Update of Focal segmental glomerulosclerosis (FSGS)

Dr. Elham Kabiri

Isfahan University of Medical Sciences

Object

- Introduction
- Pathophysiology
- Epidemiology
- Class selection
- Clinical Features
- Treatment

Introduction

FSGS is not a single disease but rather a diagnostic term for a clinical-pathologic syndrome that has multiple causes and pathogenic mechanisms.

The ubiquitous clinical feature of the syndrome is proteinuria, which may be nephrotic or non nephrotic.

pathologic feature is focal segmental glomerular consolidation or scarring, which may have several distinctive patterns

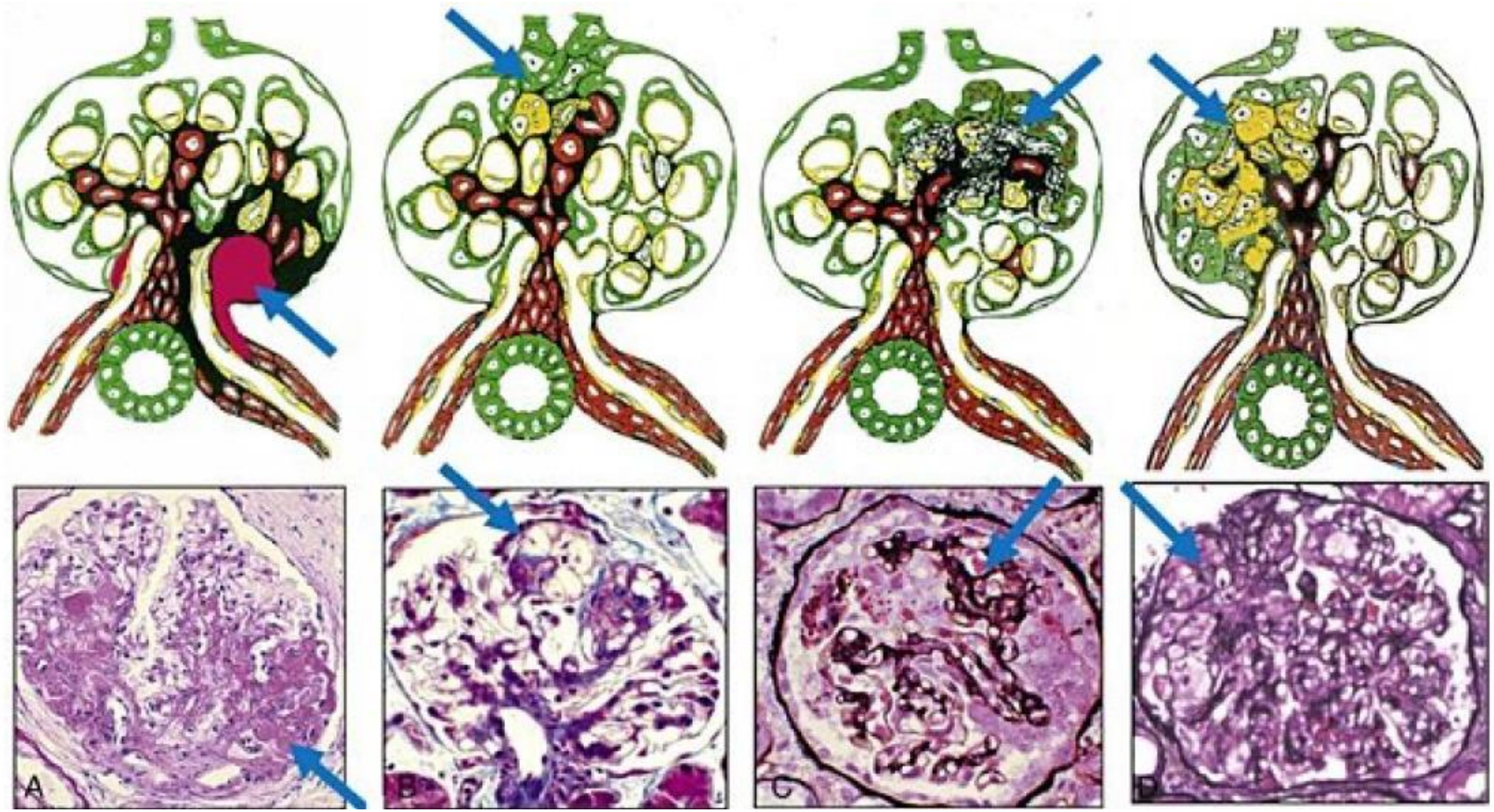
Brenner2020

Classification of Focal Segmental Glomerulosclerosis:

Which may have several distinctive patterns ,These patterns can be classified as :

- Collapsing FSGS
- Tip lesion FSGS
- Cellular FSGS
- Perihilar FSGS
- FSGS not otherwise specified (NOS)

Brenner 2020



Brenner 2020

Secondary FSGS

With human immunodeficiency virus disease
With intravenous drug abuse
With other drugs (e.g., pamidronate, interferon, anabolic steroids)
With identified genetic abnormalities (e.g., in podocin, alpha-actinin-4, TRPC6)
With glomerulomegaly:
- Morbid obesity
- Sickle cell disease
- Cyanotic congenital heart disease
- Hypoxic pulmonary disease

With reduced nephron numbers:
- Unilateral renal agenesis
- Oligomeganephronia
- Reflux-interstitial nephritis
- Postfocal cortical necrosis
- Postnephrectomy

Epidemiology

Over the past 2 decades, the incidence of FSGS has increased, whether expressed as an absolute number of patients or as a proportion of the total incident population of patients with end-stage kidney disease (ESKD).

Brenner2020

Pathology

Light Microscopy:

FSGS is characterized by focal and segmental glomerular sclerosis or consolidation.

The sclerosis may begin as segmental consolidation caused by insudation of plasma proteins causing hyalinosis, by accumulation of foam cells, by swelling of epithelial cells, and by collapse of capillaries resulting in obliteration of capillary lumens.

These events are accompanied by increased extracellular matrix material that accounts for the sclerosis component of the lesion.

Continue…..

The limited number of glomeruli in a kidney biopsy specimen may not include any of the segmentally sclerotic glomeruli that are present in the kidney.

In this case, focal tubulointerstitial injury or glomerular enlargement, which often accompanies FSGS, can be used as a surrogate marker.

For example, FSGS should be considered in kidney biopsy specimens of patients with nephrotic syndrome when there is relatively well-circumscribed focal tubular atrophy and interstitial fibrosis with slight chronic inflammation, even when there are no light microscopic glomerular lesions, no immune deposits, and no ultrastructural changes other than foot process effacement.

continue…..

- Focal segmental glomerular scarring is nonspecific. Many injurious processes can cause focal glomerular scarring and must be ruled out before making a diagnosis of FSGS.

For example:

FSGS, caused by :IgA nephropathy, lupus nephritis, or ANCA, can result in focal segmental glomerular scarring that is indistinguishable FSGS.

Findings by IF, electron microscopy, and serology, can reveal a glomerulo nephritic basis for focal glomerular scarring.

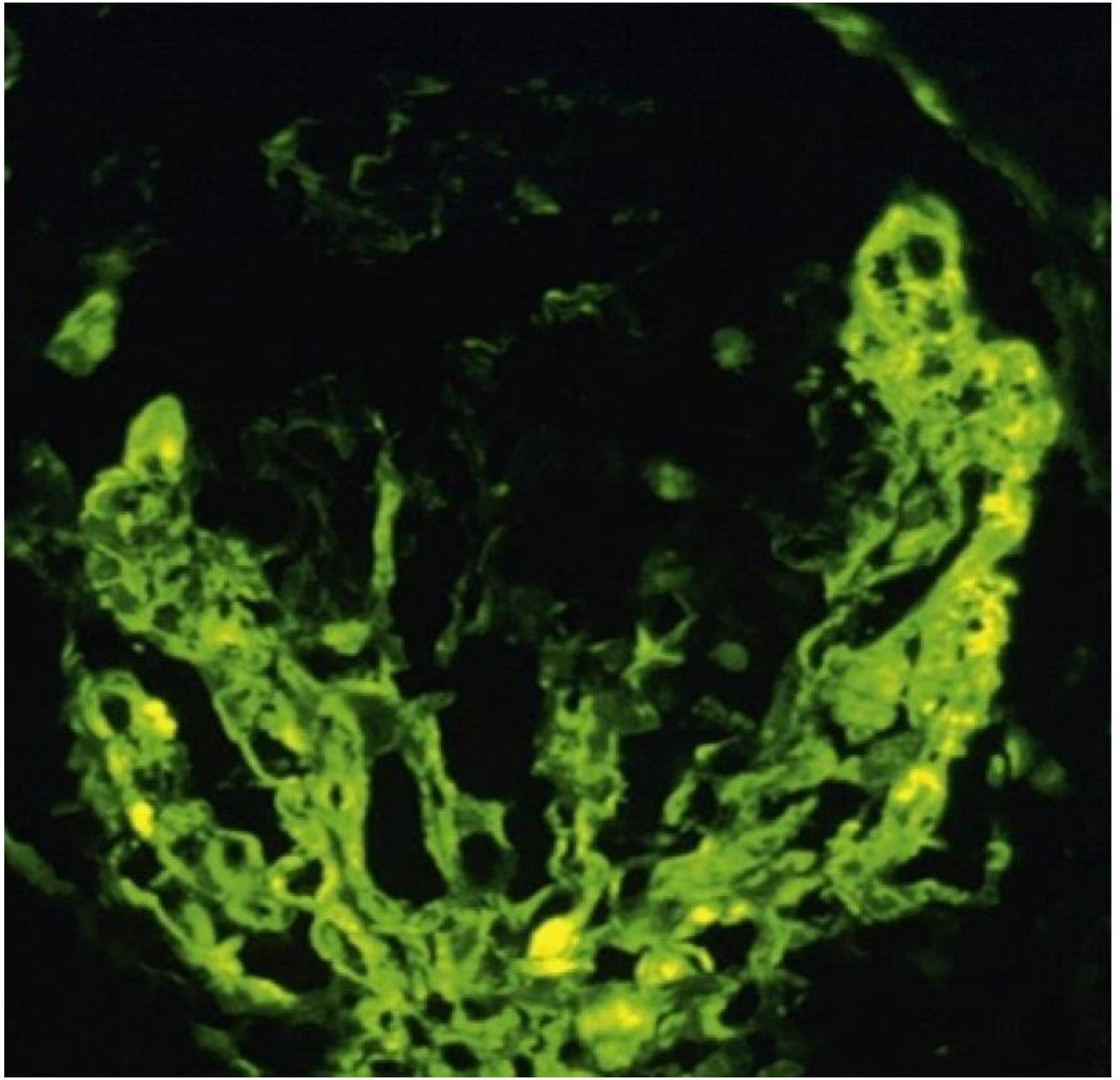
Immunofluorescence Microscopy

In all the histologic variants, nonsclerotic glomeruli and segments usually show no staining for immunoglobulins or complement.

Low-level mesangial C3 staining is less frequent, and low-level IgG and IgA staining are uncommon.

The presence of substantial staining of nonsclerotic glomeruli for immunoglobulins, especially if immune complex–type, electron-dense deposits are present, points toward the sclerotic phase of a focal immune complex glomerulonephritis rather than FSGS.

(Brenner 2020)



Electron Microscopy

- Electron microscopy plays an important role in the diagnosis of FSGS.
- Foot process effacement in FSGS affects sclerotic and nonsclerotic glomeruli and usually is more focal than in MCD.
- Foot process effacement is less extensive in some forms of secondary FSGS than in idiopathic FSGS.

Continue……

- When electron-dense material is present in sclerotic but not in non sclerotic glomerular segments, it should not be considered as evidence for immune complex– mediated glomerular disease.

- Conversely, well-defined mesangial or capillary wall electron-dense deposits in nonsclerotic segments indicate immune complex mediated glomerulonephritis with secondary scarring, which should be confirmed and further characterized by IF microscopy.

Pathogenesis

These include, but are not limited to,

- genes coding for podocin (NPHS2) nephrin (NPHS1)
- α-actinin-IV (ACTN4)
- transient receptor potential cation channel, subfamily C, member 6 (TRPC6)
- phospholipase Cε1 (PLCE1)

Clinical Features and Natural History

- Proteinuria is the hallmark feature of all forms of primary FSGS. The degree of proteinuria varies from nonnephrotic (1–2 g of protein/day) to over 10 g of protein/day, associated with all of the morbid features of nephrotic syndrome.
- Hematuria occurs in over 50% of FSGS patients .
- Gross hematuria is more commonly seen in FSGS than in MCD.
- Hypertension is a presenting feature in one-third of patients.

Children tend to have more proteinuria, whereas hypertension is more common in adults.

Brenner2020

Continue….

- Patients with collapsing FSGS have substantially more proteinuria, a lower serum albumin level, and a higher serum creatinine level than patients with perihilar FSGS.

- Pamidronate,and interferon also been reported to be associated with the development of collapsing FSGS.

Laboratory Findings

- Hypoproteinemia is common in patients with FSGS, with total serum protein reduced to varying extents.

- The serum albumin concentration may fall to below 2 g/dL,especially in patients with collapsing and glomerular tip variants of fsgs.

Continue…..

- Forms of nephrotic syndrome, levels of immunoglobulins are typically depressed
- levels of lipids are increased, especially the serum cholesterol level.
- Serum levels of complement components are generally in the normal range in FSGS.
- Circulating immune complexes have been detected in patients with FSGS
- Serologic testing for HIV infection should be obtained for patients with FSGS, especially those with the collapsing pattern.

Treatment

- Angiotensin Inhibitors:
- ACE inhibitors and angiotensin II receptor blockers (ARBs) have been evaluated in the treatment of FSGS.
- ACE inhibitors have been shown to decrease proteinuria and the rate of progression to ESKD in diabetic and nondiabetic kidney disease.

Brenner2020

Continue….

- Patients with sub nephrotic-range proteinuria have a generally good prognosis, and the initial therapy should be focused on blood pressure control, preferentially using maximal tolerated dosages of (RAAS) blockers.
- Glucocorticoids or immunosuppressive therapy should be targeted to patients with idiopathic FSGS and nephrotic syndrome.

Glucocorticoids

- As in adult patients with MCD, a longer course of therapy at higher doses of prednisone may be necessary to induce remission.

- Thus, in those series and in retrospective analyses that showed an increased remission rate, prednisone treatment was continued for 16 weeks to achieve remission. In adult patients, the median time for complete remission was 3 to 4 months.

Relapsing patients

- A portion of patients showing a positive response to corticosteroid treatment will experience relapse. Guidelines for the retreatment of relapsing patients are similar to those for treatment of patients with relapsing MCD.

- In patients whose remission prior to relapse was prolonged (>6 months, a repeat course of corticosteroid therapy may again induce a remission.

Brenner2020

Cyclophosphamide

- The International Study of Kidney Diseases in Children carefully examined the role of cyclophosphamide in the treatment of children with FSGS.

- Daily oral cyclophosphamide (2.5 mg/kg) was administered in addition to prednisone (40 mg/m2 every other day) for 12 months, and results were compared with those for prednisone alone. The addition of cyclophosphamide had no effect on the change in proteinuria or the likelihood of achieving complete resolution of proteinuria.

cyclophosphamide

- In summary, the limited, currently available data do not support the use of cyclophosphamide in patients with FSGS.

Cyclosporine

- FSGS that is resistant to prednisone may be induced into remission by cyclosporine.

- The effectiveness of cyclosporine in inducing remission of proteinuria in patients with FSGS has been demonstrated in two randomized controlled trials.

Cyclosporine

- (5 mg/kg/day for adults, 6 mg/kg/day for children) for 6 months, with the drug then tapered off by 25% every 2 months.

- Unfortunately, relapses occurred in 69% of patients after the withdrawal of cyclosporine.

How long should patients be treated with cyclosporine?

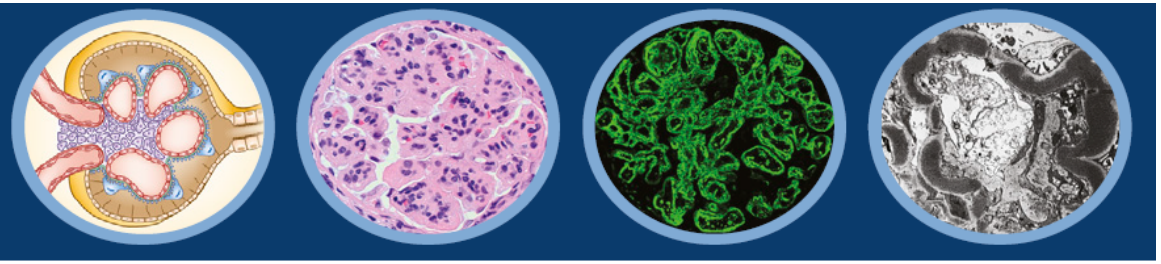
- when patients remained in remission for over 12 months, cyclosporine was slowly tapered and eventually removed, without subsequent relapse.
- long-term treatment with cyclosporine was associated with increases in tubular atrophy and interstitial fibrosis, the degree of which was positively correlated with:
- The initial serum creatinine level
- The number of segmental scars on initial biopsy specimens
- A cyclosporine dose of more than 5.5 mg/kg/day

Mycophenolate Mofetil

- The randomized controlled FSGS Clinical Trial, discussed in the cyclosporine section, showed no significant difference in outcomes when comparing cyclosporine with oral pulse dexamethasone and MMF.

Brenner2020

Glomerular Disease



Focal Segmental Glomerulosclerosis

Avi Z. Rosenberg[*†] and Jeffrey B. Kopp*[*†]

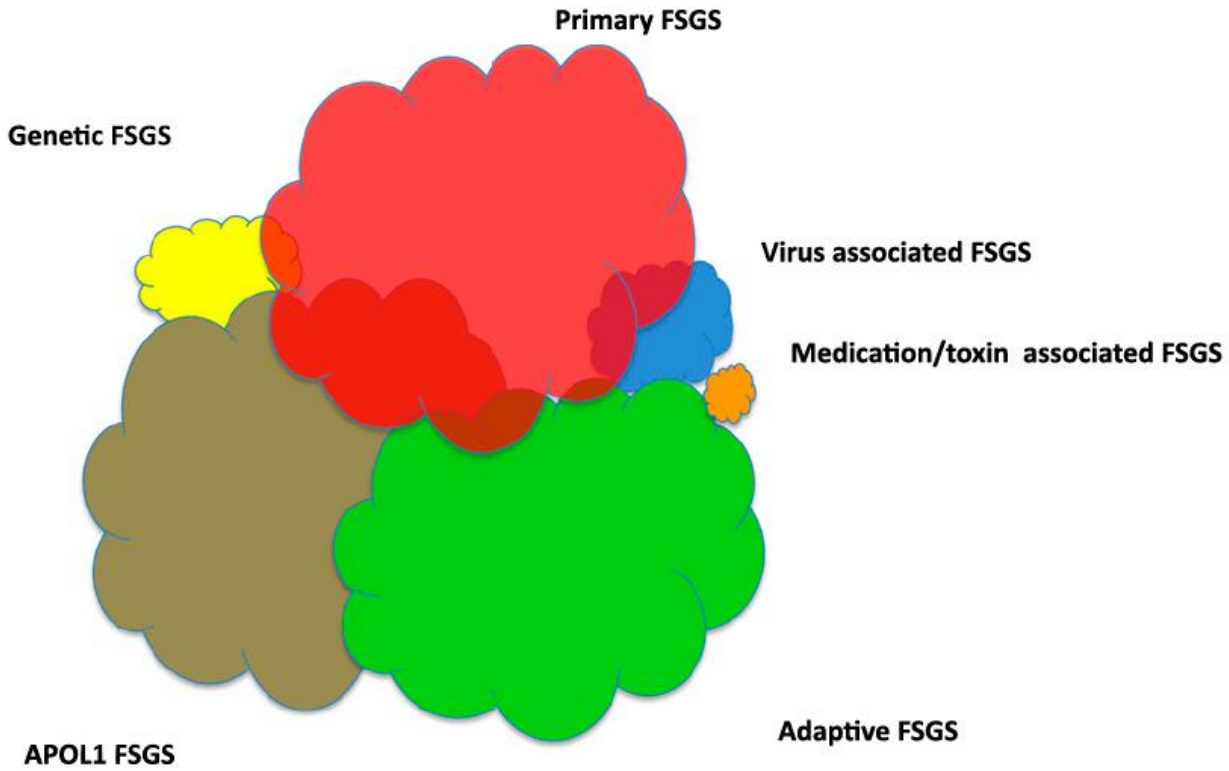
Abstract

Focal segmental glomerulosclerosis (FSGS) is a leading cause of kidney disease worldwide. The presumed etiology of primary FSGS is a plasma factor with responsiveness to immunosuppressive therapy and a risk of recurrence after kidney transplant–important disease characteristics. In contrast, adaptive FSGS is associated with excessive nephron workload due to increased body size, reduced nephron capacity, or single glomerular hyperfiltration associated with certain diseases. Additional etiologies are now recognized as drivers of FSGS: high-penetrance genetic FSGS due to mutations in one of nearly 40 genes, virus-associated FSGS, and medication-associated FSGS. Emerging data support the identification of a sixth category: APOL1 risk allele–associated FSGS in individuals with sub-Saharan ancestry. The classification of a particular patient with FSGS relies on integration of findings from clinical history, laboratory testing, kidney biopsy, and in some patients, genetic testing. The kidney biopsy can be helpful, with clues provided by features on light microscopy (*e.g.*, glomerular size, histologic variant of FSGS, microcystic tubular changes, and tubular hypertrophy), immunofluorescence (*e.g.*, to rule out other primary glomerulopathies), and electron microscopy (*e.g.*, extent of podocyte foot process effacement, podocyte microvillous transformation, and tubuloreticular inclusions). A complete assessment of renal histology is important for establishing the parenchymal setting of segmental glomerulosclerosis, distinguishing FSGS

*Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland; and †Kidney Disease Section, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney

Table 1. Data relevant in evaluating a patient with the histologic diagnosis of FSGS

Relevant Clinical History	Laboratory Data	Renal Biopsy Findings
Family history of kidney disease	Serum albumin before therapy	FSGS histologic variant
Birth weight, gestational age at birth, congenital cyanotic heart disease	Urine protein-to-creatinine ratio	Glomerular size (glomerulomegaly)
Sickle cell disease	Change in urine protein-to-creatinine ratio after maximal renin-angiotensin-aldosterone therapy and dietary sodium restriction	Electron microscopy: extent of foot process effacement; podocyte mircrovillus transformation
History consistent with reflux nephropathy or reduced renal mass	Change in urine protein-to-creatinine ratio after immunosuppressive therapy	Electron microscopy: tubuloreticular inclusions in glomerular endothelial cells (IFN effect)
Peak and present body mass index: obesity, extreme muscular development		
Viral infection: HIV, cytomegalovirus		
Medication, past or present: IFN, lithium, bisphosphonate, androgen abuse, chronic use of nephrotoxic drugs		



Adaptive FSGS

- Arises after a period of nephron-level glomerular hyperfiltration and glomerular hypertension after pathophysiology as identified

Adaptive FSGS arises from the processes described above involving increased single-nephron GFR (often with intraglomerular hypertension), leading to progressive cycles of glomerular hypertrophy; podocyte hypertrophy, stress, and depletion.

Table 5. Treatment recommendations for adults with FSGS

Setting	Therapy	Comment
Nephrotic forms of primary FSGS,[a] APOL1 FSGS, certain steroid-sensitive genetic forms of FSGS	Prednisone, initially daily or alternate days[a]	Alternate for patients at high risk for steroid complications: calcineurin inhibitors[a]
Steroid-resistant FSGS with nephrotic syndrome[a]	Calcineurin inhibitor[a] (cyclosporin and possibly, tacrolimus)	
Refractory FSGS with nephrotic syndrome[a]	Mycophenolate mofetil plus high-dose dexamethasone[a]	
All forms of FSGS with subnephrotic proteinuria	ACE inhibitor and angiotensin receptor blocker; dietary sodium restriction	Thiazide diuretic may potentiate the antiproteinuric of RAAS antagonism

KI REPORTS
KIReports.org
REVIEW

Novel Treatment Paradigms: Focal Segmental Glomerulosclerosis

Marina de Cos[1], Kristin Meliambro[1] and Kirk N. Campbell[1]

[1]Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of injury defined by the presence of sclerosis in some (segmental) of certain glomeruli (focal). On electron microscopy, it is characterized by a variable degree of podocyte foot process effacement and gaps in the coverage of the glomerular basement membrane. The pattern of injury occurs when podocytes, highly differentiated cells with limited regenerative capacity, are reduced in number. The heterogeneity in underlying causes of podocyte loss results in equally variable clinical phenotypes. Recent work acknowledging advances in defining the genetic and immunologic basis of disease has redefined the classification of FSGS. Unprecedented clinical trial activity and efficacy of repurposed agents presents hope for improved therapeutic options. This minireview summarizes recent advances with a focus on novel treatment paradigms in FSGS.

Kidney Int Rep (2023) **8**, 30–35; https://doi.org/10.1016/j.ekir.2022.10.004
KEYWORDS: FSGS; Glomerular Disease; Treatment

Current Treatment Guidelines

As a pattern of injury and not a disease, the histologic finding of FSGS in a kidney biopsy is considered the beginning of a process to identify a specific and hopefully treatable underlying cause.

microscopic changes distinguish the subtypes, but some unique clinical and pathologic features have been identified. Patients with primary FSGS typically have abrupt-onset marked proteinuria and overt nephrotic syndrome with diffuse podocyte foot process effacement

Current Treatment Guidelines

- Improving Global Outcomes practice guidelines for the treatment of FSGS recommend supportive treatment for proteinuria with the use of:
- (RAAS) blockade, optimal blood pressure control, and dietary salt restriction.
- The use of sodium glucose cotransporter 2 inhibitor therapy has emerged as an attractive supportive agent class used in conjunction with RAAS inhibitors for across the spectrum of proteinuric kidney disease.

- Prespecific analyses of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease study have shown protective benefits of dapagliflozin from estimated glomerular filtration rate decline in IgA nephropathy and FSGS

Kidney International Reports (2023)

Finerenone:

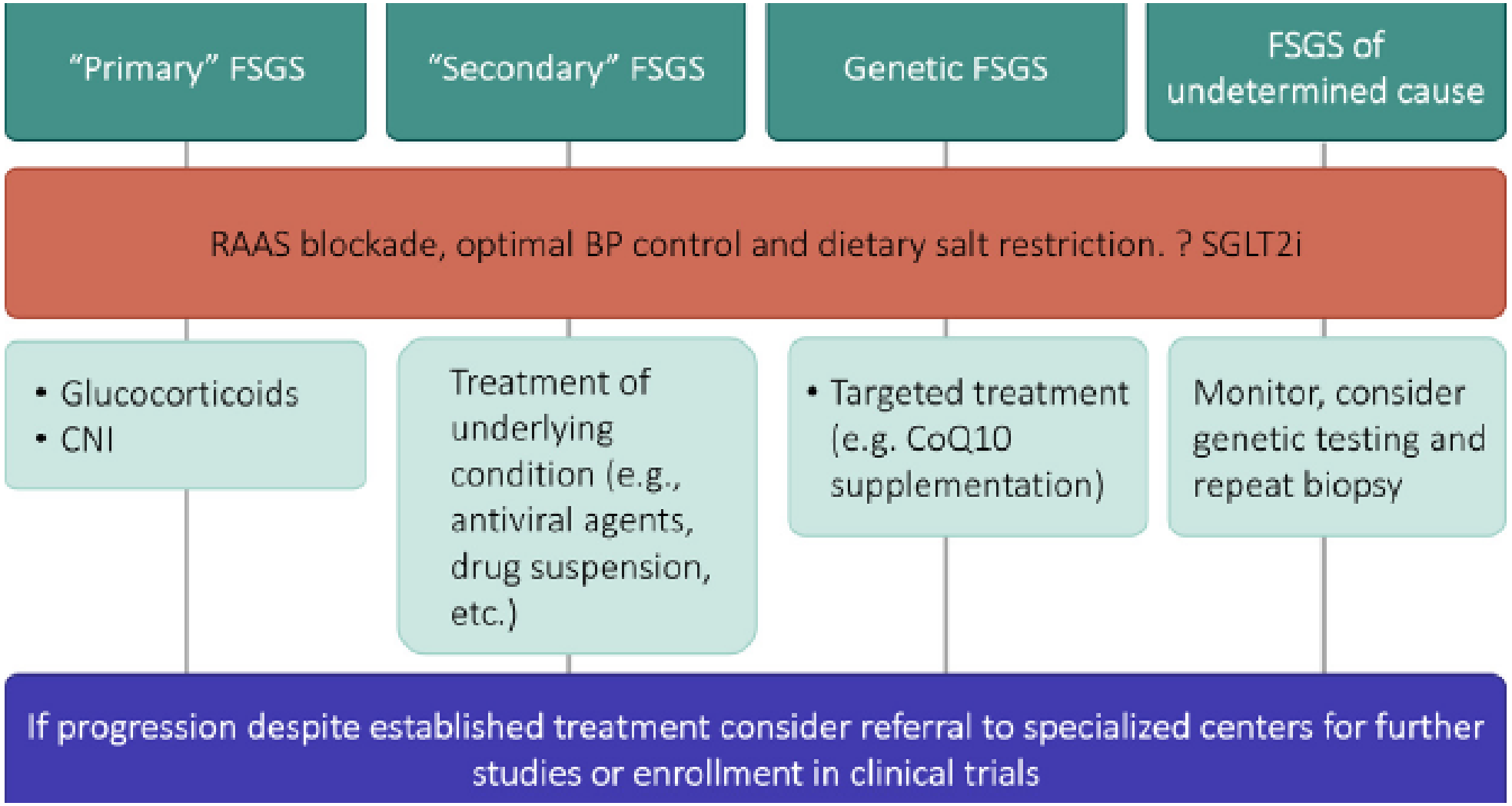
- An additional drug class likely to be considered for supportive therapy is nonsteroidal mineralocorticoid receptor antagonists.

- These agents have anti-inflammatory and antifibrotic properties with finerenone, a nonsteroidal mineralocorticoid receptor antagonist now approved by the US Food and Drug Administration for diabetic kidney disease.

Alternative therapies:

- Mycophenolate mofetil
- Adrenocorticotropic hormone
- Rituximab
- Extracorporeal therapies such as plasma exchange, Immunoadsorption, and low-density lipoprotein apheresis may have a role as adjunctive therapy for patients who fail to respond to steroids and other immunosuppressive agents.

Kidney International Reports (2023)


"Primary" FSGS
"Secondary" FSGS
Genetic FSGS
FSGS of undetermined cause
RAAS blockade, optimal BP control and dietary salt restriction. ? SGLT2i
• Glucocorticoids
• CNI
Treatment of underlying condition (e.g., antiviral agents, drug suspension, etc.)
• Targeted treatment (e.g. CoQ10 supplementation)
Monitor, consider genetic testing and repeat biopsy
If progression despite established treatment consider referral to specialized centers for further studies or enrollment in clinical trials

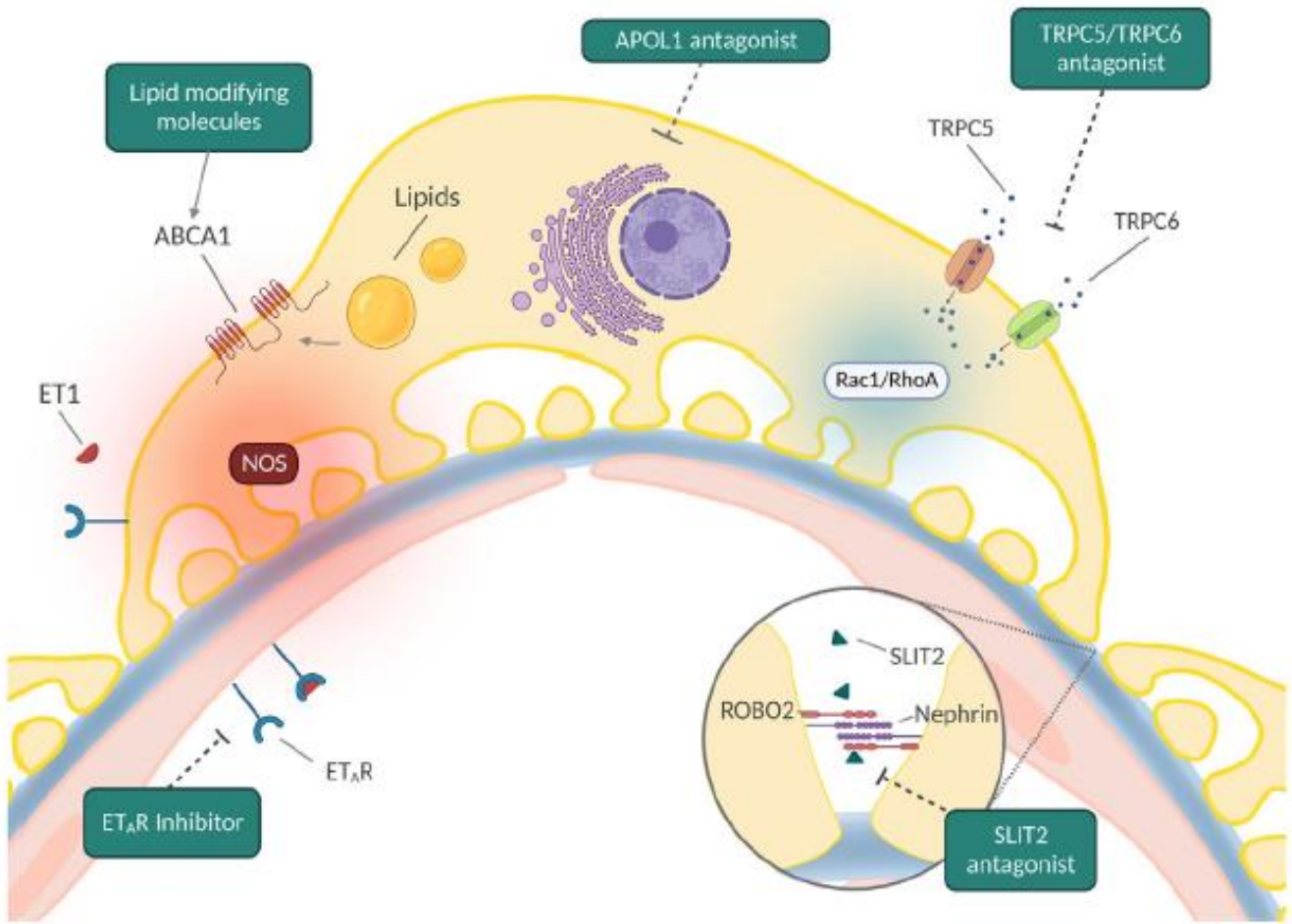
Immunosuppression (primary FSGS):	Causative directed therapies:	Podocyte specific therapies:	Antifibrotic/ hemodynamic effect:
• Glucocorticoids • CNI • Anti-CD20 antibody • ACTH • MMF • Anti-CD20 antibody • Anti-CD40 antibody • Anti-C5 antibody • B-7 costimulatory inhibitor • mTOR inhibitor • Chlorambucil • Plasma exchange	• Antiviral agents • Obesity treatment • CoQ10 supplementation • APOL1 antagonist	• TRPC5/6 channel inhibitor • SLIT2 antagonist • Lipid modifying drug	• RAS inhibitors • SGLT2 inhibitor • Endothelin antagonist • CCR2 inhibitor • Janus Kinase-STAT inhibitor • Anti-TGF-ß antibody • p38 MAPK inhibitor • Anti-human TNF-α antibody • Pirfenidone • Nrf2 activator/NF-κB inhibitor

Defining Treatment Success

There has been a lack of consensus in defining remission end points in FSGS.

- in glomerular disease clinical management and trials, a complete remission has been a reduction of proteinuria to <0.3 g/d with a stable serum creatinine and serum albumin >3.5 g/dl

- a partial remission is a reduction of proteinuria to 0.3 to 3.5 g/d and a decrease >50% from baseline.

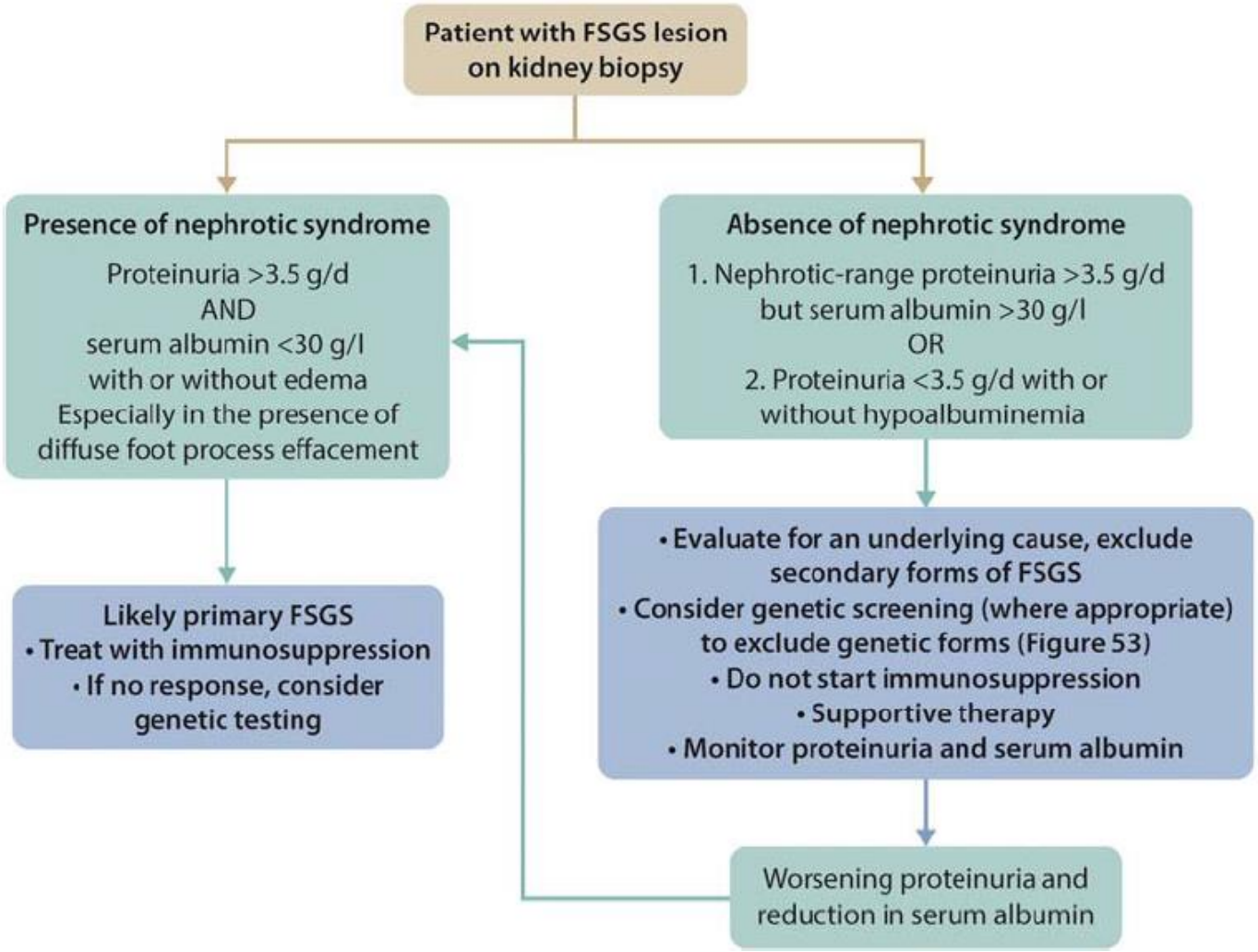


Kidney International Reports (2023)

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

Complete remission
Reduction of proteinuria to <0.3 g/d or urine PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/L)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or urine PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission
Corticosteroid-resistant FSGS
Persistence of proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for at least 16 weeks

Corticosteroid-dependent FSGS
Relapse occurring during or within 2 weeks of completing corticosteroid therapy
CNI-resistant FSGS
Persistence of proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/ml or tacrolimus treatment at trough levels of 5–10 ng/ml for >6 months
CNI-dependent FSGS
Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months


Patient with FSGS lesion on kidney biopsy
Presence of nephrotic syndrome
Proteinuria >3.5 g/d
AND
serum albumin <30 g/l
with or without edema
Especially in the presence of diffuse foot process effacement
Absence of nephrotic syndrome
1. Nephrotic-range proteinuria >3.5 g/d but serum albumin >30 g/l
OR
2. Proteinuria <3.5 g/d with or without hypoalbuminemia
Likely primary FSGS
• Treat with immunosuppression
• If no response, consider genetic testing
• Evaluate for an underlying cause, exclude secondary forms of FSGS
• Consider genetic screening (where appropriate) to exclude genetic forms (Figure 53)
• Do not start immunosuppression
• Supportive therapy
• Monitor proteinuria and serum albumin
Worsening proteinuria and reduction in serum albumin

KDigo2021

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic

Considerations for genetic testing in adults with FSGS
• When there is a strong family history and/or clinical features suggestive of a syndromal disease • Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining the risk of recurrent disease in kidney transplantation • Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants • Aiding in prenatal diagnosis

Treatment	Dose and duration
Glucocorticoids	**Starting dose:** • High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)
	High-dose glucocorticoid treatment duration: • Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier • Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment • It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects
	Glucocorticoid tapering: • If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If partial remission is achieved within 8 to 12 weeks of high-dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If the patient proves to be steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

Recommendation 6.3.1.1. For adults with corticosteroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for at least six months rather than continuing with corticosteroid monotherapy or not treating *(1C)*.

KDIGO2021

Therapeutic trials in adult FSGS: lessons learned and the road forward

An S. De Vriese, Jack F. Wetzels, Richard J. Glassock, Sanjeev Sethi and Fernando C. Fervenza

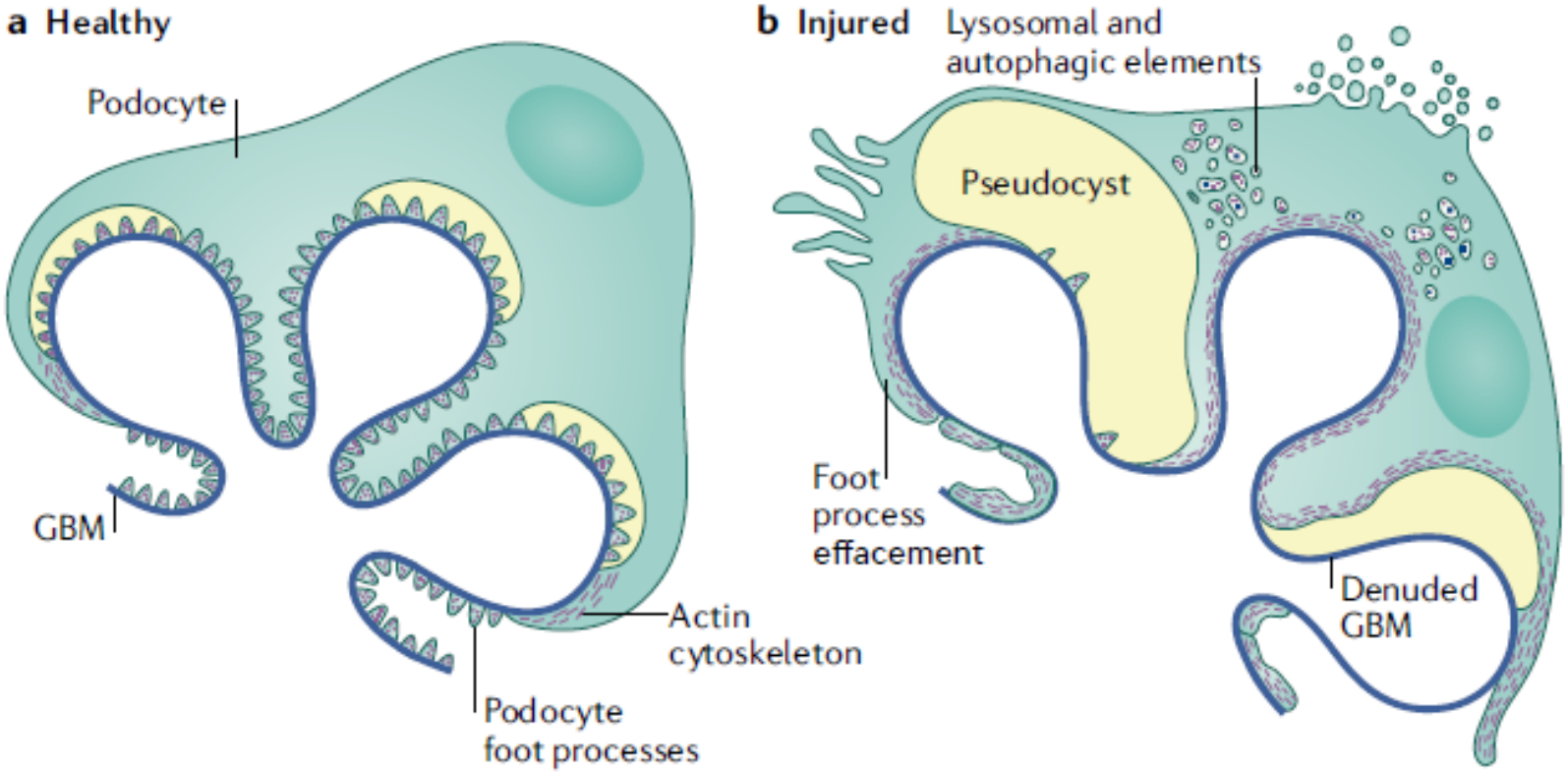
Abstract | Focal segmental glomerulosclerosis (FSGS) is not a specific disease entity but a lesion that primarily targets the podocyte. In a broad sense, the causes of the lesion can be divided into those triggered by a presumed circulating permeability factor, those that occur secondary to a process that might originate outside the kidneys, those caused by a genetic mutation in a podocyte or glomerular basement membrane protein, and those that arise through an as yet unidentifiable process, seemingly unrelated to a circulating permeability factor. A careful attempt to correctly stratify patients with FSGS based on their clinical presentation and pathological findings on kidney biopsy is essential for sound treatment decisions in individual patients. However, it is also essential for the rational design of therapeutic trials in FSGS. Greater recognition of the pathophysiology underlying podocyte stress and damage in FSGS will increase the likelihood that the cause of an FSGS lesion is properly identified and enable stratification of patients in future interventional trials. Such efforts will facilitate the identification of effective therapeutic agents.

FSGS categories

Presumed permeability factor-related FSGS. The form of FSGS traditionally termed 'primary FSGS' is presumed to be caused by a circulating permeability factor (or factors) that trigger(s) sudden and generalized injury to podocytes[5]. Given the causative role of the presumed permeability factor, we hereafter refer to this form of FSGS as ppfFSGS. Notably, despite intensive efforts, a definitive causative factor has not been conclusively identified, although several candidate molecules have been proposed, including cardiotrophin-like cytokine factor 1 (CLCF-1), soluble urokinase-type plasminogen activator receptor (suPAR), anti-CD40 antibody, apolipoprotein A1 and a soluble form of calcium/calmodulin-serine protein kinase (CASK)[6,7]. A number of in vitro assays have indirectly demonstrated the presence of a circulating permeability factor in plasma from patients with active ppfFSGS, although these assays have not been validated and their use is currently limited to the experimental setting[8,9]. This form of FSGS is most commonly

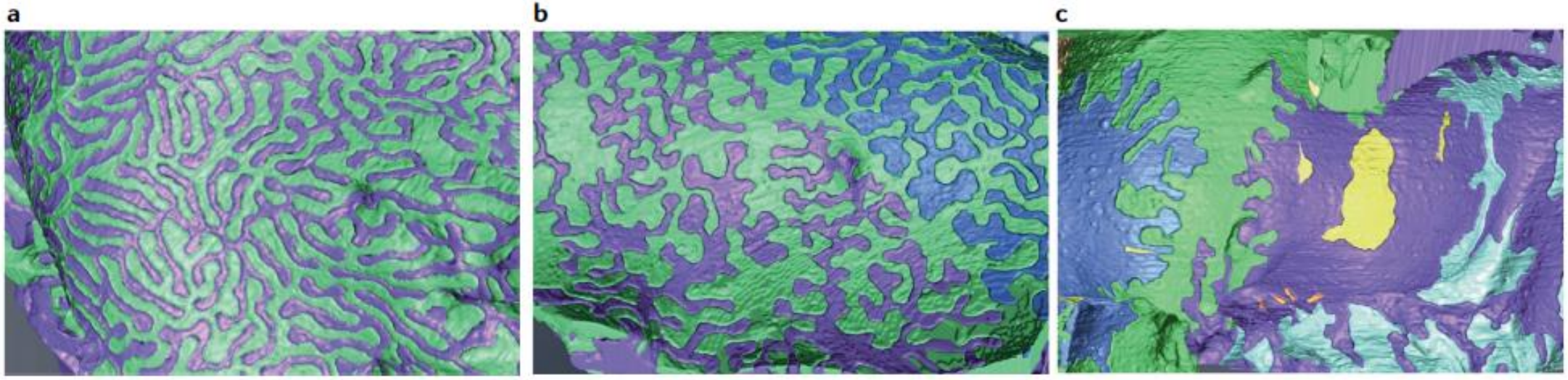
An S. De Vriese,Nature ReviewS ,2021

Podocyte structural changes in FSGS.



Nature2021

Foot process effacement in FSGS.



Axiom	Presumed permeability factor-related FSGS (ppfFSGS)	Maladaptive FSGS[a]	Genetic FSGS	FSGS of undetermined cause
Onset of disease	Sudden	Insidious; progression occurs over many years	Dependent on the type of mutation and its interaction with other genetic and environmental factors; often insidious in adults	Insidious; progression occurs over many years; often a history of hypertension
Extent of proteinuria	Typically NS level	Variable, can be high; NS is typically absent	Variable; NS is common in children but rare in adults	Variable, can be high; NS is typically absent
Findings on LM (beyond the FSGS lesion)	Generally, no other damage unless late in disease course	Often FGGS; varying degrees of chronic damage, perihilar lesions or glomerulomegaly may be present but are not diagnostic in themselves	Varying degrees of chronic damage	Often FGGS; varying degrees of chronic damage
Extent of foot process effacement on EM	Generalized (>80%) in non-sclerotic glomeruli	Mild and segmental	Either segmental or diffuse. GBM alterations may be prominent in type IV collagenopathies	Mild and segmental
Recurrence rate after kidney transplantation	High (>70%).	Low	Nil, although proteinuria may develop due to recipient versus donor immune response	Low
Response to RAS inhibition (or sparsentan)	Poor	Excellent	May be good, but has not been rigorously tested	Good
Glucocorticoids and CNIs	May induce remission	Ineffective and potentially harmful	Ineffective. Response to CNIs is anecdotal	Ineffective
Genetic tests and family history	Unrevealing	Unrevealing	May reveal mutations in podocyte or GBM proteins. Negative tests do not exclude a genetic cause	Unrevealing
Underlying cause	No evidence of a causative factor (e.g. cancer, auto-immunity, viral infection, toxins)	Evidence of a causative factor or process (e.g. unilateral renal dysplasia or agenesis, sickle cell disease, reflux nephropathy, obesity, healing phase of proliferative glomerulonephritis) is present	Mutations in genes that encode proteins involved in glomerular filtration barrier structure and function	Cannot be established, despite comprehensive evaluation

Published in final edited form as:
Adv Chronic Kidney Dis. 2015 March ; 22(2): e1–e6. doi:10.1053/j.ackd.2014.10.001.

NOVEL THERAPIES FOR FSGS: PRECLINICAL AND CLINICAL STUDIES

Laura Malaga-Dieguez, MD, PhD[1], **Diana Bouhassira**[1], **Debbie Gipson, MD**[2], **Howard Trachtman, MD**[1,*]

[1]Department of Pediatrics, Division of Nephrology, C S Mott Children's Hospital, New York NY 10016

[2]NYU Langone Medical Center, New York NY 10016

Abstract

Focal segmental glomerulosclerosis (FSGS) is a rare but important cause of end stage kidney disease in children and adults. Current therapy, consisting of corticosteroids and calcineurin inhibitors, fails to achieve a sustained remission in the majority of patients. Therefore there is a pressing need to develop new treatments for this glomerulopathy. Traditional approaches have focused on agents that modulate the immune system. In this review, we summarize pre-clinical and clinical data with newer agents that may ameliorate FSGS. We focus on drugs that inhibit immune injury or inflammation such as abatacept, rituximab, adalimumab, and stem cells. The potential of agents that block the glomerular action of circulating permeability factors as soluble urokinase receptor is reviewed. Finally, because fibrosis represents the final common pathway of

A. Rituximab

- Rituximab, a monoclonal antibody against CD20 on B-cells, was first demonstrated to induce remission of proteinuria in a single patient with a transplant-related lymphoma and recurrent FSGS after kidney transplantation.
- Subsequent reports have evaluated the effect of rituximab in case series of patients with primary FSGS. Overall, the response has been low, in the range of 20–30%, suggesting that this therapy may have a role in select patients with primary FSGS.

Rosiglitazone

- Rosiglitazone and pioglitazone are oral peroxisome proliferator-activated receptor-γ agonists that increase insulin sensitivity. They are used as hypoglycemic agents in patients with type 2 diabetes mellitus and have been shown to have antifibrotic effects in the kidney.

- Trial showed that rosiglitazone was well tolerated in children with drug-resistant FSGS and after 16 months of follow up, 71% of participants had stable GFR and reduced proteinuria.

- Future testing of peroxisome proliferator-activated receptor-γ agonists may be warranted.

PMC 2020 August 06.

Recurrence of focal segmental glomerular sclerosis (FSGS) after renal transplantation

Claudio Ponticelli

Division of Nephrology, Istituto Scientifico Humanitas, via Manzoni 56, 20089 Rozzano, Milano, Italy

Correspondence and offprint requests to: Claudio Ponticelli; E-mail: claudio.ponticelli@fastwebnet.it

Focal segmental glomerular sclerosis (FSGS) is a pathological term to indicate glomerular lesions associated with distinctive clinical features. In most cases, FSGS is primary in nature and is called idiopathic. Idiopathic FSGS is often associated with a nephrotic syndrome (NS) and may affect both children and adults. While the prognosis of FSGS is relatively good for patients with subnephrotic proteinuria, most patients with persisting proteinuria progress to end stage renal disease (ESRD) in spite of glucocorticoid or immunosuppressive treatment. For most of these patients, renal transplantation should be considered as the treatment of choice. However, in FSGS, the success of renal transplantation may be impaired by the frequent risk of recurrence of the disease on the allograft and by the poor graft survival rate in patients with recurrence.

ported that five of 13 children (38%) with inherited FSGS (nine with homozygous and four with heterozygous mutations of podocin) showed recurrence of proteinuria after renal transplantation, a rate of recurrence similar to that observed in FSGS children without mutations (12 of 27 or 44%). [14]. There are conflicting results with living donation. Baum *et al.* [15] reviewed the data of the North American Pediatric Renal Transplant Cooperative Study and found that the results of living transplants in children with FSGS were worse than in children without FSGS, the graft survival being similar to that observed in cadaveric renal transplant recipients without FSGS. Abbott *et al.* [11] reviewed the USRDS database and confirmed a higher risk of recurrence in living transplant recipients (18.7%) than in deceased donor transplant recipients (7.8%); however,

Table 1. Factors influencing the risk of recurrence of FSGS

Factors associated with increased risk of recurrence	Factors associated with low risk of recurrence
Second transplant after loss from recurrence	Familial FSGS
Childhood	Sporadic form with podocin mutation
Rapid progression to uraemia	Slow progression to uraemia
Mesangial proliferation in native kidneys	Non-nephronic proteinuria in the original disease
Living donation	
White race	
Elderly donor	

Istituto Scientifico Humanitas,NDT2010

Recurrence of FSGS

- Preemptive plasmapheresis or immunoadsorption in preventing recurrence of FSGS after transplantation. Their use is advisable particularly in patients receiving the kidney from a living donor and in those who lost a previous transplant from recurrence..

- Patients who have FSGS as their original disease should be treated as soon as possible with an intensive course of plasmapheresis (an exchange a day for 3 days, then two to three exchanges per week for the first 2 weeks, followed by one to two exchanges per week, using 5% albumin as the replacement fluid).

Trachtman *et al. BMC Nephrology* 2011, **12**:8
http://www.biomedcentral.com/1471-2369/12/8

BMC Nephrology

STUDY PROTOCOL Open Access

Novel therapies for resistant focal segmental glomerulosclerosis (FONT) phase II clinical trial: study design

Howard Trachtman[1*], Suzanne Vento[1], Debbie Gipson[2], Larysa Wickman[2], Jennifer Gassman[3], Melanie Joy[4], Virginia Savin[5], Michael Somers[6], Maury Pinsk[7], Tom Greene[8]

Abstract

Background: The lack of adequate randomized clinical trials (RCT) has hindered identification of new therapies that are safe and effective for patients with primary focal segmental glomerulosclerosis (FSGS), especially in patients who fail to respond to corticosteroids and immunosuppressive therapies. Recent basic science advances have led to development of alternative treatments that specifically target aberrant pathways of fibrosis which are relevant to disease progression in FSGS. There is a need for a flexible Phase II study design which will test such novel antifibrotic strategies in order to identify agents suitable for phase III testing.

Methods/Design: The Novel Therapies for Resistant Focal Segmental Glomerulosclerosis (FONT) project is a multicenter Phase I/II RCT designed to investigate the potential efficacy of novel therapies for resistant FSGS. Adalimumab and galactose will be evaluated against conservative therapy consisting of the combination of lisinopril, losartan and atorvastatin. The sample size is defined to assure that if one of the treatments has a superior response rate compared to that of the other treatments, it will be selected with high probability for further

Adalimumab

- TNF-a antibody: The therapeutic dose of adalimumab will be 24 mg/m2 (maximum dose: 40 mg) every other week as a subcutaneous injection for the entire treatment period.

- Although the pharmacokinetics (PK) data from the FONT Phase I Study indicated enhanced clearance of adalimumab in patients with FSGS and nephrotic-range proteinuria, the dose will not be increased above the standard amount in,order to minimize the risk of adverse events].

(TNF-a)

- (TNF-a) is an inflammatory cytokine produced by a wide range of cells including macrophages and renal tubular epithelial cells.

➢Several mechanisms for TNF-a-induced proteinuria in FSGS: recruitment of leukocytes to the site of glomerular injury,

➢ induction of cytokines and growth factors

➢generation of oxygen radicals with increased glomerular endothelial cell permeability

➢Cytotoxicity

➢ induction of apoptosis

BMC Nephrology 2011,

Conclusions

- A correct differential diagnosis between primary FSGS, secondary (maladaptive, viral or toxic) and genetic FSGS in adults requires a clinico- pathological approach.

Future work should aim to identify biomarkers that will more precisely reflect the underlying pathophysiological processes.


THANK
YOU