Chapter 10: Recurrent Kidney Disease

10.1: We suggest screening KTRs with primary kidney disease caused by FSGS for proteinuria (*2C*) at least:
- **daily for 1 week *(2D)*;**
- **weekly for 4 weeks *(2D)*;**
- **every 3 months, for the first year *(2D)*;**
- **every year, thereafter. *(2D)***

10.2: We suggest screening KTRs with potentially treatable recurrence of primary kidney disease from IgA nephropathy, MPGN, anti-GBM disease, or ANCA-associated vasculitis for microhematuria, (*2C*) at least:
- **once in the first month to determine a baseline *(2D)*;**
- **every 3 months during the first year *(2D)*;**
- **annually, thereafter. *(2D)***

10.3: During episodes of graft dysfunction in patients with primary HUS, we suggest screening for thrombotic microangiopathy (e.g. with platelet count, peripheral smear for blood cell morphology, plasma haptoglobin, and serum lactate dehydrogenase). *(2D)*

10.4: When screening suggests possible treatable recurrent disease, we suggest obtaining an allograft biopsy. (*2C*)

10.5: Treatment of recurrent kidney disease:

10.5.1: We suggest plasma exchange if a biopsy shows minimal change disease or FSGS in those with primary FSGS as their primary kidney disease. *(2D)*

10.5.2: We suggest high-dose corticosteroids and cyclophosphamide in patients with recurrent ANCA-associated vasculitis or anti-GBM disease. *(2D)*

10.5.3: We suggest using an ACE-I or an ARB for patients with recurrent glomerulonephritis and proteinuria. (*2C*)

10.5.4: For KTRs with primary hyperoxaluria, we suggest appropriate measures to prevent oxalate deposition until plasma and urine oxalate levels are normal (*2C*), including:
- **pyridoxine *(2C)*;**
- **high calcium and low oxalate diet *(2C)*;**
- **increased oral fluid intake to enhance urinary dilution of oxalate *(2C)*;**
- **potassium or sodium citrate to alkalinize the urine *(2C)*;**
- **orthophosphate *(2C)*;**
- **magnesium oxide *(2C)*;**
- **intensive hemodialysis to remove oxalate. *(2C)***

ACE-I, angiotensin-converting enzyme inhibitor; ANCA, antineutrophil cytoplasmic autoantibody; ARB, angiotensin II receptor blocker; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HUS, hemolytic-uremic syndrome; IgA, immunoglobulin A; KTRs, kidney transplant recipients; MPGN, membranoproliferative glomerulonephritis.

Background

The primary kidney disease is generally documented by pretransplant biopsy of the native kidney, or of a previous kidney transplant. Recurrence of the primary kidney disease is usually established when there is biopsy-documented involvement of the kidney allograft with the primary kidney disease.

Rationale

- Some recurrent kidney diseases cause allograft failure.
- Treatment of some recurrent kidney diseases may prevent, or delay, the onset of graft failure.
- Screening for treatable recurrent kidney disease may result in early diagnosis and treatment that may be beneficial.

Recurrence of primary kidney diseases is an important cause of morbidity and graft loss following kidney transplantation, in both adults and children. In a study of 1505 cases with both native kidney and kidney allograft biopsies documenting recurrent glomerular disease, graft loss due to recurrent glomerulonephritis was the third most frequent cause for graft failure 10 years after kidney transplantation (110). Recurrence may present as increased serum creatinine (reduced GFR), new-onset or increased proteinuria and/or hematuria. The impact of recurrence varies according to the primary kidney disease. Not all diseases recur with equal frequency. The risk of recurrence is particularly increased in FSGS, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), hemolytic-uremic syndrome (HUS), oxalosis and Fabry's disease and, to a lesser extent, with lupus nephritis, anti-glomerular basement membrane (GBM) disease and vasculitis (189). Also, the timing of recurrence and manner of presentation vary for different diseases. FSGS, HUS and oxalosis may recur in the first few days to weeks after transplantation, whereas the timing is variable in the others (127).

Table 8: Screening for recurrent diseases

Disease	Screening (in addition to serum creatinine)	Minimum screening frequency	Diagnostic tests (in addition to kidney biopsy)	Potential treatment
FSGS	Proteinuria	Daily for 1 week, weekly for 4 weeks, every 3 months for 1 year, then annually		Plasmapheresis
IgA nephropathy	Proteinuria, microhematuria	Once in the first month, every 3 months in the first year, then annually		
MPGN	Proteinuria, microhematuria		Serum complement levels	
Anti-GBM disease	Proteinuria, microhematuria		Anti-GBM antibodies	Plasmapheresis
Pauci-immune vasculitis	Proteinuria, microhematuria		ANCA	Cyclophosphamide and corticosteroids
HUS	Proteinuria, platelet count	During episodes of graft dysfunction	Platelet count, peripheral blood smear, LDH	Plasmapheresis

ANCA, antineutrophil cytoplasmic antibody; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HUS, hemolytic-uremic syndrome; IgA, immunoglobulin A; LDH, lactate dehydrogenase; MPGN, membranoproliferative glomerulonephritis.

In a majority of instances, proteinuria and/or reduced GFR provide the initial basis for suspecting disease recurrence. Since these parameters are periodically assessed in KTRs as part of their routine monitoring, a separate strategy for detection of disease recurrence is not warranted.

The modality of screening for some of these diseases, however, may vary from the usual posttransplant monitoring if timely detection is not achieved by the routine posttransplant monitoring strategies (Table 8). For example, FSGS can recur early; hence, screening for FSGS recurrence requires early and frequent monitoring for proteinuria. HUS recurrence requires looking for evidence of microangiopathic hemolysis. Screening for recurrent IgA nephropathy, MPGN, anti-GBM disease and vasculitis require examination of urinary sediment to detect microhematuria and/or presence of casts in addition to screening for proteinuria. It is appropriate to perform dipstick testing for proteinuria followed by quantitation using spot protein creatinine ratio or timed urine collection. Depending on the primary disease, biopsy evaluation may require immunofluorescence and electron microscopy in addition to light microscopy to confirm recurrence and to rule out other causes of proteinuria, hematuria or graft dysfunction (190).

There is also weak evidence (uncontrolled case studies and case reports) that disease-specific treatment may be beneficial for some recurrent diseases.

Idiopathic FSGS

Idiopathic, or primary, FSGS is characterized by typical sclerosis in a segment of glomerular tuft, along with foot-process fusion on electron microscopy. Sclerosis may not be evident in early recurrence, and light microscopy may show normal glomerular architecture. Recurrence is suspected when a patient with a documented primary FSGS in the native kidneys or a prior kidney allograft develops proteinuria and/or increase in serum creatinine, typically soon after transplantation (127).

Idiopathic FSGS recurs in 20–50% of KTRs (up to 80% if it has recurred in a prior kidney transplant) (191). It is important to distinguish idiopathic from secondary causes of FSGS that generally do not recur. Recurrence of familial FSGS has also been documented, if the donor is an obligate carrier (191). Putative risk factors for recurrence include age of onset of FSGS in native kidneys between 6 and 15 years (192), rapid course of the original disease (e.g. less than 3 years from diagnosis to CKD stage 5), diffuse mesangial proliferation on histology and non-African American ethnicity. The strongest risk factor is recurrence in a previous transplant.

The demonstration of increase in the albumin permeability of isolated rat glomeruli by sera from patients with a recurrent FSGS offers the possibility of more accurate prediction of the risk of recurrent disease (193). However, this assay is still experimental.

Idiopathic FSGS can recur at any time after transplantation, but recurrence is more common early after transplantation. Recurrent disease presents with proteinuria, which is usually heavy. About 80% of cases recur in the first 4 weeks (193). Proteinuria screening therefore needs to be more frequent in the early posttransplant period in those with CKD stage 5 due to FSGS, especially those with risk factors for recurrence. The exact frequency has not been worked out. Interpretation of proteinuria, especially in the early posttransplant period, requires knowledge of pretransplant proteinuria. Although proteinuria from the native kidneys declines after transplantation (194), the time taken for its disappearance is variable. Posttransplant proteinuria therefore should be interpreted in light of the pretransplant values.

There have been no RCTs of therapy for recurrent idiopathic FSGS. However, there have been individual cases, and uncontrolled series, reporting that patients with recurrent idiopathic FSGS may have a substantial reduction in urine protein excretion after plasma exchange (195,196). This probably occurs by removing circulating factors that alter glomerular permeability to protein. Predictors of response to plasma exchange include early initiation of treatment after recurrence, and possibly an early recurrence of disease (196). Unfortunately, proteinuria may recur after treatment, and may require additional plasma exchange, or even periodic, ongoing treatments. The presumption is that reducing protein excretion with plasma exchange will help preserve allograft function, but no studies have examined this.

It is unclear how many plasma-exchange treatments are required to reduce protein excretion, but one review found a median of nine treatments before there was a remission in proteinuria (195). In small case series, prophylactic plasma exchange has been reported, but the data are not convincing that this is effective in preventing recurrent FSGS (197,198).

High-dose CsA may induce remission of proteinuria. In one series, 14 of 17 children entered lasting remission (199). The rationale behind maintaining a high CsA blood level is to overcome the effect of high serum cholesterol often seen in patients with recurrent FSGS (lipoproteins bind CsA and reduce free CsA levels). High-dose CsA may be combined with plasmapheresis. A study concluded that plasmapheresis alone was not sufficient to induce remission except when combined with high-dose CsA (200).

For patients who do not respond to plasma exchange, or for patients who have non-nephrotic proteinuria, a reduction in proteinuria with an angiotensin-converting enzyme inhibitor (ACE-I) and/or an angiotensin II receptor blocker (ARB) may be beneficial.

IgA nephropathy

IgA nephropathy is the most common type of glomerulonephritis worldwide and is the primary cause of CKD stage 5 in 20% of KTRs in many parts of the world. Recurrent IgA nephropathy is common after transplantation. Reported incidence of recurrence varies from 13% to 53% according to differences in duration of follow-up and biopsy policy of different transplant centers, with the highest rates in centers that perform routine protocol biopsies (201). Latent IgA deposits in the donor kidney (identified on preimplantation biopsies) are responsible for 'recurrence' in some cases transplanted for kidney failure due to IgA nephropathy in areas with high disease prevalence (202). Single-nucleotide polymorphisms in the interleukin-10 and TNF-alpha genes have been shown to predict recurrence risk (203,204). The estimated 10-year incidence of graft loss due to recurrence was 9.7% (CI = 4.7–19.5%) (110). Recurrence risk in retransplants is increased if the first graft was lost due to recurrent IgA nephropathy in less than 10 years (205). There is no effective therapy for preventing recurrent IgA nephropathy. ACE-Is and ARBs have been shown to reduce proteinuria and possibly preserve kidney function in recurrent IgA nephropathy (206). In a study of 116 KTRs with IgA nephropathy, use of ATG as induction therapy was associated with a reduction in recurrence risk from 41% to 9% when compared to IL2 receptor antagonists (207).

Membranoproliferative glomerulonephritis

Secondary causes of MPGN, such as hepatitis C, should be ruled out. The histological recurrence rate in idiopathic type I MPGN is 20–30% and exceeds 80% in type 2 disease (192). Manifestations include microhematuria, proteinuria and deterioration of kidney function. Risk factors for recurrence include severity of histological lesions in native kidneys, HLA-B8DR3, living related donors and previous graft loss from recurrence (208,209). There are reports of response to long-term cyclophosphamide (210), plasmapheresis (211–213) and CsA (214).

Hemolytic-uremic syndrome

Hemolytic-uremic syndrome is defined histopathologically by intimal cell proliferation, and thickening and necrosis of the wall, thrombi and narrowed lumens of glomerular, arteriolar or interlobular artery. The severity can range from endothelial swelling to complete cortical necrosis. It manifests clinically with microangiopathic hemolytic anemia and rapid worsening of kidney function with or without involvement of other organs. HUS is often classified as diarrhea-associated (D)− HUS (atypical) and D+ HUS (typical).

Hemolytic-uremic syndrome recurs commonly in adults and in children in whom the original kidney disease was D− variant. The overall recurrence risk is less than 10% in the pediatric population; D+ HUS usually does not recur, while idiopathic D− or familial HUS may recur in 21–28% of children (215). Recurrence occurs in about 80–100% of patients with factor H or factor I mutation, while patients with a mutation in membrane cofactor protein do not have recurrence (216,217). The risk is higher in adults, with 33–56% (218–220) showing clinical manifestations and an additional 16–20% of patients demonstrating clinically silent recurrence. Recurrence is particularly frequent in adults with autosomal recessive or dominant HUS (215). Recurrence develops within 4 weeks in most cases. Most patients show microangiopathic anemia, thrombocytopenia and kidney dysfunction, whereas others present with rapidly progressive graft dysfunction without showing the classic hematologic manifestations. Platelet count should be performed during episodes of graft dysfunction in KTRs with HUS as the original cause of CKD stage 5. In those with falling counts, additional tests such as examination

of peripheral blood smear to look for fragmented cells (schistocytes), haptoglobin and lactate dehydrogenase estimation to document hemolysis are warranted. Long-term graft survival is lower (about 30%) in those with recurrence.

Treatment strategies have included plasmapheresis, intravenous immunoglobulin and rituximab. Aggressive plasmapheresis using fresh frozen plasma (40–80 mL/kg per session) increases the levels of deficient factors and has provided encouraging results, even in those with factors H and I mutations (221–223). As factor H is synthesized in the liver, combined liver and kidney transplantation (together with preoperative and intraoperative plasmapheresis using fresh frozen plasma and low-molecular-weight heparin) could reduce the risk of recurrence (222,224–226). Intravenous immunoglobulin and rituximab have been reported to rescue recurrent HUS resistant to multiple courses of plasma exchanges (227,228). There is no evidence that avoidance of CNI, mTORi and OKT3 (that may themselves cause thrombotic microangiopathy) will reduce the recurrence risk.

ANCA-associated vasculitis and anti-GBM disease

Both antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and anti-GBM disease may present with rapidly progressive CKD and crescentic glomerulonephritis. Recurrence rates are low if the disease is quiescent at the time of transplant. In an analysis of pooled data from 127 patients with ANCA-associated vasculitis, 17% of patients had recurrence, with kidney manifestation in 57.1%. Kidney dysfunction occurred in 33% of those with recurrence (229). More recent studies (230) report lower (7%) recurrence rates, most beyond the first posttransplant year with no direct or indirect impact on allograft function. ANCA-associated vasculitis relapses in the kidney allograft usually manifest as pauci-immune necrotizing glomerulonephritis, but graft function can also be affected by acute arteritis, ureteral stenosis and obstructive uropathy due to granulomatous vasculitis.

Pretransplantation disease course, disease subtype, ANCA type or titer, time of transplantation or donor type does not predict recurrence. Kidney ANCA-associated vasculitis generally responds well to high-dose prednisolone and cyclophosphamide (231–233). Other treatment modalities that have been tried include MMF, plasmapheresis with or without intravenous immunoglobulin and rituximab (234–240).

Histological evidence of anti-GBM disease can be found in biopsies in 15–50% of cases. Clinical recurrence is rare and consisted of isolated case reports only (201,241). Graft failure due to recurrence is rare (110). The incidence of recurrence may be higher in those with circulating anti-GBM antibody at the time of transplantation. Treatment of clinically active anti-GBM disease may include pulse steroids, cyclophosphamide and plasma exchange, particularly if there is potentially life-threatening pulmonary involvement (241).

Primary hyperoxaluria

Primary hyperoxaluria is caused by deficiency of hepatic peroxisomal alanine:glyoxylate aminotransferase, leading to increased synthesis and urinary excretion of oxalate, recurrent calcium oxalate urolithiasis, irreversible nephrocalcinosis and eventually CKD. In CKD, insoluble oxalates accumulate throughout the body, especially in bone and arteries. Because the enzyme defect in primary hyperoxaluria is not corrected by isolated kidney transplantation, oxalate overproduction persists, leading to recurrence of calcium oxalate deposits in over 90% of transplanted kidneys, and eventually leading to graft loss (242), unless the enzyme is replaced through a simultaneous liver transplant (243). The total body oxalate burden is very high in CKD stage 5 patients, and the urinary oxalate excretion increases greatly as soon as graft function is established. Plasma and urine oxalate levels may remain high for some period of time even in patients undergoing simultaneous kidney and liver transplantation. High urinary oxalate concentration promotes precipitation of calcium oxalate crystals first in the distal tubules, leading to graft dysfunction. This secondarily results in deposition in the parenchyma of the graft, leading to allograft failure. This risk is obviously increased further in those with primary nonfunction of the graft. Transplant protocols designed to minimize complications of recurrent disease include early posttransplant urinary dilution through aggressive fluid administration, and early and frequent dialysis in those with DGF.

Although isolated kidney transplantation is not recommended in primary hyperoxaluria, it is sometimes carried out in developing countries where liver transplantation is not available. Primary hyperoxaluria recurs invariably in those who receive kidney transplant alone and leads to graft loss. Patients with the Gly170Arg mutation are pyridoxine-sensitive, and should be given high-dose pyridoxine if they receive kidney transplant alone (244).

The disease is sometimes diagnosed for the first time after kidney transplantation when oxalate deposits are detected on biopsy in patients with graft dysfunction. Whenever possible, these patients should be referred to specialized centers for liver transplantation. In the immediate postoperative phase, extra dialysis sessions may be necessary to control oxalate blood levels until the liver is completely working (245).

Specific measures designed to increase oxalate excretion and reduce production help in minimization of recurrence, and should be in place for all patients during

the first months or years after kidney or combined liver–kidney transplantation (246). These include maintenance of urine output >3.0–3.5 L/day, and the use of alkaline citrate, neutral phosphate and magnesium oxide. Severe dietary oxalate restriction is of limited benefit (247), but intake of nutrients extremely rich in oxalate and ascorbic acid, a precursor of oxalate, should be discouraged. Pharmacological doses of pyridoxine may reduce hyperoxaluria in some patients, especially in those with a Gly170Arg mutation (244). Pyridoxine responsiveness can be assessed by observation of >30% reduction in urinary oxalate excretion to 10 mg/kg/day dose of pyridoxine (248) in patient's sibs with less severe kidney disease if it was not done at the predialysis stage. Urinary alkalinization with citrate reduces the risk of urinary calcium oxalate supersaturation by forming a soluble complex with calcium, which reduces the likelihood of binding and precipitation with other substances, such as oxalate (249). The dosage is 0.1–0.15 g/kg body weight of a sodium or sodium/potassium citrate preparation. The adequacy of therapy and patient compliance can be verified by measuring urinary pH and citrate excretion. Orthophosphate (20–60 mg/day), along with pyridoxine, has also been shown to reduce urinary calcium oxalate crystallization (250).

Fabry disease

Fabry disease is a rare, X-linked inherited disease characterized by a deficiency of alpha-galactosidase A (alpha-Gal-A), resulting in progressive systemic accumulation of glycosphingolipids. Transplantation is the treatment of choice for most patients with CKD stage 5 due to Fabry disease (251). Although patients with Fabry disease may have histological recurrence of the disease in the allograft, how often recurrence causes graft failure is not clear. In a recent US Organ Procurement and Transplantation Network registry study, 197 KTRs with Fabry disease had 74% 5-year graft survival, compared to 64% in KTRs with other kidney diseases (252). Two formulations of recombinant human alpha-Gal A are currently available: agalsidase alpha (Replagal, Transkaryotic Therapies, Cambridge, MA) and agalsidase (Fabrazyme, Genzyme, Cambridge, MA). In non-KTRs, treatment with recombinant human alpha-Gal A has been shown to reduce the rate of decline in kidney function. However, it is unclear whether treatment improves graft survival, or reduces other complications of Fabry disease in KTRs. Treatment appears to be safe in KTRs (253,254); however it is very expensive, and whether it is cost-effective for improving KTR outcomes is not known.