Universitätsmedizin Essen
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Recurrence of diseases after KTx

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Recurrent Diseases

- High risk of graft loss:
  - FSGS
  - Oxalosis (if not treated before Tx)
  - aHUS (if no Eculizumab is available)
  - C3-GN
- Limited risk of graft loss:
  - Membranous GN
  - IgAN
  - IgAV
  - ANA-GN
  - Lupus-GN

	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

♦*Denotes 5-year graft survival post-disease recurrence. Hazard ratio (HR) of death-censored allograft failure compared to kidney transplant recipients with same GN subtype but without disease recurrence post-transplant. *Denotes cumulative incidence. [#]May include recurrent and de novo GN. [θ]Denotes 5-year actuarial graft survival from time of transplant. GN, glomerulonephritis; HR, hazard ratio; MPGN, membrano-proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; ESKD, end-stage kidney disease; NR, not reported; ANZDATA, Australia and New Zealand Dialysis and Transplant registry; RADR, Renal Allograft Disease Registry; GS, graft survival; y, years; ATG, anti-thymocyte globulin.*

Lim W et al., Front Immunol 2019

EXHIBIT 5.1
CAUSES OF GRAFT FAILURE

	Index Graft Failures		Subsequent Graft Failures		All Graft Failures	
	N	%	N	%	N	%
Total transplants with graft failure	2702	100.0	343	100.0	3045	100.0
Cause of Graft Failure						
Death with functioning graft	249	9.2	27	7.9	276	9.1
Primary non-function	63	2.3	2	0.6	65	2.1
Vascular thrombosis	252	9.3	39	11.4	291	9.6
Other technical	30	1.1	4	1.2	34	1.1
Hyper-acute rejection	15	0.6	4	1.2	19	0.6
Accelerated acute rejection	33	1.2	8	2.3	41	1.4
Acute rejection	352	13.0	44	12.8	396	13.0
Chronic rejection	960	35.5	129	37.6	1089	35.8
Recurrence of original kidney disease	179	6.6	33	9.6	212	7.0
Renal artery stenosis	15	0.6	0	0.0	15	0.5
Bacterial/viral infection	47	1.7	6	1.8	53	1.7
Cyclosporine toxicity	13	0.5	0	0.0	13	0.4
De novo kidney disease	8	0.3	2	0.6	10	0.3
Patient discontinued medication	125	4.6	8	2.3	133	4.4
Malignancy	34	1.3	2	0.6	36	1.2
Other/Unknown	327	12.1	35	10.2	362	11.9

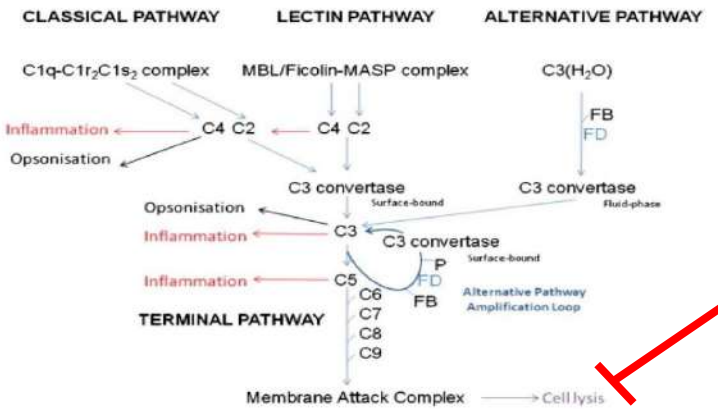
Recurrence of primary disease after the first renal transplantation

Table 1 Recurrence of primary disease after the first renal transplantation [1–11] (*FSGS* focal segmental glomerulosclerosis, *HUS* haemolytic uraemic syndrome, *IgA* immunoglobulin A, *MPGN* membranoproliferative glomerulonephritis, *SLE* systemic lupus erythematosus)

Primary disease	Recurrence rate	Graft loss to recurrence
FSGS	14–50%	40–60%
Atypical HUS	20–80%	10–83%
Typical HUS	0–1%	0–1%
MPGN type 1	30–77%	17–50%
MPGN type 2	66–100%	25–61%
SLE nephritis	0–30%	0–5%
IgA nephritis (Berger disease)	35–60%	7–10%
Henoch–Schönlein nephritis	31–100%	8–22%
Primary hyperoxaluria type 1	90–100%	80–100%

C3-Glomerulopathy

Complement pathway



Eculizumab/Ravulizumab

Cochat et al., Pediatr Nephrol, 2009

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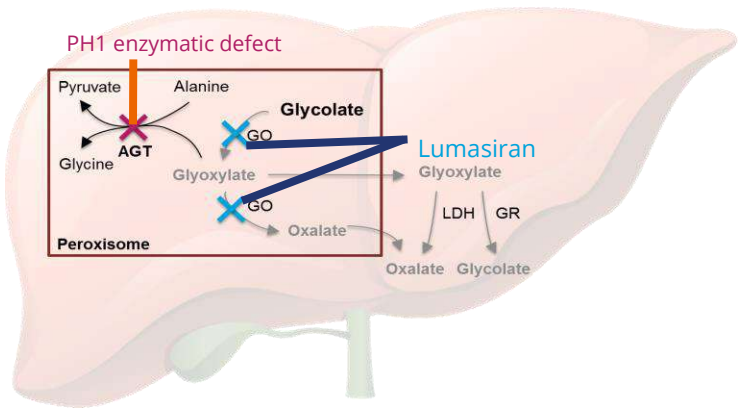
C3-Glomerulopathy

Lumasiran Therapeutic Hypothesis



Cochat et al., Pediatr Nephrol, 2009

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WILEY

SPECIAL ARTICLE

Clinical practice recommendations for recurrence of focal and segmental glomerulosclerosis/steroid-resistant nephrotic syndrome

Lutz T. Weber[1] | Burkhard Tönshoff[2] | Ryszard Grenda[3] | Antonia Bouts[4] | Rezan Topaloglu[5] | Bora Gülhan[5] | Nikoleta Printza[6] | Atif Awan[7] | Nina Battelino[8] | Rasmus Ehren[1] | Peter F. Hoyer[9] | Gregor Novljan[8] | Stephen D. Marks[10] | Jun Oh[11] | Agnieszka Prytula[12] | Tomas Seeman[13,14] | Clodagh Sweeney[7] | Luca Dello Strologo[15] | Lars Pape[9]

TABLE 1 PICO for question 1 for children with FSGS/ SRNS

Participants	Pediatric recipients of RTx (DD or LD) with FSGS and/or SRNS as primary disease
Intervention	Nephrectomy (unilateral or bilateral) with LD
Comparator	No Nephrectomy or nephrectomy with DD
Outcome	Patient survival; graft survival; primary disease recurrence

TABLE 2 PICO for question 2 for children with FSGS/ SRNS

Participants	Pediatric recipients of RTx (DD or LD) with FSGS/ SRNS as primary disease
Intervention	Immunosuppression
Comparator	Other Immunosuppression
Outcome	Patient survival; graft survival; proteinuria partial remission; proteinuria complete remission; graft function worsening in the subsequent year; infections; other side effects

SEARCH STRATEGY IN MEDLINE (OVID)

Search strategy (Search until March 04, 2019)	Hits
Patients (Pediatric recipients of kidney transplantation with focal-segmental glomerulosclerosis and/or SRNS as primary disease)	
1 exp kidney transplantation/	91 110
2 ((renal or kidney) adj1 transplant$).ab,ti.	68 693
3 1 or 2	101 198
4 (pediatric or adolescence or infant or pediatric or pediatric or adolescent$ OR child$ OR children OR young OR infant$ OR infancy).ab,ti	1 928 544
5 3 AND 4	8259
6 exp Glomerulosclerosis, Focal Segmental/	4973
7 (focal segmental glomerulosclerosis).ti,ab	3205
8 nephrotic syndrome/	15 381
9 (steroid resistant nephrotic syndrome).ti,ab	718
10 OR/6-9	20 388
11 5 AND 10	411
Intervention 1 (living-related donation and/or nephrectomy (unilateral or bilateral) / and/or re-transplantation)	
12 Exp nephrectomy/	32 806
13 nephrectomy.ti,ab	27 533
14 ((kidney) and (Liv$ adj3 donor$)).ab,ti.	6035
15 (Kidney donation).ab,ti	1358
16 retransplantation.ti,ab	3255
Intervention 2(immunosuppressive regimen)	
17 Exp immunosuppressive Agents/	302 201
18 immunosuppress$.ti,ab	124 510
19 OR/ 12-18	427 690
20 **Patients and Intervention**: 11 AND 19	**188**

SEARCH STRATEGY IN CENTRAL

Search strategy (Search until March 04, 2019)	Hits
#1 exp kidney Transplantation	193
#2 (renal or kidney) NEXT transplantation	6312
#3 #1 or #2	6410
#4 pediatric or adolescence or infant or pediatric or pediatric or adolescent* OR child* OR children OR young OR infant* OR infancy	286 448
#5 #3 AND #4	1122
#6 exp Glomerulosclerosis, Focal Segmental	5
#7 (focal segmental glomerulosclerosis)1717	157
#8 exp nephrotic syndrome	34
#9 steroid resistant nephrotic syndrome	106
#10 #6 or #7 or #8 or #9	260
#11 #5 and #10	14

TABLE 3 LoE on the basis of the Oxford Centre for Evidence-Based Medicine 2011, Levels of Evidence: Does the Intervention help? Treatment benefit

Type of study	LoE
Systematic review of RCTs	1
RCT or observational study with dramatic effect	2
Non-randomized controlled cohort/follow-up study	3
Case series, case-control studies, or historically controlled studies	4
Mechanism-based reasoning	5

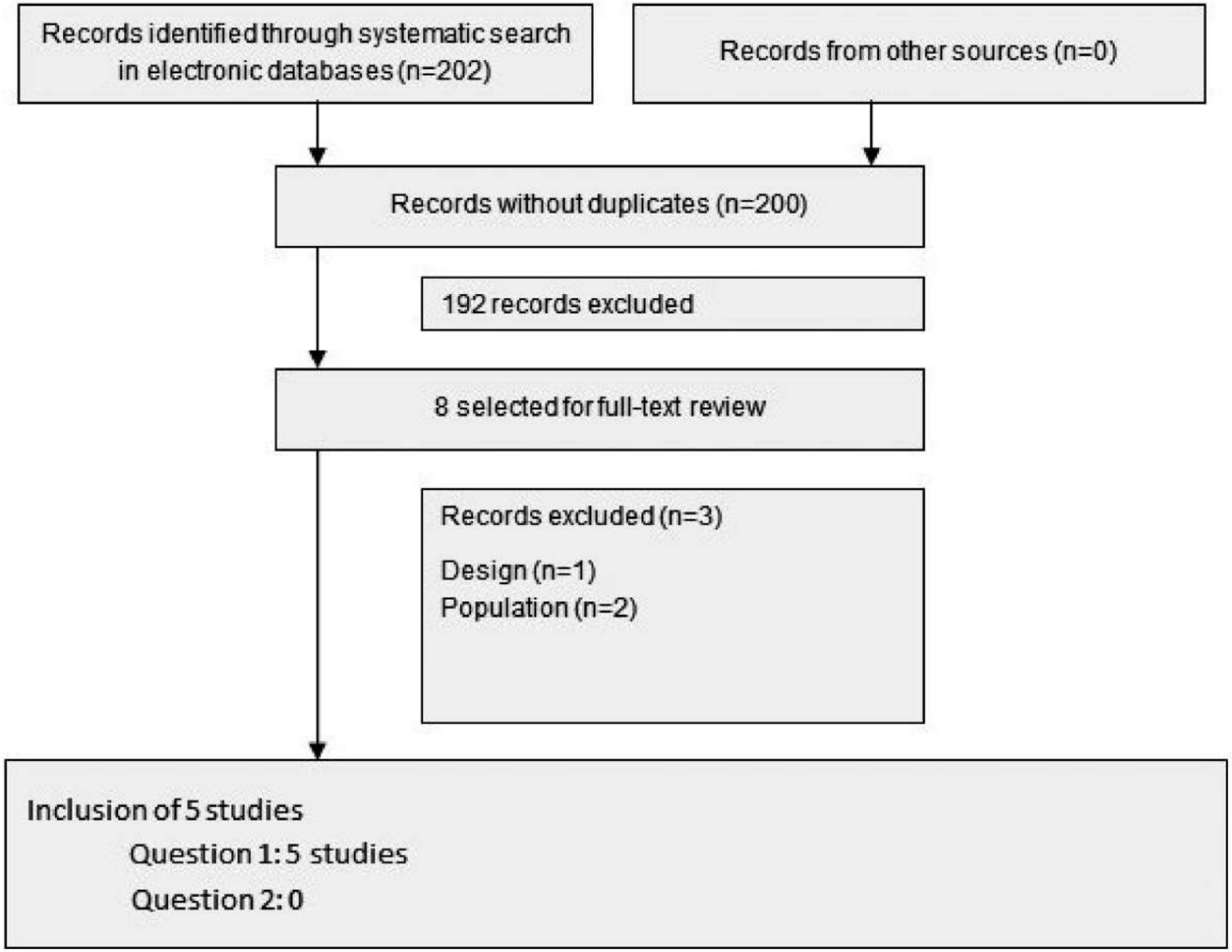


FIGURE 1 Study selection

LIST OF EXCLUDED STUDIES AFTER FULL-TEXT REVIEW

Other design **(case series without comparative analysis)**

Senggutuvan P, Cameron JS, Hartley RB, Rigden S, Chantler C, Haycock G, et al Recurrence of focal segmental glomerulosclerosis in transplanted kidneys: analysis of incidence and risk factors in 59 allografts. Pediatr Nephrol. 1990;4(1):21-8.

Other population **(12% with FSGS)**

Alexander SR, Arbus GS, Butt KM, Conley S, Fine RN, Greifer I, et al The 1989 report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 1990;4(5):542-53.

Other population (no transplant recipients)

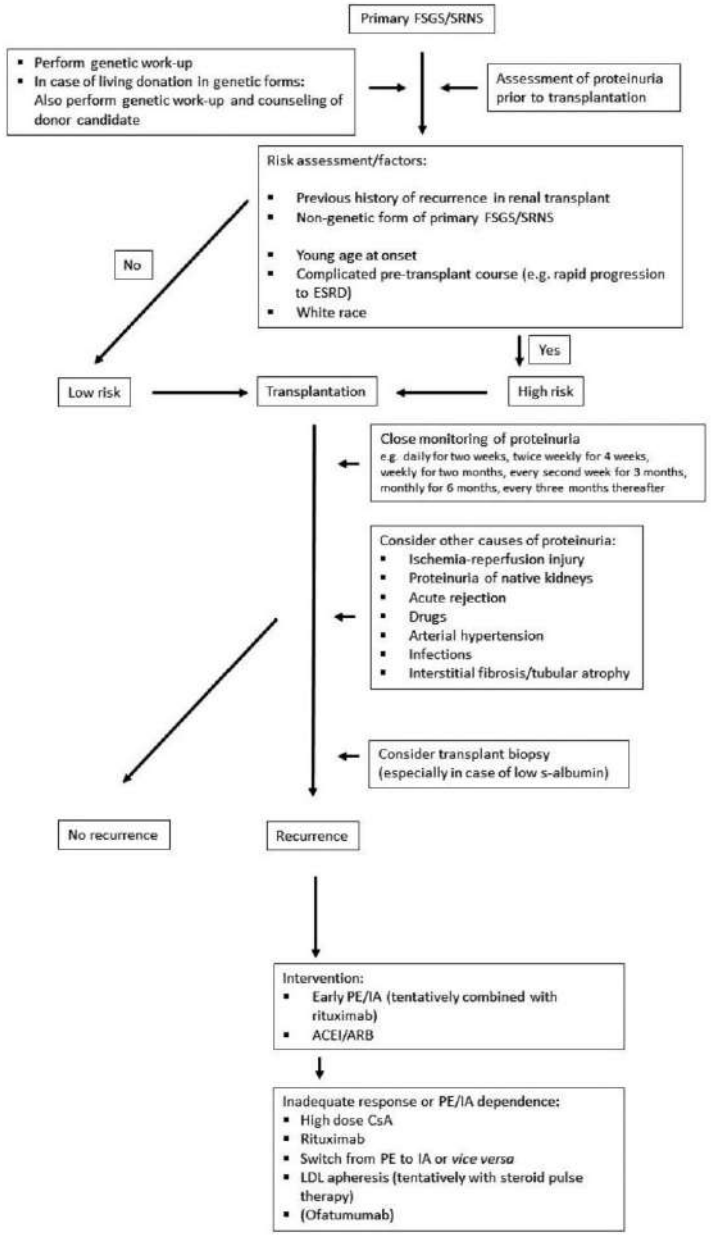
Hodson EM, Wong SC, Willis NS, Craig JC: Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database of Systematic Reviews 2016.

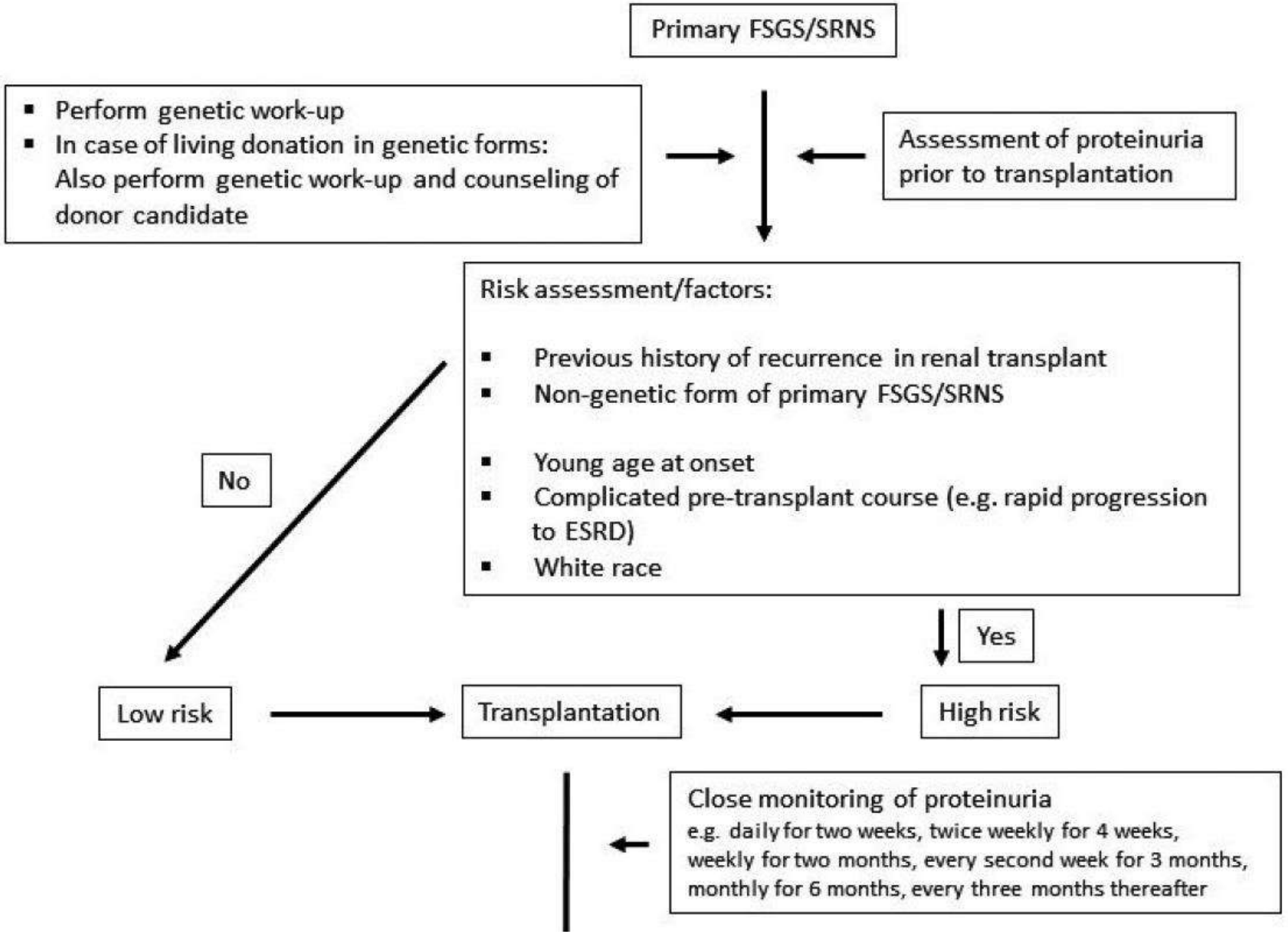
Educated statements on PICO question 1:

1. The rationale for LD grafts in children with FSGS should be based on factors other than better outcomes typically associated with LD transplantation.
2. Native kidney nephrectomy prior to kidney transplantation as a preventive measure of recurrence (unilateral or bilateral) cannot be recommended, however may decrease the risk of early graft thrombosis, and help to distinguish recurrence from persistent native proteinuria
3. Re-transplantation in case of a previous renal allograft loss due to FSGS recurrence may be associated with worse outcome.
4. Young age at disease onset and white race may be associated with a higher risk of recurrence.
5. Pediatric patients with native kidney MCD histology on initial biopsy and secondary LSRNS show an increased risk for disease recurrence following kidney transplantation.

Educated statements on PICO question 2:

1. Early initiation of PE (plasmapheresis) may be effective in treatment (probably not in prevention) of post-transplant recurrence of FSGS/SRNS.
2. Addition of the monoclonal anti-CD20–depleting antibody rituximab to PE may be considered as treatment strategy in post-transplant recurrence of FSGS/SRNS.
3. High-dose CsA may be considered for treatment of post-transplant recurrence of FSGS/SRNS.
4. RAAS blockade may be considered in post-transplant recurrence of FSGS/SRNS.


Primary FSGS/SRNS
Perform genetic work-up
In case of living donation in genetic forms: Also perform genetic work-up and counseling of donor candidate
Assessment of proteinuria prior to transplantation
Risk assessment/factors:
Previous history of recurrence in renal transplant
Non-genetic form of primary FSGS/SRNS
Young age at onset
Complicated pre-transplant course (e.g. rapid progression to ESRD)
White race
No
Yes
Low risk
Transplantation
High risk
Close monitoring of proteinuria
e.g. daily for two weeks, twice weekly for 4 weeks, weekly for two months, every second week for 3 months, monthly for 6 months, every three months thereafter
Consider other causes of proteinuria:
Ischemia-reperfusion injury
Proteinuria of native kidneys
Acute rejection
Drugs
Arterial hypertension
Infections
Interstitial fibrosis/tubular atrophy
Consider transplant biopsy (especially in case of low s-albumin)
No recurrence
Recurrence
Intervention:
Early PE/IA (tentatively combined with rituximab)
ACEI/ARB
Inadequate response or PE/IA dependence:
High dose CsA
Rituximab
Switch from PE to IA or vice versa
LDL apheresis (tentatively with steroid pulse therapy)
(Ofatumumab)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Complicated pre-transplant course (e.g. rapid progression to ESRD)
White race
No
Yes
Low risk
Transplantation
High risk
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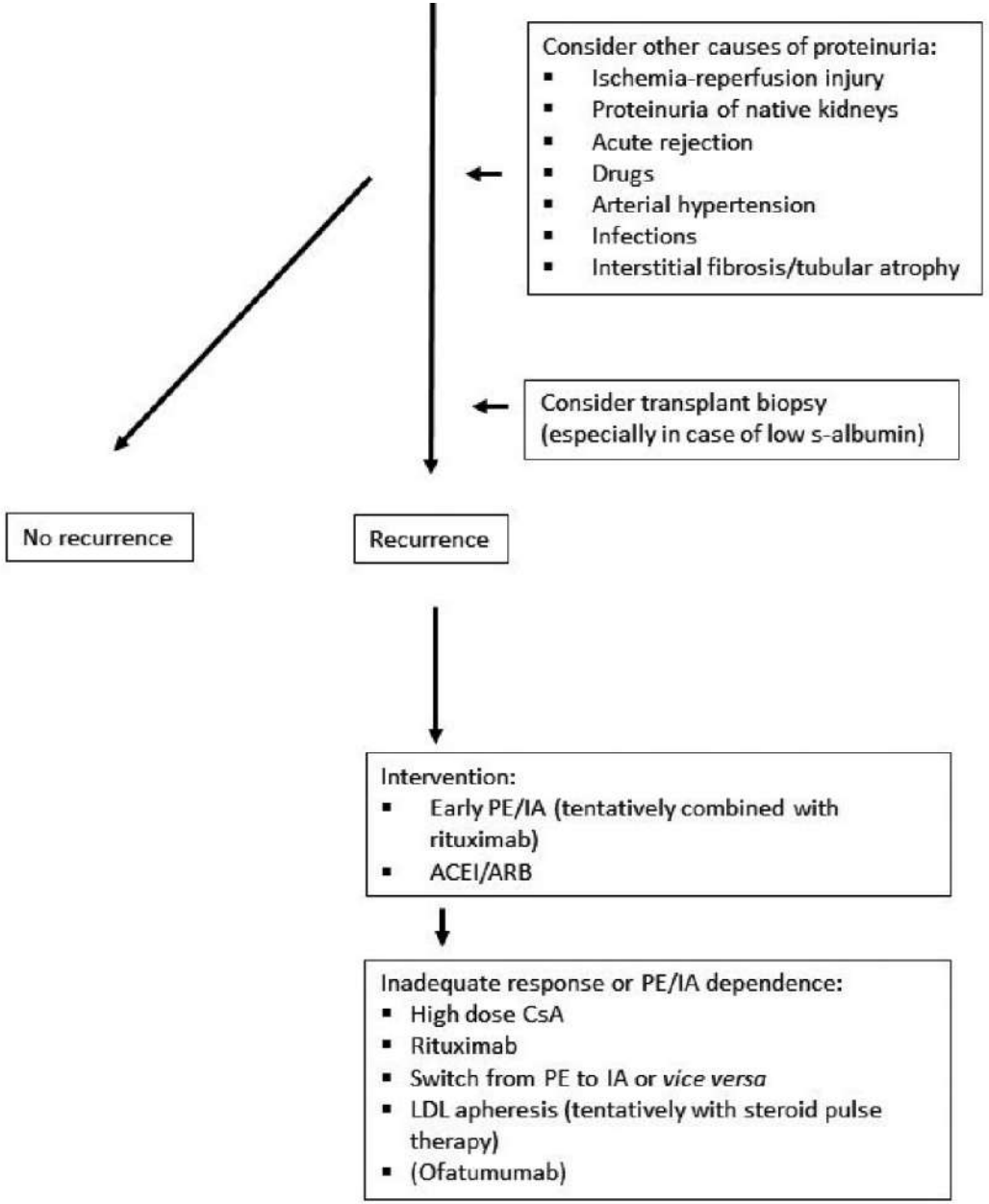
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Ischemia-reperfusion injury
Proteinuria of native kidneys
Acute rejection
Drugs
Arterial hypertension
Infections
Interstitial fibrosis/tubular atrophy
Consider transplant biopsy
(especially in case of low s-albumin)
No recurrence
Recurrence
Intervention:
Early PE/IA (tentatively combined with rituximab)
ACEI/ARB
Inadequate response or PE/IA dependence:
High dose CsA
Rituximab
Switch from PE to IA or vice versa
LDL apheresis (tentatively with steroid pulse therapy)
(Ofatumumab)

PICO 3
Hyperoxaluria

Participants	Pediatric recipients of KTx (DD or LD) with primary Hyperoxaluria as primary disease
Intervention	Kidney Tx or Combined kidney liver Tx or Liver Tx followed by kidney Tx
Comparison	another one of the options
Outcome	Patient survival; graft survival; primary disease recurrence
Study-design	4 retrospective case series (2001-2015) **LoE 3-4**

Statements

1. Liver transplantation offers a significant survival advantage to children with PH1.

2. Sequential transplantation (first liver, then kidney) is a treatment option.

3. Preemptive liver transplantation is a treatment option that can be discussed for children with chronic kidney disease stage 3 with a continuous decrease of GFR.

4. Combined liver-kidney transplantation is feasible even for small children.

Statements

1. Liver transplan to children with PH1.
2. Sequential trar ment option.
3. Preemptive live can be discussed for children with c us decrease of GFR.
4. Combined liver mall children.

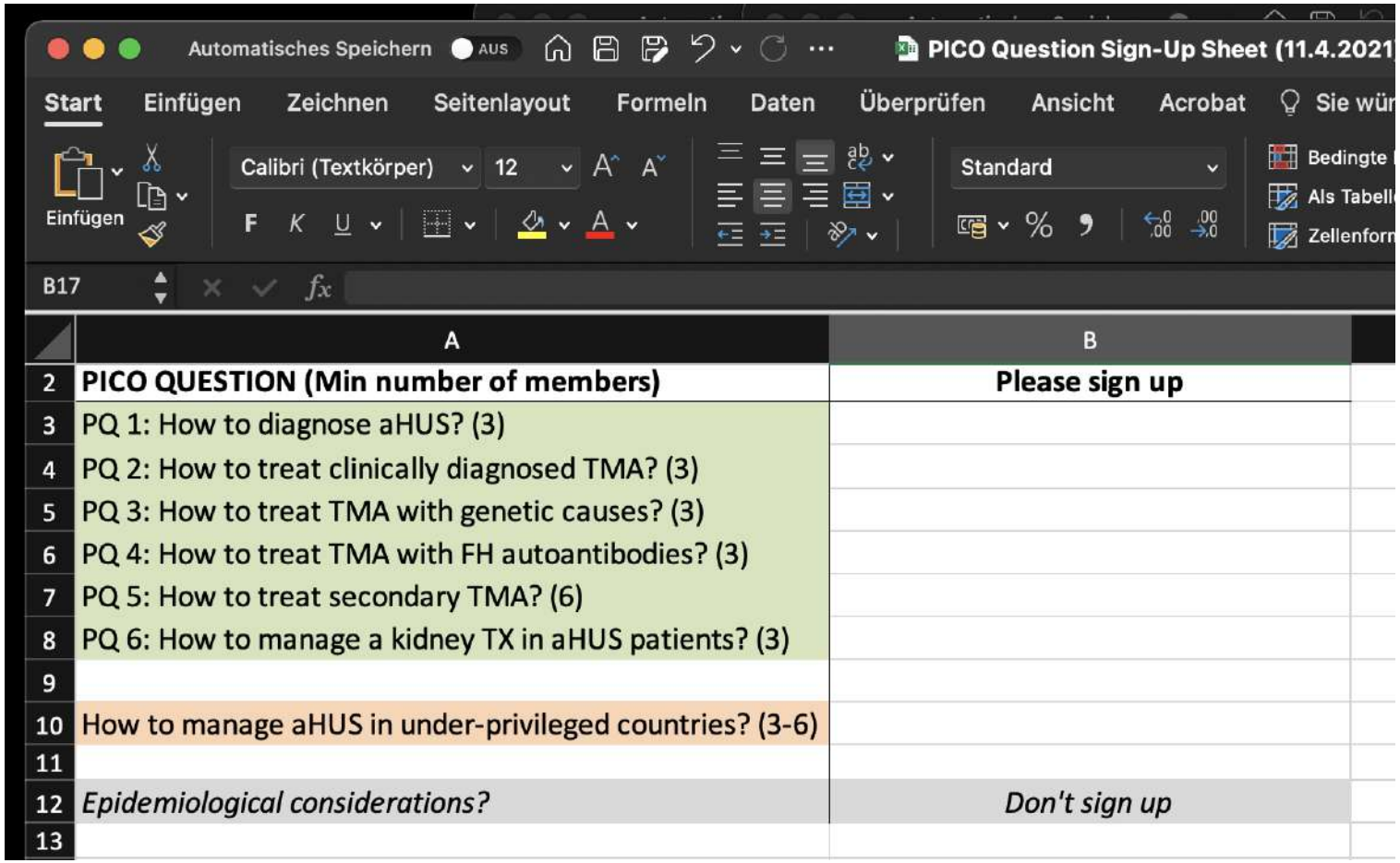
PICO 6
aHUS

Participants	Pediatric recipients of KTx (DD or LD) with aHUS as primary disease
Intervention	Eculizumab Therapy
Comparison	No Eculizumab Therapy
Outcome	Patient survival; graft survival; primary disease recurrence
Study-design	1 retrospective register analysis (2019), 1 prospective cohort study (2019) LoE 4

Statements

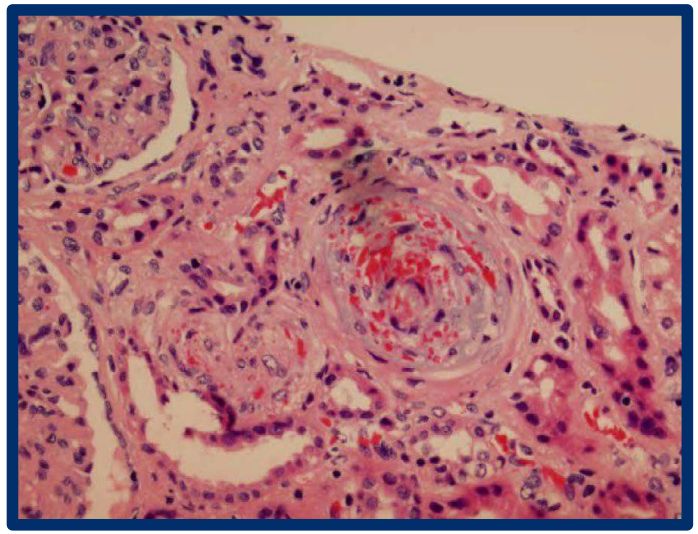
1. Eculizumab is beneficial for the treatment of patients with aHUS in the setting of transplantation.

2. Initiation of eculizumab therapy before transplantation potentially reduces rates of dialysis after transplantation.



	A	B
2	**PICO QUESTION (Min number of members)**	**Please sign up**
3	PQ 1: How to diagnose aHUS? (3)	
4	PQ 2: How to treat clinically diagnosed TMA? (3)	
5	PQ 3: How to treat TMA with genetic causes? (3)	
6	PQ 4: How to treat TMA with FH autoantibodies? (3)	
7	PQ 5: How to treat secondary TMA? (6)	
8	PQ 6: How to manage a kidney TX in aHUS patients? (3)	
9		
10	How to manage aHUS in under-privileged countries? (3-6)	
11		
12	*Epidemiological considerations?*	*Don't sign up*
13		

IPNA



2. After the results of the genetic analysis, the patient should be stratified into risk ranges for recurrence (PMID 23937869)
   a. **High-risk** patients are those who have had a recurrence in previous transplants, presence of factor H mutation or gain of function (cofactor B or C3). We recommend these patients to receive prophylactic anti-complement C5 when undergoing kidney transplantation (high, strong)
   b. Patients at **moderate risk** are those with anti-factor H antibody, factor I mutations, presence of variants of uncertain significance (VUS) or factor H polymorphisms; for this group, we recommend anti-complement C5 either prophylactically or if a recurrence ensures (medium, strong)
   c. Patients at **low risk** of recurrence have persistently negative factor H antibody titers, absence of mutations and polymorphisms (5) and do not require prophylactic use of anti-C5 therapy (medium, strong).

2. In patients with Factor H Autoantibody related aHUS (DEAP-HUS):
    a. we suggest using triple immunosuppression without anti-C5 complement prophylaxis (low, weak).
    b. We recommend close monitoring of Factor-H Abs pre and post transplant (low, weak)
    c. Anti-complement C5 treatment should be applied in case of a recurrence. (medium, strong) (Dragon-Durey, Fremeaux-Bacchi et al. 2004, Dragon-Durey, Loirat et al. 2005, Waters, Pappworth et al. 2010, Le Quintrec, Zuber et al. 2013)

3. As aHUS recurrence after kidney transplant is rare in DGKE-HUS, no C5-inhibitor prophylaxis/treatment is needed (Azukaitis, Simkova et al. 2017) (high, strong)
4. We do not recommend routine use of C5-inhibitors in case of MCP-only-mutations as recurrence after KTx does not occur (medium, strong)
(Norris).

C5 Inhibitors peri KTx & Plasmatherapy peri KTx

1. We recommend Prophylactic use of C5 Inhibitor, in patients with medium and high risk of aHUS recurrence after Kidney Tx in the periTx period.

2. We recommend treatment with C5 inhibition after recurrence of aHUS in kidney transplant patients in whom it was not used as induction therapy before transplantation (**Medium**, **Strong**)

3. We do not recommend prophylactic plasma exchange or infusion for preventing relapses of aHUS in KTx patients and instead, C5 inhibitors should be used. **(High, Strong)**

Duration of prophylactic therapy of C5 inhibitor

1. **We do not recommend withdrawal of prophylaxis therapy of C5 inhibitor after transplantation in high or intermediate risk of recurrence (high, strong)**

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.

Lim W et al., Front Immunol 2019

	Initial treatment	Other options	Trials[#]
Recurrent IgA Nephropathy	Anti-proteinuric CNI + steroid*	Alkylating agents (crescentic) (Tonsillectomy)	Induction (ATG vs. basiliximab)
Recurrent FSGS	Anti-proteinuric Plasmapheresis ± rituximab CNI	Ofatumumab Abatecept/belatacept	Pre-emptive rituximab Acthar Bleselumab Total lymphoid irradiation
Recurrent idiopathic membranous GN	Anti-proteinuric CNI Rituximab (antibody positive)	Rituximab (antibody negative) Bortezomib Alkylating agents	
Recurrent MPGN	Anti-proteinuric Treat monoclonal gammopathy (if present)	Eculizumab if C3 glomerulopathy Plasmapheresis and Immunosuppression (alkylating agent, rituximab) if immune complex MPGN	

**Optimal dose or combination of CNI type and corticosteroids unknown. [#]Trials (registered in progress/recruiting or not yet recruiting) as searched in: https://clinicaltrials.gov. GN, glomerulonephritis; CNI, calcineurin-inhibitor; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; ATG, anti-thymocyte glbulin.*

Lim W et al., Front Immunol 2019

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