

NEPHROLOGY

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Focal Segmental Glomerulosclerosis: The Need for Improved Treatment Options and the Basis for the Ongoing NIH Clinical Trial**

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A recent report by Strippoli et al revealed that the number and quality of randomized controlled trials (RCTs) in nephrology was less than those from all of the other 13 major subspecialties in internal medicine and ranked in the third lowest proportion of RCT citations.¹ The authors identified the following factors contributing to these observations: few intervention questions are asked; the number of RCTs to inform clinical decision-making is very low; the quality of reporting nephrology RCTs is suboptimal; and there has been little improvement over time. The authors surmised that there is a crisis in clinical research in nephrology and, in particular, in clinical trials. Nephrologists need to shift their attitude towards RCTs, starting with a well-trained workforce in clinical investigation in order to create a track record of successful studies. Despite the limitations related to a relatively small specialty with various rare disorders, multicenter collaborations involving larger numbers of subjects that have addressed simple goals have been successful in clinical research initiatives by both the North American Pediatric Renal Transplant Collaborative Study Group (NAPRTCS) and the European Vasculitis Study Group. In this regard, the current National Institutes of Health (NIH)-supported Focal Segmental Glomerulosclerosis Clinical Trial in Children and Young Adults (FSGS-CT) (<http://www.fsgstrial.org>) offers the opportunity to participate in a much needed RCT that may serve as a template to address many of the above factors that are critical for achieving a successful track record for future investigations into the etiology, track pathophysiology, and effective prevention and treatment of a variety of progressive kidney disorders. This issue of *Nephrology Rounds* reviews the histology, genetics, and current treatments for FSGS and the design of the FSGS-CT that will evaluate possible treatment modalities.

The histologic features of FSGS were first described in the kidney more than 80 years ago and, within a few years, this lesion was firmly associated with the clinical problem of severe nephrotic syndrome.² A more complete spectrum of FSGS presentations has been clarified over the past 20 years. The glomerular changes associated with FSGS are now recognized to occur in an array of systemic disorders: as a spontaneous illness (idiopathic), as an inherited disease, or even as a recurrent lesion in transplanted kidneys.³ It is also becoming increasingly clear that FSGS can have devastating conse-

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** Dedicated to the memory of the late Norman J. Siegel, former Chairman of the FSGS-CT Steering Committee, whose unremitting commitment to the mission of this clinical investigation, the patients it assists, and our efforts to examine the causes and best treatments for this progressive kidney disease, enabled all of us to collaborate with the sole purpose of furthering our knowledge of FSGS.

AS PRESENTED IN THE ROUNDS OF
THE NEPHROLOGY DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
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quences for affected patients and for the United States (US) healthcare system. Changes related to FSGS are recognized in native kidney biopsies much more often than in the past.⁴ Furthermore, the majority of patients with FSGS will fail to respond to steroid therapy, at least as typically employed, and these resistant patients will likely progress to end-stage renal disease (ESRD).⁵ These trends and the poor prognosis for the illness have significant bearing on the US ESRD program. The US Renal Data Systems (USRDS) data demonstrate that the incidence of new ESRD attributed to FSGS has increased 5- to 6-fold in African Americans and 5- to 8-fold in White patients. More than 75,000 patients in the US have ESRD due to idiopathic FSGS or 3.6% of the entire ESRD population.⁶ Therefore, a high priority must be placed on formally addressing new treatment options for idiopathic FSGS.

FSGS in pediatric and adult patients

Although the first autopsy reports described idiopathic FSGS in children, it is increasingly evident that the disease is important in all age groups. The disease invariably presents with proteinuria. Typically, however, macroscopic hematuria is not a major presenting feature of idiopathic FSGS across all age groups.⁷ The most important early clinical experience was from the International Study of Kidney Disease in Children, taken from renal biopsies of children in the 1960s.⁸ These studies emphasized that while only 7% of nephrotic children exhibited FSGS by renal biopsy, the bulk of these patients failed to have a remission of proteinuria with steroid treatment.⁹ This contrasts sharply with the experience from children with minimal change disease.

Subsequent series demonstrated that the FSGS glomerular lesion is present in 2%-27% of kidney biopsies across all ages and frequency extends even into the elderly age group.¹⁰ FSGS becomes less common with advancing age, but it is still a significant problem in the elderly. In a series of 1,368 renal biopsies taken from patients aged >60 years, FSGS was present in 5.4% of patients with the nephrotic syndrome.⁴ Surveys of native kidney biopsies taken from adult patients in the 1990s revealed that FSGS was increasing in prevalence and was present in 12% to 20% of cases.⁵ In addition, some observations suggest that FSGS in adults will more likely affect patients of African descent and will be associated more with reduced glomerular filtration rate (GFR) than the disease in children.¹⁰

Regardless, FSGS diagnosed at any age portends a high risk for progression to ESRD. In nearly 6,000 children with chronic kidney disease (CKD) in the NAPRTCS database, patients with FSGS carried the greatest risk of progression to ESRD, with more than half requiring renal replacement therapy within 2 years of entry.¹¹ Two large series of adult patients sug-

gest that the kidney risk is comparable when FSGS is diagnosed later in life. In cohorts of adults treated with a variety of immunosuppressive protocols, 30% of patients have evident CKD within 5 years of diagnosis, and the overall 10-year renal survival was only 67%.^{12,13} The clinical challenge is to develop an approach to treatment that is well-tolerated, safe, and effective in FSGS presenting at any age.

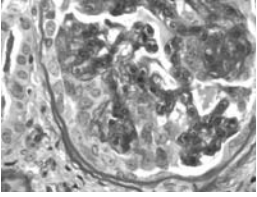
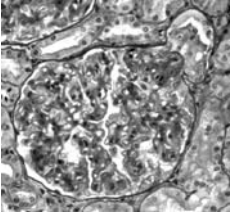
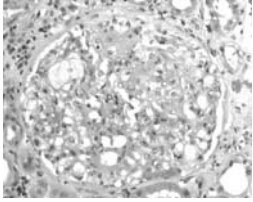
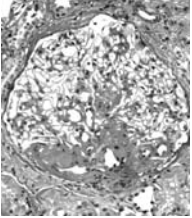
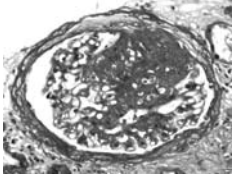
Prediction of FSGS outcome

The mainstay of management for idiopathic nephrotic syndrome, particularly in pediatric patients, has been glucocorticoid therapy.⁸ In order to avoid the long-term consequences of steroid therapy (eg, infection risk, glucose intolerance, and osteoporosis), it is desirable to predict the long-term risks of progression early in the course of FSGS. The most consistent indicator of long-term kidney survival is the ability to reduce proteinuria with initial management. It is well documented that if a nephrotic patient with FSGS has a normalization of proteinuria with immunosuppressive treatment, the likelihood of reaching ESRD is minimized. In retrospective studies, failure to achieve remission in idiopathic FSGS (predominantly after steroid therapy) is associated with a 50%-60% likelihood of ESRD; however, complete short-term remission of proteinuria is associated with no renal risk.^{14,15} More recently, these observations were extended to demonstrate that even a partial remission, namely a 50% reduction in proteinuria, was also significantly associated with improved long-term renal survival.¹⁶ The initial change in proteinuria following institution of treatment is a strong surrogate marker for long-term kidney survival.

Prediction of FSGS outcome based on histology

The term “FSGS” is applied to a pathologically diverse group of glomerular lesions with heterogeneous clinical manifestations. A recent report described the clinical and pathologic characteristics of FSGS histopathologic variants.¹⁷ The different renal diagnostic criteria had previously been outlined in a standardized pathologic classification of FSGS that confirmed the 5 categories shown in Figure 1.¹⁸ This morphologic classification of FSGS has been demonstrated to have prognostic value, with the different histological variants affecting clinical presentation and predicting outcomes after therapy. This study revealed that collapsing FSGS affected younger and, more often, Black patients.¹⁸ Collapsing and tip variants had higher proteinuria and lower serum albumin than perihilar and not otherwise specified (NOS) variants. The tip lesion variant had better renal function, less severe tubulointerstitial injury, and was more frequent in Caucasians. These patients were more likely to receive steroids and more

Figure 1: Histologic characteristics of FSGS¹⁸

<p>FSGS, Collapsing</p> <ul style="list-style-type: none">• Pre-empts other variants• Defining feature:<ul style="list-style-type: none">– Glomerular capillary tuft collapse with overlying podocyte hypertrophy and hyperplasia	
 <p>FSGS, tip</p> <ul style="list-style-type: none">• Exclude: collapsing variant• Defining feature:<ul style="list-style-type: none">– Origin of proximal tubule must be identified with adhesion or confluence of tuft lesion in the tip domain; Tuft lesion may be foam cells, endocapillary hypercellularity (<50% of tuft), sclerosis (<25% of tuft)– Presence of a “perihilar” lesion rules out tip variant	
<p>FSGS, cellular</p> <ul style="list-style-type: none">• Exclude: collapsing and tip variants• Defining feature:<ul style="list-style-type: none">– Endocapillary hypercellularity (at least 25% of tuft), typically expansile and occluding lumina, with or without foam cells.	
 <p>FSGS, perihilar</p> <ul style="list-style-type: none">• Exclude: collapsing, tip, and cellular variants• Defining feature:<ul style="list-style-type: none">– Perihilar hyalinosis, with or without sclerosis– at least 50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis	
<p>FSGS, NOS</p> <ul style="list-style-type: none">• Exclude: collapsing, tip, cellular and perihilar variants• Defining feature:<ul style="list-style-type: none">– segmental sclerosis with increased matrix obliterating capillary lumina	

often achieved complete remission (50%). After a median follow-up of 1.8 years, 23% of patients were on dialysis and 28% had renal failure. Collapsing FSGS had a worse 1-year (74%) and 3-year (33%) renal survival compared to other variants (overall cohort renal survival at 1 and 3 years: 86% and 67%).

Prediction of FSGS outcome based on genetic studies

Over the past 10 years, there has been a dramatic increase in the knowledge of genetic factors that cause glomerular disease. These discoveries raise the possibility that genetic markers will predict clinical outcome in idiopathic FSGS. Familial cases of FSGS have long

been recognized. In 1973, Habib suggested that 12% of all pediatric cases of FSGS had at least one affected sibling.¹⁹ It is now clear that mutations in structural podocyte-associated proteins account for a portion of FSGS cases. A mutation in the *NPHS2* gene, which encodes the protein podocin, was linked to autosomal-recessive steroid-resistant nephrotic syndrome in children.²⁰ However, although this link was strong in Israeli-Arab children, it was not evident in Israeli-Jewish or Japanese children with sporadic FSGS.²¹

Mutations in the α -actinin 4 gene (*ACTN4*) have been associated with autosomal-dominant FSGS in adults, a disease characterized by variable risks of progression to ESRD.²² Most recently, autosomal-dominant FSGS was linked to the gene that encodes the transient receptor potential cation channel, subfamily C, member 6 (*TRPC6*).²³ These genes are causative for FSGS and have revealed new information about the structure and function of the podocyte.²⁴

These new discoveries are also important in explaining the causes of a minority of familial FSGS cases. At this point, however, it is not clear if mutations in or expression of these genes will predict responses to therapy for long-term kidney survival.

Effective treatments in FSGS

Therapeutic interventions for FSGS have been widely reported. However, evidence-based treatment guidelines have not been developed due to the lack of controlled studies and the small number of participants included in most reports. Consequently, the choices of therapeutic interventions for the FSGS-CT were both difficult and controversial. Because strong biases exist in both pediatric and internal medicine nephrology communities, it was necessary to find therapeutic regimens that were acceptable to investigators at the participating sites who would be contributing participants to the study.

The earliest experiences in treating idiopathic FSGS involved glucocorticoids. There are clear differences between pediatric and internal medicine nephrologists with respect to the therapeutic interventions commonly employed for the treatment of patients with steroid-resistant FSGS and most other glomerulopathies. Lin recently reviewed the Metro Toronto Glomerulonephritis Registry, which indicated that adults with FSGS were less likely to be treated with steroids when compared with children (33% vs 90%), while remission rates of proteinuria were similar (39% vs 44%).^{25,26}

Over the past decade, a number of studies have reported therapies for FSGS, including corticosteroids (daily or every other day),²⁷ cyclophosphamide,²⁸ cyclosporine (CSA),²⁹⁻³¹ tacrolimus (Prograf[®]),^{32,33} mycophenolate mofetil (MMF),^{34,35} and sirolimus (Rapamycin[®]).^{36,37} The experience with MMF in the

treatment of patients with steroid-resistant FSGS has been limited to uncontrolled trials in adult patients and children.^{34,35}

Despite widely published experiences with various medications, it is notable that there have been only 4 prospective, randomized, controlled clinical trials published in idiopathic FSGS. Thus far, CsA is the only medication that has been documented to be efficacious in a controlled trial in both children and adults with steroid-resistant FSGS.^{29,30}

Rationale for study design

In evaluating the therapeutic interventions for the FSGS-CT, it was noted that no evidence-based medicine has designated a specific therapeutic intervention for steroid-resistant FSGS that significantly reduces proteinuria or preserves renal function in a substantially large proportion of patients. However, the following 4 factors were taken into consideration in the ultimate design of this clinical trial:

- an established role for CSA in the treatment of FSGS
- the potential, but unproven benefit, of intermittent high-dose corticosteroid therapy in combination with another immunosuppressive agent
- the efficacy of either therapeutic intervention to induce sustained reduction in proteinuria after withdrawal of a therapeutic agent
- the side effects and consequences of any long-term therapeutic intervention, if withdrawal of medication is unsuccessful.

Design and implementation of the NIH-FSGS treatment trial

The FSGS-CT is sponsored by the National Institutes of Health (NIH) in response to the need for rigorously-tested treatment modalities in idiopathic FSGS. It is a phase III randomized trial of children and young adults aged 2 to 40 years. The trial is being conducted at over 100 sites in North America, which are divided among 3 core networks with principal investigators, study coordinators, and a central data-coordinating center (<http://fsgstrial.org>). Eligibility criteria include a biopsy-confirmed primary FSGS, corticosteroid resistance (urinary protein/creatinine [Up/c] ratio >1.0 during minimum 4 weeks prednisone therapy with cumulative minimal dose of 56 mg/kg prednisone or equivalent), persistent proteinuria (Up/c ratio >1.0), and an estimated GFR (eGFR) ≥ 40 ml/min/1.73m² (Table 1). Exclusion criteria include secondary FSGS, prior therapy with CSA,

Table 1: Inclusion and exclusion criteria

Inclusion
<ul style="list-style-type: none">• Age 2-40 years• Estimated GFR ≥ 40 ml/min/1.73m²• Urine protein/creatinine (Up/c) ratio >1.0• Steroid resistance marked by failure to achieve a sustained Up/c ratio <1.0 during min 4 wks prednisone therapy, cumulative minimal dose 56 mg/kg• Biopsy-confirmed primary FSGS
Exclusion
<ul style="list-style-type: none">• Secondary FSGS• Prior therapy with cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, azathioprine• Obesity: BMI >97th percentile for age 2-20 yrs BMI >40 for age >21 yrs

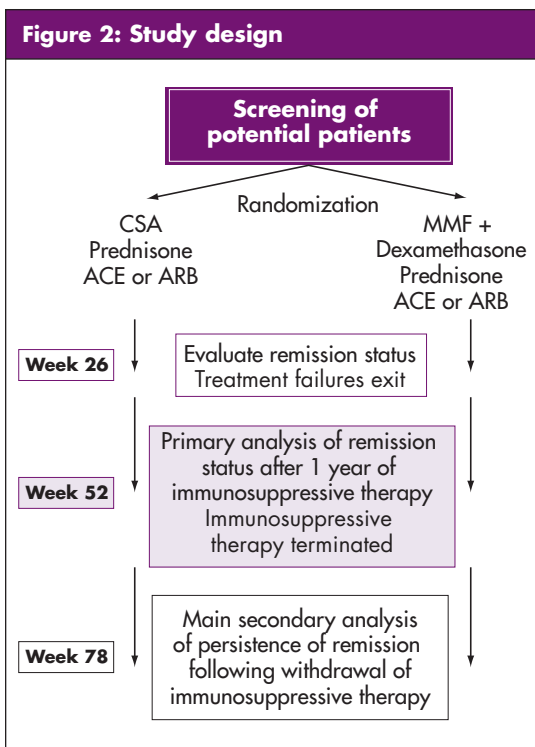
tacrolimus, MMF, sirolimus, or azathioprine, and obesity with a body mass index (BMI) >97th percentile for age 2-20 years and BMI >40 for age >21 years. Diagnostic renal biopsy material is required, consisting of a representative light microscopy (LM) slide demonstrating FSGS, an immunofluorescence (IM) report, and a representative print or digital electron microscopy (EM) of at least one glomerulus reviewed by one of the 3 core pathologists at the time of patient enrollment.

The primary outcome is attainment of partial or complete remission (6-level ordinal scale; Table 2). The main secondary outcome is relapse after withdrawal of immunosuppressive agents, followed by treatment failures, change in eGFR, side effects, decline in quality of life, and receipt of biological materials.

Patients are randomly assigned to one of two active treatment arms: CSA, or MMF + pulse dexamethasone (Figure 2). The target period for maintaining these medications is 12 months. Both study groups are also treated with either lisinopril or losartan for 18 months and low-dose alternate-

Table 2: Study outcomes

Primary outcome
<ul style="list-style-type: none">• Attainment of partial or complete remission (6-level ordinal scale)
Main secondary outcome
<ul style="list-style-type: none">• Relapse after withdrawal of immunosuppressive agents
Secondary outcomes
<ul style="list-style-type: none">• Treatment failures• Change in eGFR• Side effects• Declining quality of life• Receipt of biological materials



ACE = angiotensin-converter enzyme, ARB = angiotensin-receptor blocker, MMF = mycophenolate mofetil, CSA = cyclosporine

day steroids for 6 months. The decision to include alternate day corticosteroid therapy and inhibition of the renin-angiotensin system as background therapy for both therapeutic arms of this clinical trial reflected current standards of practice. Most therapeutic interventions in patients with steroid-resistant FSGS included these two elements irrespective of the primary therapeutic intervention. The ultimate effectiveness of a therapeutic intervention could be best appreciated, if it were possible to sustain an antiproteinuric effect when the medication is withdrawn.

The primary outcome is based on achieving a remission of proteinuria: complete remission (CR) Up/c <0.2; partial remission (PR) Up/c <50% of baseline value and <2; or no remission (NR). Patients who do not achieve a CR or PR at 6 months are defined as treatment failures for the primary outcome and exit the study. Thus, patients entering the study commit to only 6 months of therapy unless a remission is achieved. The primary outcome for the remaining patients will be assessed at month 12. The main secondary outcome is the persistence of remission after withdrawal of the CSA or MMF/dexamethasone during study months 12 to 18.

The analysis will be carried out by intent-to-treat with patients retained in their randomized

groups regardless of whether they have maintained and adhered to their randomly-assigned treatment regimen. The CSA group will be regarded as the reference group and the MMF/pulse steroid groups as the treatment group for expression of treatment effects in the primary analysis. However, due to the expectation that beneficial effects may be observed in either direction, a 2-sided test will be conducted at the 5% significance level. Sample size calculations indicate that 207 patients are needed to detect an 18% increase in CR or PR in the MMF/dexamethasone vs the CSA arm.

The FSGS-CT is the largest controlled trial of FSGS in North America and will establish a standard of therapy for corticosteroid-resistant primary FSGS. Additional benefits of the trial are the establishment of an infrastructure for the study of FSGS, the creation of a national repository of biospecimens for investigations on the pathogenesis of FSGS and the role of histological sub-classifications of FSGS in the response to therapies, and the evaluation of the efficacy of withdrawing immunosuppressive drugs while maintaining angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs). To date, 5 ancillary studies have received NIH support:

- David Kurnit – Analysis of Podocyturia in FSGS
- Howard Trachtman – Novel Therapies for Resistant FSGS
- Tej Mattoo – Tacrolimus and Plasmapheresis in Treatment-Resistant FSGS
- Lisa Guay-Woodford – Genetics and Pharmacogenetics in FSGS
- Robert Mak – Proteomics in Obesity-related FSGS.

Randomization began in November 2004 and will continue through March 1, 2008. The follow-up period for the last randomized patient ends in September, 2009. As of January 1, 2007, 139 patients were enrolled and 96 randomized with 30 excluded for biopsy readings inconsistent with primary FSGS, Up/c <1.0, and eGFR <40 mL/min/1.73m². Entry characteristics of the enrolled patients are: 57 <24 years of age; 27 African Americans, 38 white, 4 other; 39 male, 32 female; eGFR 135 mL/min/1.73m² and Up/c >6.44.

In summary, the nephrology community has been given an opportunity to participate in an important clinical trial that will serve as a template for the subsequent design and implementation of investigations into the etiologies, prevention, and treatment of a variety of progressive glomerular disorders. It is up to us to meet this challenge with a successful response.

References

1. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol* 2004;15:411-419.
2. Fahr T. *Handbuch der speziellen pathologischen Anatomie und Histologie*. Vol VI/1. Berlin, Heidelberg, New York: Springer; 1925.
3. Schnaper W. Primary focal segmental glomerulosclerosis. *Semin Nephrol* 2003;23:163-93.
4. Davison AM, Johnston PA. Glomerulonephritis in the elderly. *Nephrol Dial Transplant* 1996;11(9):34-37.
5. Hass M, Spargo BH, Coventry S. Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: a 20-year renal biopsy study. *Am J Kidney Dis* 1995;26:740-50.
6. United States Renal Data Service (USRDS). *Annual report 2005*. Minneapolis, Minn.: USRDS Coordinating Center; 2005.
7. International Study of Kidney Disease in Children. Nephrotic syndrome: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 1978;13: 159-65.
8. International Study of Kidney Disease in Children. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. *J Pediatr* 1981;98:561-64.
9. Churg J, Habib R, White RH. Pathology of the nephrotic syndrome in children: a report for the International Study of Kidney Disease in Children. *Lancet* 1979;760(1):1299-302.
10. Cameron JS. Focal segmental glomerulosclerosis in adults. *Nephrol Dial Transplant* 2003;18(6):vi45-vi51.
11. North American Pediatric Renal Transplant Cooperative Study (NAP-TRCS). *Annual report 2005*. Boston, Mass.: NAPTRCS Administrative Office; 2005.
12. Banfi G, Moriggi M, Sabadini E, Fellin G, D'Amico G, Ponticelli C. The impact of prolonged immunosuppression on the outcome of idiopathic focal segmental glomerulosclerosis with nephrotic syndrome in adults: a collaborative retrospective study. *Clin Nephrol* 1991;36:53-59.
13. Wehrmann M, Bohle A, Held H, Schumm G, Kendziorra H, Pressler H. Long-term prognosis of focal sclerosing glomerulonephritis: an analysis of 250 cases with particular regard to tubulointerstitial changes. *Clin Nephrol* 1990;33:115-122.
14. Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course and response to treatment. *Am J Kidney Dis* 1995;25(4):534-42.
15. Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. *J Am Soc Nephrol* 2004;15(8):2169-77.
16. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J Am Soc Nephrol* 2005; 16(4):1061-8.
17. Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006;69:920-926.
18. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004;43:368-382.
19. Habib R. Editorial: focal glomerular sclerosis. *Kidney Int* 1973; 4:355-61.
20. Frishberg Y, Rinat C, Megged O, Shapira E, Feinstein S, Raas-Rothschild A. Mutations in NPHS2 encoding podocin are prevalent cause of steroid-resistant nephrotic syndrome among Israeli-Arab children. *J Am Soc Nephrol* 2002;13:400-05.
21. Maruyama K, Iijama K, Ikeda M, et al. NPHS2 mutations in sporadic steroid-resistant nephrotic syndrome in Japanese children. *Pediatr Nephrol* 2003;18:412-16.
22. Kaplan JM, Kim SH, North KN, et al. Mutations in ACTN4, encoding α -actinin-4, cause familial focal segmental glomerulosclerosis. *Nat Genet* 2000;24:251-56.
23. Winn MP, Daskalakis N, Spurney RF, Middleton JP. Unexpected role of TRPC6 channel in familial nephrotic syndrome: does it have clinical implications? *J Am Soc Nephrol* 2006;17:378-87.
24. Barisoni L, Kriz W, Mundel P, D'Agati V. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 1999;10(1):51-61.
25. Lin J. Focal segmental glomerulosclerosis. *Nephrology Rounds* 2006; 4(5).
26. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P. Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. *Am J Med* 1987;82(5):938-44.
27. Korbet SM. Treatment of primary focal segmental glomerulosclerosis. *Kidney Int* 2002;62(6):2301-10.
28. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. *Pediatr Nephrol* 1996;10(5):590-3.
29. Liberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol* 1996;7(1): 56-63.
30. Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int* 1999;56(6):2220-6.
31. Heering P, Braun N, Mullejans R, et al; German Collaborative Glomerulonephritis Study Group. Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. *Am J Kidney Dis* 2004; 43(1):10-8.
32. Duncan N, Dhaygude A, Owen J, et al. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004;19(12):3062-7.
33. Sinha MD, MacLeod R, Rigby E, Clark AG. Treatment of severe steroid-dependent nephrotic syndrome in children with tacrolimus. *Nephrol Dial Transplant* 2006;21(7):1848-54.
34. Cattran DC, Wang MM, Appel G, Matalon A, Briggs W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. *Clin Nephrol* 2004;62(6):405-11.
35. Choi MJ, Eustace JA, Gimenez LF, et al. Mycophenolate mofetil treatment of primary glomerular diseases. *Kidney Int* 2002;61(3):1098-114.
36. Fervenza FC, Fitzpatrick PM, Mertz J, et al; Mayo Collaborative Committee. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulonephritis. *Nephrol Dial Transplant* 2004;19(5):1288-92.
37. Tumulin JA, Miller D, Near M, Selvaraj S, Hennigar R, Guasch A. A prospective, open-label trial of sirolimus in the treatment of focal segmental glomerulosclerosis. *Clinical J Am Soc Nephrol* 2006;1(1): 109-17.

Upcoming Scientific Meetings

1-3 June 2007

International Society for Peritoneal Dialysis

Westin Diplomat Resort, Hollywood, Florida

CONTACT: Northpointe Meetings & Incentives

Tel.: 866-512-8801

Website: www.ispd.org

21-24 June 2007

World Congress of Nephrology 2007

XLIV European Renal Association

Dialysis and Transplant Association Congress 2007

CONTACT: Email: registrations@era-edta.org

Website: www.eraedta2007.org

31 October – 5 November 2007

American Society of Nephrology

Renal Week 2007

Moscone Convention Center, San Francisco, California

CONTACT: Tel. 202-367-1190

Website: www.asn-online.org

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