

## CHAPTER 8.8 Recurrence of primary kidney disease

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### 1 Focal segmental glomerulosclerosis (FSGS)

**Pathophysiology:** Podocyte damage leads to mesangial matrix proliferation, allowing protein leakage and resulting in sclerosis and scarring of the glomerulus [1].

**Frequency:** FSGS is one of the most common diseases to recur with rates ranging from 30% to 60%, increasing to 86% after re-transplantation. In genetic forms of FSGS, recurrence occurs very rarely [2].

**Clinical appearance:** FSGS presents with nephrotic-range proteinuria shortly after transplantation. Gross haematuria is rare, although microscopic haematuria may occur [3].

**Monitoring:** Frequent monitoring of urine protein-to-creatinine ratio.

**Therapy:** Plasmapheresis is postulated to reduce the circulating permeability factor. It may be used with or without rituximab [4]. Supportive measures: Sodium and protein restriction, blood pressure control, use of RAAS inhibitors, and management of dyslipidaemia. SGLT2 inhibitors may offer kidney protection, but evidence is limited. Diuretics for oedema and adequate nutrition [5].

### 2 C3 glomerulopathy (C3G)

**Frequency:** The recurrence rate of C3 glomerulopathy after kidney transplantation varies, but studies suggest that it may occur in up to 50% of patients [6].

**Pathophysiology:** The high risk of recurrence after kidney transplantation is due to the continued activation of the complement system, which is damaging even in the new kidney. Some patients may have genetic predispositions that affect complement regulation, increasing the likelihood of recurrence in the transplanted kidney.

**Monitoring:** Close monitoring is essential for early detection and management of recurrence in transplant recipients with a history of C3 glomerulopathy:

1. Clinical monitoring: Assessment of kidney function, proteinuria, and haematuria.
2. Kidney biopsy: If there are signs of recurrence, a kidney biopsy is the most definitive way to diagnose C3-glomerulopathy.
3. Complement studies: Testing for complement levels (C3, sC5b-9, C3d, autoantibodies (C3/C4/C5Nef, anti-CFH), etc.) can provide insight into the ongoing complement activation that is a hallmark of C3-glomerulopathy [7].

**Therapy:** Treatment of recurrent C3 glomerulopathy after kidney transplantation typically involves several approaches:

1. Immunosuppressive therapy: Adjustment of immunosuppressive medication can help control the immune response. This may include increasing the dose of existing medications or adding new agents.
2. Plasmapheresis: This procedure can be used to remove pathogenic factors, including complement components and antibodies, from the blood. It may be effective in reducing recurrence and controlling symptoms.
3. Complement blocker therapy: Monoclonal antibodies blocking the terminal complement cascade such as eculizumab or ravulizumab have limited efficacy [7]. New more specific complement inhibitors such as iptacopan or pegcetacoplan might have better efficacy and will soon achieve regulatory approval [8].
4. Supportive care: Control of blood pressure and proteinuria and close monitoring of kidney function are essential to prevent further damage.

### 3 IgA nephropathy (IgAN)

**Pathophysiology:** IgAN is the most common primary glomerulonephritis worldwide and is characterised by impaired IgA1 glycosylation (due to galactose-deficient IgA1, immune complex deposition, genetic predisposition [e.g. *C1GALT1* or *IGAN1*] or familial predisposition) [9].

**Frequency:** Recurrence is highly variable time-dependent. The cumulative incidence in a large retrospective study was 19% at 10 years und 23% at 15 years [10, 11].

**Clinical appearance:** Patients with recurrent IgAN usually present with persistent microscopic haematuria. New or worsening proteinuria or, occasionally, an increase in the serum creatinine may also be seen [12].

**Monitoring:** In IgAN, increased urinary protein excretion indicates a higher risk of disease progression [13].

#### Therapy:

1. Glucocorticoid withdrawal may increase the risk of recurrence in IgAN [14].
2. ACE inhibitors/AT1 antagonists to reduce proteinuria and blood pressure [15]. Treatment of cardiovascular risk factors [16].
3. Standard immunosuppressive regimens (e.g., tacrolimus, mycophenolate, corticosteroids) have limited effect on the risk of recurrence.
4. High-dose glucocorticoids may be considered for treatment of aggressive glomerulonephritis. Experimental options include rituximab [17] and SGLT2 inhibitors as nephroprotective agents [18].

### 4 Atypical/complement-mediated haemolytic uremic syndrome

**Pathophysiology:** Many patients with atypical haemolytic uraemic syndrome (aHUS) have underlying genetic mutations affecting complement regulation (e.g., in the genes encoding for CFH, CFI etc.). In addition, aHUS can be triggered by anti-FH antibodies. Persistent dysregulation of the complement system before and/or after transplantation is associated with a high risk of recurrence in the transplanted kidney.

**Frequency:** Depending on the underlying cause, recurrence of aHUS after kidney transplantation occurs in approximately 30% to 50% of cases [19]. Close monitoring and proactive management, including the peri-transplant use of complement inhibitors such as eculizumab or ravulizumab can help to reduce the risk of recurrence and improve outcomes for transplant recipients [20].

**Prevention:** Preventing the recurrence of atypical haemolytic uremic syndrome (aHUS) after kidney transplantation involves a multifaceted approach:

1. Genetic screening: Identifying patients with genetic mutations associated with aHUS can help tailor prevention strategies. Understanding a patient's specific genetic risk can guide management.
2. Complement inhibitors, plasmapheresis: Drugs such as eculizumab or ravulizumab may be used to prevent or treat recurrence. If these are not available, plasmapheresis might be considered.
3. Adequate immunosuppression: It is important to ensure optimal immunosuppressive therapy post-transplant. This may help to prevent an immune response that could trigger aHUS or a recurrence of anti-FH antibody-induced aHUS.
4. Monitor for early signs: Regular monitoring of urine (proteinuria, haematuria), kidney function, and blood tests for haemolysis (such as LDH and haptoglobin) and thrombocytopenia, can help detect early signs of recurrence.
5. Kidney biopsy: If there are no laboratory signs of recurrence, a kidney biopsy can provide definitive evidence of thrombotic microangiopathy (TMA).

**Therapy:** Treatment of recurrent aHUS after kidney transplantation typically involves several strategies: A complement inhibitor is now considered to be the first-line treatment. It can help to prevent further complement-mediated damage and control haemolysis. Plasmapheresis may be used, if complement inhibitor therapy is not available or to remove circulating factors contributing to aHUS, such as complement components or antibodies.

**Patient education:** Educating patients about recognising early signs of recurrence, including urine testing, and the importance of adherence to follow-up care can facilitate prompt intervention.

## 5 Lupus nephritis (LN)

**Pathophysiology:** LN is a manifestation of systemic lupus erythematosus (SLE) and results from an immune dysregulation with autoantibody and immune complex formation.

**Frequency:** LN recurs in approximately 2–11 % of cases after kidney transplantation [21, 22]. It manifests at a median of 4.3 years [23].

**Clinical features:** Proteinuria, microhaematuria, deterioration of graft function [21]. Systemic manifestations of SLE recurrence such as arthralgias, skin lesions, fatigue and serological activity (e.g. increased anti-dsDNA antibodies) may also occur.

**Monitoring:** Monitor proteinuria and (micro-)haematuria. Complement levels (C3 and C4), anti-dsDNA antibodies and ANA indicate serological activity. Kidney biopsy is required if a relapse is suspected [24].

**Therapy:** Treatment of recurrent LN follows the same guidelines as for the primary disease: High-dose steroids to control acute inflammation. Mycophenolate mofetil (MMF) as preferred maintenance therapy. Calcineurin inhibitors (tacrolimus, cyclosporine) may be used in combination with MMF. Cyclophosphamide for aggressive relapses or lupus nephritis (class III/IV). Rituximab is used in refractory cases and reduces the production of autoantibodies. Eculizumab in severe cases with complement activation. Supportive therapy with ACE inhibitors/AT1 antagonists to reduce proteinuria; control blood pressure, cholesterol levels and cardiovascular risk factors. In the presence of antiphospholipid syndrome, consider anticoagulation to prevent thrombotic events.

## 6 Primary hyperoxaluria (PH1)

**Pathophysiology:** Primary hyperoxaluria is a genetic disorder affecting oxalate metabolism in the liver. If isolated kidney transplantation is performed, the underlying metabolic defect persists, resulting in continued overproduction of oxalate leading to (rapid) recurrence in the transplant. Therefore, sequential or combined liver and kidney transplantation (SLKT/CLKT) are current transplantation strategies [25]. Alternative approaches using isolated kidney trans-

plantation under pyridoxine and/or siRNA therapy in responsive patients may be considered [25]. If a patient has a significant pretransplant oxalate burden, oxalate may be deposited in the transplanted kidney even after SLKT/CLKT. Oxalate levels may remain elevated even years after transplantation.

**Monitoring/therapy:** Therefore, certain measures should be taken after transplantation:

1. Short-term management: Lowering oxalate levels is critical to prevent recurrence after transplantation. Therefore, haemodialysis/-filtration may be necessary after transplantation, especially if graft function is delayed.
2. Long-term management: Hydration and urine alkalinisation should be optimised even years after transplantation. In patients with isolated kidney transplantation on pyridoxine and/or siRNA therapy it is imperative to continue these therapies. Plasma and urinary oxalate levels should be monitored after transplantation. Ultrasound should be used to assess for kidney stones or calcifications. If there are significant signs of recurrence, a biopsy may be performed to check for oxalate deposits in the renal tissue.

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