Recurrent Renal Disease After Transplantation

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Shanthi S. Balani and Paul R. Brakeman

18.1 Introduction

In the pediatric population, primary glomerulonephritis diseases, including focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranoproliferative GN (MPGN), are the second most common cause of end-stage renal disease (ESRD), representing 21.1% of all pediatric ESRD patients [1]. In addition, secondary glomerular diseases, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV), and complement-mediated glomerular disease, are the fourth leading cause of ESRD, representing 8.0% of pediatric patients with ESRD [1]. These conditions can recur after transplantation with varying effects on the allograft and long-term transplant outcomes (Table 1). The goal of this chapter is to describe the epidemiology, pathophysiology, treatment options, and allograft outcomes for patients in whom these conditions recur after transplant.

18.2 Focal Segmental Glomerulosclerosis

Focal segmental glomerular sclerosis (FSGS) is the most common acquired glomerular disease causing ESKD in pediatric and adult patients. FSGS is a histopathologic description of glomerular scarring with a heterogenous pathogenesis. FSGS can be genetic, primary/idiopathic, or secondary with post-transplant recurrence primarily occurring in primary/idiopathic forms of FSGS [2, 3]. FSGS recurrence is common, affecting up to 55% of first pediatric transplants and up to 80% of subsequent transplants after FSGS has recurred in a previous transplant [4–6].

S. S. Balani
Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

P. R. Brakeman (✉)
Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA
e-mail: paul.brakeman@ucsf.edu

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The molecular pathogenesis of primary FSGS is incompletely understood, with the central event being podocyte damage leading to podocyte loss and glomerular scarring. The mechanism for primary FSGS likely involves a circulating factor that causes increased glomerular permeability. The hypothesis that there is a circulating factor that can trigger increased glomerular permeability is supported by data that plasma from a human with FSGS can trigger increased glomerular permeability when infused into a rat and that FSGS recurrence can occur within hours of implantation of a renal allograft. There has been exhaustive work to identify this circulating factor or factors; however, to date the definitive identification of this factor remains elusive [7]. Podocyte damage occurs in secondary FSGS as a result of viruses, hyperfiltration related to obesity or drug toxicity, and other environmental factors [2]. It is likely that some patients with presumed primary FSGS have an unidentified secondary cause for their FSGS.

18.2.1 Incidence

The overall reported rate of recurrent FSGS in children is 6–58% [4, 6]. This large variability may reflect different definitions of recurrence (clinical versus biopsy-proven) and/or incomplete reporting of data in large data sets. Center-specific retrospective pediatric cohort studies show generally high rates of recurrence between 30% and 55% [8–10]. Most recurrences occur within the first week after transplant and can occur as early as post-operative day 1 [8, 11].

18.2.2 Risk Factors

Risk factors for recurrence include younger age at onset of disease, more rapid progression to ESRD, white race, and previous recurrence in an allograft [4–6]. Of note, many patients with very-early onset FSGS will have a genetic cause for their disease and are unlikely to recur, although recurrence has been reported for a small number of patients with identified homozygous mutations in *NPHS2* [12, 13]. The use of a living donor or deceased donor has not been observed to affect disease recurrence [9].

18.2.3 Diagnosis and Treatment

Identification of FSGS recurrence is usually made based on significant new proteinuria and/or reduced allograft function after transplantation. After transplantation, patients should be monitored daily, then weekly, and eventually monthly with a spot urine protein/creatinine ratio [14]. An elevated protein/creatinine ratio should be confirmed with a 24-h urine collection. In order to reduce thrombotic risk and also to allow for identification of recurrence, transplant recipients with ongoing nephrotic-range proteinuria should undergo native nephrectomy prior to transplant

or have pre-transplant urinary protein loss aggressively reduced with renin-angiotensin-aldosterone system blockade (RAASB) and/or non-steroidal anti-inflammatory medications such as indomethacin followed by native nephrectomy at the time of transplant [15]. There are no specific guidelines for which patients should undergo nephrectomy prior to transplantation. Definitive diagnosis requires allograft biopsy which early on usually shows histologic features of minimal change disease with normal-appearing glomeruli on light microscopy with foot-process effacement on electron microscopy. Serial biopsies of patients who do not respond to therapy show progressive development of podocyte detachment and epithelial hypercellularity, accumulation of intracapillary foam cells, and the segmental scarring that is classic for FSGS in native kidneys [16].

Management of FSGS recurrence is difficult due in part to a lack of randomized clinical trials as well as specific guidelines. Based on the evidence for a circulating factor, plasmapheresis has been a commonly used treatment for FSGS recurrence since 1985. To date there are still few randomized trials evaluating plasmapheresis, but there have been many case series reporting efficacy in inducing remission of recurrent FSGS that often persists even after discontinuation of plasmapheresis [4, 5, 11, 17]. A typical plasmapheresis regimen is plasmapheresis with 5% albumin replacement daily for 3 days followed by alternate day treatment (3 times per week) for a total of nine treatments or longer depending on response [14]. Treatment is more likely to be successful if started early on in a relapse. In a meta-analysis of many, primarily adult, case series, plasmapheresis induces complete remission (<0.5 G/day) of proteinuria in 47% of patients and partial remission (<1 G/day) of proteinuria in 28% of patients [11]. Studies in pediatric cohorts are limited, but plasmapheresis also appears to be efficacious in pediatric patients [4–6, 18].

Additional management strategies for recurrent FSGS include immunoadsorption instead of plasmapheresis, intensifying immunosuppression with cyclosporine, and using rituximab or similar biologics such as ofatumumab [4–6]. Immunoadsorption is an alternate extra-corporal option for acute therapy for recurrent FSGS [19–21], and a recent case series in children demonstrated efficacy similar to plasmapheresis [19]. Some authors have advocated using high-dose cyclosporine as part of prevention and treatment of FSGS recurrence, but there are no randomized trials directly comparing cyclosporine-based immunosuppression to tacrolimus-based regimens [15, 22]. There have been many case series and case reports describing the use of rituximab for FSGS recurrence reporting generally good success [5, 6]. The appropriate dosing and frequency of rituximab administration is variable and still not completely defined, with one case report even demonstrating efficacy with a single low dose of rituximab [23]. Rituximab is an anti-CD20 antibody B-cell-depleting agent; however, its efficacy in FSGS may be via immune and non-immune mechanisms as it has been shown to bind directly to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein and regulate acid sphingomyelinase activity in the podocyte [24, 25]. Ofatumumab is another B-cell-depleting agent that has also demonstrated efficacy in FSGS although with only a few cases reported [26, 27]. Ofatumumab may be a useful option for patients who do not tolerate rituximab due to anaphylaxis.

Pre-transplant regimens to prevent recurrence have also been evaluated, as the recurrence rate for the highest risk patients is very high [28, 29]. One regimen that has been reported in a relatively large prospective cohort of patients included giving 1–2 doses of 375 mg/m^2 of rituximab and giving 3–10 sessions of therapeutic plasma exchange in the perioperative period [29]. This trial demonstrated similar rates of recurrence for very high-risk patients receiving this regimen compared to lower-risk patients receiving no pre-emptive preventative therapies [29]. Recurrence of FSGS in subsequent allografts remains a nearly insurmountable problem in patients where a prior allograft has failed due to FSGS recurrence and requires further clinical investigation.

18.2.4 Prognosis

Allograft survival for pediatric patients with FSGS is reduced. Using data from the USRDS from 2000 to 2009, Wang and colleagues reported a 5-year allograft survival of 64% for pediatric patients with FSGS compared to 79% for other causes of ESRD [30]. These differences persisted, with 10-year allograft survival being 47% for pediatric patients with FSGS compared to 61% for other causes of ESRD [30]. Similar data have been reported by Koh and colleagues using the NAPRTCS database with a 5-year allograft survival of 74% for pediatric patients with FSGS compared to 87% for other patients with other glomerular diseases [31]. Encouragingly, both of these studies report improved allograft survival for transplants performed after 2000.

18.3 IgA Nephropathy

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and recurs at a high rate post-transplantation with recurrence rates as a high as 50% reported for pediatric patients [32–34]. IgAN in the native kidney often progresses slowly and IgAN recurrence in the allograft can likewise have an indolent presentation. However, IgAN recurrence does lead to significant allograft dysfunction in a small percentage of patients, and there is some evidence that treatment of recurrent IgAN can prolong allograft survival.

The pathogenesis of IgAN Nephropathy in the native kidney is not completely defined and involves generation of aberrantly glycosylated IgA1, development of anti-glycan autoantibodies and deposition of these IgA-antibody complexes in the glomeruli. This deposition of IgA1-antibody complexes in the glomeruli leads to the pathognomonic finding of diffuse mesangial IgA1 staining that is the hallmark of IgAN. These immune complexes then trigger inflammation mediated by complement as well as other inflammatory mediators such as B cell activation factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) [32, 34]. The pathogenesis of IgAN recurrence appears to involve these same mechanisms.

18.3.1 Incidence

The overall reported rate of recurrent IgAN in adults is between 10 and 61 percent [34, 35] with most authors citing about a 30% recurrence rate [34–37]. Most studies have reported the time to recurrence to be between 3 and 5 years [34]. The variability in the reported recurrence rate is likely related to variability in performing biopsies as well as variability in assigning a diagnosis of recurrent IgAN. Some case series have defined recurrence of IgAN as having hematuria and/or proteinuria, while others have only required the presence of IgA deposits on biopsy to define recurrence of IgAN. In one small case series comparing adult and pediatric kidney transplant patients, the pediatric recurrence rate (age < 20) was reported to be 53.8% compared to only 23.3% for patients >20 years old [33].

18.3.2 Risk Factors

Young age at renal transplantation, male gender, and rapidly progressive original disease have all been associated with a higher risk of IgAN recurrence [34, 35, 38]. The presence of crescents in the native kidney has also been shown to be predictive of post-transplant recurrence [38]. There is conflicting evidence on whether living-donor kidneys are more likely to have recurrence [34, 35, 39], and a further lack of data that living donation affects patient or allograft survival in patients with ESKD due to IgAN [34]. Currently, IgAN is not listed as a contraindication to living-donor transplantation in several transplant guidelines.

Large registry reviews as well as smaller case series have demonstrated that use of steroid-based immunosuppression is associated with a lower rate of IgAN recurrence [40–44]. Use of other specific immunosuppressive agents has not been shown to definitively affect the rates of IgA recurrence, although there is some evidence that the use of tacrolimus and mycophenolate over cyclosporine and azathioprine may be associated with lower rates of IgAN recurrence [34, 35].

Post-transplant IgAN appears to have the same pathophysiologic mechanism as native IgAN. Post-transplant serum IgA1 levels are predictive of post-transplant recurrence of IgAN [45], and serum levels of galactose-deficient immunoglobulin (Ig)A1 also predict IgAN recurrence [46]. Increased levels of APRIL have been shown to precede transplant recurrence of IgAN [47].

18.3.3 Diagnosis and Treatment

In most cases IgAN recurrence is identified based on biopsies performed for other clinical indications; however, IgAN recurrence may be identified during evaluation for proteinuria and/or allograft dysfunction. Diagnosis can only be made based on biopsy findings of IgAN. Histopathology for IgAN recurrence is very similar if not identical to IgAN in the native kidney, and the Oxford classification system also predicts outcome for recurrent IgAN [48]. Interestingly,

not all patients with IgAN recurrence on biopsy have hematuria or proteinuria [49, 50], although more severe histological disease is almost always associated with proteinuria [50].

There are no treatments for recurrent IgAN that have been tested in randomized-controlled trials. As with primary IgAN, treatment of IgA recurrence is focused on limiting proteinuria and achieving a tight blood pressure control as recommended in KDIGO transplant guidelines [34, 35, 51, 52]. KDIGO guidelines for primary IgAN are to control blood pressure with an angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor (ARB) blocker, with a goal to lower the blood pressure to less than 130/80 mm Hg in patients with protein less than 1 g per day and less than 125/75 in patients with protein greater than 1 g per day. For pediatric patients younger than 13 years of age, blood pressure should be lowered ideally to 50% for age, gender, and height. For patients with recurrent IgAN, this tight blood pressure control should be the goal but may be impossible due to unacceptable decreases in GFR with aggressive renin-angiotensin-aldosterone system blockade (RAASB) or other side effects such ass hyperkalemia. With or without hypertension, in those with proteinuria greater than 0.5 g per day, RAASB should be initiated. There is some evidence in small trials that this treatment strategy is efficacious [53–56].

While steroid withdrawal and steroid avoidance have been associated with IgAN recurrence, there is no randomized trial demonstrating efficacy for treatment of recurrent IgAN with either IV or oral steroids. Data to support use of tonsillectomy post-transplant to treat recurrent IgAN are limited and have generally only been reported in Japanese patients; thus the validity in other ethnicities has not been confirmed [34]. In severe cases of IgAN recurrence rescue therapy with steroids, eculizumab and cyclophosphamide have been attempted with variable success [3, 4, 20].

18.3.4 Prognosis

Outcome of recurrent IgAN is highly variable. Some patients have detectable IgA deposition on biopsy and never develop hematuria or proteinuria, while in other patients recurrent IgAN is associated with development of proteinuria and early allograft failure. Short-term allograft outcomes are generally unaffected by recurrence of IgAN; however, 10- and 15-year death-censured allograft survival are moderately reduced in patients with IgAN recurrence [57–59]. Worse prognosis is predicted by more severe histopathologic classification, presence of crescents, and heavier proteinuria similar to primary IgAN [50, 51, 57, 60–62].

18.4 Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) has a higher rate of allograft failure compared to other glomerulonephritides, and recurrence contributes to a significant proportion of allograft failure [63, 64]. Studies have shown variable rates of

MPGN recurrence from 27% to 65%. This large variability is attributed to small numbers, lack of protocol biopsies, presence of different subtypes, and variable periods of observation [65].

MPGN was previously classified into three types: Type 1, Type 2, and Type 3 based on location of immune complex deposition found on electron microscopy. However, with increased pathophysiologic understanding of the disease, the classification has evolved to be based on the mechanism of glomerular injury and distinguishable by immunofluorescence. The new proposed classification includes immune complex-mediated glomerulonephritis characterized by deposition of immunoglobulins and complement components, or complement-mediated glomerulonephritis characterized by complement deposition in the absence of immune complexes mediated by abnormal activation of the alternate complement pathway [66, 67]. Rarely, a third type without immune complexes or complement is seen, caused by endothelial injury.

Recurrence of MPGN post-kidney transplantation is now being studied in the light of the new classification. This is very helpful since the risk of recurrence, prognosis, and treatment differ substantially among subtypes.

18.5 Immune Complex-Mediated MPGN

18.5.1 Incidence

The overall reported rate of recurrent idiopathic MPGN is between 19% and 48% [65, 68, 69], with over 50% of recurrences occurring within the first 2 years after transplantation [70]. MPGN with polyclonal immunoglobulin deposits has a relatively low rate of recurrence of 30–35% and tends to have a more benign course [71]. MPGN with monoclonal immunoglobulin deposits has a higher rate of recurrence, closer to 66% with a more aggressive course [72, 73].

18.5.2 Risk Factors

Several studies have raised concern of MPGN recurrence being higher among recipients of living-related-donor kidneys, compared with deceased-donor kidneys [65, 69, 74–76] and recommend exercising caution with living donation. This was attributed to a possible common genetic predisposition. However, this was not corroborated in a large cohort study [63]. The data on living donation continue to remain limited and conflicting, and currently living donation is not listed as a contraindication in several transplant guidelines.

Risk of recurrence is also found to be associated with persistent or recurrent hypocomplementemia – either C3 or C4 or both, especially in MPGN with polyclonal immunoglobulin deposits [65, 68, 69].

A few other studies reported increased risk of recurrence with the presence of serum monoclonal globulins [65, 68, 69]. There was one study which showed an

association between the human leukocyte antigen phenotype B8DR3 and recurrent disease [75].

ATG induction therapy was found to be associated with a lower risk of recurrence of MPGN [77].

18.5.3 Diagnosis and Treatment

A strong index of suspicion is necessary in patients with ESRD from MPGN who develop hematuria/proteinuria or declining renal function of the allograft.

Diagnosis is confirmed with biopsy with a special importance of immunofluorescence staining patterns. It should be distinguished from transplant glomerulopathy (which may have similar appearance on light microscopy) by the presence of electron dense deposits on EM.

It is also important to rule out secondary causes of MPGN – including infections (Hep B, Hep C, HIV), autoimmune conditions, and monoclonal gammopathies.

No specific guidelines exist on treatment, and it is usually based on the severity of the disease process.

ACEi/ARB may be sufficient in mild disease cases (proteinuria <3.5 g/day), similar to treatment offered in primary MPGN.

In moderate disease with proteinuria >3.5 g/day or steadily declining renal function, immunosuppression is intensified in addition to ACEi/ARBs. Options available include high-dose steroids, cyclophosphamide [78], rituximab [79], antimetabolites (azathioprine/mycophenolate), and plasmapheresis [80]. Rituximab may be specifically beneficial in monoclonal IgG MPGN [65, 79].

Recurrent MPGN can be poorly responsive to immunosuppressive therapy, with less than half of patients responding to high-dose steroids, rituximab and/or plasmapheresis, or eculizumab to preserve their renal allografts, as shown in a study published in 2016 [69].

Thus, it is important to fully characterize the GN pre-transplant, as it will direct management and prognosis post-transplant.

18.5.4 Prognosis

Recurrent MPGN in the transplant kidney has a grave prognosis, with a 5-year allograft survival post-recurrence of only 30% [81]. There is a higher incidence of graft loss in MPGN associated with monoclonal IgG deposits of about 50% [72, 73], whereas MPGN associated with polyclonal IgG has a better prognosis with graft loss of 10% [71].

One study showed the mean duration of graft survival following the diagnosis of recurrent disease was 40 months [75].

MPGN recurrence increases the risk of recurrence in subsequent transplants. Four out of five patients who received a second transplant after losing the previous allograft due to recurrent MPGN showed recurrence in the second allograft [75].

18.6 Complement-Mediated MPGN (C3GN/Dense Deposit Disease)

C3 glomerulopathy [comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD)] is characterized by the glomerular deposition of C3 in the absence of immunoglobulin deposition. The underlying abnormality is uncontrolled activation of the alternate pathway of the complement system. Both can be morphologically distinguished by the nature and ultrastructural characteristics of these electron dense deposits.

18.6.1 Incidence

The reported recurrence rate of C3 glomerulonephritis (C3GN) is greater than 50 percent, and the recurrence rate of dense deposit disease (DDD) is much higher and approaches approximately 80 to 100 percent [82–84].

The timing and clinical presentations of patients with C3GN and DDD are different; DDD is more likely to recur later in the post-transplant period and is often associated with no clinical manifestations other than allograft dysfunction.

A large cohort study with long-term follow-up contested the largely held belief that Type 2 MPGN has a higher recurrence rate and poorer outcome. They demonstrate that rather than the MPGN type, the severity of initial glomerular injury, particularly younger age at diagnosis and the presence of cellular crescents on the initial biopsy, influenced renal survival [85].

18.6.2 Risk Factors

Monoclonal gammopathy is associated with earlier and more aggressive recurrent disease and was seen in 21% of patients with recurrent C3 glomerulopathy in one case series of patients [82].

Persistent or development of new hypocomplementemia and living donation is also shown to be associated with a higher risk of recurrence in the case of immune complex-mediated MPGN [69].

Levels of C3 nephritic factors have not been shown to correlate with disease activity or recurrence risk [86].

18.6.3 Diagnosis and Treatment

A biopsy with analysis of tissue by light microscopy, immunofluorescence, and electron microscopy should be performed in all transplant recipients who have either DDD or C3GN as a cause of end-stage renal disease (ESRD) in the native kidney and who present with unexplained new or worsening proteinuria, hematuria, or worsening renal function.

It is very important to perform a comprehensive genetic and functional evaluation of the complement system if this has not been done previously, as the identification of an abnormality in the alternative complement pathway informs immunosuppressive therapy.

Mild disease (stable renal function and non-nephrotic-range proteinuria) can be managed with the addition of ACEi/ARBs.

However, most recurrences tend to be moderate to severe in presentation, and due to the rarity of the disease and small numbers of recurrent disease, no treatment options have been rigorously tested in clinical trials.

It is unclear if intensification of immunosuppression, especially nonspecific agents such as cyclophosphamide or mycophenolate, is beneficial. Chronic infusions of fresh frozen plasma to replace missing complement factors may be beneficial in cases of genetic mutations in CFH. Rituximab and plasma exchange can be trialed in cases of pathogenic antibodies.

The role of eculizumab is rapidly evolving in the prevention and treatment of recurrent C3 glomerulopathy since the first reported study showing benefit in 2012 [87]. Several studies since have shown variable response to eculizumab. Six patients with C3GN and DDD, of whom three had recurrent disease, from a prospective single-arm pilot study were given eculizumab for 1 year, and all responded to therapy [88].

Eculizumab binds to C5 and blocks its binding to a second surface-bound C3b, making it very effective in aHUS. However, the pathophysiology of C3GN is less well understood and substantially more complex than in aHUS. Eculizumab is effective in patients in whom the dominant process is activation of C5 convertase and the terminal complement cascade. Conversely, in C3G patients in whom the dominant process is upstream dysregulation at the level of C3 convertase, as evidenced by elevated levels of C3 split product, it is likely not to be effective.

This again highlights the importance of disease characterization pre-transplant, so that it may aid in treatment post-transplant. However, efforts to prevent post-transplant recurrence with either rituximab or eculizumab have not been shown to be consistently effective [71].

18.6.4 Prognosis

There is a high rate of graft loss associated with post-transplant recurrence for both C3GN and DDD, with over 50% of patients reported to experience allograft failure, although the number of patients in these studies was relatively small with a median time from recurrence of disease to failure of 18 months [82, 89].

Transplant recipients with DDD have been shown to have a significantly reduced allograft survival. In a series of 75 pediatric patients, Braun et al. demonstrated a 5-year allograft survival of 50% compared to 74% in their transplant cohort as a whole [83]. The UNOS review reported a 10-year death-censored allograft survival

of 57.5% for recipients whose primary pathology was DDD compared to 65.2% for those with other forms of glomerulonephritis [90].

When patients with failed allografts from recurrent C3GN are evaluated for a second transplant, the risk of recurrence may be deemed to be unacceptably high [89].

18.7 Anti-neutrophil Cytoplasmic Antibody-Associated Vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small- to medium-vessel vasculitic conditions associated with the presence of ANCA on serologic testing. The vasculitis seen in AAV can cause necrotizing inflammation in multiple organs, including the kidneys, lungs, upper airway tissue, gastrointestinal tissue, joints, eyes, skin, and/or nervous system [91]. The specific antibodies that have been identified are anti-proteinase 3 (anti-PR3) and anti-myeloperoxidase (anti-MPO) antibodies which are found in the cytoplasmic region of the neutrophil. The identified AAV conditions include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), renal limited vasculitis, and eosinophilic granulomatosis with polyangiitis with GPA and MPA being the most common AAV syndromes to cause ESKD in children.

While there is a strong association of AAV and ANCAs, the pathophysiology is incompletely understood, as ANCA titers do not consistently vary with disease activity, nor do specific ANCAs always associate and/or segregate with the specific AAV syndromes (i.e., GPA versus MPA). Passive transfer of anti-MPO antibodies can cause AAV in mouse models; however, the pathogenesis of AAV elucidated in these anti-MPO models also involves activation of neutrophils, adherence and degranulation of neutrophils in the microvasculature, endothelial injury, complement activation, and release of other inflammatory cytokines and chemoattractants [92, 93]. Interestingly, robust PR3-AAV animal models do not currently exist, and while there are many in vivo data indicating that human PR3-AAV pathophysiology is similar to MPO-AAV disease, this has not been validated in animal models [92].

18.7.1 Incidence

Relapse of AAV is rare post-transplant. In adult series of patients, relapse rates vary between 0.006 and 0.1 per patient per year with time to relapse ranging from 5 days to more than 13 years [94]. Similar data are limited for pediatric patients, but in two recent small series there were no relapses reported [95, 96]. At the University of California, San Francisco, we have had one pediatric patient with a relapse of AAV post-transplant and can report anecdotally, at least, that recurrence of AAV post-transplant for pediatric patients is possible and can be treated successfully.

18.7.2 Risk Factors

With such limited data available for pediatric patients, risk factors for recurrence have not been defined. For adult patients, it appears that modern mycophenolate-based immunosuppression has yielded lower rates of recurrence compared to azathioprine-based immunosuppression regimens [97, 98], indicating that more intensive immunosuppression likely reduces recurrence. Ongoing disease activity is also thought to be a risk for recurrence, and there is a KDIGO recommendation to perform renal transplant in AAV only if the disease has been quiescent for at least 1 year [52]. It is important to note that complete elimination of ANCA is not required to achieve quiescence and to be ready for kidney transplantation [52]; however, there is some evidence that persistent ANCA positivity is associated with a higher recurrence rate post-transplant and thus patients with persistent positivity should be carefully monitored for clinical signs of disease activity before and after kidney transplantation [99].

18.7.3 Diagnosis and Treatment

Recurrence of AAV can be identified post-transplant by unexplained decrease in allograft function, new significant hematuria and proteinuria, allograft biopsy, and/or new-onset extra-renal symptoms such as pulmonary hemorrhage [94, 99]. Identification of recurrent extra-renal symptoms of AAV such as new cough with anemia can be difficult, as these symptoms can be subtle and often mimic infection. Ultimately, renal recurrence is diagnosed by allograft biopsy. There is no standard monitoring protocol for AAV post-transplant, but a reasonable monitoring schedule could include ANCA testing monthly for the first 6 months and then q3 months after that, with urinalysis at every visit to evaluate for new-onset hematuria and/or proteinuria that would trigger further evaluation.

Treatment for recurrent AAV disease should be similar to treatment for primary disease [94, 99]. Severe AAV has been treated with high-dose IV glucocorticoids, plasma exchange, and/or cyclophosphamide and these therapies can be considered for severe transplant recurrence as well [94, 98, 99]. More recently, data have suggested that rituximab provides similar outcomes to cyclophosphamide, with an improved safety profile [91, 99]. There are case reports describing the successful use of rituximab post-transplant for both recurrent and de novo AAV [100, 101] and rituximab can be considered for use as the sole induction agent for recurrent AAV depending on the severity of the recurrence.

18.7.4 Prognosis

In general, the prognosis for kidney transplantation for patients with AAV is good based on recent adult data. Patient and graft survival is at least as good for AAV patients as it is for patients with non-diabetic ESKD [99, 102]. In addition, the many

case reports and case series describing AAV recurrence in adult patients report generally good success treating AAV recurrence, although these reports are likely to be significantly biased.

18.8 Lupus Nephritis

Although the incidence of ESKD from lupus nephritis (LN) has decreased as a result of advances in lupus treatment, it still affects 10–20% of children 10 years after diagnosis and accounts for 4% of kidney transplants [103]. It is generally agreed that remission of lupus activity is important prior to proceeding with transplantation, and most patients with recent significant renal or extra-renal activity and ESRD receive a period of dialysis to achieve "burn out." However, there are currently no established guidelines for how long a patient with ESKD from LN should wait before undergoing kidney transplantation. This remains a source of debate, since it has been shown that serological activity does not always correlate with clinical activity to determine transplant eligibility [104]. Studies have also shown that pre-emptive transplantation is a safe option in LN patients who are in remission and is associated with superior graft survival and patient outcomes [105].

18.8.1 Incidence

The incidence of clinically significant recurrent LN (rLN) is 2–11%, but can range from 0% to 44% depending on the study [106]. Pediatric specific recurrence data are scarce and thought to range from 0% to 30% [107]. It may, in fact, be more prevalent, as suggested by a surveillance biopsy study in which 54% had biopsy-proven recurrence of LN. The majority of the cases were subclinical and characterized as class I/class II LN [105, 108].

Recurrent LN can occur as early as 5 days and up to 16 years post-transplant, with the median time to recurrence approximately 4 years post-transplant [106, 109, 110]. The clinical and histologic pattern of recurrence varies, although it is usually more benign in histology and clinical manifestation than the patient's original disease [111].

18.8.2 Risk Factors

A large OPTN study of kidney transplant recipients with ESKD due to LN revealed a 1.88-fold higher risk for non-Hispanic black race, a 1.70-fold increased risk for female gender, and a 1.69-fold greater risk for recipients younger than 33 years old [112]. A surveillance biopsy study reported a higher association of recurrence in patients with lupus anticoagulant [108]. There are no studies that have been published describing the risk factors in the pediatric population. Post-transplant recurrence is not found to be reliably predicted by serological measures such as complement and anti-double-stranded DNA antibody levels.

18.8.3 Diagnosis and Treatment

Recurrent LN can present as an increase in serum creatinine, new-onset proteinuria, and/or new-onset hematuria. A kidney biopsy has to be obtained to make a definitive diagnosis, as it is recognized that serology can be inconsistent and is not adequate to make a diagnosis [109]. Additionally, a kidney biopsy must include light microscopy, immunofluorescence, and electron microscopic examination to maximize diagnostic yield, as light microscopic findings may be subtle or non-specific [110]. The histopathologic lesion with rLN may be different than that in the native kidney and is usually less severe, with mesangial proliferation or Class II being the most common [106, 109]. A study of allograft biopsies from patients with LN demonstrated that while typical immune complex GN was frequently observed, atypical pauci-immune proliferative GN and segmental glomerular sclerosis were also observed, implying a role for nonimmune complex-mediated glomerular injury in rLN [113].

Patients who have subclinical disease (Class I or II) do not need any change to their immunosuppression regimen unless there is clinical evidence of a lupus flare. Patients with proteinuria >0.5 g/day, similar to nontransplant patients, should be treated with renin-angiotensin-aldosterone system inhibition to reduce proteinuria and slow the progression of renal disease. Patients having clinically evident disease with deterioration of kidney function in the setting of Class III or IV LN may be treated with higher doses of mycophenolate mofetil (MMF) 2–3 g/day. If they fail to respond or have severe crescentic lesions on biopsy, IV cyclophosphamide can be used in place of the prescribed antimetabolite with pulse dose steroids. Some authors suggest a trial of rituximab in refractory cases although there are no published reports supporting its benefit [106, 109]. Due to the lack of evidence supporting the benefit of further immunosuppression, caution should be exercised to avoid the complications associated with overimmunosuppression such as BK nephropathy, opportunistic infections, and malignancy.

18.8.4 Prognosis

Patients with rLN had a fourfold increased risk of graft failure as reported by a UNOS study [112], but only 7% of graft failure events were attributed to rLN. Other single-center studies have similarly found that graft loss and patient survival are not adversely affected by rLN [111, 114–116]. Although allograft survival was comparable between lupus and non-lupus recipients in a pediatric study, it was associated with a worse patient survival rate, with a 1.8 relative risk of mortality [117].

18.9 Idiopathic Membranous Nephropathy

Idiopathic membranous nephropathy (IMN) is a glomerular disease that usually presents with nephrotic syndrome and is characterized histopathologically by extensive foot-process effacement and subepithelial deposits on electron microscopy and

glomerular basement membrane matrix spike formation that progresses over time [118]. IMN is found in ~1–9% of all pediatric native kidney biopsy samples [119–121] and progresses to ESKD in about 30% of pediatric patients within 10 years [119]. Pediatric membranous nephropathy is often a secondary disease caused by other primary diseases such as SLE, infections such as hepatitis B or C, and/or various medications [121]. Secondary MN does not typically recur post-transplant. Since 2009, it has been demonstrated that auto-antibodies against multiple antigens are the primary driver of IMN [122, 123]. Anti-M-type phospholipase A2 receptor (PLA2R) is the most common antigen in IMN with ~70% of adult patients [122] and ~45–75% of pediatric patients [124, 125] with IMN having measurable anti-PLA2R antibodies and/or glomerular PLA2R staining. Antibodies against these antigens lead to histologic changes by in situ binding to glomerular components, formation of immune complexes, and activation of the immune system [123].

18.9.1 Incidence

Recurrence of MN post-kidney transplant is estimated to occur in 10–50% of adult patients [86, 126, 127]. The rate of recurrence in pediatric patients is not clear, as <1% of pediatric kidney transplants are performed for ESKD secondary to IMN, with only 10 transplants reported for ESKD secondary to IMN in the United States from 2015 to 2019 [1]. In addition, in the adult kidney transplant population de novo MN occurs in ~2% of adult transplants and may have a different pathophysiology, being associated with rejection and other types of inflammation [128, 129].

18.9.2 Risk Factors

With such limited data available for pediatric patients, risk factors for recurrence in the pediatric population have not been defined. For adult patients, both pre-transplant and post-transplant titers of anti-PLA2R antibodies predict recurrence in the allograft [130–133]. In addition there may be a donor-genetic component to recurrence as specific single nucleotide polymorphisms (SNPs) in the HLA-DRB1, HLA-DQA1, HLA-D, and the PLA2R1 loci of the donor are associated with recurrence of IMN in the allograft [134].

18.9.3 Diagnosis and Treatment

Recurrence of IMN is usually first identified by recurrence of proteinuria, and periodic monitoring for proteinuria using a monthly spot urine protein to creatinine ratio for the first 1–3 years after transplant is recommended [131, 132]. An elevated protein/creatinine ratio should be confirmed with a 24-h urine collection. Given the association between anti-PLA2R-ab and recurrence, some centers also routinely monitor anti-PLA2R titers [132].

MN recurrence tends to occur 1–3 years post-transplant, and it is important to note that other causes of proteinuria several years into the life of an allograft include acute rejection, transplant glomerulopathy, overweight/obesity, diabetes mellitus, malignant hypertension, mTOR inhibitors, and/or chronic CNI toxicity. Definitive diagnosis is made by allograft biopsy including staining for IgG subtypes and PLA2R antigen [131, 132]. Many times subclinical de novo or recurrent MN (rMN) is diagnosed on surveillance biopsies.

Treatment of rMN is similar to treatment for primary IMN in terms of the use of rituximab; however, there is no significant evidence that additional steroids, alkylating agents, calcineurin inhibitors, and mycophenolic acid provide any benefit in rMN [132]. All patients with rMN should receive supportive care including RAS blockade, strict blood pressure control, statin therapy if nephrotic with hyperlipidemia, symptomatic treatment with diuretics, and anticoagulation if indicated. Many centers reserve additional immunosuppression to higher-risk rMN where there is persistent proteinuria of >1 G/day despite treatment with RAS blockade. Multiple case series in adult patients have described good responses to rituximab using most commonly 1 G of IV rituximab for 2 doses of 375 mg/m^2/dose [131, 132].

18.9.4 Prognosis

In general, the prognosis in kidney transplantation for patients with rMN is guarded compared to patients with primary IMN. Most subclinical rMN progresses to overt proteinuria over time, and the likelihood of achieving a spontaneous remission is reduced in rMN compared to IMN in native kidneys [131, 132]. One large study by Pippias and colleagues in >700 adult patients with IMN (both with and without rMN) demonstrated a relative risk for death-censured graft loss of 1.60 (1.34–1.91) at 10 years and 1.65 (1.40–1.95) at 15 years compared to ADPKD controls with no risk for recurrent disease [135]. Death-censored kidney allograft survival rates were also lower in 167 patients in the Australia and New Zealand Dialysis and.

Transplant (ANZDATA) Registry, although overall patient survival post-transplant was better for patients with MN than for patients with ESKD due to other causes [126].

18.10 Conclusion

There is significant variability in allograft survival across subtypes of disease recurrence in pediatric transplantation. Our current strategies for treatment of the most common recurrent diseases such as FSGS and IgA nephropathy are good enough that disease recurrence can usually be treated and/or attenuated with only mild to moderate effects on allograft survival for most patients. Other recurrent diseases such as complement-mediated C3GN are associated with severely reduced allograft survival. Definitive data from randomized trials on the efficacy of specific therapeutic strategies do not exist for any recurrent disease in

pediatric kidney transplantation. Therefore, recurrent disease in pediatric kidney transplantation is generally treated using the same modalities we use to treat primary disease. While we await more complete and informative data from pediatric trials on recurrent disease post-kidney transplantation, with small numbers of patients being transplanted for most recurrent diseases and with only a portion of these patients having recurrent disease, we are unlikely to see significant randomized trials in pediatric patients for most types of recurrent disease. We likely will need iterative improvement strategies with standardized treatment protocols rather than randomized clinical trials to lengthen allograft survival in patients with rare and severe recurrent conditions.

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