Recurrent Disease in Pediatric Renal Transplantation

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Abstract The risk of disease recurrence (DR) after renal transplantation (Tx) is relatively high in children and may lead to graft loss (GL), representing 7–8 % of all graft failures. Recurrence of the full disease may be associated with either a high risk of GL (focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, oxalosis, atypical hemolytic uremic syndrome) or with a low risk of GL (IgA nephropathy, lupus, ANCA-associated glomerulonephritis). Recurrence may also occur with a delayed risk of GL, such as insulin-dependent diabetes mellitus and sickle cell disease. Adequate strategies should therefore be added to kidney Tx, such as pre-Tx genotyping, adequate donor selection, specific immunosuppression and/or biotherapy, associated liver Tx, etc. Under such conditions, very few patients would be excluded from kidney Tx only because of a major risk of DR. In the future, the issue of DR after kidney Tx may benefit from alternatives to organ Tx.

Keywords Disease recurrence · Renal transplantation · Child · Focal segmental glomerulosclerosis · Hemolytic uremic syndrome · Membranoproliferative glomerulonephritis · Systemic lupus erythematosus · Primary hyperoxaluria

Renal transplantation (Tx) is the treatment of choice for stage 5 chronic kidney disease (CKD) and end-stage renal disease (ESRD). Disease recurrence has a greater prevalence in children than in adults [1•], therefore increasing patient morbidity, graft loss and sometimes mortality. The current overall graft loss to acute rejection has become comparable to the rate of graft loss to disease recurrence, mainly due to primary glomerular diseases. Relative risk for graft failure from recurrent and de novo disease approximates 2 times compared to the non-recurrent population, but changes in immunosuppression protocols during the last decades have not significantly influenced the incidence of recurring diseases post-Tx.

The spectrum of recurrence is rather wide and mainly depends on the primary disease itself, ranging from a recurrence of the full disease—with variable risks of graft loss—to a recurrence of specific features of the disease (Table 1). In addition, some renal complications post-Tx may mimic recurrence but are based on different mechanisms.

Unfortunately, there is limited evidence on the management of post-Tx disease recurrence, and clinical practice is usually based on non-randomized and uncontrolled case series [1•, 2].

Recurrence of the “Full Blown” Disease

Recurrence with a High Risk of Graft Loss

Nephrotic Syndrome (NS)

Epidemiology Of children with NS, 10 to 15 % do not respond to corticosteroids, and 10–15 % of children with ESRD first presented with NS. Most of them present with

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Table 1 Recurrence of primary disease after the first renal transplantation [1•, 2, 9, 21••, 27, 28•, 44, 45]

Primary disease	Recurrence rate (%)	Graft loss to recurrence (%)
Focal segmental glomerulosclerosis	14–50 (average 30)	40–60
Atypical hemolytic uremic syndrome	17 (MCP)–90 (CFH, CFI)	10 (MCP)–86 (CFH, CFI)
Typical hemolytic uremic syndrome	0–1	0–1
MPGN type 1	30–77	17–50
MPGN type 2	66–100	25–61
Lupus nephritis	0–30	0–5
IgA nephropathy (Berger disease)	32–60	3–7
Henoch–Schönlein nephritis	31–100	8–10
Primary hyperoxaluria type 1	90–100	80–100

CFH complement factor H, CFI complement factor I, MCP membrane cofactor protein, MPGN membranoproliferative glomerulonephritis

idiopathic focal segmental glomerulosclerosis (FSGS). The risk of recurrence in a first graft is 14–50 % with a risk of graft loss of 40–60 %, i.e., a relative risk for graft failure from post-Tx FSGS is around 2 compared to non-recurrent diseases [1•, 3, 4•]. The risk of recurrence in a second graft after a first graft loss to recurrence is 60–100 %. Some risk factors have been reported (Table 2). The current knowledge on pathophysiology of the NS suggests that it may be either an immunological or a genetic disorder, with a common histological pattern (FSGS) but a different risk of recurrence.

Pathophysiology The risk of recurrence mainly affects patients with primary idiopathic FSGS involving T- and B-cell dysfunction and a putative circulating factor. Several candidate agents have been proposed, such as tumor necrosis factor- α , soluble form of the urokinase receptor, etc.; all of them may have the same target, i.e., the podocyte and related integrins [5•, 6, 7••].

A growing number of genes involved in the structure and function of the podocyte have been identified so far but their role in the development of FSGS is incompletely understood. However those patients with a genetic disease causing podocin mutation use to have no recurrence [1•, 8].

Clinical Spectrum The presentation of recurrence includes early massive proteinuria (often as early as the first urine from the graft) and sometimes graft failure and arterial hypertension. The onset of FSGS lesion is a secondary phenomenon that can occur early following recurrence of proteinuria.

Table 2 Risk factors for recurrence/graft loss in patients with steroid-resistant NS [1•, 3, 4•, 24]

Proven increased risk	Independent/controversial risk factors	Proven decreased risk
	Gender	
	Mesangial hypercellularity	
	Age at onset over 6 years	
Recurrence in a first graft ++	Presence of FSGS circulating factor	Start of RRT <6 years of age
Start of RRT >12 years of age	Donor source	African-American recipients
White and Asian recipients	HLA typing/matching	Genetic and syndromic NS
Rapid course to ESRD (<3 years)	Time interval on dialysis prior to Tx	
	Type of immunosuppressive therapy	
	Use of induction therapy	
	Bilateral nephrectomy of native kidneys	

ESRD End-stage renal disease, FSGS focal segmental glomerulosclerosis, NS nephrotic syndrome, RRT renal replacement therapy, Tx transplantation

The prognosis of untreated recurrent NS is poor and there is no current evidence for any kind of treatment but some therapeutic options have been advocated including active treatments, preventive measures and rescue treatments.

Global Approach to Transplantation Some general measures are available: (i) an exact diagnosis is required, (ii) DNA should be analysed/stored, (iii) in patients with persistent NS, preemptive Tx is not recommended because of the risk of both graft thrombosis and delayed diagnosis of recurrence, (iv) pre-Tx bilateral nephrectomy is therefore recommended in patients with persistent proteinuria [1•].

Kidney Tx provides a unique environment since immunosuppressive agents that have not been successful on native kidneys may be effective to prevent post-Tx recurrence. Indeed their late use in the presence of advanced glomerular damage leads to drug-resistance whereas there is a potential benefit of early immunological intervention prior to Tx regarding the onset of glomerular damage into the graft.

Active Treatment of Overt Recurrence Plasmapheresis (around 10 sessions within 2 weeks, then weekly sessions for a total of 2 months, then adapted to individual response) has been successful in many patients [1•, 3, 9, 10]. The use of more sophisticated methods such as immunoabsorption has

no superior benefit. Plasmapheresis has been used with or without cyclophosphamide for an average of 12 weeks. Around 60 % of patients are in complete remission and the success rate is higher when plasmapheresis starts during the first 3–4 days post-Tx.

Randomized controlled studies in children with primary steroid resistant NS have shown that ciclosporin (CsA) is effective in inducing remission since it may act on immunological basis and inhibit the effect of a glomerular permeability factor [2]; it may also act through vasoconstriction. High dose CsA (either orally or with continuous infusion in order to avoid nephrotoxic peak levels; blood concentration between 200 and 350 ng/mL) for a period of 1–3 weeks has given stimulating results. The rationale for maintaining high CsA blood concentration is to overcome the effect of high serum LDL that binds CsA and is further responsible for low free CsA. However, some patients have required further plasmapheresis and others have experienced CsA nephrotoxicity. In the long term, around 60 % of the patients are in complete remission. The use of CsA as a first step treatment may limit the efficacy of plasmapheresis that may be therefore postponed.

The benefit of tacrolimus on native kidney NS is scarce. Its interest on post-Tx recurrent NS has not been demonstrated so far and some patients with a successful post-Tx strategy using CsA have experienced a late recurrence at the time of switching CsA to tacrolimus.

Antibody induction therapy using either thymoglobulin or basiliximab has given controversial results but rituximab—a chimeric monoclonal antibody that acts by inhibiting CD₂₀-mediated B cell proliferation and differentiation—has been successful in a significant number of patients with or without combined plasmapheresis [2, 9, 11–15]. Pediatric patients were given $375 \text{ mg/m}^2 \times 1\text{--}6$ without significant short-term side effect, in order to achieve long-lasting B-CD₁₉ cell depletion [16, 17].

Preventive Measures Pre-treatment with CsA, plasmapheresis, and rituximab requires the use of a living donor in order to initiate therapy prior to Tx; encouraging results have been obtained from limited series [18, 19, 20]. However living donation should not be recommended in the absence of any preventive measures.

Rescue Treatments Angiotensin-converting enzyme inhibitors, angiotensin 2-receptor blockers as well as non-steroidal anti-inflammatory drugs may partially reduce proteinuria without affecting significantly graft survival [1].

Many alternative individual approaches have been proposed, especially in case of recurrence in a second graft, including low-density lipoprotein apheresis [15].

Hemolytic Uremic Syndrome (HUS)

Most children with HUS present with a ‘typical’ form (due to Shiga toxin *Escherichia coli*) with a 5–10 % rate of ESRD, but 5–10 % have an ‘atypical’ course (aHUS) with a high risk of developing chronic kidney disease (CKD) so that aHUS is the primary diagnosis of 2–5 % of children with ESRD. Indeed >50 % of patients with aHUS progress to ESRD and the overall outcome of kidney Tx is poor. However aHUS are a group of distinct diseases that may be due to either deficient von Willebrand factor-cleaving protease (ADAMTS 13), metabolic disorders or to various disorders of complement regulation. Complement abnormalities are identified in 50–70 % of cases and include specific gene mutations in factor H (CFH, 20–30 %), membrane cofactor protein (MCP, 10–15 %), factor I (CFI, 10–15 %), factor B (CFB), C3 and thrombomodulin; no gene mutation is found in one-third of the patients [21•, 22•]. In addition, around 5–10 % of aHUS are due to the presence of anti-FH antibodies leading to a secondary form of FH deficiency [21•, 23]. Patients with aHUS should therefore undergo complement factors determination, genotyping and determination of anti-FH antibodies prior to renal Tx in order to evaluate the risk for graft failure.

Graft failure is mostly due to endothelial damage, i.e., vascular thrombosis and disease recurrence. Disease recurrence is <1 % in children with typical HUS versus 20–80 % in aHUS [21•, 22•]. The average time to recurrence is around 1 month but can be later; it may be triggered by viral or bacterial infection as well as by allograft rejection. Patients who start renal replacement therapy before the age of 6 years have a higher risk of graft loss to recurrence but graft survival has significantly improved during the last decade [24]. Clinical symptoms of recurrence are often severe but the overall management and the risk of post-Tx recurrence are strongly linked to the underlying genotype and associated pathophysiology.

Patients with ADAMTS-13 deficiency use to present either with neonatal onset HUS or with recurrent thrombotic thrombocytopenic purpura-like course. Few of them have been transplanted but recurrence was rather frequent and can benefit from fresh frozen plasma infusion.

In case of MCP mutation, HUS usually presents in children older than 1 year of age as a recurrent disease on native kidneys. The transplanted kidney brings normal MCP so that the risk of recurrence is limited, and the option of using a living donor should not be ruled out when MCP mutation has been proven in the recipient and excluded in the donor [21•].

In case of CFH, CFI or CFB mutation, the presentation is characterized by early symptoms, i.e., during the first 3 months of life. The recurrence rate in children with FH deficiency is 66–80 % and 77–93 % of them will lose their

graft, so that living donors should be excluded [21•, 25] (Table 1). Comparable poor results have been found in patients with factor I mutation: 80–88 % recurrence rate with 100 % graft loss, very few patients with CFB or C3 mutation have been transplanted but the risk of recurrence is rather high [1•].

aHUS with complement mutations may be regarded as contraindication to kidney Tx. However, aggressive treatment with plasmapheresis using fresh frozen plasma has provided interesting results [26] but patients with graft loss despite plasma therapy require either long-term dialysis or another innovative therapeutic option. Human plasma-derived FH concentrate has been suggested but is not yet available whereas the recent use of anti-C5 humanized monoclonal antibodies (eculizumab) has given encouraging results [22•, 27–29, 30•]. It has been proposed either as a treatment for overt post-Tx recurrence of aHUS or as a prophylactic measure [31, 32]. In most cases, eculizumab is given every 2 weeks and cannot be discontinued in the absence of alternative treatment [33, 34]. Because complement factor synthesis comes from the liver, combined liver and kidney Tx (together with pre and intraoperative plasma therapy) has been proposed to selected patients with severe forms of HUS with variable results, but indications for such an option may become limited to very limited cases because of promising results of eculizumab in CFH mutations [21•, 27, 28•, 30•].

Patients with anti-FH autoantibodies are also likely at risk of recurrence, but monitoring of antibodies associated with a combination of plasmapheresis and rituximab may be successful but there is no room for eculizumab [21•, 23].

Membranoproliferative Glomerulonephritis (MPGN) [35]

MPGN type 1 accounts for around 2 % of the primary diagnoses of children who receive a renal Tx. The rate of recurrence in children has been reported between 30 and 77 %, with graft failure to recurrence in 17–50 % (Table 1). Time to recurrence is 0.5–2 years, and the first sign of recurrence is proteinuria that may lead to NS and further graft loss. There is no evidence for any successful treatment despite anecdotal response to plasmapheresis or cyclophosphamide in adults but eculizumab has recently given interesting results [36].

MPGN type 2 is an uncommon form of complement-dependent acquired renal disease often leading to ESRD. It is known to recur almost universally and up to one quarter of patients loses their graft from recurrence (Table 1) [37]. The risk of recurrence and graft loss is independent of both pre-Tx presentation and C3 concentration, but is strongly associated with the presence of proteinuria, which is the hallmark of clinical recurrence. There is no available treatment of MPGN-2 recurrence but the use of eculizumab

has also allowed some encouraging results from case reports [38].

Recurrence has not been reported in very rare patients with lipodystrophy-associated MPGN type 2.

Membranous Nephropathy

In adults, the risk of post Tx recurrence of membranous nephropathy approximates 30 % at 3 years, without evidence for specific risk factors; such a recurrence is associated with graft loss in half of patients. No available treatment has been reported.

Lipoprotein Glomerulopathy

ESRD due to lipoprotein glomerulopathy is an exceptionally rare condition in children. In adults, the risk of post-Tx recurrence approximates 100 % and the risk of graft loss to recurrence involves most patients. Neither specific treatment nor prevention has been advocated but lipid lowering and ACE inhibitor therapy. The use of living donors therefore cannot be recommended.

Primary Hyperoxaluria (PH)

PH-1 is a recessive autosomal disease caused by a deficiency of hepatic peroxisomal alanine: glyoxylate aminotransferase (AGT; cofactor: pyridoxal phosphate) which catalyses the conversion of glyoxylate to glycine. This leads to overproduction of oxalate and massive urinary excretion of calcium oxalate. Once CKD has been reached due to progressive stone disease, insoluble oxalate accumulates throughout the body and mainly skeleton and vessels. Since the metabolic defect is in the liver, isolated kidney Tx cannot correct the primary metabolic defect but only the damaged target organ, so that the risk of recurrence in the absence of liver Tx is 90–100 % (Table 1) with a 5-year graft survival of only 14 % in children from the ESPN/ERA-EDTA registry [39]. A combined liver and kidney Tx is therefore required in most patients. However, in patients with a long period of ESRD, oxalate release from the body may jeopardize the renal graft mimicking recurrence despite the metabolic correction associated with synchronous liver Tx. This is the reason why PH-1 patients should be transplanted as early as CKD stage 4. Some patients who are transplanted after a long period of time on dialysis may benefit from a sequential liver and kidney Tx in order to clear systemic oxalate by dialysis between liver and kidney Tx procedures [40•].

In any patient, the diagnosis has to be confirmed from DNA analysis before considering any procedure of organ Tx. Indeed some patients may present with hyperoxaluria without AGT deficiency, leading to a diagnosis of PH-2,

PH-3 or another unidentified type of PH where Tx strategy has not been clearly delineated.

Recurrence with a Low Risk of Graft Loss

IgA Nephropathy

Up to 25 % of patients with IgA nephropathy develop ESRD, and 32–60 % will experience a histological recurrence of the disease [1•, 41••]. These recurrent patients present with persistent microhematuria and proteinuria, and renal transplant biopsy often shows mesangioproliferative glomerulonephritis, and not only silent recurrent mesangial IgA deposits from protocol biopsy. The risk of recurrence is not correlated with donor status, recipient age, race, or gender; full DR match as well as the use of ciclosporin may limit the risk of recurrence [41••]. Younger adult patients seem to be more prone to the risk of recurrence but recurrence rate in children has not been documented enough; however the percentage of graft loss to recurrence is 3–7 % [1•, 41]. In all patients, proteinuria is associated with progressive loss of function in patients with recurrent IgA nephropathy.

The recurrence rate of Henoch–Schönlein nephropathy post-Tx in children is common on protocol biopsies (Table 1). There is an increased risk of disease recurrence in case of an aggressive progression to ESRD and when a living-related donor has been used, but there is no influence of the type of post-transplant immunosuppression [1•].

Systemic Lupus Erythematosus (SLE)

Results of kidney Tx in SLE are rather good since there is no significant risk of clinical recurrence (Table 1). Some series report on a 30 % histological rejection rate and a greater risk of thrombotic complications (particularly in patients with antiphospholipid antibody syndrome). Such an overall favourable outcome is probably due to the adequate immunosuppressive effect of antirejection regimens that keeps SLE silent [42]. In children, SLE is responsible for around 3 % of ESRD leading to kidney Tx in North America; allograft survival is not different from non-lupus renal diseases but patient survival is worse.

ANCA-Associated Small Vessels Vasculitides

Recurrence of idiopathic pauci-immune ANCA-associated necrotizing glomerulonephritis after renal Tx is rare thanks to the adequacy of immunosuppression, so that the overall results are good. A combination of cyclophosphamide, corticosteroids and sometimes plasmapheresis has been successful from case reports [43].

Wegener granulomatosis is a very rare cause of graft loss in children. The experience of renal Tx in adults shows that the risk of graft loss to recurrence ranges is low, with a comparable outcome to other non-diabetic primary diseases.

Methylmalonic Acidemia (MMA)

Kidney Tx has provided acceptable results in the small number of patients with ESRD due to MMA. However, systemic production of MMA persists after kidney Tx despite dietary protein restriction so that plasma MMA remains at a lower range than before Tx according to post-Tx GFR but still many times greater than in normal subjects.

Recurrence with a Long-Term Risk of Graft Loss

Insulin-Dependent Diabetes Mellitus, Sickle Cell Disease, Endemic/Balkan Nephropathy

Some renal diseases may lead to ESRD during late childhood or early adulthood with a high risk of recurrence as long as the primary disease causing disorder is present. Such a recurrence is a delayed phenomenon and always occurs in adulthood, many years after the primary renal Tx.

Adenine Phosphoribosyl-Transferase Deficiency

Very few patients with adenine phosphoribosyl-transferase deficiency and 2,8-dihydroxyadenine tubulointerstitial lesions present with ESRD of ‘unknown origin’ and no history of nephrolithiasis. Some of them are therefore transplanted in adulthood with a risk of post-Tx stone recurrence and around 10 % have a diagnosis after disease recurrence post-Tx [46]. Once the diagnosis has finally been established, a treatment based on allopurinol, purine restricted diet and hydration uses to be efficient.

Recurrence/Occurrence of Specific Features of the Primary Disease

A large number of hereditary renal diseases may lead to ESRD and kidney Tx. In general, due to their pathophysiology, there is no risk of disease recurrence, except for some patients in which graft function may be jeopardized by the occurrence of specific autoantibodies.

Genetic Forms of NS

Proteinuria

Due to constitutional glomerular abnormalities, there is no risk of recurrence of the primary disease in inherited NS after

Tx of a “new kidney”. This has been shown in most patients with dominant FSGS and in patients with syndromic NS (*WT1*-associated NS, Schimke disease, Pierson syndrome, Galloway syndrome, Charcot-Marie-Tooth disease).

However some patients with genetic NS present with proteinuria post-Tx in the absence of specific features of the primary disease; this may be due to antibody-mediated glomerular injury leading to increased permeability and proteinuria. Such a complication has been found in patients with the Finnish-type NS (anti-nephrin antibodies in *Maj/Maj* homozygous patients) and recessive FSGS (anti-podocin antibodies).

Cancer

Patients with *WT1* mutations have an increased intrinsic risk of cancer in residual tissues, so that target organs must be removed prior to Tx, i.e., bilateral nephrectomy in Denys-Drash syndrome and bilateral gonadectomy in Frasier syndrome. In case of tumor prior to Tx, a 1–2-year time interval between the last specific treatment course and Tx is recommended.

Anti-Glomerular Basement Membrane (GBM) Antibodies-Associated Glomerulonephritis

Anti-GBM antibodies occasionally occur in Alport patients after renal allograft Tx. The association of high titers of anti-GBM antibodies and vascular rejection may be important so that anti-GBM antibodies should be sought in the presence of vascular rejection in Alport patients.

Goodpasture syndrome is a rare cause of ESRD in children. Graft loss to recurrence has been reported in adults but the recurrence of anti-GBM nephritis has rarely been documented. However some patients with recurrent fulminant anti-GBM nephritis also show a reappearance of circulating anti-GBM antibodies at the time of recurrence.

Graft Involvement as a Consequence of Lower Urinary Tract Abnormality

A normal bladder acts as a low pressure, good volume urinary reservoir that is continent, sterile and empties freely and completely. When such an environment is not achieved, infection and renal impairment may occur and recur after kidney Tx. Abnormal bladders must therefore be assessed urodynamically prior to Tx.

From most series in adults as well as in children, patients with abnormal bladder (posterior urethral valves)

or urinary diversion experience worse graft function than those with primary renal diseases but graft survival is comparable. Graft dysfunction may sometimes be due to both repeated urinary tract infection and abnormal urinary pressure regime, so that limited surgical interventions prior to Tx and post-Tx antibiotic prophylaxis are recommended.

Different from Recurrence

De novo lesions can also occur and may mimic disease recurrence, e.g., focal segmental glomerulosclerosis, membranous glomerulonephritis, thrombotic microangiopathy, IgA nephropathy, and even diabetic nephropathy [1•, 28•]. However, these lesions occur regardless of the primary disease so that the diagnosis can be determined.

In some rare inherited diseases, isolated specific deposits can be observed, such as cystine crystals within the interstitial tissue in patients with nephropathic cystinosis or GL3 in those with Fabry's disease. However there is no risk of recurrence of the primary disease in the graft but renal Tx does not correct the underlying metabolic defect in other organs.

Conclusions

Disease recurrence is currently one of the most challenging issues in pediatric renal transplantation. However, graft loss and patient morbidity may benefit from better approaches to disease pathophysiology, better risk evaluation, and improved individualized treatment strategies. DNA analysis should be performed as far as available and adequate material should be stored for immediate approach to the risk of post-transplant recurrence and for further investigations. Specific strategies should be added to kidney transplantation if necessary, such as transplantation strategy (less preemptive procedure), donor selection, associated liver transplantation, plasmapheresis, specific immunosuppression protocols, use of specific monoclonal antibodies, etc. Therefore, very few patients may be excluded from kidney transplantation only because of a major risk of disease recurrence and repeated graft loss. In the near future, the issue of disease recurrence after kidney transplantation may benefit from new approaches to alternatives to organ transplantation such as biotherapy, cell therapy, gene therapy, chaperone molecules, etc. The use of international registries and databases is of major concern in any project including interventional study.

Conflict of interest No potential conflicts of interest relevant to this article were reported.

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