بسم الله الرحمن الرحيم

RECURRENT GLOMERULONEPHRITIS AFTER KIDNEY TRANSPLANTATION

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Review

Recurrent Glomerulonephritis after Renal Transplantation: The Clinical Problem

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Kidney Transplantation
Long-Term Management Challenges

Recurrent Glomerular Disease after Kidney Transplantation
Diagnostic and Management Dilemmas

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Recurrent and *de novo* Glomerulonephritis After Kidney Transplantation

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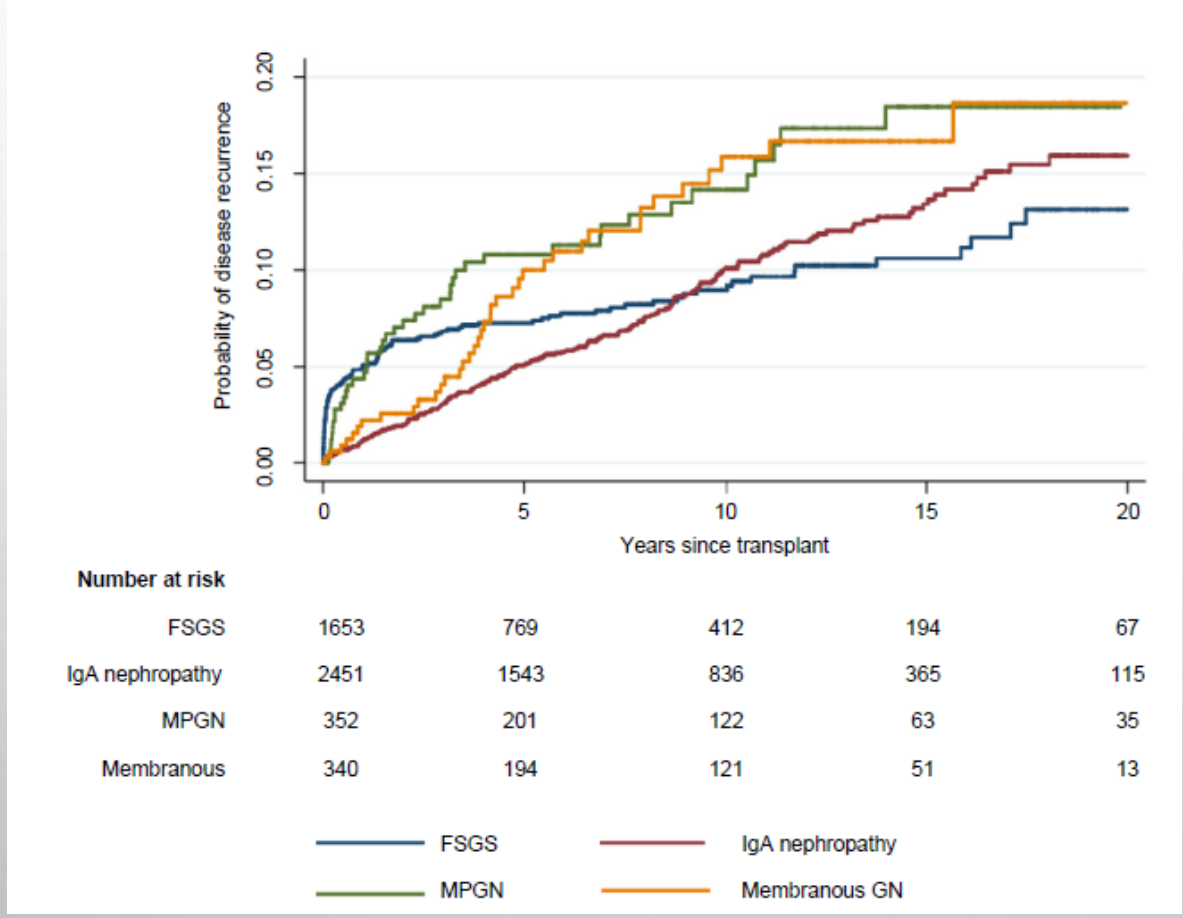
Epidemiology And Risk Factors Of Recurrent GN

- Third most common cause of graft failure 10 years after TX.
- Recurrence of a glomerular disease : 10–20%
- 50% of them show a graft loss on long term follow up.
- 8.4% recurrence-related allograft loss within 10 years after kidney transplantation (ANZDATA).
- Recurrent disease … twice allografts loss compared to those without recurrence
- Risk of disease recurrence:
- Increase in age at transplantation…… 2% reduction risk of recurrence
- Steroid use at baseline (protective for IgAN)
- Longer total ischemic time (protective for IgAN)

TABLE 1 | Prevalence, risk of allograft failure and clinical predictors of glomerulonephritis recurrence post-kidney transplantation.

	Overall[#]	IgA Nephropathy	FSGS	Membranous GN	MPGN
Prevalence of GN recurrence					
ANZDATA (1985–2014) (5)	10.3%	10% at 10 y, 15% at 15 y	9% at 10 y, 11% at 15 y	16% at 10 y, 18% at 15 y	16% at 10 y, 19% at 15 y
Mayo/Toronto[*] (4)	39.5% at 5 y	42% at 3 y, 51% at 5 y	31% at 3 y, 35% at 5 y	45% at 3 y, 55% at 5 y	41% at 3 y, 41% at 5 y
British Columbia (1990–2005) (9)	13% at 10 y, 18% at 15 y	15.4%	9.7%	10%	4.8% (type I MPGN only)
Korea (1995–2010)(11)	17.8%	14.8%	6.3%	0%	12.5%
France (single center) (15)	NR	36% at 10 y	NR	NR	NR
Allograft failure following GN recurrence					
ANZDATA (1985–2014) (5)	55%♦	58%♦	57%♦	59%♦	30%♦
RADR (1987–1996) (14)	5 y GS[θ]:40% (vs. 68% without)	Allograft failure 41%	Allograft failure 65%	Allograft failure 44%	Allograft failure 66%
Mayo/Toronto[#] (4)	HR: 2.6 (1.9, 3.6)	HR: 3.4 (1.2, 9.7)	HR: 5.0 (2.4, 10.1)	HR 1.4 (0.3, 6.8)	HR 6.8 (2.7, 17.2)
British Columbia (1990–2005) (9)	HR: 7.5 (5.5, 10.2)	NR	NR	NR	NR
Korea (1995–2010) (11)	HR: 4.0 (1.7, 9.3)	NR	NR	NR	NR
Clinical predictors of GN recurrence (5, 9, 11, 15, 16)	Primary ESKD secondary to GN, male gender, younger age, non-white ethnicity, steroid-free	Younger age, steroid-free, early steroid-withdrawal, no induction therapy (ATG protective)	Younger age, rapid progression of initial ESKD	Presence (and titer) of anti-PLA2R autoantibody pre-transplant	C3-glomerulopathy subtypes, presence of monoclonal gammopathy, poor response to treatment and rapid progression to ESKD of native disease

Kaplan–Meier estimates of disease recurrence, stratified by glomerulonephritis (GN) types



FSGS; Rate And Clinical Manifestations Of Recurrence

- Primary form…. 30–50% (children, increasing graft failure rate)
- Five-fold higher risk of graft loss
- Early graft failure from 12% to 27%
- Treatment …..Better outcome only half of the cases
- Two clinical manifestations :average time of recurrence… 2 weeks in children and 7.5 months in adult
  - Early (clinical, histology)
  - Late(rare, Donor High-risk APOL-1 (DDX:CNI ,obesity, hypertension, diffuse effacement of foot processes is less obvious)
  - Recurrence in the second graft … 80% in a second TX, exponentially greater.

Risk Factors And Biomarkers Of FSGS Recurrence

- Younger age, rapid progression to ESRD ,mesangial proliferation , steroid resistance , older donor , pre-transplant bilateral nephrectomy (absorber of permeability factors) , ethnicity
- The histologic type of FSGS (±; collapsing FSGS ….Low risk)
- living-related donation (±; particularly in the pediatric recipients)
- Antibodies: suPAR, CD40 (greater risk of recurrence), PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2.
- Monitoring suPAR : poorly defined.

FSGS/ Genetic Testing Before TX

- Monogenic or familial FSGS (NPHS2, TRPC6,APOLipoprotein L-1) ….0% recurrence (exception NPHS1 30%)
- * Children higher prevalence of monogenic or familial genetic FSGS , availability of comprehensive and low-cost genetic testing , should be considered an important tool for the risk stratification of FSGS recurrence.
- **Adult-onset FSGS when there is uncertainty regarding the likelihood of primary (atypical clinical/pathological features or poor response to immunosuppressive treatment) and secondary (no obvious causes identified) FSGS or when there is a clear family history of FSGS.
- Cost:.. It may be more practical to consider screening for patients with a clear family history of FSGS or those with a potential live-related donor for transplantation, including undertaking genetic screening of the donors for the same genetic mutations.

FSGS; Treatment

- Daily measurements of proteinuria in the first 1–2 weeks .
- **Plasmapheresis (immediately**), anti-proteinuric therapy,
- CNI regimen: ± ; inhibition of the dephosphorylation of synaptopodin.
- **Rituximab**: Preservation of podocyte SMPDL-3b expression.
- Ofatumumab, abatacept (all with positive B7-1 immunostaining of podocytes)
- Monoclonal antibodies anti TNF.
- Prophylactic treatment :avoid , insufficient data for pre-emptive use of plasmapheresis ± rituximab.
- Nephrectomy of native kidneys: only children, refractory hypoalbuminemia and continuous requirement for albumin)

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

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

MPGN; Rate And Risk Factors Of Recurrence

- Recurrent MPGN ….27–65% (in 24 month) …..Graft loss in up to 50% .
- 5-year allograft survival post-disease recurrence of only 30%.
- C3 glomerulopathy: recurrent disease in 67%–84% , DDD usually recurs later than C3GN
- **RF**: monoclonal paraprotein, lower serum complement level, HLA B8, DR3, B49, and DR4, higher proteinuria, presence of crescents in the native kidney biopsy (C3Nef levels not related to the risk of recurrence)
- **High risk of graft loss**: such as those with worsening or high-grade proteinuria and/or progressive decline in kidney function.

MPGN/Complement Testing

- The pathogenesis of C3 glomerulopathy :
- **gene mutations:** CFH, factor I, membrane cofactor protein (MCP), CFHR5
- Acquired **antibodies** : C3Nef, antibodies against factor B, CFH, and C3 convertase.
- **No data** exist to support an association between **complement testing** and recurrent disease after transplantation

Treatment Of C3 Glomerulopathy

- A **recent systematic review** : included 12 studies comprising 122 patients with C3 glomerulopathy:
- 50% did not receive treatment due to stable kidney function.
- For treated patients, the pooled rate of allograft loss :
- 33% with **eculizumab**,
- 42% with plasma exchange,
- 81% with rituximab.
- Eculizumab was associated with lower rates of graft loss in C3 glomerulonephritis (22% versus 56% for tpe and 70% for rituximab), with limited data in dense deposit disease (53% rate of allograft loss with eculizumab).
- The pooled risk of allograft loss for those who did not receive treatment was 32%.
- s**MAC**….Only seven patients. 80% of those with **elevated sMAC** levels responded to eculizumab, and all responders normalized sMAC levels after treatment.

MPGN/ Treatment

- The use of **cyclophosphamide and mycophenolate** mofetil may be advantageous in **native disease**,
- In patients with C3 glomerulopathy due to **genetic mutations in CFH, chronic infusions of FFP**
- **Plasmapheresis and/or rituximab** in the treatment of recurrence due to pathogenic antibodies is **controversial** .
- Immunosuppressive treatment: **corticosteroids and mycophenolate**.
- Consideration of **plasmapheresis and anti-B cell therapy for immune complex-mediated GN or those with monoclonal gammopathy**
- **Consider eculizumab for C3 glomerulopathy**

MPGN With Monoclonal Gammopathy

- Up to 70% of patients with immune-mediated GN and **monoclonal deposits** have no evidence of plasma cell dyscrasia , 30% “monoclonal gammopathies of renal significance”.
- Monoclonal gammopathy may be present in both **immune complex-mediated and complement mediated** MPGN)
- For immune-mediated MPGN, serum monoclonal proteins , with and without low complement levels (±glomerular C4d deposition), the presence of glomerular **monoclonal Ig deposits** (typically IgG3K and IgG3l, but IgG2l has been reported): was associated with **poorer prognosis**, characterized by early disease recurrence and substantially greater risk of premature allograft failure .

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PGNMID

- 20 recipients with PGNMID. Histologic recurrence in 18 of 20 recipients (90%), a median of 7 (1 to 65) months post transplant. Four of the 18 patients with recurrence did not progress and were not treated. Another 4 patients with recurrences were treated with cyclophosphamide with or without plasmapheresis, and 2 of these grafts were lost from glomerulonephritis. Nine patients with recurrences were treated with anti-cd20 antibodies (rituximab) alone, resulting in improvements in estimated glomerular filtration rate (31.5 ± 16 versus 38.8 ± 13.3 ml/min/1.73 m2, P = 0.011) and proteinuria (1280 versus 168 mg/24 h, P = 0.012) although complete clinical remission was rare.

AL Amyloidosis

- AL amyloidosis who do not have cardiac involvement and who otherwise meet criteria for transplantation should be considered for kidney transplantation, particularly those **who have achieved complete or very good partial hematologic responses**.
- Angel-korman ….Comprising 49 patients at boston university, graft survival at 1, 3, and 5 years was 94%, 89%, and 81%, respectively.

HUS

Previously renal transplantation was contraindicated (**recurrent** 75–80%).

- genetic; acquired or idiopathic form: **mutations** of the type **“loss of function**” :CFH, CFI, membrane cofactor protein (MCP, CD46), and thrombomodulin (THBD) and mutation of the type “**gain of function**” in genes that encode C3 and CFB.
- **Autoantibodies** against the CFH**.**
- Mutation of membrane-bound factors, for example **MCP (renal endothelium)**, have an **extremely low risk** of developing recurrence (20%).
- Mutation of **circulating factors**, for example **CFH and CFI**, have **a higher risk of developing recurrence leading to graft loss** in 80–90% of cases. These factors are mainly produced by the **liver**;
- These data support that **genetic complement testing should be performed** in all patients with ahus who are undergoing kidney transplant evaluation.

HUS, Treatment

- KDIGO controversies conference recommends starting prophylactic **eculizumab** at the time of transplant,(prophylactic or pretransplant strategies)
- And meta-analysis comprising 380 adult kidney transplant recipients who received eculizumab for **prevention or treatment** of aHUS revealed a pooled estimated rate of allograft loss of **6%** in the prophylaxis group compared with **23%** in those treated after disease recurrence .
- **RF of recurrence of aHUS** : **infections** (CMV, influenza virus, parvovirus B19, BK virus); the use of immunosuppressive **drugs** such as CNI and less frequently mTORI, **rejection**.
- **Prevention:** eculizumab, screening in the living-related donor to exclude genetic mutation. Plasmapheresis, as a prophylactic treatment is still a topic of discussion (**combination)**.
- **Combined liver-kidney transplant.**

HUS

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

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

membranous GN

- **Recurrence** in patients with idiopathic membranous GN : **more than 40% and graft loss rates of over 10–15% at 10 years.**
- **Proteins localized in podocyte** : neutral endopeptidase (NEP) and m-type phospholipase a2 receptor (PLA2R).
- **20%** ….**Do not have** detectable autoantibodies to PLA2R or THSD7A. **70%** Anti-**PLA2R Ab.**
- Direct relationship between the circulating **levels of anti-PLA2R** autoantibody and the risk **of recurrence**
- Anti-**PLA2R** antibodies **tend to decline post-transplant** (adsorption into the allograft or the effect of immunosuppression).
- At the time of **initial transplant evaluation, and at the time of transplant,** following PLA2R ab levels **every 3–6 months is likely to detect trends to guide further monitoring** (to predict disease progression, determine response to treatment**)**

membranous GN/ Treatment

- **Rituximab**: up to 80% achieving complete or partial remission, for early disease recurrence.
- **Indication:** in the setting of worsening kidney function, overt nephrotic syndrome, and/or thromboembolic complications of nephrotic syndrome, (monitoring CD19 counts and PLA2R antibody) levels.
- Single case of complete clinical remission with **bortezomib** (rituximab resistant).
- **Pre-emptive use of rituximab**: ± high pre-transplant levels of anti-PLA2R antibody,

(Likely not necessary) high levels of anti-PLA2R antibody with prior allograft failure

persistent high or increasing levels of circulating anti-PLA2R Ab post- transplant with early histological recurrence.

membranous GN

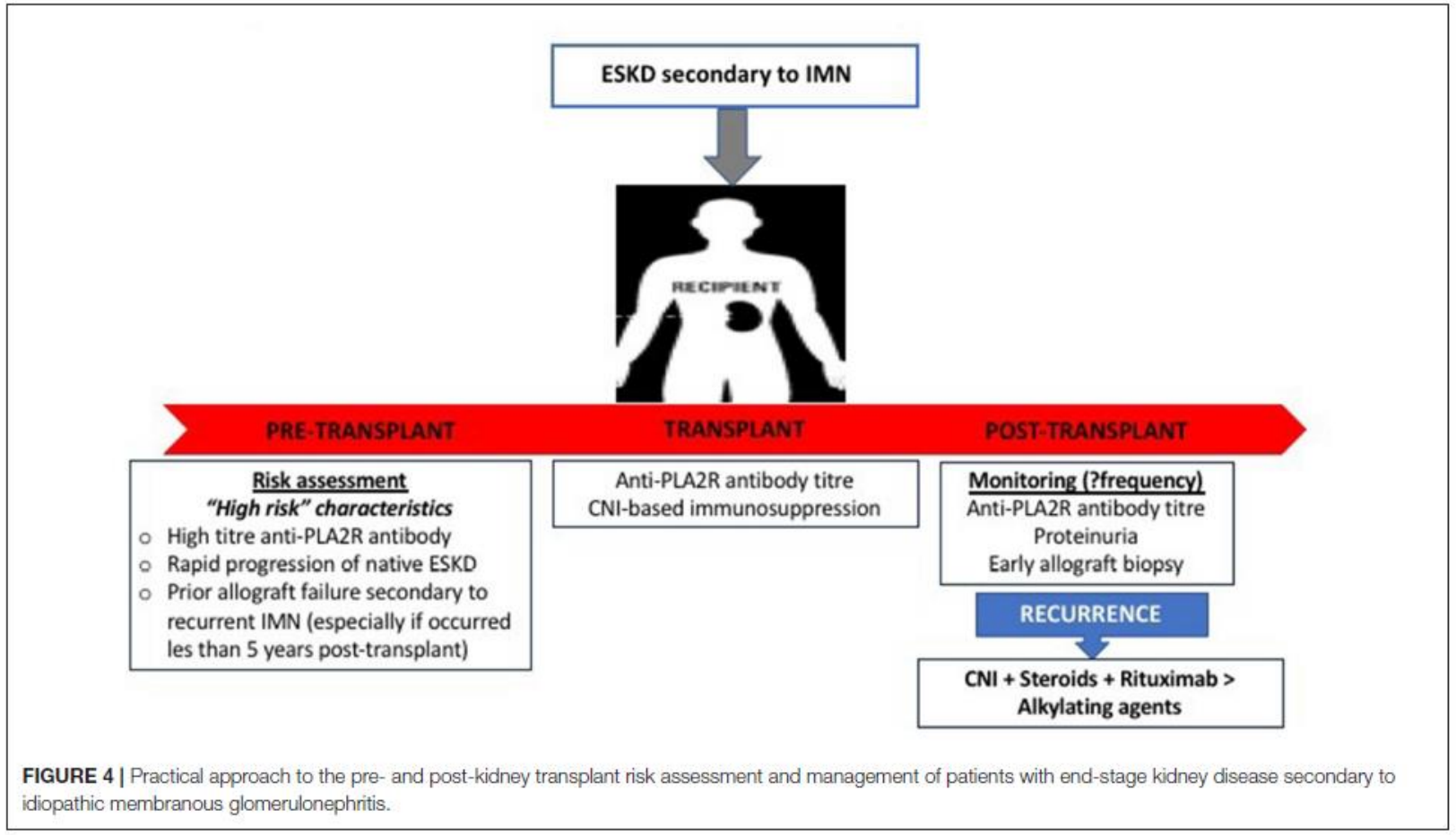

FIGURE 4 | Practical approach to the pre- and post-kidney transplant risk assessment and management of patients with end-stage kidney disease secondary to idiopathic membranous glomerulonephritis.

IgA Nephropathy

- **Recurrence:** 9% to 61% (3 years after TX)
- Graft dysfunction in 13% and graft loss in 5% of cases (long term).
- **RF**: antibodies against galactose-deficient IgA1 (IgG), zero-HLA mismatched live-related donor kidney, steroid-avoidance or early steroid-withdrawal immunosuppressive regimens, male gender, rapidly progressive course of the original disease, number of crescents in the native biopsy, degree of proteinuria, HLA-B35/DR4, and higher levels of circulating gd-IgA1 and IgA-IgG immune complexes, soluble CD89 (disease progression)
- No clinical signs , histological only with mesangial IgA deposits with or without mesangial proliferation.

IgA Nephropathy/ Treatment

- ACE/ ARB .
- ATG: Incidence of recurrence of IgAN, 9% in patients with **ATG**, in comparison with 41% in patients without induction therapy . (also, ATG in comparison with basiliximab and alemtuzumab induced patients).
- Maintenance therapy, steroid , combination of mycophenolate and tacrolimus may also be protective for graft survival.
- Crescentic rapidly progressive IgA nephropathy….**Cyclophosphamide or rituximab** may be considered but this is largely **unproven and unlikely to successfully** reverse the disease process.

ANCA Associated Vasculitis

- **Recurrence**: 0.02 per patient-years, about 17% and incidence of allograft loss is about 7.7%.
- Patients with ANCA associated vasculitis should be in **clinical remission for at least 12 months,** however, persistent ANCA positivity is not a contraindication to transplantation
- Positive antiproteinase-3, require continuous monitoring.
- In both patients with native and transplanted kidney **rituximab may be a treatment of choice**.

SLE/ Anti-GBM

- In patients with **SLE** rate of recurrence is about 30% and allograft loss is uncommon .
- higher risk : female gender, and young age. Patients with antiphospholipid (aPL) autoantibodies and those receiving the kidney from living donors .
- Generally **no change of therapy** is necessary
- Clinical manifestations and severe histopathologic lesions: additional immunosuppressive treatment with bolus of steroid and higher doses of mycophenolate mofetil or cyclophosphamide intravenously in case of rapid renal deterioration with crescentic lesions and severe extra renal disease such as pulmonary hemorrhage and central nervous system involvement.
- In patients with **anti-GBM** rate of recurrence is about 50% when circulating antibodies are still present before transplantation, instead if these antibodies are absent for **at least 12 months** recurrence is rare, when anti-GBM recurs the graft loss is rapid.

TABLE 2 | Prognostic and predictive biomarkers for glomerulonephritis and recurrence of disease post-kidney transplant.

Potential predictive biomarkers in GN subtypes	Clinical utility	Predict post-transplant recurrence
IgA nephropathy		
Serum IgA level (33)	↑ Post-transplant predicts recurrence	Yes
Serum galactose-deficient IgA1 (26)	↑ Pre-transplant predicts post-transplant recurrence	Yes
Serum IgA-IgG complexes (26)	↑ Pre-transplant predicts post-transplant recurrence	Yes
Serum IgA-sCD89 complexes (26)	↓ Pre-transplant predicts post-transplant recurrence	Yes
Normalized Gd-IgA1-specific autoantibody (34)	↑ Pre-transplant predicts post-transplant recurrence	Yes
Serum APRIL (35)	↑ Post-transplant predicts recurrence	Yes
#*Urine proteomics (SERPINA1, Transferrin, APOA4, and RBP4)* (36)	↑ Post-transplant predicts recurrence	Yes
FSGS		
Serum suPAR (37)	↑ Pre-transplant predicts post-transplant recurrence	Yes
Urine suPAR (38)	↑ Post-transplant predicts recurrence	Yes
Anti-CD40 autoAb (39)	↑ Pre-transplant predicts post-transplant recurrence	Yes
Urine apolipoprotein A-1b (40, 41)	↑ In relapses	No data
A1AT (42)	Differentiate from other causes	No data
CLC-1 (43)	↑ Recurrent disease	No data
Anti-AT1R Ab	↑ Pre-transplant predicts post-transplant recurrence	Yes
Membranous GN		
PLA2R *antibody* (44)	↑ Pre-transplant predicts post-transplant recurrence	Yes
THSD7A autoantibody (45, 46)	↑Primary membranous GN	No data
Autoantigens of AR, SOD2, αENO (47)	↑Primary membranous GN	No data
MPGN		
Complements and C3NF (48–50)	Possible association with disease recurrence	Uncertain

#Denotes abstract. GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; CLC-1, Cardiotrophin-like cytokine 1; THSD7A, Thrombospondin type 1 domain-containing 7A; AR, aldose reductase; αENO, α-enolase; AT1R Ab, angiotensin receptor II type 1 antibodies; PLA2R, phospholipase A2 receptor; C3NF, C3 nephritic factor; Gd, galactose-deficient; APRIL, a proliferation-inducing ligand; suPAR, soluble urokinase receptor; Ig, immunoglobulin.

THANK YOU