organ Procurement and Transplantation Network [OPTN] and Australian and New Zealand Dialysis and Transplant Registry [ANZDATA]) found a reduced risk of graft losses due to IgA nephropathy with continued steroid use, and also reported a higher number of graft loss due to chronic allograft nephropathy and rejection. Furthermore, these studies only investigated recurrences that led to graft loss, and the immunosuppressive regimens used in the ANZDATA study are not comparable to current standard of care transplant immunosuppression. Contrarily, two United States Renal Data System registry studies did not find an association of steroid withdrawal with graft loss due to recurrent IgA nephropathy (69) or overall graft loss (70).

Two single-center studies evaluating IgA nephropathy recurrence and steroid withdrawal have similar limitations, such as large differences in groups at baseline (including immunosuppression), no or limited multivariable analysis, IgA deposits that were not defined as recurrence when rejection was present in the biopsy, a higher risk of rejection in the steroid group, and possible selection bias of which patients received the steroid free regimen (71,72). Unfortunately, there are no prospective studies that look at early steroid withdrawal and recurrent IgA with protocol biopsies, although a retrospective study with protocol biopsies by Ortiz *et al.* found an overall IgA nephropathy recurrence rate of 32%, with no association between IgA recurrence and steroid withdrawal (73). In TANGO, early steroid withdrawal was prescribed in 76 out of 504 patients with native IgA nephropathy and was not associated with recurrence of IgA nephropathy after kidney transplantation in a multivariable analysis.

In conclusion, the evidence for an association between early steroid withdrawal and IgA nephropathy recurrence has significant limitations. Because there is some evidence that the incidence of recurrent disease has decreased over time (74), newer trials are required to investigate the association between steroid withdrawal and recurrent IgA nephropathy in the modern era.

Exciting advances over the last decade have clearly improved our insight and treatment for many post-transplant glomerular diseases, yet significant dilemmas still exist for both clinicians and patients. International collaborative research efforts hold great promise to revolutionize our understanding, management, and, most importantly, patient outcomes for these rare and challenging conditions.

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