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# European Society of Pediatric Nephrology survey on current practice regarding recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation

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## Abstract

**Introduction:** Primary FSGS is an important cause of ESRD in children. FSGS recurrence after kidney transplantation is associated with early graft loss. No guidelines for treatment of FSGS recurrence exist. We conducted a survey to gain insight into variation of treatment between centers.

**Methods:** A survey was sent to all members of the ESPN on behalf of the "Renal Transplantation" and "Idiopathic Nephrotic Syndrome" working groups.

**Results:** Fifty-nine nephrologists from 31 countries responded, reporting 807 FSGS patients, with 241 (30%) FSGS recurrences after transplantation. Recurrence varied from 0% to 100% between respondents. Native nephrectomy before or during transplantation was performed, respectively, always (37%), never (39%), or on clinical indication (17%). Half of the respondents started preventive treatment before transplantation, using PF (n = 10); R (n = 4); PF or IA, plus R (n = 9); cyclosporine (n = 2); or unknown (n = 4). Immunosuppressive therapy for patients without known mutations consisted of a combination of steroids, tacrolimus/cyclosporine, and MMF, with or without IL-2R-blockade in, respectively, 61% and 86% of the respondents. Sixty-three percent applied a similar regimen to patients with known mutations. FSGS recurrence was treated with PF or IA, plus R by 66% of respondents; 54% observed no response. Complete remission in >50% of patients was reported by 41% of the respondents.

**Discussion:** FSGS recurrence after transplantation is common, but varies greatly between centers. We found great variability in preventive and therapeutic treatment regimens. Future research should focus on predisposing factors, including biopsy findings and genetic mutations, and standardized treatment.

KEYWORDS

children, focal segmental glomerulosclerosis, kidney transplantation, recurrence, steroid resistant nephrotic syndrome

**Abbreviations:** ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; CNI, calcineurin inhibitor; Cs, corticosteroids; ESPN, European Society of Pediatric Nephrology; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; IA, immunoadsorption; IL-2R, interleukin-2-receptor; IVIG, intravenous immunoglobulin; LDL, low-density lipoprotein; MCD, minimal change disease; MMF, mycophenolate mofetil; PF, plasmapheresis; R, rituximab; SRNS, steroid-resistant nephrotic syndrome.

## 1 | INTRODUCTION

The treatment of primary FSGS and its recurrence after kidney transplantation remains challenging, since many patients are refractory to treatment with steroids and other immunosuppressive therapy.[1-3] FSGS is a histologic feature, rather than a specific disease entity, and is the most common pathological finding in children with SRNS. FSGS is classified as a secondary, genetic, or idiopathic form of SRNS.[4-6] In children, secondary forms are extremely rare. Instead, 40%-50% of pediatric patients with SRNS have an underlying genetic defect, while the remaining present with so-called idiopathic or primary FSGS. In idiopathic FSGS, the injury to the podocyte is thought to be caused by epigenetic reorganizations, immune system dysregulations, and a circulating factor(s).[4] The hypothesis of an immune origin is supported by the efficacy of drugs that affect immune cells, like glucocorticoids, CNIs, and anti-proliferative agents. The circulating factor theory is supported by a vast body of clinical and experimental evidence,[7] most notably by a striking case in which a kidney was transplanted into a recipient with FSGS, proteinuria developed. When the kidney graft was removed and transplanted into a second patient without FSGS, the graft showed disappearance of foot process effacement and there was no development of proteinuria.[8]

Between 30% and 70% of children with idiopathic FSGS develop recurrent disease after renal transplantation.[2,6,9-13] The onset of FSGS recurrence sometimes occurs within minutes after kidney transplantation. However, it is generally accepted that the risk of recurrence is not high enough to contraindicate the transplantation procedure. Factors that are reported to be associated with a higher risk of recurrence are as follows: (a) progression to ESRD within 3 years; (b) mesangial hypercellularity on biopsy; (c) pediatric age at onset; (d) the presence of a circulating permeability factor; (e) non-genetic forms of FSGS; (f) native kidney nephrectomy before or at the time of transplant; (g) histology of MCD on initial renal biopsy; (h) lower serum albumin at initial diagnosis; and (i) initial responsiveness to Cs treatment.[3,12,14-16] Treatment of recurrent disease is still empirical with none of the multiple approaches providing consistent efficacy.[17-19] Randomized controlled trials are lacking, and disease definitions, treatment regimens, and definitions of response to therapy vary greatly. Therapeutic strategies consist of methylprednisolone, high-dose cyclosporine, cyclophosphamide, PF, plasma filtration, IA, LDL-apheresis, IVIG, R, and ofatumumab.[17,19-26] In this study, we investigated local preventive and/or therapeutic policies of recurrent FSGS after renal transplantation through a survey sent to all members of the ESPN.

## 2 | METHODS

### 2.1 | Data collection

We investigated current practice through a web-based survey (SurveyMonkey Inc, San Mateo, California, USA) on behalf of the working groups "Idiopathic Nephrotic Syndrome" and "Renal Transplantation" of the ESPN. All ESPN mailing list addresses were contacted via e-mail. The survey was carried out between the 20th of December 2017 and 12th of March 2018. An invitation by e-mail and two reminders with the aim of the survey and a personal link to https://es.surveymonkey.com), an Internet questionnaire service provider, were sent to the ESPN members. The survey consisted of 20 questions (both open and multiple choice) addressing the current practice regarding recurrent FSGS after pediatric kidney transplantation (see Appendix S1).

### 2.2 | Ethical approval

The study was approved by the council of the ESPN. Requests for approval by the ethics committees of each center were not considered necessary since the survey aimed to investigate variations in local practice on FSGS recurrence post-transplantation and not to collect patient-specific data. Also, patients were not approached and data collected could not be traced to an individual patient.

### 2.3 | Statistical analysis

Responses of the participants were collected in an electronic database. The following statistical analysis was performed: data were only plotted to check for normal distribution. Calculations were made using R Studio (RStudio Team, 2016. RStudio: Integrated Development for R. RStudio, Inc, Boston, MA). Continuous variables were expressed as median and range as no normal distribution was observed, and frequencies were reported as percentages. Pie charts were used to visualize data.

## 3 | RESULTS

In total, 59 (pediatric) nephrologists from 31 countries responded to the survey (Table 1). Four double entries by the same respondent were removed from the database (two Italy, one Saudi Arabia, one Greece). The response rate was 15% (59 respondents of 391 ESPN members). Results from all respondents were analyzed. Altogether, 807 children with FSGS who underwent transplantation were reported. The reported number of transplanted FSGS children per respondent varied between 0 and 130 in a median (range) time-period of 14 years (1-38 years). The median (range) number of transplanted FSGS patients per year was 0.7 (0.1-3.8). The reported number of transplanted FSGS children with recurrence after transplantation varied between 0 and 40 (total 240) in a median (range) time-period of 11 years (0-38 years). The median (range) number of FSGS recurrence after transplantation per year was 0.25 (0-3). Post-transplantation recurrence of FSGS was reported to occur in 30% of the children (240 out of 807). Fourteen (24%) respondents do not routinely perform mutation analysis in FSGS patients. Fifty-four pediatricians never experienced a post-transplant recurrence of FSGS in children with a known mutation; still, five reported recurrence in

**TABLE 1** Number of respondents, FSGS patients, and recurrences per country

| Country | Respondents | FSGS patients | FSGS patients per year | FSGS recurrences | FSGS recurrences per year | Country | Respondents | FSGS patients | FSGS patients per year | FSGS recurrences | FSGS recurrences per year |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Australia | 1 | 3 | 0.17 | 2 | 0.11 | Japan | 1 | 2 | 0.12 | 0 | 0 |
| Belarus | 1 | 8 | 0.89 | 4 | 0.44 | Lithuania | 1 | 11 | 0.85 | 2 | 0.29 |
| Bulgaria | 1 | 3 | 0.21 | 0 | 0 | Macedonia | 1 | 3 | 0.17 | 1 | 0.11 |
| Canada | 1 | 4 | 0.29 | 2 | 0.40 | Netherlands | 2 | 7 | 1.31 | 5 | 1.19 |
| Colombia | 1 | 19 | 0.95 | 16 | 0.80 | Norway | 1 | 6 | 0.43 | 2 | NA |
| Croatia | 2 | 28 | 0.43 | 8 | 0.26 | Poland | 1 | 130 | 3.82 | 40 | 0.26 |
| Czech Republic | 1 | 12 | 0.67 | 4 | NA | Romania | 1 | 5 | 0.46 | 2 | 0.50 |
| Denmark | 1 | 4 | 0.20 | 1 | 0.05 | Saudi Arabia | 1 | 5 | 1.00 | 1 | 0.05 |
| France | 8 | 159 | 1.26 | 67 | 0.65 | Slovenia | 1 | 3 | NA | 2 | NA |
| Germany | 3 | 14 | 0.97 | 5 | 0.43 | South Korea | 1 | 5 | 0.28 | 3 | 0.17 |
| Greece | 3 | 2 | 0.20 | 0 | 0 | South Africa | 1 | 20 | 2.00 | 2 | 0.20 |
| Hungary | 1 | 6 | 0.75 | 2 | 0.25 | Spain | 1 | NA | NA | NA | NA |
| Iran | 2 | 26 | 1.88 | 5 | 1.00 | Sweden | 1 | 9 | 0.50 | 2 | 0.11 |
| Ireland | 1 | 5 | 0.31 | 3 | 0.19 | Turkey | 6 | 105 | 1.49 | 11 | 0.19 |
| Israel | 1 | 8 | 0.44 | 4 | NA | United Kingdom | 3 | 19 | 0.97 | 7 | 1.50 |
| Italy | 8 | 176 | 1.10 | 37 | 0.26 | | | | | | |

NA, not available.

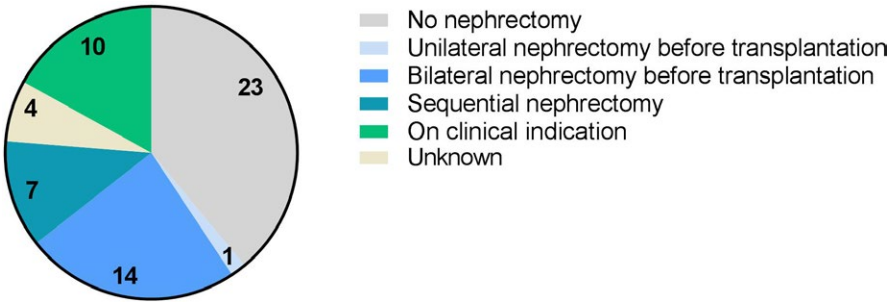


**FIGURE 1** Policy on nephrectomy of native kidney(s) as reported by 59 respondents

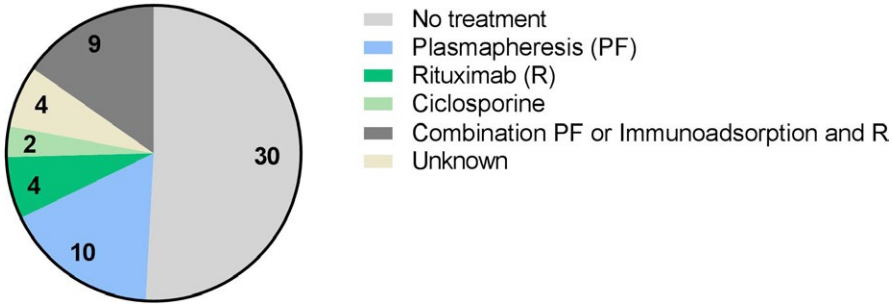


**FIGURE 2** Treatment before transplantation to prevent FSGS recurrence post-transplantation as reported by 59 respondents

children with (heterozygous) mutations of NPHS1 (n = 1), NPHS2 (n = 2), NUP93 (n = 1) or a not reported mutation (n = 1).

The policy regarding nephrectomy when the patient has nephrotic proteinuria before transplantation is shown in Figure 1. Of the patients with nephrotic proteinuria, 39% (23/59) did not undergo nephrectomy before transplantation or during the transplantation procedure. A unilateral, bilateral, or sequential (before transplantation and during transplantation procedure) nephrectomy was performed in 37% (22/59) of the children with proteinuria. Nephrectomy on clinical indication only was reported by 17% (10/59) of all respondents.

Treatment before transplantation to prevent recurrence after transplantation was performed by 20 respondents (34%), and another six respondents performed preventive treatment on clinical indication (eg, living-donor transplantation, quick evolution to end-stage renal failure or idiopathic FSGS), while about half of the respondents (29/59) did not perform any preventive treatment. The choice of preventive treatment before transplantation is shown in Figure 2.

As first-choice treatment, 14% (8/59) preferred living-related renal transplantation, whereas 29% (17/59) preferred deceased donor renal transplantation. The policy regarding the type of donor and transplantation is shown in Figure 3. The standard immunosuppressive regimen at the time of transplantation in children without a known mutation was a combination of glucocorticoids (steroids), CNI, and MMF with or without IL2R blockade induction therapy in the vast majority (50/59) of the respondents (Figure 4). In case of kidney transplantation in FSGS children with a known mutation, the same initial immunosuppressive therapy was used in 63% (37/59) of the respondents, and four respondents did not administer or stopped Cs within 1 week after transplantation. One respondent commented that the use of Cs was discussed case by case. Five respondents used tacrolimus instead of cyclosporine. The maintenance immunosuppressive regimen during follow-up in children without a known mutation was a combination of steroids, CNI, and MMF in 73% (43/59) of the respondents. Steroids were prescribed for different durations: (a) life-long in 22 (37%); (b) during 3-12 months in 10 (17%); (c) 1-2 years in 9 (15%); and (4) other or unknown in 18 (31%). The maintenance immunosuppressive regimen during follow-up in children with a known mutation consisted of a regimen with steroids, CNI, and MMF in 29 (49%) of all respondents, whereas 16 (27%) used a steroid-free regimen. One respondent switched from tacrolimus to cyclosporine when recurrence occurred after transplantation. Delayed graft function requiring dialysis after renal transplantation in children with FSGS was observed by 18 (31%) of the respondents, not observed by 37 (63%), (four unknown).

The median reported (46/59 respondents) percentage of patients with FSGS that recurred after renal transplantation was 20% (range: 0%-100%; Figure 5). If recurrence occurred, 9/32 respondents (28%) reported a recurrence rate of 100% within 1 week. Of all respondents, 34 (58%) routinely performed a kidney biopsy in case of a recurrence post-transplantation, whereas 17 (29%) did not (eight unknown or other). The treatment policy for recurrence of FSGS post-transplant is shown in Figure 6A,B. The majority (39/59) used a combination of PF or IA and R with concomitant therapy: ACE inhibitor and/or ARB, and/or steroids, and/or switch to other immunosuppressive therapy. The response to treatment of FSGS recurrence post-transplant is shown in Figure 7. The definition of response was not specified in the questionnaire. Complete remission after treatment in >50% of the patients has been achieved by 21 (36%) respondents. No correlation can be made between the response rate and different treatment modalities. No response to recurrence treatment was observed by 32 (54%) respondents, whereas 19 (32%) did observe a response.

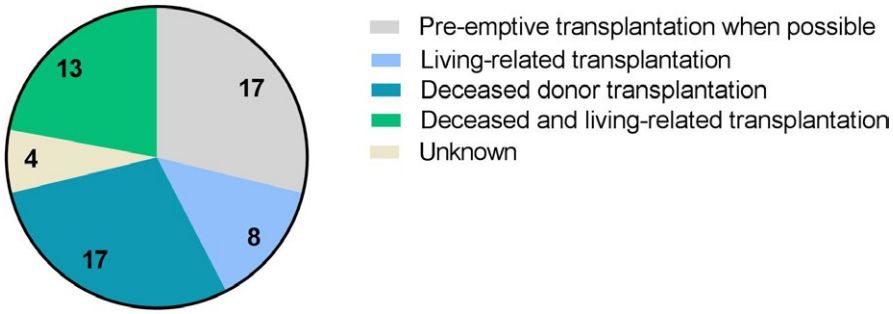


**FIGURE 3** Preferred policy regarding donor choice and transplantation procedure as reported by 59 respondents

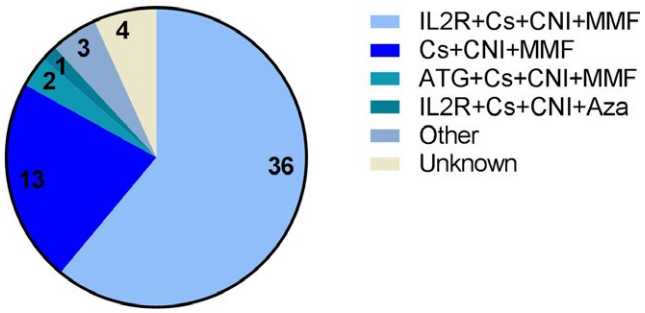


**FIGURE 4** Standard immunosuppressive therapy at time of transplantation for FSGS patients without proven mutation as reported by 59 respondents. ATG, anti-thymocyte globulin; Aza, azathioprin

## 4 | DISCUSSION

This survey among ESPN members gives insight into the frequencies of kidney transplantation in children with FSGS, the post-transplant recurrence of the disease, and the variation in policies regarding the prevention and treatment of FSGS recurrence. The response rate was 15% (59/391 active members), mostly all by pediatric nephrologists. After initial treatment, idiopathic nephrotic syndrome is steroid-resistant in approximately 15% of the patients. Of the non-responders who undergo a kidney biopsy, FSGS is the predominant histopathological finding in SRNS and accounts for 15% of all children with ESRD.[27,28] FSGS is a non-specific lesion reflecting irreversible injury of the podocytes. In general, renal transplantation is the therapy of choice for all children with ESRD. Unfortunately, FSGS often recurs in the kidney transplant recipient, mainly in the primary non-genetic or idiopathic form of FSGS. These patients are supposed to have dysfunction of T- and B-lymphocytes and a circulating factor that adversely affects podocyte function and glomerular permeability.[4,7,29] The first cases of FSGS recurrence after transplantation were reported by Hoyer et al.[30] Electron microscopy analysis of an early graft biopsy showed only diffuse podocyte foot process effacement. In our survey, the majority of the respondents performed a renal biopsy after transplantation in case of recurrence of FSGS.

The reported post-transplant recurrence of FSGS in our survey was 30%. Previously reported recurrence rates vary between 30% and 60%.[3,10,31] Almost one-third of the respondents (54% response rate) reported recurrence within 1 week after transplantation in all of their FSGS patients. In the literature, risk factors for recurrence include younger age at onset, a rapid progression to ESRD in the native kidney, heavy proteinuria and lower serum albumin, histology of MCD in renal biopsy, initial steroid responsiveness (late SRNS), non-black race, and the loss of previous allografts to recurrence.[9,12,18,19,32] Disease recurrence is associated with poor graft outcomes. Graft loss within 5 years after transplantation occurs in 50% of the patients.[9] Historically, the prognosis of SRNS was mainly based on histopathological findings. However, recent findings show that the presence or absence of genetic mutations in FSGS patients and the response to immunosuppressive therapy are important

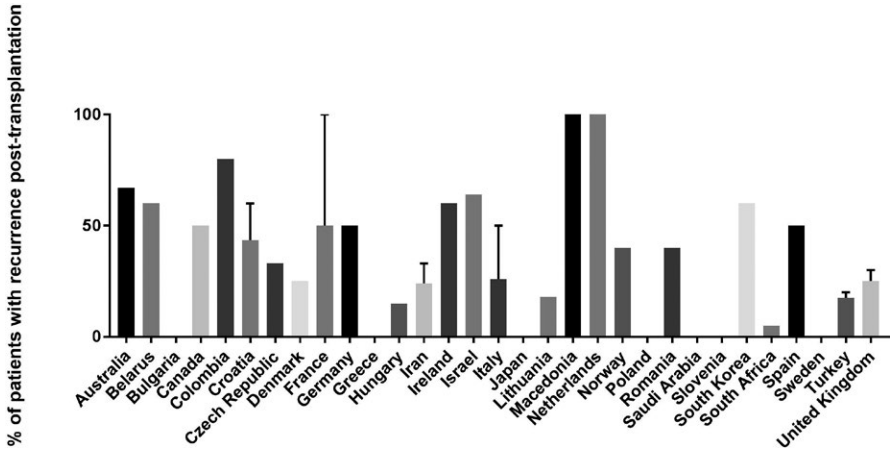


**FIGURE 5** Reported percentage of patients with FSGS recurrence post-transplantation as reported by 46 respondents (medians and ranges)

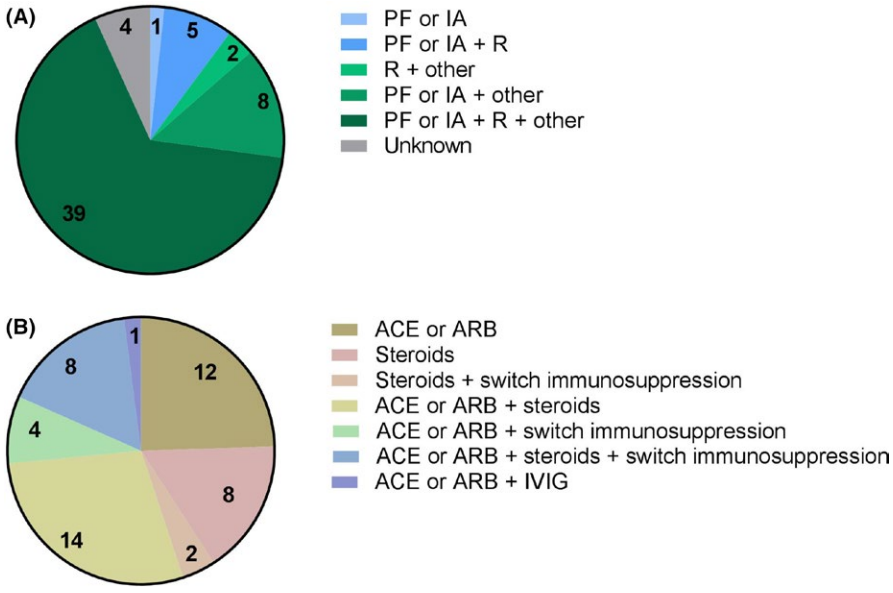


**FIGURE 6** A, Treatment of FSGS recurrence post-transplantation as reported by 59 respondents. Other = ACE, ARB, steroids, switch immunosuppression or IVIG. B, Other treatment for FSGS recurrence post-transplantation as reported by 49 respondents

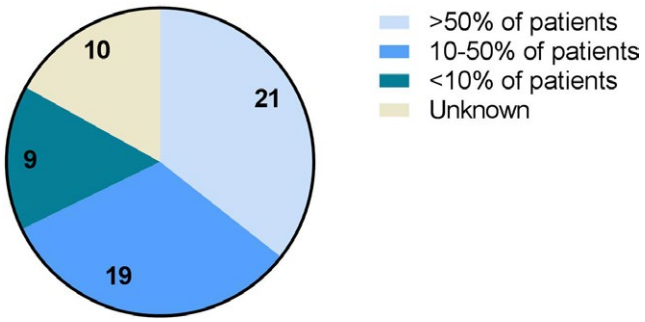


**FIGURE 7** Number of patients that achieved complete remission after FSGS recurrence treatment as reported by 59 respondents

prognostic factors. Theoretically, there is no risk of recurrence in cases with a known mutation, except in children with a homozygous NPHS1 mutation (Finnish type NS) who might develop anti-nephrin antibodies after kidney transplantation in up to 25% of the cases.[33] In this survey, two-thirds of all respondents routinely perform mutation analysis in FSGS patients before transplantation. Less than 10% of the respondents observed a recurrence in children with a known, albeit heterozygous, mutation of NPHS1, NPHS2, or NUP93. Published data on post-transplantation recurrence in genetic FSGS show variability. The recurrence rate in homozygous or compound heterozygous NPHS2 mutations is very low, while in heterozygous NPHS2 mutation recurrence rate was almost 40%, which is almost similar to idiopathic FSGS.[34-37] The latter should be considered as non-genetic FSGS cases. Therefore, patients with heterozygous NPHS1 or NPHS2 mutations should be treated similarly to patients with idiopathic FSGS. Moreover, antibodies against podocin have never been identified.[34,37,38]

In our survey, the majority of the respondents used the same immunosuppressive therapy in FSGS patients regardless of the presence or absence of a mutation. Few respondents reported the use of tacrolimus instead of cyclosporine and/or cessation of steroids in FSGS cases with a proven mutation. Because of the high risk of post-transplant recurrence, preventive treatments before renal transplantation might be considered, such as PF/IA, R, and avoiding nephrectomy. In this survey, one-third of the respondents treated pre-emptively with PF and/or R or cyclosporine. The use of cyclosporine is the only evidence-based treatment for SRNS/FSGS before transplantation.[39,40] Theoretically, cyclosporine might have an antiproteinuric effect through vasoconstriction of afferent arterioles in addition to its CNI effect. Combination therapy of cyclosporine and PF has been reported favorable in children with FSGS recurrence. However, a better outcome with the use of tacrolimus has also been reported.[41] In our survey, unilateral or bilateral nephrectomy was performed by 37% of the respondents. We have no information collected on the outcome of children with or without nephrectomy before or during transplantation. In order to reduce the risk of recurrence of FSGS, some investigators have suggested bilateral native nephrectomy before renal transplantation.[15] However, others could not confirm this.[16] Persistence of nephrotic syndrome and risk of thrombosis remain indications for nephrectomy before renal transplantation. Unfortunately, no effective treatment for FSGS recurrence post-transplantation exists. A large number of therapies have been attempted, but randomized controlled trials on the treatment of FSGS recurrence are still lacking. In this survey, the majority of respondents used a combination of PF or IA together with R as first-choice treatment for post-transplant recurrence. The survey did not ask for the duration of PF therapy and the effect of this specific therapy on the response. Good results are reported with a PF treatment protocol for FSGS recurrence with various duration with or without a switch to high-dose cyclosporine and methylprednisolone.[2,10,17,42] However, Verghese et al[43] demonstrated no additional benefit from pre-emptive PF. Concomitant therapy

consisted mainly of ACE-inhibitor and/or angiotensin receptor blocker. Although FSGS is a steroid-resistant disease, more than half of the respondents used steroids as recurrence treatment. The switch of immunosuppressive therapy was mainly a switch of tacrolimus to cyclosporine. Although some encountered more often delayed graft function requiring dialysis after transplantation, the majority did not. In the study from Cleper et al,[2] a higher number of children with post-transplant recurrent FSGS needed renal replacement therapy compared to the children without recurrence. More than one-third of the respondents achieved complete remission after treatment in >50% of their patients. However, the definition of complete remission was not investigated. Furthermore, more than 50% of the respondents encountered that one or more patients showed no response at all upon recurrence treatment. With the results from this survey, it is not possible to analyze the correlation between the response rate and different recurrence treatment modalities.

Some of the survey questions requested specific information about patients, including number and proportions for outcomes. The decision on responding by recall or by checking a local registry was up to the respondent. There are therefore some risks for reporting bias and recall errors in regard to the reported outcomes, which is a limitation of our study.

In conclusion, this survey gives global insight into the variation of current practice of the treatment of FSGS and its recurrence after transplantation. A more detailed, retrospective analysis of the incidence, renal histopathology, genetics, treatment, and outcome of FSGS and its recurrence after transplantation in all participating centers from this survey will help guideline development. This will be done by using the CERTAIN registry, a registry for pediatric renal transplantation cases in Europe. An upcoming project will be a study on the incidence, treatment, and outcome of recurrent FSGS after pediatric kidney transplantation. Both retrospective and prospective data will be collected. But more importantly, more randomized clinical trials are needed in order to develop an evidence-based treatment.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.


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