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SPECIAL ARTICLE

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

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Abstract

Recurrence of primary disease is one of the major risks for allograft loss after pediatric RTx. The risk of recurrence of FSGS/SRNS after pediatric RTx in particular can be up to 86% in idiopathic cases. There is a need for consensus recommendations on its prevention and treatment. The CERTAIN study group has therefore performed a thorough literature search based on the PICO model of clinical questions to formulate educated statements to guide the clinician in the process of decision-making. A set of educated statements on prevention and treatment of FSGS/SRNS after pediatric RTx

Abbreviations: ACEI, Angiotensin-converting enzyme inhibition; ARB, angiotensin receptor blocker; ATG, Antithymocyte globulin; AWMF, Association of Scientific Medical Societies in Germany; CERTAIN, Cooperative European Paediatric Renal Transplant Initiative; CsA, Ciclosporin; DD, deceased donor; ERKNet, European Reference Network for Rare Kidney Diseases; ESKD, End-stage kidney disease; ESPN, European Society for Paediatric Nephrology; FSGS, Focal and segmental glomerulosclerosis; IA, Immunoadsorption; LD, Living donor; LDL-A, Low-density lipoprotein apheresis; LoE, Level of evidence; LSRNS, Late steroid-resistant nephrotic syndrome; MCD, minimal-change disease; mTOR, Mammalian target of rapamycin; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; PE, Plasma exchange; PICO, Population/Intervention/Comparison/Outcome; RAAS, Renin-angiotensin-aldosterone System; RCT, Randomized controlled trial; RTx, Renal transplantation; SRNS, Steroid-resistant nephrotic syndrome.

Luca Dello Strologo and Lars Pape contributed equally to this work.

has been generated after careful evaluation of available evidence and thorough panel discussion. We do not recommend routine nephrectomy prior to transplantation; neither do we recommend abstaining from living donation. Special attendance needs to be given to those patients who had already experienced graft loss due to FSGS/SRNS recurrence. Early PE or IA with or without high-dose CsA and/or rituximab seems to be most promising to induce remission. The educated statements presented here acknowledge that FSGS/SRNS recurrence after pediatric RTx remains a major concern and is associated with shorter graft survival or even graft loss. The value of any recommendation needs to take into account that evidence is based on cohorts that differ in ethnicity, pre-transplant history, immunosuppressive regimen, definition of recurrence (eg, clinical and/or histological diagnosis) and treatment modalities of recurrence.

KEYWORDS

children, focal-segmental glomerulosclerosis, recurrence, renal transplantation, steroid-resistant nephrotic syndrome

1 | INTRODUCTION

Recurrence of primary disease is one of the major risks for premature allograft loss after pediatric RTx.[1,2] The CERTAIN study group has therefore addressed this topic in its annual meetings and has performed a thorough literature search based on the PICO model of clinical questions to formulate educated statements to guide the clinician in the process of decision-making. The following working groups have been assembled (Appendix A):

FSGS/SRNS: RG, AA, AN, CS, JO, NB, GN, RT, NP, AB, AP, BG, SM, TS, and BT.

Atypical hemolytic uremic syndrome: AA, JO, GN, NP, BG, and RT.

Hyperoxaluria: AP, NB, NP, SM, and BT.

The entire process was coordinated by LP, LDS, and LTW (Appendix A).

This work represents a consensus report of the CERTAIN study group in cooperation with the working groups on transplantation of the ESPN and the ERKNet.

The risk of recurrence of FSGS/SRNS after pediatric RTx is low in children with a causal mutation of genes encoding podocyte-associated proteins, but can be up to 86% in idiopathic cases.[3-5] Recurrence occurs particularly early within the first two weeks after transplantation in children.[6] If time to recurrent proteinuria is more than 3 months after RTx, also de novo FSGS has to be taken into account. This group decided to use the histological description of FSGS and the clinical definition of SRNS for the literature search taking into account that not all FSGS are steroid-resistant and not all SRNS show histopathological lesions of FSGS.

2 | METHODS

2.1 | Systematic search

For this consensus report, two electronic databases (Medline (Ovid) and CENTRAL) were searched until March 2019. In November 2019, the literature search was repeated for inclusion of all relevant evidence. The references of included studies were additionally screened for further eligible studies. The systematic search was based on PICO questions from Tables 1 and 2. Search strategies in Medline (Ovid) and CENTRAL are reported in the Appendix (Appendix B and Appendix C).

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

Question 1: Should a living-related donation and/or nephrectomy (unilateral or bilateral) and/or re-transplantation in case of a recurrence be performed in patients with FSGS and/or SRNS?

Question 2: What is the optimal immunosuppressive regimen in patients with FSGS and/or SRNS?

2.2 | Screening

All references were screened on the basis of their titles and abstracts. All potentially relevant studies were read as full texts and judged on the basis of inclusion criteria from Tables 1 and 2.

2.3 | Table of evidence

The table of evidence used was adapted from the standard of the AWMF. Information was extracted on setting, study type, main aim of the studies, participants, intervention and control, outcomes, results, and LoE. The LoE was judged by a clinical epidemiologist (see acknowledgements) on the CebM criteria (https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf) as summarized in Table 3.

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

The LoE was graded on the basis of study quality, imprecision, indirectness (study does not match PICO questions), inconsistency between studies, or because the absolute effect size was very small. For each study, we added the conclusions of the authors and a summarized judgment of the reviewer on the resulting LoE.

A total of 200 references were identified from the systematic search, and eight records were selected for full-text review (Figure 1). This process yielded five eligible studies on FSGS and/or SRNS.

The table of evidence for the association between type of donation and outcome of RTx in children with FSGS/SRNS can be found in the supplementary material (Table S4). Excluded studies after full-text review are listed with their reasons for exclusion (Appendix D). One study reported results on recurrence of FSGS after transplantation without comparative analyses between groups of living and DD transplantation. A second US study included children after RTx, but only 12% of children were diagnosed with FSGS. A third study (Cochrane review) did not report on pediatric renal transplant recipients.

The results of the systematic literature search were discussed in detail by the CERTAIN study group on 6 December 2019. This discussion led to educated statements based on the PICO questions (Tables 1 and 2). The particular comment on each statement also considered evidence that had been compiled by the group as well as such published after March 2019 when appropriate (see comments below). The quality of included studies was discussed following the criteria of the Delphi method expressing the degree of agreement (strongly disagree, disagree, neither agree/disagree, agree,

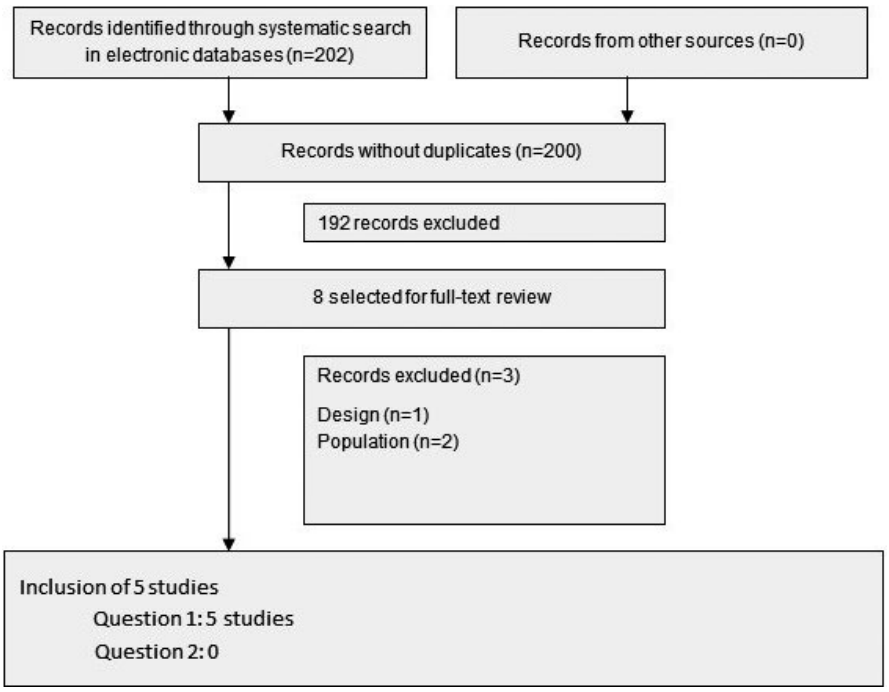

FIGURE 1 Study selection

strongly agree).[7] Systematic literature search, annual discussions between 2017 and 2019 and Delphi method resulted in the educated key statements given in the results/clinical recommendations section below. Final approval by the group was obtained on 14th of September 2020.

3 | RESULTS/CLINICAL RECOMMENDATIONS

PICO Question 1: Should a living-related donation with or without nephrectomy (unilateral or bilateral) and/or re-transplantation in case of a previous graft loss due to FSGS recurrence be performed in patients with FSGS and/or SRNS?

The evidence table (Table S4) of PICO question 1 can be found in the Table S4 summarizes the results from five cohort studies[8-12] that are based on a retrospective analysis of different databases from the United States and Canada.

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.

3.1 | Comment

All results are based on retrospective analyses, but four of these analyses also include prospective collected data in a registry.[8-11] Consequently, results on recurrence of FSGS/SRNS and on graft function were judged with the LoE 3, whereas results on the outcome criteria acute rejection, graft survival and overall survival were judged with LoE 4.

The impact of FSGS/SRNS recurrence on renal allograft survival in children is greatest in transplants after living donation, resulting in loss of expected LD graft survival advantage. The rationale for LD grafts in children with FSGS/SRNS should therefore be based on factors other than better outcomes typically associated with LD transplantation[8] as, for example, availability of grafts from DDs, severe complications of chronic dialysis therapy beside others.

FSGS/SRNS has a negative impact on graft survival in adolescents. Recurrence of FSGS/SRNS results in a loss of the expected living graft survival advantage in adolescents. Furthermore, adolescents with FSGS/SRNS have decreased graft survival compared to younger children with FSGS/SRNS, irrespective of recurrence. These data suggest that the rationale for LD transplantation in adolescents with FSGS/SRNS should also be based on factors other than the increased graft survival typically seen with LD transplantation.[9]

In order to reduce the risk of recurrence, some experts have recommended bilateral native kidney nephrectomy prior to transplantation.[13,14] Others have not confirmed this recommendation.[6,15] In a recent survey for the ESPN on current practice regarding recurrent FSGS/SRNS after pediatric kidney transplantation, Bouts et al[16] reported that 37% of respondents perform unilateral or bilateral nephrectomy prior to RTx. The structured literature search did not reveal any eligible evidence for or against native kidney nephrectomy. The group decided not to recommend this measure, acknowledging that there might be other reasons than reducing the risk of recurrence for performing native kidney nephrectomy prior to pediatric RTx, such as persistence of nephrosis and risk of thrombosis.

Overall experience shows that the risk of recurrence of FSGS/SRNS in the second graft is very high, when the first graft had been lost due to recurrence,[2] in some series reaching 100%.[17] The group therefore felt it to be important to indicate this special risk, as special strategies should be considered to protect the second graft (see PICO question 2 below).

Younger age is associated with a higher likelihood of post-transplantation recurrence as is white race.[10,11] The risk of recurrence is also higher in patients with SRNS and the initial histological pattern of MCD.[12] Likewise, children with nephrotic syndrome, who primarily responded to steroid therapy but developed secondary steroid resistance, are at increased risk for recurrence compared to those with primary SRNS. Even though the latter finding was no longer statistically significant after adjusting for sex, race, histology, time to ESKD, and transplant type, this association was regarded to be of clinical significance, especially as late SRNS had also been associated with recurrence in two European studies. Ding et al[18,19] showed that children with late steroid resistance were 3.1 times more likely to have post-transplant disease recurrence, while Bierzynska et al showed a 1.6 times increased risk of recurrence. These findings may in part be explained by the immunological pathogenesis of these different subclassifications of nephrotic syndrome.

Recent data from the NAPRTCS registry confirmed the inferior 5-year renal allograft survival of children with FSGS compared to other glomerulopathies. Living donation was not advantageous. The renal allograft survival risk was associated with re-transplantation and recipient age.[20]

PICO question 2: What is the optimal immunosuppressive regimen in patients with FSGS and/or SRNS?

The eligible review to answer PICO question 2 (Appendix C) was not selected by the group, because this review did not address therapy of FSGS/SRNS in the transplanted but the native kidneys. The educated statements given below are a result of thorough review

of the available literature performed by the group according to the Delphi method described above and final discussion during the annual meetings. Available literature consisted of reviews, case series and case reports. LoE therefore was judged as 4.

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.

3.2 | Comment

Idiopathic FSGS/SRNS may recur in the transplanted kidney immediately or within days or weeks after RTx. A circulating permeability factor is discussed as potential cause of recurrence, especially in early recurrence. Although the evidence for the benefit of PE or IA in terms of inducing remission is scarce and there is no RCT addressing this topic in pediatric patients, many centers use PE or IA in this group of patients. Some retrospective case series that differ in numbers treated, underlying immunosuppressive regimen, ethnicity of patients, definition of recurrence, and treatment modalities of PE indicate a positive effect of PE on inducing remission,[21-24] but not as a preemptive measure.[24,25]

No study has been performed on the comparison of PE or IA for the treatment of recurrent FSGS/SRNS in children after RTx. Case series in heterogeneous groups of patients indicate comparable efficacy of IA compared to PE.[26-28] Nevertheless, the role of IA in recurrent FSGS needs to be further elucidated, especially since the exact mechanism of IA remains unclear.[29]

Case series have been published indicating efficacy of rituximab added to PE in pediatric renal transplant recipients suffering from recurrence of idiopathic FSGS/SRNS.[30-33] The optimal timing of rituximab administration remains as unclear as the required number of doses. The correlation between CD19/CD20 B-cell depletion and clinical efficacy has not been demonstrated.[31] It must be pointed out that not all patients respond to rituximab, but approximately 50% reach complete remission and another 25% reach partial remission. Patients achieving remission show a favorable long-term graft survival. Rituximab seems to be effective after failure of PE as well as for weaning from PE.[31] In any individual patient, a careful risk/benefit assessment is required, as side effects of rituximab such as first dose reactions,[32] severe infections[33] and even rituximab-associated lung injury with fatal consequences[34] have been reported.

Retrospective series have demonstrated that approximately 75% of pediatric renal transplant recipients with recurrent FSGS/SRNS achieve complete remission when CsA was administered in high dose.[35-37] At the same time, there is no consensus on the definition of *high-dose* CsA *High-dose* CsA varies between initial CsA-area under the concentration vs time curve within the first 4 hours after administration (CsA-AUC_{0-4}) of 4500-5500 ng h/mL,[35] an oral CsA dose of up to 25 mg/kg body weight per day,[36] and continuous iv CsA application to maintain whole blood levels of 250-350 ng/mL.[37] It needs to be pointed out that around 20% of patients additionally received PE therapy with *high-dose* CsA. The clinician needs to be aware of calcineurin inhibitor-associated nephrotoxicity when high-dose CsA is given (especially as iv application).

RAAS blockade has shown to be beneficial to slow down the progression of proteinuric as well as non-proteinuric renal diseases in childhood.[38] Furthermore, RAAS blockade is recommended to decrease proteinuria in pediatric renal transplant recipients.[39] Angiotensin is suggested to play a role in the pathogenesis of recurrent FSGS.[40] Hubsch et al[41] have shown maximal benefit from PE in combination with RAAS blockade and mycophenolate mofetil in pediatric renal transplant recipients with recurrent FSGS. Despite the rather low LoE, this group of experts recommends the use of RAAS blockade in case of recurrent FSGS/SRNS.

Small case series presume a beneficial (rescue) effect of the fully humanized anti-CD20 antibody ofatumumab in multidrug-resistant refractory courses of recurrence. Ofatumumab has the theoretical advantage of higher affinity binding to B lymphocytes and may be less prone to the development of antibodies against a murine fragment. However, it seems to be less effective in the post-transplant setting than it is in native kidneys.[42,43] The manufacturer took ofatumumab off the market in 2019 due to low demand.

LDL-A has also been discussed as rescue therapy in refractory FSGS recurrence in pediatric renal transplant recipients. Efficacy in terms of induction of remission was heterogeneous, and numbers treated were small.[44,45]

The question on when a rescue therapy is justified is difficult to answer. An inadequate response to a previous therapy is defined at the discretion of the treating physician and may take into account worsening of proteinuria after transient improvement or unsatisfactory response to therapy within a certain time frame that may comprise about 3 months or 20 PE sessions. The decision is certainly dependent on accompanying clinical factors such as the presence of acute kidney injury.

4 | DISCUSSION

The CERTAIN Study Group in association with the working groups "Transplantation" of the ESPN and ERKNet encountered the lack of RCTs as major limitation of this pediatric RTx guideline development. Heterogeneity of patients and definitions of FSGS/SRNS were additional drawbacks. Therefore, the LoE was expected to be low. The idea of highly graded guidelines based on solid scientific evidence had to be replaced by broadly discussed consensus recommendations summarized in form of a clinical practice recommendation.

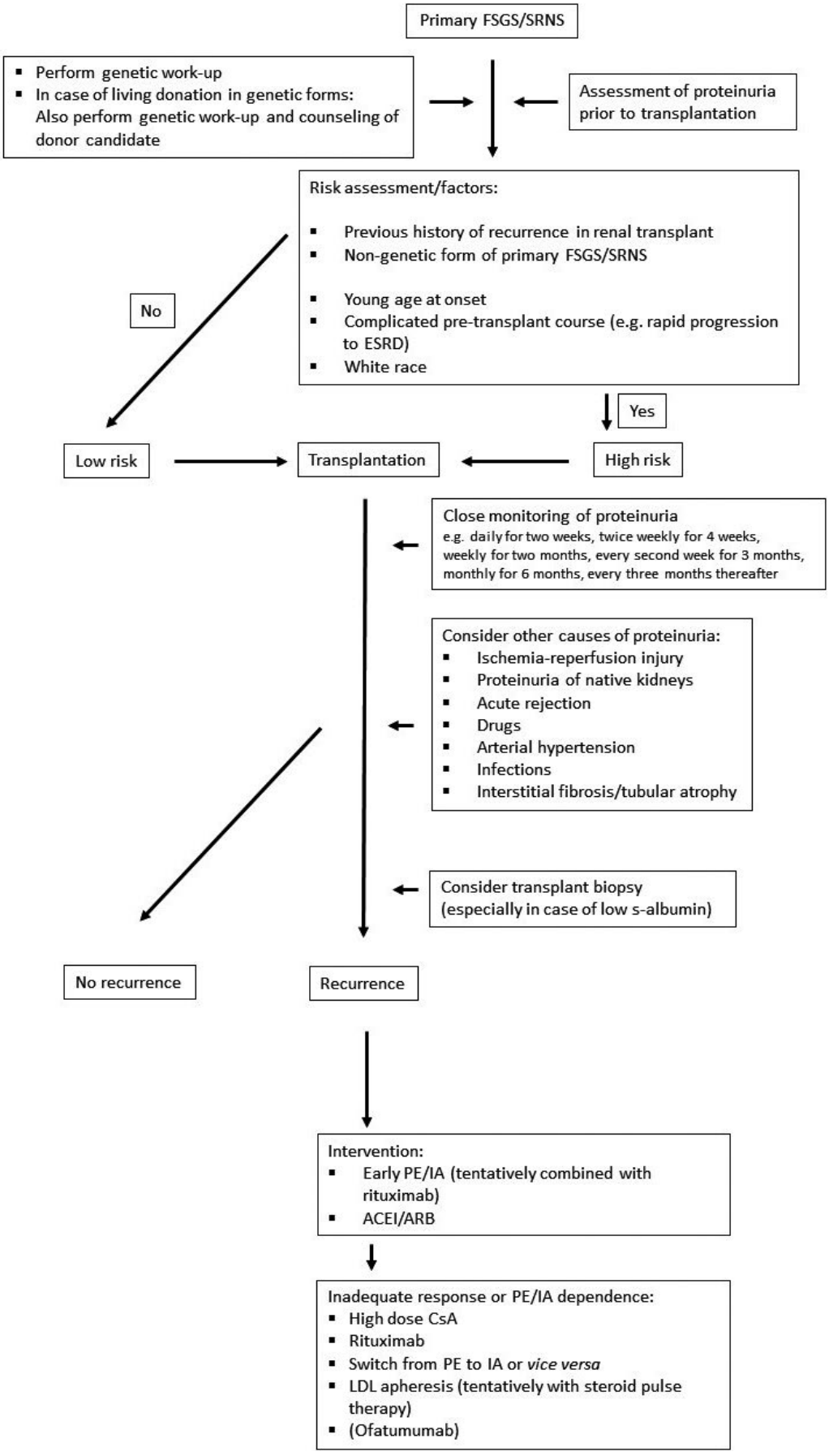

FIGURE 2 Algorithm on management of RTx in children suffering from primary FSGS/SRNS

Nevertheless, the group tried to prepare the best possible scientific basis to generate the current recommendations on recurrence of FSGS/SRNS in pediatric renal transplant recipients as there is an obvious need in daily clinical practice. For this purpose, the study group performed a structured dialogue including working groups for different topics to generate PICO questions. According to these questions, a structured literature search by a medical epidemiologist (SU) was performed, followed by rating of the evidence and composition of educated statements by the working group and their final discussion by the entire study group according to the Delphi method. In addition, a thorough literature review had been performed by the group and evidence was assessed according to the Delphi method described above. This work and the corresponding dialogue were done by e-mail communication and during several annual meetings between 2017 and 2019.

The educated statements presented here acknowledge that FSGS/SRNS recurrence after pediatric RTx remains a major concern and is associated with shorter graft survival or even graft loss. The value of any recommendation needs to take into account that any scientific report is based on cohorts that differ widely in ethnicity, pre-transplant history, immunosuppressive regimen, definition of recurrence (eg, clinical and/or histological diagnosis) and treatment modalities of recurrence.

Nowadays, genetic workup of patients suffering from FSGS/SRNS[46] is standard of care at many sites. Since genetic forms of FSGS/SRNS virtually never recur post-transplant, the differentiation of genetic from idiopathic forms of FSGS/SRNS will help to assess the individual risk of recurrence in the future. In case of living-related kidney donation, a careful genetic workup and genetic counseling of the potential donor should also be performed. For example, the risk for donors carrying heterozygous *NPHS2* mutations may be modified by variants such as R229Q, which are considered to have a dominant-negative impact that might theoretically pose a risk to the donor to develop FSGS.[47] The presence of this variant must be evaluated and taken into account during the evaluation process of the donor and weighed against the recipient´s characteristics and chance to receive a DD transplant.

The pathogenesis of recurrent FSGS/SRNS post–RTx is multifactorial and has not been fully elucidated.[3,48] It may therefore help the clinician to consider the following risk factors of recurrence for the individual patient management. However, it needs to be pointed out that none of the following factors has ever been shown to be valid or reliable enough to be included in the educated statements given above.

1. Aggressive course of idiopathic FSGS/SRNS prior to transplantation with fast progression to end-stage renal disease within 48-72 months.[17,49]
2. Higher incidence of recurrence with the use of ATG as induction therapy[50]
3. Higher risk of recurrence in patients with mesangial hypercellularity and fewer sclerotic glomeruli in the native kidney biopsy.[51,52]

The precondition for an adequate decision on treatment of recurrent FSGS/SRNS is a reliable diagnosis. There is no doubt that pre-transplant assessment of proteinuria and its regular post-transplant monitoring (random or spot urinary protein/creatinine ratio) are mandatory for an early diagnosis of FSGS/SRNS recurrence. The clinician has to take into account other causes of post-transplant proteinuria, differentiating recurrence of primary disease from secondary forms of FSGS, including ischemia-reperfusion injury (higher risk in FSGS patients[53]), renal vein obstruction or thrombosis, proteinuria of native kidneys, acute rejection, drugs (eg, mTOR inhibitors), arterial hypertension, infections such as BK polyomavirus nephropathy and chronic interstitial fibrosis. The definition of recurrence of FSGS/SRNS differs among studies by being based on either clinical (nephrotic syndrome[22]) and/or histological (50% podocyte effacement[25]) assessment. This further complicates interpretation of evidence.

There are only small case series with few patients reporting on the use of cyclophosphamide for induction of remission in patients with recurrent FSGS/SRNS post-transplant.[51,54,55] Cyclophosphamide is afflicted with major long-term side effects such as malignancies and gonadal toxicity, both associated with the cumulative dose. Of note, several patients might have a history of high-dose cyclosphosphamide given during treatment of nephrotic syndrome of their native kidneys. In a recent survey of the ESPN, cyclophosphamide did not play a role for post-transplant management of recurrent FSGS/SRNS.[16]

In summary, recurrence of primary idiopathic FSGS/SRNS remains a major clinical concern in pediatric RTx. We do not recommend routine nephrectomy prior to transplantation, neither do we recommend to abstain from living donation. Special attendance needs to be given to those patients who had already experienced graft loss due to FSGS/SRNS recurrence. Early PE or IA with or without high-dose CsA and/or rituximab seems to be most promising to induce remission. Figure 2 proposes an algorithm on the management of RTx in children suffering from primary FSGS/SRNS.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

LTW, LDS, and LP: Coordinated the entire process and are primarily responsible for manuscript writing. LTW, BT, RG, AB, RT, BG, NP, AA, NB, RE, PFH, GN, SDM, JO, AP, TS, CS, LDS, and LP: Collected and evaluated the evidence. LTW, BT, RG, AB, RT, BG, NP, AA, NB, PFH, GN, SDM, JO, AP, TS, CS, LDS, and LP: Involved in preparation and discussion of statements. LTW, BT, RG, AB, RT, BG, NP, AA, NB, RE, PFH, GN, SDM, JO, AP, TS, CS, LDS, and LP: Involved in in-depth revision of draft. BT and LP: Organized and hosted annual meetings of the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) study group. RE: provided technical and formal support.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

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APPENDIX B

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**

APPENDIX C

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**

APPENDIX D

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.