



## Approach to Diagnosis and Management of Primary Glomerular Diseases Due to Podocytopathies in Adults: Core Curriculum 2020

Woojin Ahn and Andrew S. Bomback

Podocyte injury is the initiating step in the pathway toward clinically evident forms of nephrotic syndrome known as podocytopathies, represented as either minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). There are hallmark differences in the histologic appearances of MCD and FSGS, which in turn represent distinct pathogenic models after initial podocyte injury (eg, no change in podocyte number in MCD vs podocyte detachment and death in FSGS). However, MCD and FSGS also share a number of common causes, supporting the theory that these diseases lie along a shared podocytopathy spectrum. In this installment of *AJKD's* Core Curriculum in Nephrology, we demonstrate how the podocytopathies can be classified according to pathogenesis and treatment response as an alternative to histologic description. Using case examples, we show how these alternative classification schemes can assist not only diagnosis, but also long-term management of podocytopathies.

Complete author and article information provided at end of article.

*Am J Kidney Dis.*  
75(6):955-964. Published  
online April 21, 2020.

doi: [10.1053/j.ajkd.2019.12.019](https://doi.org/10.1053/j.ajkd.2019.12.019)

© 2020 by the National  
Kidney Foundation, Inc.

### Introduction

The podocyte is a visceral epithelial cell that is the core component of the glomerular filtration barrier. Podocytopathy is the state of injury to podocytes. The most frequent histopathologic findings of primary injury to podocytes are minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). However, MCD and FSGS are morphologic descriptions that can be caused by various pathogenic pathways.

Shared causes of podocytopathies, such as drugs, infections, and genetic mutations, support the theory that MCD and FSGS exist on a spectrum of podocyte injury instead of being 2 distinct conditions. The observation of “MCD-like” biopsy specimens immediately after transplantation (ie, normal light microscopy with moderate to severe foot-process effacement on electron microscopy) in patients with early recurrent FSGS suggests that MCD may be an “early” podocytopathy and FSGS may be an advanced late form of podocyte injury.

Using the terms “primary” and “secondary” to describe podocytopathies is common yet problematic. KDIGO defined “primary FSGS” as idiopathic disease without identifiable cause. However, KDOQI suggested that FSGS due to known genetic mutations should also be called primary FSGS because the effect of the mutation is primarily damage to podocytes. To complicate things further, many authorities restrict the term “secondary

FSGS” for only an adaptive hyperfiltration form of FSGS with segmental foot-process effacement. Absence of identifiable cause or inability to perform testing (eg, genetic test) should not define the podocytopathy. A more accurate and practical classification system is necessary.

Rather than dividing into primary and secondary forms, we recommend classifying podocytopathies by pathogenesis (Table 1). In the following, we discuss this pathogenesis-based classification system and review how renal pathology and clinical response to treatment relate to the diagnosis and management of podocytopathies.

### Pathogenesis-Based Classification of Podocytopathy

#### Permeability Factor–Mediated Podocytopathy

In 1974, Shalhoub proposed the theory that abnormal T-cell production of a circulating permeability factor may mediate podocyte injury. This theory resulted from the observation that nephrotic syndrome associated with Hodgkin lymphoma often resolves in patients who contract rubeola (measles), a virus that dampens T-cell activity. The idea of a pathogenic circulating factor has gained additional credence from studies of animals and humans that show immediate nephrotic syndrome recurrence after transplantation in some patients with FSGS (suggesting the

**FEATURE EDITOR:**  
Asghar Rastegar

**ADVISORY BOARD:**  
Ursula C. Brewster  
Michael Choi  
Ann O'Hare  
Manoocher Soleimani

*The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.*

**Table 1.** Pathogenesis-Based Classification of Podocytopathies

Type of Podocytopathy	Causes and Pathogenesis	Pathology	Clinical Manifestation	Treatment	Recurrence After Transplantation
Permeability factor–mediated	Circulating factor causing podocyte injury	MCD, FSGS with extensive FPE	Sudden-onset nephrotic syndrome	Immunosuppression, plasma exchange	Common; sometimes immediate
Toxic	Direct toxicity or cytokine mediated $\pm$ APOL1 overexpression	MCD, FSGS (frequently collapsing) $\pm$ endothelial tubuloreticular inclusions	Variable clinical course; slowly progressing CKD or nephrotic syndrome	Removal of toxic injury	Possible; usually several months later
Genetic	Mutation causing structural or functional abnormalities of podocytes	MCD, MesGN, FSGS	Steroid-resistant nephrotic syndrome	RAS inhibitors	Rare
Hyperfiltration-mediated	Adaptive changes due to excessive nephron workload	FSGS (frequently perihilar) with glomerulomegaly and segmental FPE	Slowly progressive proteinuria without edema and hypoalbuminemia	RAS inhibitors	Rare

Abbreviations: CKD, chronic kidney disease; FPE, foot-process effacement; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MesGN, mesangioproliferative glomerulonephritis; RAS, renin-angiotensin system.

presence of a circulating factor in the recipient that immediately damages the new graft). Furthermore, in one such patient with immediate graft failure after transplantation, the allograft was explanted and retransplanted into a second recipient who did not have FSGS and the graft functioned normally. These phenomena strongly suggest that some cases of FSGS are caused by an extrarenal circulating pathogenic permeability factor that injures podocytes.

The relatively lower incidence of early recurrent FSGS in African Americans supports that a permeability factor–mediated FSGS is a different entity from FSGS associated with renal risk variants of the apolipoprotein L1 gene (APOL1). Several molecules (including soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine factor 1, and anti-CD40 antibody) have been proposed as the circulating factor that causes podocyte injury, but we still do not have a convincing candidate that can be measured and followed up in clinical practice. The inability to identify the permeability factor has made it difficult to identify patients with this subtype of podocytopathy and has precluded clinical trials for effective treatments.

In terms of clinical presentation, permeability factor–mediated podocytopathy features a relatively sudden onset of nephrotic syndrome. The hallmark clinical scenario is early recurrence of nephrotic-range proteinuria after transplantation. On biopsy, MCD and all histologic variants of FSGS (ie, collapsing, cellular, and not otherwise specified [NOS]) can be found. Initial responsiveness to immunosuppression and/or plasma exchange is often seen, and frequent relapses are common during the disease course.

### Additional Readings

- Maas RJ, Deegens JK, Wetzels JF. Permeability factors in idiopathic nephrotic syndrome: historical perspectives and lessons for the future. *Nephrol Dial Transplant*. 2014;29(12):2207-2216.
- Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet*. 1974;2(7880):556-560.
- Wada T, Nangaku M. A circulating permeability factor in focal segmental glomerulosclerosis: the hunt continues. *Clin Kidney J*. 2015;8(6):708-715.

### Genetic Forms of Podocytopathy

Genetic variants of proteins that form the glomerular filtration barrier can cause FSGS, MCD, mesangioproliferative glomerulonephritis (MesGN; also known as diffuse mesangial hypercellularity), or diffuse mesangial sclerosis. Genetic testing is the only method to diagnose this form of podocytopathy and should be considered in patients with a family history of nephrotic syndrome or kidney disease, as well as patients with extrarenal manifestations suggesting a particular genetic syndrome. Routine genetic testing during initial workup is currently not recommended by any formal guideline but declining costs and easier access to genetic screening may soon make this a standard part of practice in all patients with podocytopathy. In some instances, knowing the type of mutation present may guide treatment, as in coenzyme Q10 supplementation when there is a coenzyme Q10 biosynthesis-associated mutation and vitamin B<sub>12</sub> in the context of a cubilin mutation. Identification of a pathologic variant may thus prevent unnecessary use of immunosuppressive agents and morbidity from their adverse effects.

Mutations in type IV collagen (COL4A) genes, which have been causally linked to Alport syndrome, may be the

**Table 2.** Selected Genetic Mutations Causing Podocytopathies

Gene (Inheritance Pattern)	Product	Clinical Manifestations
COL4A3/4/5 (AD, AR, XL)	Type IV collagen	Alport syndrome: bilateral anterior lenticonus, dot-and-fleck retinopathy, spherophakia, high-frequency sensorineural hearing loss
NPHS1 (AR)	Nephrin	Early-onset SRNS
NPHS2 (AR)	Podocin	Early- or late-onset SRNS
WT1 (AD)	Wilms tumor 1	Denys-Drash syndrome: Wilms tumor, male pseudohermaphroditism Frasier syndrome: gonadoblastoma, male pseudohermaphroditism
PLCE1 (AR)	Phospholipase C $\epsilon$ 1	Early-onset SRNS
LAMB2 (AR)	Laminin $\beta$ 2	Pierson syndrome: microcoria, neuromuscular junction defects
CD2AP (AD)	CD2-associated protein	Early-onset SRNS
ACTN4 (AD)	$\alpha$ -Actinin 4	Early- or late-onset SRNS
TRPC6 (AD)	Transient receptor potential cation channel 6	Late-onset SRNS
INF2 (AD)	Inverted formin 2	Charcot-Marie-Tooth disease: motor and sensory nerve manifestations with distal leg weakness, foot deformities (pes cavus, hammer toes), late-onset SRNS
MT-TL1, MT-TL2, MT-TY (mitochondrial)	Mitochondrial tRNA	MELAS syndrome: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes
LMX1B (AD)	LIM homeobox transcription factor 1- $\beta$	Nail-patella syndrome: hypoplastic patella, dystrophic nails, dysplasia of elbows Collagenofibrotic glomerulopathy
ITGB4 (AR)	$\beta$ 4 integrin	Epidermolysis bullosa
CD151 (AR)	Tetraspanin CD151	Epidermolysis bullosa, sensorineural hearing loss, nail dystrophy
SCARB2 (AR)	Lysosomal integral membrane protein 2	Action myoclonus-renal failure syndrome: ataxia, myoclonus
CUBN (AR)	Cubilin: intrinsic factor-cobalamin receptor	Megaloblastic anemia secondary to vitamin B <sub>12</sub> deficiency, SRNS
COQ6 (AR)	Coenzyme Q6	Sensorineural hearing loss
MYH9 (AD)	Nonmuscle myosin 11a	Bleeding diathesis, macrothrombocytopenia, progressive sensorineural deafness, $\uparrow$ liver enzyme, cataract
SMARCA1 (AR)	SMARCA-like protein	Schimke immune-osseous dysplasia

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; SRNS, steroid-resistant nephrotic syndrome; tRNA, transfer RNA; XL, X-linked.

most common (44%–56%) cause of genetic FSGS in adults. It is estimated that collagen mutations account for ~30% of genetic forms of chronic kidney disease (CKD), though many affected patients are not diagnosed as having a hereditary condition. Other common mutations causing late-onset podocytopathies found in adults occur in ACTN4, TRPC6, INF2, and NPHS2 (the genes encoding  $\alpha$ -actinin 4, transient receptor protein 6, inverted formin 2, and podocin). Extrarenal manifestations may provide diagnostic clues before genetic testing (Table 2).

About 60% of patients with steroid-resistant nephrotic syndrome (SRNS) who manifest clinical signs of disease in the first year of life have genetic causes of podocytopathy. This number declines with older age, but genetic podocytopathies can be diagnosed in adulthood. Typical presentations are SRNS or proteinuric CKD.

Immunosuppressive therapy does not have direct beneficial effects in patients with genetic causes of MCD and FSGS, although the cytoskeleton stabilization effect of calcineurin inhibitors (CNIs) can lead to reductions in proteinuria in some. Renin-angiotensin system (RAS) inhibitors may slow progressive glomerulosclerosis by

reducing glomerular hyperfiltration. Recurrence after kidney transplantation is rare.

### Additional Readings

- > Buscher AK, Kranz B, Buscher R, et al. Immunosuppression and renal outcome in congenital and pediatric steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol*. 2010;5(11):2075-2084.
- > Gast C, Pengelly RJ, Lyon M, et al. Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. *Nephrol Dial Transplant*. 2016;31(6):961-970.
- > Gribouval O, Boyer O, Hummel A, et al. Identification of genetic causes for sporadic steroid-resistant nephrotic syndrome in adults. *Kidney Int*. 2018;94(5):1013-1022.
- > Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med*. 2019;380(2):142-151.
- > Lovric S, Ashraf S, Tan W, Hildebrandt F. Genetic testing in steroid-resistant nephrotic syndrome: when and how? *Nephrol Dial Transplant*. 2016;31(11):1802-1813.
- > Preston R, Stuart HM, Lennon R. Genetic testing in steroid-resistant nephrotic syndrome: why, who, when and how? *Pediatr Nephrol*. 2019;34(2):195-210.

- Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. *J Am Soc Nephrol*. 2015;26(6):1279-1289.
- Trautmann A, Bodria M, Ozaltin F, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. *Clin J Am Soc Nephrol*. 2015;10(4):592-600.

### Toxic Podocytopathy and ApoL1 Nephropathy

Drugs, infections, hematologic malignancies, and systemic inflammatory states can cause toxic podocytopathies by varied mechanisms. Collapsing glomerulopathy (CG), a histologic subtype of FSGS named for the shrunken appearance of the glomerular tufts, is a frequent pathologic finding in toxic podocytopathies, but MCD and other histologic variants of FSGS have also been reported.

One of the most well-described infection-related podocytopathies is human immunodeficiency virus (HIV)-associated nephropathy (HIVAN). HIV induces cell proliferation in glomerular epithelial cells, including podocytes. Classically, HIVAN manifests histopathologically as CG in patients with poorly controlled HIV infection. MCD and other histologic subtypes of FSGS besides CG have also been described. The majority of patients who develop HIVAN are of African descent. This racial disparity has recently been explained in large part by genetic variations in APOL1, for which the gene product participates in defense mechanisms. Specifically, having the G1 or G2 risk allele of APOL1 increases resistance to *Trypanosoma brucei*, the parasite that causes trypanosomiasis or sleeping sickness. The detrimental effects of having 2 risk alleles is increased susceptibility to HIVAN, FSGS, the entity previously called hypertensive kidney disease, and other forms of nondiabetic CKD. About 10% to 13% of African Americans carry 2 risk alleles, and 20% of these double carriers will develop kidney failure. This incomplete penetrance suggests that a second “hit” or injury process is required for APOL1-related kidney diseases to develop, a phenomenon that distinguishes it from other genetic causes of podocytopathies, which show higher if not full penetrance.

Administration of interferon is associated with CG with endothelial tubuloreticular inclusions, and retrospective genetic analyses revealed that many patients with these interferon-associated lesions have 2 risk alleles of APOL1. A subsequent study showed that APOL1 expression is driven by interferon, which explains its association with various interferon-mediated viral infections such as HIV, as well as autoimmune diseases such as lupus and hemophagocytic lymphohistiocytosis that can result in the pathologic lesion of FSGS. Patients with 2 APOL1 risk alleles and interferon-associated podocytopathies have worse kidney disease outcomes than those with 1 or no risk allele, including greater propensity to kidney failure.

Not all toxic podocytopathies are associated with APOL1 variants. Pamidronate intravenous infusions, used for multiple myeloma and malignancy-associated hypercalcemia, can cause podocytopathies. As is the case with

HIVAN, CG is the classic histologic lesion, but other forms of FSGS and MCD have been reported. Unlike HIVAN, the risk for developing pamidronate-associated FSGS is not related to race or ethnicity. Additionally, tubuloreticular inclusions are not frequently seen on biopsy, suggesting a different mechanism of injury.

When possible, identification and removal of the toxic agent is the most important treatment strategy. For example, in HIVAN, initiation of appropriate antiretroviral therapy should be prioritized. Immunosuppressive therapy may be beneficial by reducing cytokine activation. There is no known difference in immunosuppressive treatment response according to APOL1 status, and there is currently no targeted treatment for APOL1-associated kidney diseases.

### Additional Readings

- Arrestier R, Satie AP, Zhang SY, et al. Minimal change nephrotic syndrome in patients infected with human immunodeficiency virus: a retrospective study of 8 cases. *BMC Nephrol*. 2018;19(1):331.
- Freedman BI, Limou S, Ma L, Kopp JB. APOL1-associated nephropathy: a key contributor to racial disparities in CKD. *Am J Kidney Dis*. 2018;72(5)(suppl 1):S8-S16.
- Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*. 2011;22(11):2129-2137.
- Kopp JB, Winkler CA, Zhao X, et al. Clinical features and histology of apolipoprotein L1-associated nephropathy in the FSGS Clinical Trial. *J Am Soc Nephrol*. 2015;26(6):1443-1448.
- Lescure FX, Flateau C, Pacanowski J, et al. HIV-associated kidney glomerular diseases: changes with time and HAART. *Nephrol Dial Transplant*. 2012;27(6):2349-2355.
- Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. *Clin J Am Soc Nephrol*. 2015;10(7):1291-1299. ★ **ESSENTIAL READING**
- Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med*. 2001;344(26):1979-1984.

### Hyperfiltration-Mediated (Adaptive) FSGS

When there is a reduced total number of functioning nephrons, due either to acquired disease or congenital abnormalities, hyperfiltration by remaining nephrons is adaptive in that it preserves physiologic homeostasis. However, glomerular hyperfiltration and resultant adaptive glomerulomegaly can progress to segmental glomerulosclerosis. This has been described in reflux nephropathy, obesity, sickle cell anemia, and solitary kidney from unilateral renal agenesis or surgical removal.

Hyperfiltration-mediated (adaptive) FSGS typically manifests with proteinuria without nephrotic syndrome features, such as hypoalbuminemia or edema. The usual biopsy findings include glomerulomegaly and perihilar variant of FSGS on light microscopy, with segmental foot-process effacement on electron microscopy.

Not all patients with obesity and solitary kidneys, including kidney donors, develop FSGS, which shows the importance of compensatory reservoir. Low birth nephron



endowment, suggested by glomerular enlargement and low glomerular density, may be an important contributing factor.

Treatment of hyperfiltration-mediated FSGS should focus on reduction of glomerular hyperfiltration through inhibition of angiotensin II–mediated efferent arteriole vasoconstriction, by using RAS inhibitors including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Weight loss in obese patients is often encouraged as well.

### Additional Readings

- D'Agati VD, Chagnac A, de Vries AP, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. *Nat Rev Nephrol.* 2016;12(8):453-471. ★ **ESSENTIAL READING**
- D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med.* 2011;365(25):2398-2411. ★ **ESSENTIAL READING**
- Mallamaci F, Ruggenenti P, Perna A, et al. ACE inhibition is renoprotective among obese patients with proteinuria. *J Am Soc Nephrol.* 2011;22(6):1122-1128.
- Rennke HG, Klein PS. Pathogenesis and significance of non-primary focal and segmental glomerulosclerosis. *Am J Kidney Dis.* 1989;13(6):443-456.

## Classification Based on Treatment Response

**Case 1:** A 45-year-old Latino man presented with generalized edema for 2 weeks. Laboratory studies showed serum creatinine (Scr) level of 2.5 mg/dL, serum albumin level of 3.0 mg/dL, and random urinary protein-creatinine ratio (UPCR) of 7 g/g. Findings from review of medications and physical examination were unremarkable. Kidney biopsy showed FSGS NOS. Treatment with oral prednisone, 120 mg, every other day was started. Six weeks after the initiation of prednisone therapy, random UPCR is 8 g/g, and Scr level is 3.0 mg/dL. He has some increased appetite and insomnia.

### Question 1. What would you recommend at this point?

- (a) Continue prednisone at same dose
- (b) Replace prednisone with oral cyclophosphamide
- (c) Replace prednisone with mycophenolate mofetil (MMF)
- (d) Replace prednisone with rituximab
- (e) Stop prednisone and recommend plasma exchange

For the answer to the question, see the following text.

Depending on response to steroid therapy, podocytopathies can be classified as steroid-sensitive nephrotic syndrome (SSNS) or SRNS (Box 1). Adult podocytopathies may take up to 4 months to remit and therefore steroid resistance should not be declared until after 4 months of steroid use.

In the pediatric population, kidney biopsy is usually not performed and nephrotic syndrome is classified based on treatment response. Among children with SRNS who undergo biopsy, FSGS has been reported as the most common histopathologic finding (56%), followed by MCD (21%) and MesGN (12%). Therefore, SSNS and SRNS are not synonyms of MCD and FSGS, respectively.

In adults, classification by steroid responsiveness is also used when describing histopathologic diagnosis

### Box 1. Definitions of Various Conditions in Nephrotic Syndrome in Adults

**Steroid-sensitive nephrotic syndrome (SSNS):** nephrotic syndrome that had remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use within 4 mo

**Steroid-resistant nephrotic syndrome (SRNS):** nephrotic syndrome that failed to achieve remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use for 4 mo

**Steroid dependence (SD):** 2 consecutive relapses during steroid therapy or within 2 wk of ceasing therapy

**Frequent relapse (FR):** ≥2 relapses within 6 mo of initial response or 4+ relapses within any 12-mo period

**Infrequent relapse:** 1 relapse within 6 mo of initial response, or 1-3 relapses in any 12-mo period and treated with steroids

**Remission:** reduction of proteinuria to < 3.5 g/d with stable serum creatinine level (change < 25%)

(eg, steroid-resistant FSGS) because classification by pathogenesis is often not possible in the absence of genetic testing. Genetic podocytopathies always manifest as SRNS, but SRNS is not always due to a genetic problem. For example, permeability-mediated podocytopathy may present as SSNS or SRNS. In addition, SSNS can progress to SRNS, which may reflect progression from FSGS to diffuse global glomerulosclerosis.

In randomized clinical trials of adults with steroid-resistant FSGS, there was no significant difference in treatment response to CNI versus mycophenolate/dexamethasone. Rituximab and other immunosuppressive therapies do not have satisfactory efficacy on SRNS. A substantial proportion of patients with SRNS may have genetic podocytopathies or podocyte injuries that cannot be reversed by immunosuppressive therapy. Clinicians managing SRNS should closely monitor side effects and weigh the risks and benefits of continuing or withdrawing immunosuppressive therapy.

The presence or absence of relapses, as well as their frequency, during tapering of steroid therapy has been used to define phenotypes of steroid-sensitive MCD and FSGS (Box 1). The steroid-dependent and frequently relapsing nephrotic phenotypes require alternative steroid-sparing treatment to reduce the adverse effects of long-term glucocorticoid use. CNIs have been traditionally used, but immediate relapse after their withdrawal (so-called CNI dependence) is also frequent, and long-term use of these agents may cause chronic tubulointerstitial damage and CKD. Rituximab has been successfully used in this setting, as well as alkylating agents (cyclophosphamide preferred to chlorambucil) outside childbearing years. Podocytopathies with infrequent relapses are treated with steroids.

For Question 1, the correct answer is (a) because adult podocytopathies may respond to corticosteroid therapy up to 4 months from initiation of treatment, and steroid resistance should not be declared until that time.

### Additional Readings

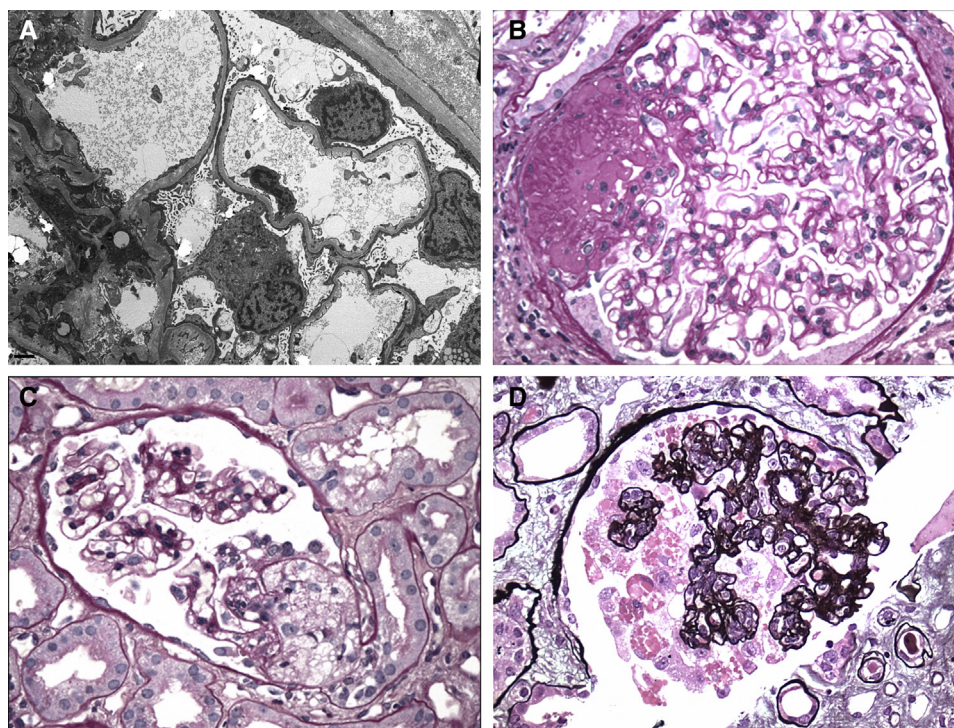
- Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int.* 2011;80(8):868-878.
- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl.* 2012;2:139-274.

### Classification of Podocytopathies Based on Histopathology

MCD is the most common histopathologic finding in nephrotic syndrome in pediatric and geriatric ( $\geq 80$ -year-old) populations. Light microscopy and immunofluorescence evaluation demonstrate no abnormalities other than tubular proteinaceous material and occasional acute tubular necrosis. Electron microscopy reveals extensive foot-process effacement and is required for the diagnosis.

FSGS is incomplete (“segmental”) scarring seen in some (“focal”) but not all glomeruli. It is characterized by intracapillary obliteration by matrix accumulation and/or hyaline deposition. It is the most common kidney biopsy finding in adults aged 18 to 80 years with nephrotic syndrome in the United States. The incidence rate of FSGS is increasing for unclear reasons. FSGS lesions are classified histopathologically into collapsing, cellular, tip, and NOS variants (Fig 1).

CG or collapsing-variant FSGS has parietal epithelial cell hyperplasia presumably from injury to precursors of podocytes. Electron microscopy may reveal endothelial tubuloreticular inclusions when the lesion is associated with interferon from drug administration, HIV or parvovirus B19 infection, systemic lupus erythematosus, and hemophagocytic lymphohistiocytosis. CG is typically found with acute kidney injury (AKI) alongside nephrotic-range proteinuria. This lesion is frequently seen in African American patients with 2 *APOL1* risk alleles. The CG lesion is usually accompanied clinically by severe proteinuria, hypoalbuminemia, and reduced glomerular filtration rate and not surprisingly has been associated with the worst kidney outcomes of the FSGS subtypes. However, kidney



**Figure 1.** Kidney biopsy findings across a spectrum of podocytopathies. (A) Electron microscopy showing diffuse near-complete effacement of the podocyte's foot processes is the hallmark finding for minimal change disease when light microscopy shows no glomerular lesions. (B) Segmentally sclerotic glomerulus picked up by periodic acid–Schiff stain on a case of focal segmental glomerulosclerosis (FSGS), not otherwise specified. (C) The tip lesion variant of FSGS is noted by the presence of segmental sclerosis of the glomerulus at the tubular pole, shown in hematoxylin and eosin stain. (D) The silver stain (Jones methenamine silver) on light microscopy highlights the hallmark feature of collapsing variant of FSGS in which segmental obliteration of the glomerulus is caused by collapse of the glomerular basement membrane. Images courtesy Dr Dominick Santoriello (Columbia University Irving Medical Center).

survival in CG is similar to that of the NOS variant of FSGS after adjusting for immunosuppressive treatment and baseline characteristics such as serum creatinine and proteinuria. Therefore, if clinically appropriate, immunosuppressive treatment should be considered after ruling out contributions of infections, drugs, and systemic conditions.

The perihilar variant of FSGS is frequently associated with hyperfiltration-mediated FSGS. Tip-variant FSGS (also referred to glomerular tip lesion) commonly manifests as SSNS, a phenotype similar to MCD. Even when a glomerular tip lesion case demonstrates steroid resistance, prognosis is still better than other forms of steroid-resistant FSGS. The NOS and cellular variants of FSGS are the most and the least common subtypes of FSGS, respectively.

Although pathologic classification, along with degree of segmental and glomerular sclerosis, interstitial fibrosis, and tubular atrophy, are important for prognostication, these findings do not always give clues for pathogenesis. For example, a genetic form of FSGS cannot be differentiated from other forms by morphology. Steroid-resistant FSGS with 2 APOL1 risk alleles could have any variant of FSGS. A proliferative glomerulonephritis that involves segmental portions of glomeruli, such as immunoglobulin A (IgA) nephropathy or antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, may cause segmental scarring that is morphologically FSGS. A biopsy late in the disease course of such entities after remission of serologies (eg, ANCAs) or other pathologic features (eg, mesangial proliferation or crescents replaced by segmental sclerosis) may look like FSGS, but these entities should not be regarded as podocytopathies. Likewise, FSGS lesions are frequently seen in biopsy-confirmed diabetic glomerulosclerosis.

Diffuse mesangial sclerosis, MesGN without immune deposits, C1q nephropathy, and IgM nephropathy are less common pathologic findings of podocytopathy. A small proportion of SRNS from a genetic podocytopathy in the pediatric population has diffuse mesangial sclerosis and MesGN on light microscopy.

Although immunosuppressive agents are commonly used in the treatment of podocytopathies, MCD and FSGS do not have consistent histologic evidence of antigen-antibody immune complexes, complement activation, or inflammation with leukocyte infiltration unless they accompany other conditions, as in lupus podocytopathy or MCD superimposed on IgA nephropathy. Sometimes mesangial nonspecific trapping of immunoglobulins is observed, but this is usually not regarded as an immunologic reaction.

### Additional Readings

- Laurin LP, Gasim AM, Derebail VK, et al. Renal survival in patients with collapsing compared with not otherwise specified FSGS. *Clin J Am Soc Nephrol*. 2016;11(10):1752-1759.
- Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2017;12(3):502-517.
- Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. *Clin J Am Soc Nephrol*. 2017;12(2):332-345.

## Clinical Manifestations of Podocytopathies

**Case 2:** An 86-year-old white man presented with shortness of breath. Laboratory studies showed Scr level elevation to 4.75 mg/dL (from 1.2 mg/dL 2 months earlier), potassium level of 6.0 mEq/L, serum albumin level of 2.1 g/dL, and random UPCR of 15 g/g. Urine output declined despite large doses of loop diuretics. After 3 sessions of hemodialysis, kidney biopsy was performed, which showed global glomerulosclerosis in 4 of 20 sampled glomeruli without segmental glomerulosclerosis, mild to moderate (30%) interstitial fibrosis and tubular atrophy, acute tubular injury, and unremarkable vessels. Electron microscopy revealed extensive foot-process effacement. Treatment with prednisone, 60 mg, daily was started. Four weeks later, he remains dialysis dependent with no urine output.

### Question 2: What would you recommend for long-term kidney replacement therapy plan?

- (a) Taper prednisone and refer to kidney transplantation
- (b) Taper prednisone and place arteriovenous fistula
- (c) Taper prednisone and start CNI
- (d) Continue prednisone and hemodialysis via dialysis catheter

*For the answer to the question, see the following text.*

MCD and tip-variant FSGS typically present with sudden-onset nephrotic syndrome with anasarca and weight gain. Gastrointestinal manifestations (nausea, abdominal pain, ascites, and umbilical hernia) sometimes lead to unnecessary extensive workup and interventions. CKD from any mechanism, congestive heart failure, and cirrhosis may cause salt retention and fluid overload, mimicking nephrotic syndrome. Edema from use of vasodilators (eg, dihydropyridine calcium channel blockers, hydralazine, and minoxidil) and glucocorticoids should be considered in the differential diagnosis. When urine studies and serum albumin level are unavailable, a sudden decrease in calcium level due to hypoalbuminemia could indicate the initial presentation or relapse of nephrotic syndrome.

Not all podocytopathies present with nephrotic syndrome. Workup for asymptomatic proteinuria with or without reduced glomerular filtration rate may lead to the diagnosis of a podocytopathy, especially in genetic or hyperfiltration-mediated conditions. Albumin-dominant proteinuria is the cardinal sign of glomerular injury. Microscopic hematuria may be present in any podocytopathy, including MCD.

AKI with tubular injury can be seen in some podocytopathies with severe hypoalbuminemia and proteinuria, particularly in geriatric patients. CG and bilateral renal vein thromboses also may cause AKI in nephrotic syndrome. Overall, AKI accompanies MCD in 25% to 33% of adult patients with MCD (a similar prevalence is expected in the much rarer glomerular tip lesion cases), and recovery from dialysis dependence can span from weeks to 6 months.



**Box 2.** Suggested Initial Laboratory Tests for Nephrotic-Range Proteinuria

- Complete blood cell count
- Basic metabolic panel
- Total protein and albumin
- Hemoglobin A<sub>1c</sub>
- Erythrocyte sedimentation rate
- Antinuclear antibody
- C3 and C4
- Ferritin
- PT/INR and aPTT (for kidney biopsy)
- Lipid panel
- Phospholipase A<sub>2</sub> receptor antibody
- HBsAg, anti-HBs, anti-HBc
- Hepatitis C virus antibody
- HIV ELISA
- Serum and urine protein electrophoresis and immunofixation
- κ:λ free light chain ratio
- Spot urine albumin, urine protein, urine creatinine
- Urinalysis with sediment evaluation

Abbreviations: aPTT, activated partial thromboplastin time; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; INR, international normalized ratio; PT, prothrombin time.

Returning to question 2, treatment with corticosteroids and close monitoring of kidney recovery should be continued; thus (d) is the correct answer. It is too early to place permanent dialysis access because acute tubular necrosis associated with MCD or glomerular tip lesion may take months for recovery (in this case, the patient recovered after 6 weeks' use of prednisone and was able to stop dialysis then).

**Additional Reading**

- Meyrier A, Niaudet P. Acute kidney injury complicating nephrotic syndrome of minimal change disease. *Kidney Int.* 2018;94(5):861-869.

**Diagnosis and Workup of Podocytopathies**

Clinically, any glomerular disease that causes nephrotic syndrome may mimic podocytopathies. There are a few situations for which biopsy can be bypassed. For example, nephrotic syndrome with amyloidosis found in other organs, such as fat pad or bone marrow, or nephrotic syndrome with detectable phospholipase A<sub>2</sub> receptor antibody can be sufficient for the diagnosis of renal amyloidosis and membranous nephropathy, respectively. However, podocytopathies cannot be diagnosed by exclusion, and kidney biopsy is the only way to diagnose these entities definitively.

Diagnostic evaluation (Box 2) should be tailored based on age, background, and medical history. All potential causes of nephrotic syndrome (Box 3) should be considered. Failure to identify the underlying cause of the

**Box 3.** Known Causes of Podocytopathies**Drugs**

Nonsteroidal anti-inflammatory drugs (NSAIDs)  
Lithium  
Interferon (alpha, beta, gamma)  
Pamidronate  
Anabolic steroids  
Sirolimus  
Anthracyclines

**Infectious diseases**

HIV  
EBV  
CMV  
Parvovirus B19  
Syphilis  
Ehrlichiosis  
Mycoplasma  
Strongyloides  
Leishmaniasis  
Filariasis

**Systemic noninfectious diseases**

SLE  
Mixed connective tissue disease  
Adult-onset Still disease  
Hemophagocytic lymphohistiocytosis/macrophage activation syndrome  
Thymoma  
Atopy/eczema  
Hodgkin lymphoma  
Non-Hodgkin lymphoma  
Acute myeloid leukemia (acute monoblastic leukemia)  
Acute lymphoblastic leukemia  
Chronic lymphoblastic leukemia  
Polycythemia vera  
Essential thrombocytosis  
Primary myelofibrosis

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

nephrotic syndrome may lead to treatment failure and deterioration of unidentified conditions due to inappropriate treatment.

**Treatment of Podocytopathies**

**Case 3:** A 23-year-old woman presents for continued management of MCD. She developed nephrotic syndrome with generalized edema, hypoalbuminemia, and nephrotic-range proteinuria when she was 8 years old. Kidney biopsy done when she was 18 years old showed MCD without significant interstitial fibrosis or tubular atrophy. Her symptoms and laboratory abnormalities improved with prednisone therapy. Her previous nephrologist added tacrolimus therapy. She reports that every time she tries to taper prednisone, her proteinuria increases, with generalized edema. She has been taking prednisone, 7 mg, daily for 15 years and tacrolimus, 3



*mg, twice daily for 10 years. Laboratory data shows Scr level of 1.0 mg/dL, albumin level of 4.4 g/dL, and random UPCR of 0.1 g/g. The last prednisone tapering trial was 1 year ago.*

**Question 3: What would you recommend?**

- (a) Continue current treatment
- (b) Try another prednisone tapering
- (c) Increase tacrolimus dose and try another prednisone tapering
- (d) Continue current treatment and add MMF
- (e) Rituximab infusion and then try prednisone tapering

*For the answer to the question, see the following text.*

The goal of treatment of podocytopathies is resolution of nephrotic syndrome and prevention of kidney failure. Achievement of proteinuria remission is associated with reduction of kidney failure. A novel definition of partial remission (40% proteinuria reduction and UPCR < 1.5 g/g) portends a better kidney outcome than the conventional definition of partial remission (50% reduction and UPCR < 3.5 g/g). Data from randomized clinical trials to guide the treatment of podocytopathies are limited.

Edema in podocytopathies is mediated mainly by sodium retention. There is additional translocation of fluid into the interstitial compartment due to low oncotic pressure, especially when serum albumin level is <2 g/dL. Salt intake should be restricted for control of proteinuria and edema. Loop diuretics are used while addressing causes and initiating any necessary immunosuppressive agents. Albumin infusion can be considered with diuretics for profound hypoalbuminemia, although the data supporting this practice are limited to small series with mixed results.

Inhibition of the RAS is the most important component of treatment in hyperfiltration-mediated FSGS. It is not recommended for known cases of SSNS that have already demonstrated a pattern of remitting relatively quickly. If blood pressure remains elevated after control of volume overload with diuretics, RAS inhibitors should be used to reduce hyperfiltration of residual glomeruli.

Immunosuppression is the mainstay of treatment of permeability factor-mediated podocytopathy. Glucocorticoids remain the first choice of immunosuppressive treatment. Initial presentation and infrequent relapse of MCD or FSGS in adults are treated with prednisone, 1 mg/kg (maximum 80 mg), daily or 2 mg/kg (maximum 120 mg), every other day for at least 4 weeks and at most 4 months, unless patients have contraindications or severe side effects, such as glucose intolerance or mood disorder. The steroid dose should be slowly tapered if used for longer than 3 weeks; rapid tapering or discontinuation may cause adrenal insufficiency with nausea, vomiting, and low blood pressure. Long-term use of high-dose steroids (longer than 4 months) in podocytopathies should be avoided to prevent avascular necrosis, osteoporosis, bone fracture, and atrophic striae.

The CNIs cyclosporine and tacrolimus are used frequently as second-line agents in the treatment of podocytopathies. Inhibition of calcineurin results in inhibition of nuclear factor of activated T cells and downstream cytokine production. They may exert non-nuclear factor of activated T cell-mediated inhibition of cathepsin L-driven degradation of synaptopodin, which is important in podocyte actin cytoskeleton rearrangement. This action may explain how CNIs have proteinuria reduction effects even in some forms of genetic podocytopathies. Major side effects are vasoconstriction of the afferent and efferent glomerular arterioles, thrombotic microangiopathy, tremor, headache, hyperlipidemia, hyperkalemia, hypertension, and hypertrichosis. Long-term use can cause arterial hyalinosis, interstitial fibrosis, and tubular atrophy. Therapeutic drug monitoring can confirm adherence and avoid subtherapeutic or toxic doses. Due to their long-term nephrotoxicity, CNIs are usually avoided in patients with reduced kidney function, especially when there is significant tubulointerstitial damage on pathology. CNIs or MMF may be used as steroid-sparing agents (allowing lower doses of prednisone) in steroid-responsive and steroid-resistant podocytopathies. MMF is preferred in patients with advanced CKD.

Rituximab is a chimeric anti-CD20 monoclonal antibody that targets B cells. It is particularly useful as a steroid-sparing option in steroid-dependent or frequently relapsing podocytopathies. One or 2 doses of 375 mg/m<sup>2</sup> of body surface area (lower than doses for ANCA-associated glomerulonephritis and membranous nephropathy) has been shown to work successfully in SSNS. There has been no report to date of progressive multifocal leukoencephalopathy after rituximab use in podocytopathy. Hepatitis B virus status should be checked before rituximab administration to prevent its reactivation. In the recovery state of hepatitis B virus infection, entecavir can be used for prophylaxis. Patients without immunity (ie, hepatitis B surface antibody negative) should be vaccinated before rituximab infusion because B-cell antibody production capacity will be reduced by infusion, and those who progress and require in-center hemodialysis will be susceptible to Hepatitis B virus infection.

Corticotropin may act on the melanocortin receptor in podocytes, reducing proteinuria in addition to its intrinsic glucocorticoid-releasing effect. Corticotropin therapy is approved by the US Food and Drug Administration for the edematous state in nephrotic syndrome. As with other medications used in podocytopathies, no large-scale randomized clinical trial data are available for corticotropin, which usually is reserved for refractory cases of FSGS due to its cost.

Cyclophosphamide may be used in steroid-dependent or frequently relapsing podocytopathies. It is not routinely used in podocytopathies in adults due to its side effects, such as malignancy, hemorrhagic cystitis, leukopenia, and infertility. Resistance to steroids and other

immunosuppressants is usually associated with resistance to cyclophosphamide as well.

Plasma exchange may remove a permeability factor. This intervention is usually reserved for recurrent podocytopathies after kidney transplantation. Sometimes these patients become dependent on plasma exchange, which may still be preferable to dependence on kidney replacement therapy. Some clinicians use plasma exchange in severe forms of nephrotic syndrome with AKI in the native kidney that is nonresponsive to initial attempts at immunosuppression; anecdotal reports of success in this setting are rare.

The best answer to question 3 is (e). In steroid-dependent nephrotic syndrome, rituximab can facilitate tapering and ideally discontinuation of prednisone and CNI treatment.

### Additional Readings

- Chavez-Mendoza CA, Nino-Cruz JA, Correa-Rotter R, Uribe-Uribe NO, Mejia-Vilet JM. Calcineurin inhibitors with reduced-dose steroids as first-line therapy for focal segmental glomerulosclerosis. *Kidney Int Rep.* 2019;4(1):40-47.
- Remy P, Audard V, Natella PA, et al. An open-label randomized controlled trial of low-dose corticosteroid plus enteric-coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults (MSN Study). *Kidney Int.* 2018;94(6):1217-1226.
- Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a

Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019;95(2):281-295. ★

### ESSENTIAL READING

- Ruggenenti P, Ruggiero B, Cravedi P, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *J Am Soc Nephrol.* 2014;25(4):850-863.
- Troost JP, Trachtman H, Nachman PH, et al. An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol.* 2018;13(3):414-421.

### Article Information

**Authors' Full Names and Academic Degrees:** Woojin Ahn, MD, PhD, and Andrew S. Bomback, MD, MPH.

**Authors' Affiliation:** Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY.

**Address for Correspondence:** Andrew S. Bomback, MD, Columbia University College of Physicians and Surgeons, Division of Nephrology, 622 W 168th St, PH 4-124, New York, NY 10032. E-mail: [asb68@columbia.edu](mailto:asb68@columbia.edu)

**Support:** None.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Peer Review:** Received September 4, 2019, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form December 21, 2019.