

Recurrent FSGS Postkidney Transplant: Moving the Needle Forward

Sandra Amaral* and Alicia Neu[†]

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Primary FSGS is a common cause of steroid-resistant nephrotic syndrome in both children and adults, and it is the most common primary glomerular cause of ESRD in the United States (1–3). Over the last 20 years, we have dramatically increased our understanding of the spectrum of genetic factors, histology, and podocyte injury that contributes to similar clinical phenotypes (1,2,4–6). Although this increased knowledge has improved our diagnostics, it has made our management somewhat more complex, with tremendous lack of evidence to inform clinical decision making with respect to who benefits the most from aggressive management of their primary disease versus who will regardless progress to ESRD. Similarly troublesome is understanding who benefits the most from transplantation versus who is a greatest risk for post-transplant recurrence. Understanding transplant recurrence risk is particularly poignant for children and young adults who run the risk of early transplant failure and sensitization.

A great challenge in achieving optimal post-transplant outcomes in patients with FSGS is in the prevention and management of recurring disease after transplant. Most commonly, FSGS recurrence portends negative graft survival, and although knowledge is being gained regarding the various forms of FSGS, particularly with respect to genetic mutations, much more data are needed to truly understand how to predict risk of recurrence and inform transplant approaches to mitigate the effects of recurrence when it happens.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Francis *et al.* (7) report the results of a large retrospective cohort study of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) that examined adults and children with FSGS in Australia and New Zealand who received first kidney transplants between 1992 and 2011. The authors sought to achieve three aims: (1) to assess the incidence of FSGS recurrence post-transplant, (2) to determine the effect of donor source on recurrence, and (3) to determine the effect of donor source on graft survival.

For the first aim, the authors defined recurrence as biopsy-proven FSGS. In their registry, these data are reported monthly. They defined recurrence on the basis of histology (renal biopsy or graft nephrectomy) and time of recurrence as the date of onset of nephrotic-range proteinuria with a decrease in serum albumin or

the date of tissue biopsy confirmation. Using this strict definition of recurrence, they found that only 10.3% of patients (76 of 736) recurred, among them 51 adults and 25 children, with the majority of recurrence occurring within the first 2 years post-transplant. Compared with other studies, this incidence is relatively low. Several other cohort studies suggest that the incidence is closer to 15%–30% across racial/ethnic groups and for children and adults (8–11). Because in clinical practice, recurrence is generally made as a clinical diagnosis with evidence of increased proteinuria post-transplant, this study likely underestimates true rates of disease recurrence and may be capturing patients in whom recurrence was more severe, perhaps including patients with delayed graft function or other indications for biopsy. The authors also found that younger age, non-white ethnicity (primarily Asian and Indigenous), and having a living donor were independent risk factors associated with recurrence. The findings associated with age and race/ethnicity have been fairly consistent across studies, although in most United States studies, the nonwhite populations comprise blacks, who may be at greater likelihood of having genetic forms of FSGS, including Apolipoprotein L1 mutations (12–17). The ANZDATA Registry does not collect genetic testing results, and thus, patients with known mutations would have been included in the cohort, with less risk of recurrence, biasing toward lower rates of recurrence in the overall cohort. Additionally, the authors did not have data on early treatment, which may have halted or prevented early recurrence before biopsy was needed. Again, this limitation likely results in an underestimate of true recurrence rates. Taken together, the study's incidence estimates are likely lower than the true event rates across the spectrum of disease recurrence.

The second aim of the study by Francis *et al.* (7) was to determine the effect of donor source on recurrence. This has been a longstanding area of controversy, because prior studies have produced conflicting results (13,18–20). Additionally, there are valid ethical concerns in using living related donors who may harbor some genotypes with greater risk for future renal disease development (21). Francis *et al.* (7) found having a living donor to be an independent risk factor for recurrence across the combined adult and pediatric cohort, although there was no difference in FSGS recurrence rates by donor source among the pediatric subgroup.

*Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and [†]Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland

Correspondence: Dr. Alicia Neu, Johns Hopkins University School of Medicine—Pediatrics, Division of Nephrology, 200 North Wolfe Street, Rubenstein Child Health Building, Baltimore, MD 21287. Email: aneu@jhmi.edu

Beyond recurrence rates, for their third aim, the authors examined the effect of donor source on graft survival. They found that, although recurrence rates were higher among living donor recipients, median graft survival among living donor recipients was 14.8 versus 12.1 years among deceased donor recipients. Notably, Francis *et al.* (7) had no data on the treatment and management of FSGS recurrence, such as plasma exchange or rituximab, which may have affected outcomes (22–24). With respect to donor source, preemptive intervention strategies before transplant are generally only feasible among living donor recipients and may or may not alter the short-term outcome of recurrence and long-term allograft function (25,26). Nevertheless, the results of the study by Francis *et al.* (7) support the consideration of living donors for adults and children with FSGS—although as we learn more about donor risk, we must weigh the potential genetic risk for ESRD among donors as well as the benefit to the recipients with FSGS.

Of note, the graft survival at 5 years was only 52% (95% confidence interval, 40% to 63%) among those who recurred. In pediatrics, very few children with FSGS are transplanted preemptively, having to wait on dialysis to burn out their active nephrosis or stabilize after nephrectomy; this likely affects their health going into transplant and may affect graft and patient survival (27). Although Francis *et al.* (7) are likely selecting out the worst cases by limiting to those with biopsy-proven recurrence diagnoses, these results are a stark reminder of the work that needs to be done to reduce the long-term effect of recurrence on graft outcomes.

Current treatment approaches to recurrence are most frequently reactive and strikingly inadequate, waiting and watching for the development of *de novo* (or increased) proteinuria post-transplant. For example, a recent analysis of data from the Nephrotic Syndrome Study Network (NEPTUNE) revealed only modest correlation between random urine protein-to-creatinine ratios and 24-hour urine protein excretion (28). The authors showed that a simple log₁₀ transformation of the urine protein-to-creatinine ratio increased the correlation with 24-hour urine excretion (28). Chang *et al.* (29) recently reported that foot process effacement can be observed within minutes after reperfusion in patients with kidney transplants and FSGS and may be an early predictor of disease recurrence. Kachurina *et al.* (30) have also proposed an assay to identify serum podocyte-toxic activity that may increase recurrence risk. Obviously, larger prospective studies are required to validate the prognostic value of such tools, but these and other strategies to improve early diagnostics of recurrence are greatly needed and may inform targeted therapies. In addition, when patients do recur, we must better understand the utility and benefits of standard treatments, such as plasma exchange and rituximab, and novel approaches, such as B7–1 blockade, through more controlled study designs (31).

Beyond improving recognition and optimizing treatment paradigms for patients with recurrent FSGS, the key to improving the long-term health of children and adults with this challenging diagnosis will rely on better characterization of the underlying disease pathophysiology and greater understanding of genotype-phenotype relationships (32). With long-term cohort studies, such as the NEPTUNE, and other glomerular disease networks that collect genetic, histologic, and clinical data, we will be able to create more precise risk stratification

models and increase understanding of the relationships between genotype and clinical phenotype for both recipients and potential living donors (1,33). In turn, risk stratification informed by the pathogenesis of the condition and not solely by a final common pathologic lesion can move the needle forward toward preemptive strategies to reduce recurrence altogether.

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Disclosures

None.

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