Focal Segmental Glomerulosclerosis: Primary vs. Secondary Disorders

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Focal Segmental Glomerulosclerosis: Primary vs. Secondary Disorders

Learning Objectives

By the end of this module, you will be able to:

1. **Define** FSGS and its classification systems
2. **Distinguish** primary FSGS from secondary forms
3. **Identify** genetic variants associated with familial FSGS
4. **Apply** risk-based treatment approaches for steroid-responsive vs. steroid-resistant disease
5. **Recognize** diagnostic pitfalls and appropriate workup algorithms

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Definition and Core Concepts

Focal Segmental Glomerulosclerosis (FSGS): - Pathological pattern characterized by sclerosis (scarring) of **portions of glomeruli** (segmental) that are **present in some glomeruli but not others** (focal) - One of the most common causes of nephrotic syndrome in adults - Highly variable clinical course: some patients remit spontaneously, others progress rapidly to ESRD

Key Point: FSGS is a **pathologic pattern**, not a disease etiology. The same histologic picture can result from widely different causes, each requiring different treatment approaches.

Classification of FSGS: Columbia Classification

Modern FSGS classification based on predominant lesion pattern identifies different prognoses and treatment responses:

Variant	Histologic Feature	Prevalence	Steroid Response	Prognosis
Not Otherwise Specified (NOS)	No defining features	40-45%	50-60% response	Intermediate

Variant	Histologic Feature	Prevalence	Steroid Response	Prognosis
Perihilar (PHFS)	Lesions at hilar region	15-20%	Better response	More favorable
Cellular (CFSGS)	Endocapillary hypercellu-larity	10-15%	Good response	Favorable
Tip Lesion	At tubular pole of glomerulus	10-15%	Excellent response	Most favorable
Collapsing (ColFSGS)	Glomerular capillary collapse	5-10%	Poor response	Worst prognosis

Clinical Pearl: Collapsing FSGS, particularly in African Americans, shows minimal response to steroid therapy and rapidly progresses to ESRD.

Primary vs. Secondary FSGS: Critical Distinction

Primary (Idiopathic) FSGS

Definition: FSGS occurring without identifiable external etiology

Clinical Characteristics: - Nephrotic syndrome with full syndrome features - Usually presents with proteinuria 5-10+ g/day - Variable GFR decline - Normal serum albumin despite significant proteinuria (sometimes)

Genetic Basis: - Multiple gene mutations identified in 10-15% of primary FSGS - Suggests inherent glomerular dysfunction - May present as familial disease

Treatment Response: - 40-50% respond to corticosteroid monotherapy - Remaining 50-60% are steroid-resistant and require alternative agents

Secondary FSGS

Definition: FSGS resulting from identifiable stress or toxin injuring podocytes

Key Principle: Secondary FSGS typically does NOT respond to immunosuppression because the injurious process is not immune-mediated.

Causes of Secondary FSGS: Complete Classification

Viral Infections

HIV-Associated Nephropathy (HIVAN) **Epidemiology:** - Predominantly affects individuals of African descent - Collapsing variant most common - Often presents with nephrotic syndrome and profound proteinuria (>10 g/day)

Pathophysiology: - Direct infection of glomerular epithelial cells - Viral replication within podocytes - Triggers podocyte apoptosis and death

Management: - Antiretroviral therapy (HAART) is FIRST-line and often only necessary therapy - ACE inhibitors/ARBs for proteinuria reduction - Corticosteroids may provide temporary benefit but not curative - Most patients stabilize or improve with viral suppression alone

Prognosis: With effective antiretroviral therapy, many patients achieve remission without additional immunosuppression

Other Viral Causes

- Parvovirus B19
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Hepatitis B and C (rare)

Drug and Toxin-Induced FSGS

Heroin Nephropathy **Historical Significance:** - Common cause of FSGS in IV drug users - May actually relate to adulterants or contaminants rather than heroin itself

Management: - Discontinuation of heroin use - Supportive care and rehabilitation - Immunosuppression generally ineffective

Outcome: Variable; some patients stabilize after drug cessation, others progress despite abstinence

Other Drug/Toxin Causes

- Anabolic steroids
- Pamidronate/bisphosphonates
- Lithium
- Interferon
- Sirolimus/mTOR inhibitors
- NSAIDs (rare)
- Mercury exposure

Management Principle: Remove offending agent; immunosuppression generally unhelpful

Adaptive/Hyperfiltration FSGS

Obesity-Related Glomerulopathy **Pathophysiology:** - Glomerular enlargement (glomerulomegaly) prominent feature - Increased single-nephron GFR compensating for reduced nephron mass - Proteinuria often modest (<3.5 g/day) despite significant histologic changes - Perihilar variant common

Distinguishing Features: - Often presents without full nephrotic syndrome - Peripheral edema less prominent relative to proteinuria level - Serum albumin normal despite significant proteinuria

Management: - Weight loss (dietary or surgical) - RAAS blockade - Immunosuppression generally ineffective - Prognosis depends on ability to achieve sustained weight loss

Other Hyperfiltration States Solitary Kidney or Renal Agenesis: - Remaining single kidney undergoes compensatory hypertrophy - Increased glomerular filtration pressure leads to FSGS - Proteinuria develops over years

Reflux Nephropathy: - Scarring from vesicoureteral reflux - Reduced functioning renal mass - Remaining nephrons hyperfiltrate

Low Nephron Mass Conditions: - Prematurity with low birth weight - Oligomeganephronia - Sickle cell disease - Cyanotic congenital heart disease

Management: Address underlying cause; ACE-I/ARB reduce hyperfiltration injury

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Genetic FSGS: When to Suspect Hereditary Disease

Podocyte Gene Mutations

Associated Genes: - **NPHS2** (podocin) — most common genetic cause - **NPHS1** (nephrin) - **WT1** (Wilms tumor suppressor) - **TRPC6** (ion channel) - **ACTN4** (alpha-actinin-4) - **INF2** (formin family protein)

Clinical Clues Suggesting Genetic Disease: - Family history of FSGS or unexplained ESRD - Early disease onset (childhood/young adulthood) - Bilateral disease - Steroid-resistant presentation - Multiple family members affected

Prognosis: Generally steroid-resistant; genetic mutations target structural proteins, not immune pathology

Management: Supportive care with RAAS blockade; immunosuppression ineffective

APOL1 Risk Variants

Relevance: High-risk APOL1 alleles (G1/G2) associated with: - Higher prevalence of FSGS in African Americans - Faster progression to ESRD - Collapsing variant more common

Clinical Significance: - Explains racial disparity in FSGS progression - No specific targeted therapy; supportive care remains foundation - Genetic testing may help prognostication

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Clinical Distinction: Primary from Secondary FSGS

Features Favoring Primary FSGS

- Full nephrotic syndrome features
- Preserved or near-normal serum albumin initially
- Variable GFR at presentation
- Steroid-responsive phenotype (in some)
- Family history of kidney disease
- No identifiable secondary cause

Features Suggesting Secondary FSGS

- Absence of full nephrotic syndrome
- **Less peripheral edema relative to proteinuria**
- Normal serum albumin despite significant proteinuria (key clue)
- Slower progression to ESRD
- **Identifiable causative factor** (obesity, HIV, drugs, low nephron mass)
- Steroid-resistant phenotype (typical)

Histologic Clues

Suggesting Primary FSGS: - IgM and C3 deposits on immunofluorescence - Extensive foot process effacement on electron microscopy - Absence of other pathologic features

Suggesting Secondary FSGS: - Glomerulomegaly (obesity-related) - Perihilar variant (hyperfiltration) - Collapsing variant (HIV, viral infection) - Less foot process effacement - Absence of immunoglobulin deposits

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Treatment Approaches by FSGS Type

Primary FSGS: Steroid-Responsive Disease

Initial Treatment: - Prednisone 1 mg/kg/day (maximum 80 mg) or 2 mg/kg every other day - Duration: 8-16 weeks minimum before determining resistance - Taper slowly over 6+ months after response achieved

Expected Response: - 40-50% achieve complete remission - 15-20% achieve partial remission - 30-40% are steroid-resistant

Complete remission rate reaches 60% if extended to 6 months therapy in some patients.

Primary FSGS: Steroid-Resistant Disease

First-line (per KDIGO 2021): - **Calcineurin inhibitors (CNI)** — cyclosporine or tacrolimus - Cyclosporine: 5-10 mg/kg/day targeting trough 125-175 ng/mL - Tacrolimus: 0.1-0.2 mg/kg/day divided doses - Complete remission rates: 70-81% with tacrolimus

Alternative Approaches: - **CNI + Low-dose corticosteroids** — reduces steroid exposure while maintaining efficacy - **Mycophenolate mofetil (MMF)** — for CNI-intolerant patients, but lower response rates - **Rituximab** — anti-CD20 B-cell antibody, emerging data for steroid-resistant FSGS - **Sirolimus** — mTOR inhibitor, can reduce proteinuria in steroid-resistant disease

Key Advantage: CNI-based approach reduces corticosteroid exposure while maintaining response-to-therapy rates similar to high-dose steroid regimen.

Secondary FSGS: General Principles

Fundamental Principle: Remove the offending agent or treat underlying condition.

HIVAN: - Antiretroviral therapy is first-line (viral suppression often sufficient) - ACE-I/ARB for proteinuria reduction - Corticosteroids controversial; may provide temporary benefit - Immunosuppression not first-line unless CNI used as part of broader renal protocol

Obesity-Related: - Weight loss (dietary or bariatric surgical) - RAAS blockade - Avoid unnecessary immunosuppression - Prognosis depends on achievement of weight reduction

Drug-Induced: - Discontinue offending agent - Supportive care - Most recover proteinuria gradually if agent withdrawn early

Hyperfiltration States: - RAAS blockade to reduce glomerular pressure - Protein restriction (modest, 0.8 g/kg) - Address underlying condition where possible - Immunosuppression generally ineffective

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Practice Questions

Question 1: A 42-year-old male with BMI 38 presents with proteinuria 2.1 g/day and serum albumin 3.8 g/dL. Kidney biopsy shows FSGS with glomerulomegaly and perihilar variant. Which is the most appropriate first-line intervention?

A) High-dose prednisone (1 mg/kg/day)
B) Calcineurin inhibitor therapy
C) Dietary weight loss with RAAS blockade
D) Rituximab therapy

Correct Answer: C — The clinical and pathologic findings (glomerulomegaly, perihilar variant, modest proteinuria without severe hypoalbuminemia, obesity) indicate secondary FSGS from obesity-related glomerulopathy. Weight loss is first-line. Immunosuppression ineffective for secondary FSGS.

Question 2: A 28-year-old with steroid-resistant primary FSGS achieves complete remission on tacrolimus but experiences recurrent hematuria after dose reduction. Which approach is most appropriate?

A) Discontinue tacrolimus and switch to rituximab
B) Increase tacrolimus back to previous dose; maintain long-term therapy
C) Add mycophenolate mofetil to enable CNI dose reduction
D) Initiate high-dose steroids despite prior steroid resistance

Correct Answer: B — Steroid-resistant FSGS responding to CNI often requires prolonged maintenance therapy. Flares during dose reduction common. Increasing dose back to therapeutic level with longer maintenance period is appropriate. CNI response in steroid-resistant disease indicates need for long-term CNI therapy.

Question 3: A 34-year-old HIV-positive patient with HIVAN presents with 7 g/day proteinuria and collapsing FSGS on biopsy. CD4 count 85 cells/μL; viral load >100,000 copies/mL. What is the most appropriate initial therapy?

A) High-dose prednisone + cyclophosphamide
B) Antiretroviral therapy (HAART) to achieve viral suppression
C) Immediate calcineurin inhibitor therapy
D) Rituximab induction therapy

Correct Answer: B — HIVAN is pathophysiologically related to HIV replication. Antiretroviral therapy achieving viral suppression is first-line and often sufficient to achieve remission of proteinuria. Immunosuppression not first-line. High-dose corticosteroids problematic with CD4 <200.

Clinical Pearls

1. **FSGS is a pathologic pattern, not a disease** — determine etiology before selecting therapy
2. **Primary FSGS steroid-responsive** — 40-50% achieve remission with steroids
3. **Steroid-resistant FSGS** ☐ CNI first-line per KDIGO (70-81% remission rates)
4. **Secondary FSGS** ☐ immunosuppression generally ineffective; treat underlying cause
5. **Collapsing FSGS** ☐ worst prognosis; African Americans particularly affected
6. **Obesity-related FSGS** ☐ weight loss first-line; immunosuppression unhelpful
7. **HIVAN** ☐ antiretroviral therapy primary therapy; viral suppression often sufficient

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Related Topics

See Also

Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Glomerular Treatment Principles
- Kidney Biopsy Essentials
- Immunosuppressive Therapy in Nephrology

Clinical Content (01-Clinical-Medicine/Nephrology)

- Glomerular Diseases Hub
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

- Clinical Recognition and Differential Diagnosis
- Specific Management of Renal HIV Disease
- When Steroids Fail

Summary

Focal segmental glomerulosclerosis presents a diagnostic and therapeutic challenge due to its multiple etiologies producing identical histologic patterns. The critical distinction between primary idiopathic FSGS and secondary forms fundamentally affects treatment strategy. Primary FSGS in 40-50% of patients responds to corticosteroid monotherapy, while steroid-resistant disease requires calcineurin inhibitors achieving 70-81% remission rates. Secondary FSGS due to obesity, HIV, drugs, or hyperfiltration states typically does not respond to immunosuppression; rather, treatment focuses on addressing the underlying cause. Understanding FSGS variants by Columbia classification helps predict steroid responsiveness, with tip lesions having best outcomes and collapsing FSGS having worst prognosis. For medical students, FSGS exemplifies the critical importance of determining disease etiology before selecting therapy—the same histologic pattern requires dramatically different treatments depending on whether it represents primary idiopathic disease or secondary injury.