

### Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:

<https://reachmd.com/programs/cme/fsgs-in-practice-patient-centered-decision-making/35713/>

Released: 06/02/2025

Valid until: 06/02/2026

Time needed to complete: 15 Minutes

### ReachMD

[www.reachmd.com](http://www.reachmd.com)

[info@reachmd.com](mailto:info@reachmd.com)

(866) 423-7849

### FSGS in Practice: Patient-Centered Decision-Making

#### Dr. Trachtman:

Welcome to CME on ReachMD. This activity titled FSGS In practice decision-making is provided by intelligence prior to beginning the activity. Please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

#### Dr. Trachtman:

This is CME on ReachMD. I'm Dr. Howard Trachtman, and joining me today is Dr. Kenneth Lieberman. Our discussion today will focus on the optimal management of focal segmental glomerulosclerosis, or FSGS.

We'll start our discussion with a case. Ken, here's a patient for you. A 42-year-old man presents to a mini-ER with an ankle sprain after playing touch football with his friends. He's treated for an ankle sprain and given analgesics. During the visit, he's noted to have a blood pressure of 146 over 92. It is attributed to stress and no further assessment is done. Three months later, he notices that his legs are swollen. He consults his internist who does a urinalysis and detects 4+ proteinuria, prompting referral to a nephrologist. The only medication he takes is intermittent NSAIDs for muscle aches. He exercises regularly, drinks socially, and does not smoke. Blood tests reveal the following. His serum creatinine is 1.4 mg/dL. His eGFR is 76. His serum albumin is 2.6. He has an elevated cholesterol level of 302, and his C3 is normal at 98 mg/dL. The urine protein-to-creatinine ratio is 4.8. A biopsy is done and reveals FSGS not otherwise specified subtype with 20% interstitial fibrosis and tubular atrophy.

What would your diagnostic approach be if the patient had been Black? What are your thoughts on this case, Ken?

#### Dr. Lieberman:

So the definitive diagnostic test has been done. They did the biopsy and made the diagnosis histologically of FSGS, which is the way that diagnosis is definitively made. We're stuck with the classification system of the histologists of old who were basically describing histopathology that they saw under their microscopes. So this is characterized as a lesion of glomerular sclerosis that is patchy and doesn't involve the entire glomerulus, hence the name FSGS. More recently, there's been an attempt to classify the different types of FSGS histologically, and this patient has one of those subtypes that you told us about. This lesion that's described here is kind of intermediate and potentially amenable to ameliorative treatment. Let me just make one other comment about the heterogeneity of FSGS.

Again, we're stuck with some of these classifications in nephrology, again, which are holdovers from when the whole world was described histologically by appearance, membranous nephropathy and so on. But we've recognized how heterogeneous FSGS is as a category, and we recognize at this point 3 major etiologic subsets and I would credit Jeffrey Kopp here in putting together what I think is the schema that most people are comfortable with these days. And you alluded to it when you dropped me this hint about what if the patient were Black in the importance of the genetic types. And that's still a work in progress. It seems like every other week there's a new gene, and it may very well be. It already is to a certain extent that where you're going to do a genetic test, perhaps, up front, you may even be able to not biopsy everybody. And so genetics, particularly in individuals of African or Afro-Caribbean descent, there's the concern for APOL1 mutations, which are predisposed to kidney dysfunction, hypertension, and FSGS is the histologic lesion.

#### Dr. Trachtman:

And I think excellent work is being done mining the heterogeneity of FSGS to drill down beyond the histology and even these clinical

categories but to the actual mechanism of disease that's injuring the podocyte, which we both know is the central site of injury in patients with FSGS, and hopefully using this more mechanistic information to understand the disease, to hopefully target therapies to patients that are more likely to work.

**Dr. Lieberman:**

Yes, absolutely.

**Dr. Trachtman:**

I think we want to emphasize the importance of attempting, as much as possible, early identification of this disease to ostensibly allow patients to get the advantage of medical intervention as early as possible. I think we want to emphasize that this is a disease that's a devastating entity whether you're 5, whether you're 25, or whether you're 55. And the outcome of FSGS is fairly unoptimistic, fairly worrisome, regardless of age. And I think the challenge is in early identification. I think the case that I presented showed that they weren't really paying attention to that elevated blood pressure and a simple urinalysis might have been very, very helpful.

Why is it important for patients to be identified is because we do believe that proteinuria is the key driver. It's the key sign of the disease. It's indicative that the podocyte is not working the way it's supposed to and that the glomerular filtration barrier is disturbed, leading to protein leak.

I think there's a consensus in the community that the objective of therapy is to lower proteinuria as safely and as effectively as we possibly can. We know that complete remissions of proteinuria augur very promising for the patient for a favorable outcome and most regulatory authorities see that as – in a drug that could achieve that on a consistent basis, that would be the answer to our prayers; do you agree, Ken?

It's important for the community to identify patients with FSGS as early as possible in the clinical trajectory so that interventions can be started that can lower proteinuria and hopefully protect the kidney parenchyma.

**Dr. Lieberman:**

We are both pediatric nephrologists, and I think we have a different vision of the life course of disease. That's essentially the essence of our field, and we're very concerned, obviously, about the impact of the disease itself in real time on the patient, but also the implications of chronic kidney failure, eventual ESRD, even something that might be a decade down the line. And so we recognize in peds that we have this opportunity for early intervention in potentially chronic diseases. I would like to emphasize as part of therapy here, that there certainly are more likely to be steroid and immunosuppressive responsive individuals in the pediatric arena, in the pediatric age range. And so the use of steroids, CNIs, calcineurin inhibitors, other immunosuppressive agents, anti B cell agents may be thought of more readily on the part of pediatricians because we are looking for the potential of remittive therapy. We certainly don't want to miss that opportunity.

And I would take this opportunity, again, to reemphasize the genetic perspective in that we certainly have a pretty good sense that the genetic causes in peds, especially the younger children, is particularly prevalent and that has important impacts on therapy even today. Even if it's just saying you have a genetic form and so I'm not going to take a lot of time making you steroid toxic. And that for me, frankly, has been a very positive intervention over the years, just being able to tell somebody that steroids is not for them in terms of the impact on the child. So in terms of standard of care, certainly steroids and CNIs and maybe more CNIs, calcineurin inhibitors, has become a mainstay in addition to the use of anti-RAS therapy, which is ACE inhibitors and angiotensin receptor blockers. And those have a long, long usage in the treatment of these diseases.

**Dr. Trachtman:**

Unfortunately, we live in a time where there are no FDA-approved therapies for FSGS and there's this huge unmet need. All the therapies that we as nephrologists are able to offer to our patients, they're all offered based on empiric evidence with minimal quality clinical trial evidence that they work. We try steroids first. I think that's much more readily applied in pediatrics than in the adult population. The second-line therapy, I think we both agree, would be calcineurin inhibitors, as you said. And then after that, I think most doctors are on their own. And I would want to advocate for continued ongoing participation of the clinicians around the United States, around the globe, in clinical trials to augment our understanding of what are the optimal therapies for this disease.

Standard of care, I think we need as a community to get answers to this as quickly as possible and figure out the optimal combinations of therapy because I don't think any of us want to give our patients 55 meds if we can avoid it. We should mention that sparsentan is potentially a promising addition to the armamentarium for standard conservative therapy. It's a drug that has this dual action blocking both endothelin and angiotensin II. And we have good data from colleagues from Sinai that have shown that there is an interaction between these 2 signaling systems and blocking them both may potentiate the beneficial effect of these 2 drugs.

So that being said, we know we are in a difficult situation with treatment.

Ken, how should patients be monitored while you're treating them?

**Dr. Lieberman:**

As far as monitoring goes, certainly we've more than once mentioned how central proteinuria is, and I think that can't be stressed enough. It has been demonstrated and, in fact, re-demonstrated recently that proteinuria not only has negative immediate consequences for the patients, nephrotic syndrome is no simple matter in terms of the impact on patients, but also reduction of proteinuria in and of itself is a marker for potentially improved outcomes of disease.

We certainly do monitor eGFR, which is going to be ultimately the true functional outcome here. But there are a number of other parameters which are important to not forget. Certainly blood pressure for the effect on secondary end-organ damage as well as the amplification effect it has on kidney injury. And fortunately anti-RAS therapy as well as sparsentan also have antihypertensive benefits. I think that's of importance.

And certainly in all of our patients, but especially children, what is the impact of the disease in all of this therapy on them? I found over the years, I mentioned it already, steroids is really number one here in terms of – ask any patient, lupus patient, ask anybody on multiple meds what drug do they want to get rid of? And it is always steroid, and I think we need to be sensitive to how the disease and how our treatments are affecting patients, and that will influence us as we continue to have more available treatment options.

**Dr. Trachtman:**

I agree wholeheartedly with what you've said. Just to supplement that, I think that one of the things we're learning is to listen to the patient voice and, I think, where the incorporation of patient-reported outcomes into clinical trials and our regular assessment of patients should be part of standard of care. A lot of studies have shown that patients with FSGS and nephrotic syndrome, they suffer pain, they suffer fatigue, and they suffer significant difficult symptoms that interfere with their daily living. And I would just want to point out in this regard, we've highlighted the importance of edema, and there is a FDA-sponsored study called Prepare-NS, which is being done by a colleague of mine and is developing an instrument that will be validated that can be used in clinical practice to assess the severity of edema and to use this as a tool both in clinical care and as a research tool to assess the efficacy of drugs.

So with all that said, Ken, you mentioned, I think, before – I think we've both said the word sparsentan as a potential new therapy for FSGS. Can you review for us what the clinical data were from the DUET, the phase 2, and DUPLEX, the phase 3, trial of sparsentan.

**Dr. Lieberman:**

So both DUET and DUPLEX were randomized clinical trials. In both cases they were done in a double-blind fashion during the double-blind phase, and in both cases the control arm was irbesartan, which is a pretty widely used ARB.

So they were both similar in that regard. There was also, both of them, both studies use an outcome indicator called FSGS remission of proteinuria, and this is an endpoint that is essentially what most of us would think of as a partial remission. And in the DUET trial there was 25% versus 9% reaching of this partial remission endpoint of sparsentan versus irbesartan. This gave encouragement to move ahead with the clinical trials agenda to move to DUPLEX, which is a longer-term, larger phase 3 trial, almost 400 patients.

And similarly to the results in DUET, there was both significant greater reductions in proteinuria in the sparsentan arm versus the irbesartan arm. And this was at the 2-year mark. There was a greater number of patients achieving this partial remission endpoint. And there were a couple of subsets that were looked at initially and later on. The pediatric subset was looked at separately, and the genetic etiology patients were looked at separately, obviously smaller numbers, but both of those subset groups, both of those cohorts indicated the same sort of proteinuria reduction effect. Both groups had stable GFRs, there was a numerically less decline, smaller decline in eGFR in the sparsentan group, but more data is certainly needed to see as much as possible what the longer-term outcomes are going to be in these groups as well as perhaps other subsets.

**Dr. Trachtman:**

I think that what's encouraging about the DUPLEX trial is that it enrolled a representative population of patients with FSGS. It represented the way patients with FSGS represent themselves to nephrologists and to general practitioners. I think I'm extraordinarily encouraged by the safety signal that there was no significant worsening of edema or other organ toxicity that might've been associated with the endothelin blockade component of the drug. We think of it as a non-immunological drug, but I think we always have to keep in mind that by blocking angiotensin II and endothelin, these signaling molecules do have an effect on the immune system as well. And I think this underscores the fact that this is a very, very pluripotent drug. It does a lot of things and it has a lot of aspects to its effort.

And also to highlight, even to connect with what you said before, that there is evidence that this drug works in the substantial subset of patients within DUPLEX who had genetic causes for FSGS, and follow-up analyses have demonstrated that the sparsentan worked even

in that subgroup just as effectively as in the non-genetic group. And then finally, I think it's important we knew that in contrast to IGA, where we were able to document the efficacy of sparsentan in actually reducing the rate of decline in GFR, there was this dissociation in DUPLEX between the antiproteinuric effect, lowering proteinuria successfully in a sustained fashion, and a statistically significant preservation in GFR. But thankfully the community rallied behind this finding, and I think it has stimulated the PARASOL initiative, which I think will represent an important gain for the entire nephrology community and especially those of us who are engaged in the care of patients with FSGS.

The disease has significant variability and therefore it's just unfeasible to use eGFR slope as an endpoint in the context of clinical trials. What that triggered was an analysis to find an endpoint that was feasible in the context of clinical trials that could be carried out in a reasonable time frame that would be acceptable to patients. And that analysis looked at changes in proteinuria. And the PARASOL initiative has documented a level of proteinuria achievable at 2 years that has a highly significant association with a reduction in the risk of progression to kidney failure. And this represents an important advance to our community because it really potentially opens the door to pharmaceutical companies that are interested in engaging in the space of FSGS because they now know that they have a realistic objective.

Just in summary, I think what we would want to emphasize to our listeners is the importance that FSGS, though it's a rare disease, it's a disease with high health burden, and it would be really important for practitioners to keep this in mind and to work hard at identifying the disease as early as they can because this offers the opportunity to introduce interventions that can lower proteinuria, which are the most important prognostic indicator of altering the trajectory of their disease. Unfortunately, currently, there are no approved therapies. Most of the therapies are selected based on non-strong clinical evidence, and there's a need for patients to participate in clinical trials to help us move the field forward. And finally, to emphasize that patients should articulate their life experience and that doctors should be receptive and recognize the importance of responding to that in when they manage patients with FSGS. Look beyond just the lab data, see the whole patient, and hopefully this will lead to the optimal outcomes for each one of them.

Ken, thanks so much for participating in this with me. Thanks to all of you for joining us today. We hope this discussion will be useful for you and your practice. Thank you very much.

**Dr. Lieberman:**

It's been a pleasure.

**Dr. Trachtman:**

You have been listening to CME on ReachMD. This activity is provided by Medtelligence. To receive your free CME credit or to download this activity, go to [reachmd.com/cme](https://reachmd.com/cme). Thank you again for listening.