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

Wooin 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.

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

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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-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


### Genetic Forms of Podocytopathy

Genetic variants of proteins that form the glomerular filtration barrier can cause FSGS, MCD, mesangiproliferative 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 B₁₂ 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
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 α-actinin 4, transient receptor potential 6, inverted formin 2, and podocin). Extrarenal manifestations may provide diagnostic clues before genetic testing (Table 2).

Table 2. Selected Genetic Mutations Causing Podocytopathies

<table>
<thead>
<tr>
<th>Gene (Inheritance Pattern)</th>
<th>Product</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL4A3/4/5 (AD, AR, XL)</td>
<td>Type IV collagen</td>
<td>Alport syndrome: bilateral anterior lenticonus, dot-and-fleck retinopathy, sphericalia, high-frequency sensorineural hearing loss</td>
</tr>
<tr>
<td>NPHS1 (AR)</td>
<td>Nephrin</td>
<td>Early-onset SRNS</td>
</tr>
<tr>
<td>NPHS2 (AR)</td>
<td>Podocin</td>
<td>Early- or late-onset SRNS</td>
</tr>
<tr>
<td>WT1 (AD)</td>
<td>Wilms tumor 1</td>
<td>Denys-Drash syndrome: Wilms tumor, male pseudohermaphroditism Frasier syndrome: gonadoblastoma, male pseudohermaphroditism</td>
</tr>
<tr>
<td>PLCe1 (AR)</td>
<td>Phospholipase Cε1</td>
<td>Early-onset SRNS</td>
</tr>
<tr>
<td>LAMB2 (AR)</td>
<td>Laminin β2</td>
<td>Pierson syndrome: microcoria, neuromuscular junction defects</td>
</tr>
<tr>
<td>CD2AP (AD)</td>
<td>CD2-associated protein</td>
<td>Early-onset SRNS</td>
</tr>
<tr>
<td>ACTN4 (AD)</td>
<td>α-Actinin 4</td>
<td>Early- or late-onset SRNS</td>
</tr>
<tr>
<td>TRPC6 (AD)</td>
<td>Transient receptor potential channel 6</td>
<td>Late-onset SRNS</td>
</tr>
<tr>
<td>INF2 (AD)</td>
<td>Inverted formin 2</td>
<td>Charcot-Marie-Tooth disease: motor and sensory nerve manifestations with distal leg weakness, foot deformities (pes cavus, hammer toes), late-onset SRNS</td>
</tr>
<tr>
<td>MT-TL1, MT-TL2, MT-TY (mitochondrial)</td>
<td>Mitochondrial tRNA</td>
<td>MELAS syndrome: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes</td>
</tr>
<tr>
<td>LMX1B (AD)</td>
<td>LIM homeobox transcription factor 1-β</td>
<td>Nail-patella syndrome: hypoplastic patella, dystrophic nails, dysplasia of elbows Collagenofibrotic glomerulopathy</td>
</tr>
<tr>
<td>ITGB4 (AR)</td>
<td>β4 integrin</td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td>CD151 (AR)</td>
<td>Tetraspanin CD151</td>
<td>Epidermolysis bullosa, sensorineural hearing loss, nail dystrophy</td>
</tr>
<tr>
<td>SCARB2 (AR)</td>
<td>Lysosomal integral membrane protein 2</td>
<td>Action myoclonus-renal failure syndrome: ataxia, myoclonus</td>
</tr>
<tr>
<td>CUBN (AR)</td>
<td>Cubilin: intrinsic factor-cobalamin receptor</td>
<td>Megaloblastic anemia secondary to vitamin B_{12} deficiency, SRNS</td>
</tr>
<tr>
<td>COQ6 (AR)</td>
<td>Coenzyme Q6</td>
<td>Sensorineural hearing loss</td>
</tr>
<tr>
<td>MYH9 (AD)</td>
<td>Nonmuscle myosin 11a</td>
<td>Bleeding diathesis, macrothrombocytopenia, progressive sensorineural deafness, ↑ liver enzyme, cataract</td>
</tr>
<tr>
<td>SMARCAL1 (AR)</td>
<td>SMARCA-like protein</td>
<td>Schimke immune-osseous dysplasia</td>
</tr>
</tbody>
</table>

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

Additional Readings


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


Hyperfiltation-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.

Hyperfiltation-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 effenter 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**


### 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 (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.

**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%)
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

Classification of Podocytopathies Based on Histopathology

MCD is the most common histopathologic finding in nephrotic syndrome in pediatric and geriatric (≥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 as 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, ANCA) 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.

**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/L. 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.
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


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 A2 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 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, daily for 3 years. She is otherwise well and has no history of any other medical conditions.

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/m² 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**


**ESSENTIAL READING**


**Article Information**

* Authors’ Full Names and Academic Degrees*: Wooin 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: aab68@columbia.edu

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