How Do Patients with FSGS Present?

By Ellen McCarthy, MD

Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disease, resulting in heavy proteinuria and leading to ESRD. The term FSGS refers to a morphologic pattern of injury rather than a distinct disease. Sclerotic lesions are present in <50% of all glomeruli on light microscopy (hence focal), with <50% of the glomerular tuft affected (hence segmental). FSGS can be primary or secondary to a variety of physiologic, anatomic, or environmental factors. Primary FSGS is characterized by rather acute onset of heavy proteinuria, with other features of the nephritic syndrome, renal impairment, and resistance to treatment in many patients. The incidence of FSGS as cause for ESRD is increasing (1). Spontaneous remission rate is low (<5%) and progression to ESRD within a few years (5 to 8 years) of diagnosis is common (50%) in patients who do not respond to therapy (2).

There are several histologic variants described in the Columbia classification: FSGS not otherwise specified (NOS), collapsing, tip, perihilar, and cellular variants (3). In spite of initial hopes, this classification, although useful, has not consistently correlated with natural history or response to therapy. FSGS NOS is the most commonly seen variant. In general, collapsing variant has the worst prognosis, whereas tip lesion has the best prognosis and is often responsive to immunosuppressive therapy.

How can one differentiate primary FSGS from secondary FSGS?

FSGS describes the histologic appearance of glomeruli and is nonspecific with regard to etiology of primary or secondary in origin. Differentiating primary from secondary FSGS is important, in that doing so will have significant implications in treatment of patients (4). Primary FSGS is characterized by absence of glomerular mesangial expansion, and the onus is on the clinician to carefully examine the clinical, biochemical, and pathologic data to rule out secondary FSGS.

FSGS can be secondary to acquired or congenital reduced renal mass (single kidney, oligomeganephronia, renal agenesis), or as a feature of physiologic changes (such as increased body mass), genetic mutations, drug toxicity, infections, or the course of other glomerular diseases. Nephritic syndrome, defined as proteinuria greater than 3.5 g/24 hours and hypoalbuminemia, is more commonly seen in patients with primary FSGS. Patients with secondary FSGS are more likely to have nephritic-range proteinuria without the marked hypoalbuminemia and edema of nephrotic syndrome. Patients with primary FSGS and those with HIV-associated nephropathy, collapsing glomerulopathy, or drug toxicity, including toxicity of pamidronate, often have nephrotic syndrome and rapid progression of renal failure, whereas other forms of secondary FSGS may have only proteinuria and exhibit a slower course. Hypertension may be seen more commonly in patients with secondary FSGS.

Important data are obtained from kidney biopsy, in that tip and collapsing lesions are seen in primary FSGS, whereas perihilar lesions more commonly characterize secondary FSGS. However, no histologic subtype is diagnostic for primary FSGS, and secondary causes must be excluded, irrespective of subtype. On electron microscopy (EM), diffuse foot process effacement characterizes primary FSGS, whereas sporadic or patchy foot process effacement is more common in secondary FSGS. It is, therefore, important to ensure that EM be obtained if at all possible in patients with suspected FSGS.

The pathologic processes occurring in primary and secondary FSGS are likely different as well. Primary FSGS is believed to result from diffuse podocyte injury with podocyte loss and formation of synchiae. Secondary FSGS is characterized by glomerular and podocyte hypertrophy, with podocytes becoming attenuated in covering a larger area of the basement membrane, although with preservation of foot processes. Treatment differs in primary versus secondary FSGS. Patients with secondary FSGS should be treated conservatively, with an emphasis on good BP control, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, weight loss if above healthy weight, smoking cessation, low-sodium diet, and control of hyperlipidemia with a statin in particular. These same measures should be taken in patients with primary FSGS in addition to immunosuppressive therapy if indicated. Patients with secondary FSGS do not respond to immunosuppressive therapy and are exposed to potential harm if treated unnecessarily with these medications.

What are important familial forms of FSGS in adults?

Just as a wide variety of nongenetic factors can lead to the histologic lesion of FSGS, a broad range of genetic mutations can also lead to FSGS (5). Inherited forms of FSGS consist of autosomal recessive disorders that usually present in infancy or early childhood and autosomal dominant disorders that usually have a later onset. Although there are patients with recessive disorders not presenting until adulthood, most familial FSGS encountered in adults is caused by autosomal dominant disorders. The most common mutation leading to FSGS in adults is in the gene for inverted formin 2. FSGS can also be caused by mutations in the actin crosslinking protein α-actinin-4 or the cation channel TRPC6. Patients with genetic forms of FSGS rarely respond to immunosuppressive drugs, although information about response to treatment is largely anecdotal. Recurrence of proteinuria after renal transplantation is uncommon.

Although not a Mendelian form of FSGS, variants of the apolipoprotein A1 gene confer increased risk of developing FSGS. These variants are found in patients of African descent. Homozygotes or compound heterozygotes for the G1 or G2 allele have a seven- to tenfold increased risk of developing FSGS.

What are important familial forms of FSGS in children?

The goal of nonspecific and specific therapies in both primary and secondary FSGS is to minimize proteinuria. Achieving complete remission is ideal, although even partial remission portends a better renal outcome (6). Treatment guidelines for primary FSGS were recently published by Kidney Disease Improving Global Outcomes (KDIGO) (7). Treatment for primary FSGS in adults is largely on the basis of controlled trials done in children and consists of immunosuppressive therapy. Initial treatment consists of high-dose corticosteroids for up to 16 weeks or until complete remission; about 50% of adult patients respond to corticosteroid therapy. Calcineurin inhibitors (CNIs) can be used in patients resistant to or intolerant of corticosteroids. The role of alkylating agents in treatment of adults with FSGS has not been substantiated; likewise, the use of mycophenolate mofetil has not been substantiated. Rituximab has been studied in small uncontrolled series in adults with mixed results. Despite the fact that the KDIGO guidelines report that there is insufficient evidence to support recommending alkylating agents, rituximab, or mycophenolate mofetil in adults with FSGS, it is possible that there may be a role for these agents as well as others, including galactose or adenosinocorticotropic hormone, in patients who are resistant or intolerant of recommended therapies.

What is the pathogenesis of FSGS?

FSGS is a podocytopathy, and injury to the podocyte (glomerular epithelial cell) is thought to be the central and initiating event in disease development (8). The nature of the initial insult is unclear, but in some patients, it may be related to a circulating injurious substance or substances, or perhaps, absence of a protective substance.

Podocyte injury is first seen on EM in the form of foot process effacement and cell body atrophy. Injury may then lead to cell death and/or detachment from the glomerular basement membrane (GBM), a resultant decrease in podocyte number, and subsequent mismatch between podocytes and GBM to be covered. Podocyte depletion is a critical event in the pathogenesis of FSGS. Some weeks to months after the initial insult, naď adhesion between parietal epithelial cells and denuded GBM is seen by light microscopy. It has been suggested that misdirected filtration then can occur between the glomerular capillary and the area outside Bowman’s space and along the tubular basement membrane. The role of parietal epithelial cells in FSGS, whether protective or injurious, is currently actively debated.

The podocyte is a terminally differentiated cell, and therefore, hypertrophy (not proliferation, which is quite limited) is the response to increase in glomerular size seen in obesity and reduced nephron number, such as that seen in patients with history of low birth weight. Glomerular hypertrophy as well as increased fluid flow shear stress that occurs in glomerular hyperfiltration may each play an important role in development of secondary FSGS.

What is the role of circulating factor or factors in recurrent FSGS?

Proteinuria recurs in renal allografts of about 30% of patients with primary FSGS in native kidneys. The risk of recurrence in subsequent allografts is over 80% if there has been a previous recurrence (9). There are several observations that strongly implicate a circulating substance that initiates disease recurrence in these patients: 1) proteinuria may be seen within minutes or hours of transplantation, 2) plasmapheresis or immunoadsorption may reduce recurrent proteinuria, 3) injection of patient serum or plasma or fractions thereof into experimental animals results in increased proteinuria, 4) proteinuria that spontaneously resolved was seen in a neonate born of a mother with FSGS, and 5) absence of proteinuria in a second recipient who received an allograft from an initial recipient with native FSGS and rapid recurrence of proteinuria after transplantation. The identity of possible circulating factors has been earnestly sought for decades. Possible candidates include T-cell-derived mediator, soluble uronikase-like plasminogen activator receptor, or cardiotoxin-like cytokine factor 1 (10).

Risks of recurrent FSGS include young age and rapid progression to advanced chronic kidney disease. There are intriguing data to suggest that presence of circulating factor(s) before transplantation may predict recurrence.
Recurrence in focal segmental glomerulosclerosis (FSGS) can lead to graft failure, although aggressive treatment may prolong the life of the allograft.

**What is the treatment of recurrent FSGS?**

Treatments that can be effective for primary FSGS, such as angiotensin blockers or CNIs, have not shown great efficacy in the treatment of recurrent FSGS. Plasmapheresis has been the cornerstone in treating recurrent FSGS as well as prophylaxis against recurrence in both children and adults (11). It is considered standard of care currently, despite lack of randomized, controlled trials. Plasmapheresis is generally well tolerated and safe. Plasmapheresis alone will not induce remission in most patients and must be used in conjunction with other interventions. Such interventions include aggressive use of CNIs.

Rituximab is emerging as a promising agent in treating recurrent FSGS, although thus far, data are limited to small studies and numerous case reports. Published reports suggest a 79% response rate when rituximab is used in recurrent FSGS. It is postulated that the direct effect of rituximab on the podocyte via modulation of sphingomyelinase activity accounts for the benefit seen in decreasing proteinuria. Randomized, controlled trials are needed to elucidate the role of rituximab in treatment of recurrent FSGS in adults and children. Agents, such as CNIs and rituximab, may alter podocyte responses as well as act on the immune system. Study is ongoing to understand the mechanism of these agents.

**Future directions**

Several areas in the diagnosis and treatment of primary and recurrent FSGS are in need of high-quality randomized, controlled trials. It is of vital importance to distinguish primary from secondary FSGS, because many subsequent treatment decisions are on the basis of this initial dichotomy. Accurate categorization would prevent exposing patients to immunosuppressive drugs who are unlikely to benefit from them. Identification of accurate and reliable biomarkers would enhance our ability to determine whether a patient has primary or secondary FSGS and enable appropriate therapy. Likewise, identification and characterization of causative factors in the circulation would ultimately allow for diagnosis, treatment, and prevention of recurrence. The recommended treatment protocols for FSGS in adults are largely on the basis of studies done in children. Verification of applicability to adults seems important. It is crucial to be able to predict which patients are at risk for recurrence of FSGS to institute preventive and/or therapeutic measures in a timely fashion. Finally, evidence-based treatment protocols for recurrent FSGS are needed. These gaps in our understanding of FSGS pose an exciting challenge for those of us who study the condition and care for those patients afflicted with FSGS (Table 1).  

![Ellen McCarthy, MD, is affiliated with the University of Kansas Medical Center, Division of Nephrology and Hypertension and Kidney Institute, Kansas City, KS.](image)

References


Table 1: Treatment of FSGS

<table>
<thead>
<tr>
<th>Treatment target</th>
<th>Intervention</th>
<th>Primary FSGS</th>
<th>Secondary FSGS</th>
<th>Recurrent FSGS after transplant</th>
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</thead>
<tbody>
<tr>
<td><strong>All FSGS</strong></td>
<td></td>
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<tr>
<td><strong>Hemodynamic changes</strong></td>
<td>ACEI, ARB, PGE2 receptor blockade</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hemodynamic changes and vascular metabolism</strong></td>
<td>Normalize systemic BP stop smoking</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hemodynamic changes, inflammation</strong></td>
<td>Treat metabolic syndrome, obesity, hyperlipidemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Podocyte injury</strong></td>
<td>Calcineurin inhibitor</td>
<td>Yes</td>
<td>Yes; protect synaptopodin and actin cytoskeleton</td>
<td></td>
</tr>
<tr>
<td><strong>Podocyte integrity, immunosuppression</strong></td>
<td>Prednisone, ACTHAR gel</td>
<td>Yes</td>
<td>Yes; glucocorticoid and melanocortin receptors</td>
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<tr>
<td><strong>Immunosuppression</strong></td>
<td>Mycophenolate</td>
<td>Yes</td>
<td>Potential (often used in routine immunosuppression)</td>
<td></td>
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<tr>
<td><strong>Podocyte integrity, immunosuppression</strong></td>
<td>Rapamycin</td>
<td>Potential</td>
<td>Potential; inhibit mTOR, protect autophagy</td>
<td></td>
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<tr>
<td><strong>Podocyte integrity, immunosuppression</strong></td>
<td>Rituximab</td>
<td>Yes</td>
<td>Potential; inhibit sphingomyelinase</td>
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<tr>
<td><strong>Circulating Focal Sclerosis Permeability Factor (FSPF)</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Down-regulate synthesis of FSPF</strong></td>
<td>Immunosuppression/cytotoxic agents/stem cell transplant</td>
<td>Potential</td>
<td>Potential</td>
<td></td>
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<tr>
<td><strong>Remove FSPF</strong></td>
<td>Plasmapheresis, plasma exchange, or lipopheresis</td>
<td>Potential</td>
<td>Yes</td>
<td></td>
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<tr>
<td><strong>Bind or block FSPF/interaction with receptor</strong></td>
<td>Galactose; a specific antibody or cytokine trap</td>
<td>Potential</td>
<td>Potential</td>
<td></td>
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<tr>
<td><strong>Inhibit signaling such as Jak/STAT activation</strong></td>
<td>Kinase inhibitor</td>
<td>Potential</td>
<td>Potential</td>
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</tbody>
</table>

**Abbreviations:** ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, PGE2 = prostaglandin E2, FSPF = FSGS permeability factor.