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Management of adult patients with podocytopathies

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are best regarded as histopathological patterns of podocyte injury rather than distinct disease entities, and are therefore grouped under the broader category of podocytopathies. MCD predominantly affect children and accounts for only 10–15% of nephrotic syndrome cases in adults. In contrast, FSGS is one of the leading causes of nephrotic syndrome in the adult population. Although FSGS can be subdivided into several histological variants, these classifications do not reliably reflect the underlying etiology. MCD may arise in primary or genetic forms, with primary disease generally considered to be immune-mediated. FSGS, on the other hand, is classified as primary, secondary, genetic, or of undetermined cause when the underlying mechanism cannot be clearly defined. Immunofluorescence studies are typically negative in these lesions, whereas electron microscopy provides critical diagnostic information by revealing characteristic ultrastructural changes.

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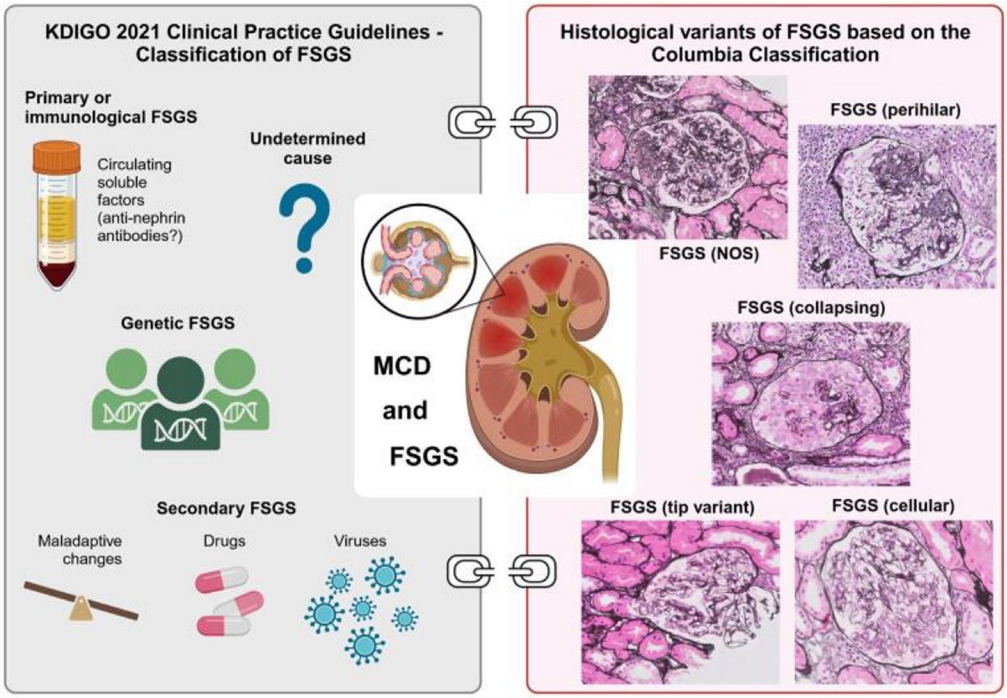


Figure 1.
Etiologic and Histologic Classification of Minimal Change Disease and FSGS within Podocytopathies (Mirioglu et al. 2024)

The degree of foot process effacement (FPE) reflects the extent of podocyte injury and is defined as the percentage of the glomerular capillary wall covered by flattened foot processes. In primary FSGS, effacement is typically diffuse (>80%), whereas in genetic or secondary disease, it is usually less extensive (<50%). However, these thresholds are not absolute, as overlap exists, with some genetic cases showing extensive effacement and occasional primary cases presenting with lower degrees of podocyte injury.

Etiology and pathogenesis of podocytopathies

Pathogenesis of podocytopathies involves injury to the glomerular filtration barrier, composed of the endothelium, the glomerular basement membrane, and the podocyte foot processes. The slit diaphragm, situated between adjacent foot processes, is a key structural element. Nephrin constitutes its backbone and is anchored to the actin cytoskeleton via podocin and synaptopodin proteins. Disruption of this highly specialised complex can compromise barrier integrity, resulting in proteinuria and the development of MCD and FSGS lesions. production

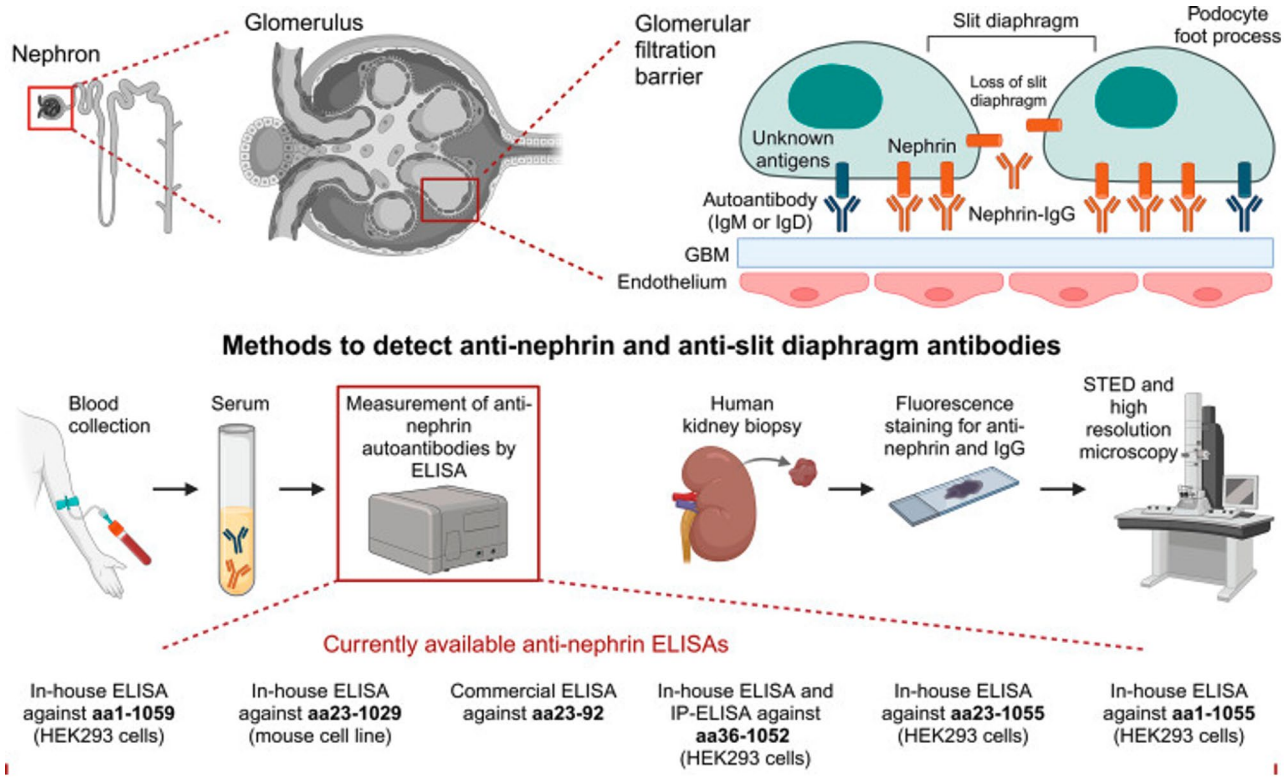


Figure 2.
Currently available methods to detect anti-nephrin and anti-slit diaphragm antibodies (Mirioglu et al. 2025)

The identification of anti-nephrin autoantibodies in 2021 marked a significant advance, with such antibodies detected in approximately 30% of patients with MCD and declining during remission. Since then, multiple studies have reported higher positivity rates, reaching up to 90% in treatment-naïve children, although detection remains challenging due to low antibody titers and lack of standardized assays. Ongoing efforts to improve assay performance include immunoprecipitation-based ELISA techniques, while advanced imaging methods remain largely restricted to specialized centers. In addition to anti-nephrin, autoantibodies targeting other slit diaphragm proteins, such as podocin and Kirrel1, have also been described, although their clinical relevance remains to be established.

Current and emerging therapeutic strategies for podocytopathies

Management of podocytopathies begins with comprehensive supportive care. Dietary sodium restriction is recommended to reduce both proteinuria and blood pressure, while renin–angiotensin system inhibitors (RAASi) should be titrated to the maximally tolerated dose. In addition, sodium–glucose cotransporter 2 (SGLT2) inhibitors are now an established part of standard supportive therapy. Large trials, including DAPA-CKD and EMPA-KIDNEY, have demonstrated notable renal benefits in patients with glomerular disease, but such effects were not clearly evident in the FSGS subgroup, possibly related to the limited sample size. Additional data suggest that SGLT2 inhibitors may stabilize kidney function and reduce proteinuria in patients with podocytopathies.

Additional strategies to manage proteinuria have been explored in the phase III DUPLEX trial. Their results showed that dual endothelin–angiotensin receptor antagonist sparsentan significantly reduced proteinuria compared with irbesartan. However, the primary endpoint of

eGFR slope was not met, and longer follow-up may be necessary to assess its full impact. Supportive care also includes management of complications related to nephrotic syndrome. Patients are at increased risk of thromboembolic events (10–40%) and should be considered for prophylactic anticoagulation where appropriate. Management should also address hyperlipidaemia and oedema, while infection risk should be mitigated, including vaccination under selected circumstances.

Beyond supportive care, treatment of primary podocytopathies relies on immunosuppressive therapy. Current KDIGO guidelines recommend glucocorticoids as first-line therapy in MCD. In frequently relapsing or steroid-dependent disease, cyclophosphamide may be considered in patients without prior exposure, while calcineurin inhibitors (CNIs), mycophenolate mofetil, or rituximab represent effective alternatives. Although cyclophosphamide is effective, its toxicity profile often favours the use of rituximab or CNIs. Similar principles generally apply to FSGS.

The dose and duration of glucocorticoid therapy are critical, as prolonged high-dose exposure is associated with significant morbidity. KDIGO recommends gradual tapering over at least 24 weeks, although shorter regimens are increasingly used in practice, as reflected in the low-dose arm of the TURING trial. Steroid resistance occurs in approximately 8–25% of patients with MCD and is more common in FSGS, affecting up to 50%. In steroid-resistant cases, genetic causes are identified in up to 20% of patients and are associated with a high risk of progression to kidney failure. Lack of response to glucocorticoids remains a key determinant of prognosis. CNIs are used in both steroid-dependent and steroid-resistant disease and are typically continued for at least 12 months in responders. However, relapse after withdrawal is common, and long-term use is limited by nephrotoxicity. Lack of response after six months is generally considered indicative of CNI resistance.

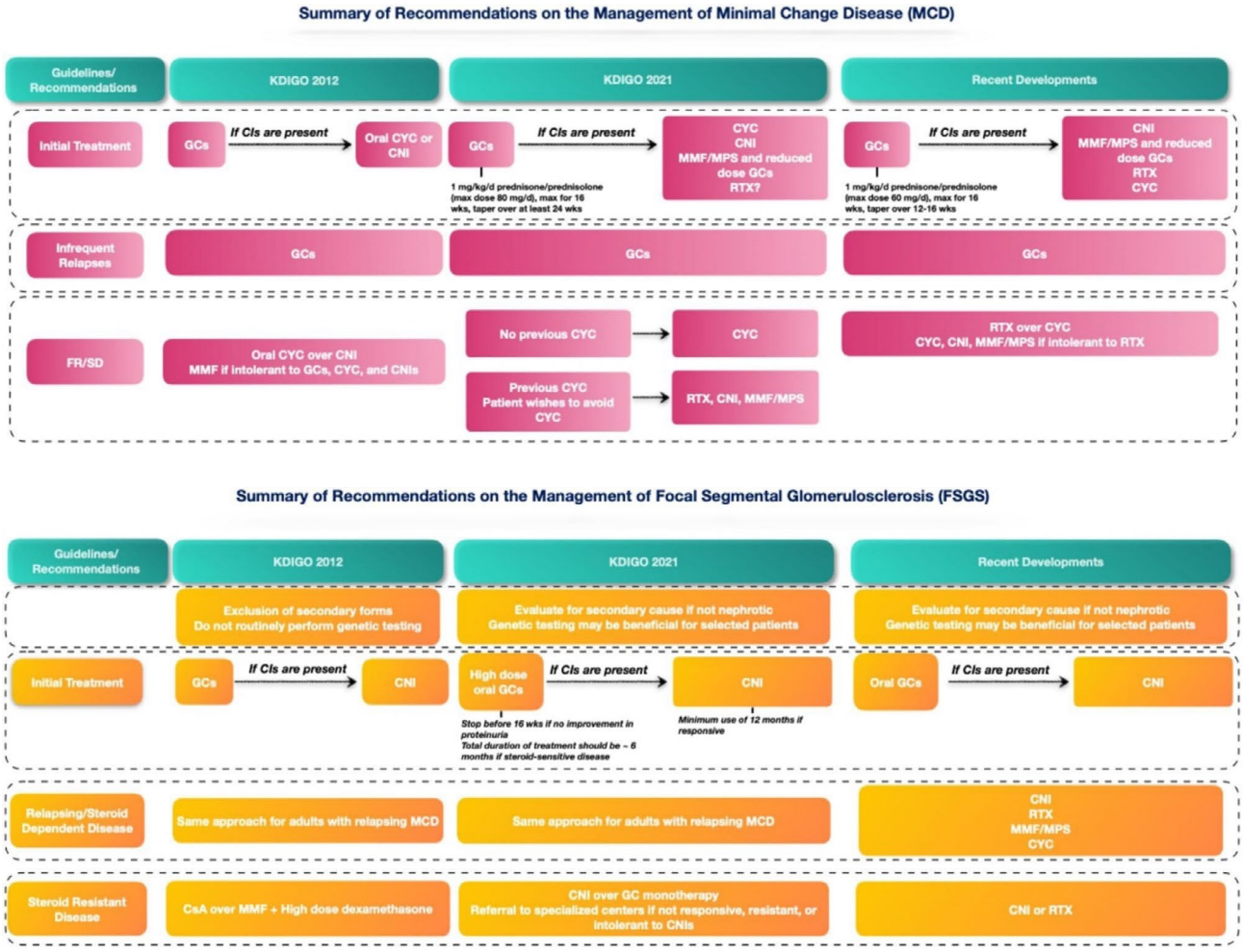
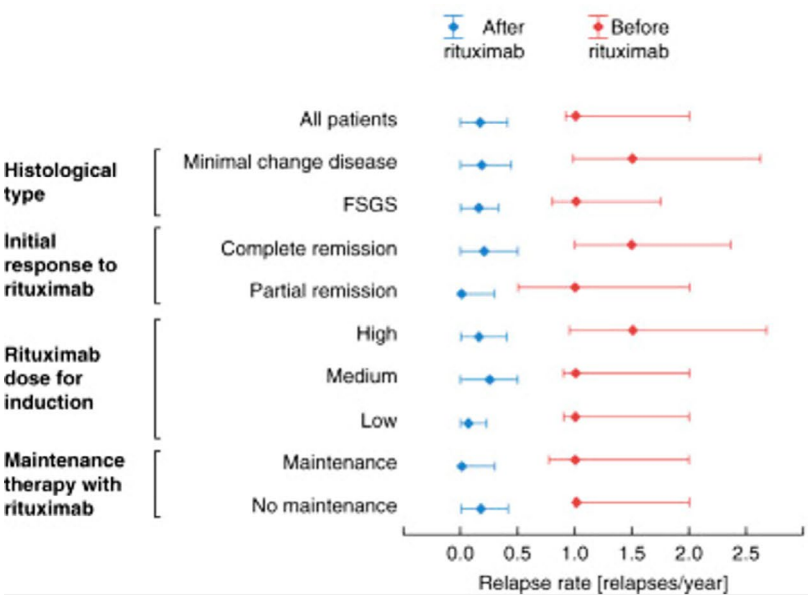


Figure 3.
Recommendations on the management of MCD and FSGS in 2021 KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. Legend: CI: contraindication; CNI: calcineurin inhibitor; CYC: cyclophosphamide; FR: frequently relapsing; GC: glucocorticoid; MMF: mycophenolate mofetil; MPS: mycophenolate sodium; KDIGO: Kidney Disease: Improving Global Outcomes; RTX: rituximab; SD: steroid-dependent (Mirioglu et al, 2024)

Among immunosuppressive strategies, B-cell–targeted therapies have garnered increasing attention. Rituximab reduces relapse rates in steroid-dependent and frequently relapsing nephrotic syndrome, although most evidence derives from cohorts dominated by MCD patients. In FSGS, efficacy is more limited, with more favourable responses observed in steroid-dependent than in steroid-resistant cases. Steroid resistance should prompt evaluation for genetic or secondary causes. These patterns are reflected in larger cohort studies. The RITERM study, which included 183 patients with podocytopathies, reported an overall response rate of 82% over a follow-up period of at least three years. Outcomes differed by subgroup, with lower response rates in steroid-resistant patients (51%) and complete remission in only 18%, particularly in those with FSGS. Maintenance rituximab was associated with longer relapse-free survival, whereas non-response correlated with progressive decline in kidney function.



		Relapse rate		
	n	Before	After	*P* - value
All patients	106	1.00 (0.92-2.00)	0.17 (0.00-0.41)	< 0.001
Minimal change disease	80	1.50 (0.98-2.63)	0.18 (0.00-0.45)	< 0.001
FSGS	26	1.00 (0.80-1.75)	0.16 (0.00-0.33)	< 0.001
Complete remission	79	1.50 (1.00-2.36)	0.20 (0.00-0.50)	< 0.001
Partial remission	27	1.00 (0.50-2.00)	0.00 (0.00-0.30)	< 0.001
High	68	1.50 (0.96-2.68)	0.16 (0.00-0.41)	< 0.001
Medium	29	1.00 (0.90-2.00)	0.25 (0.00-0.50)	< 0.001
Low	8	1.00 (0.90-2.00)	0.25 (0.00-0.50)	0.01
Maintenance	24	1.00 (0.78-2.00)	0.00 (0.00-0.30)	< 0.001
No maintenance	82	1.02 (1.00-2.00)	0.18 (0.00-0.50)	< 0.001

Figure 4.
Relapse rates before and after initiation of rituximab therapy in rituximab responders, RITERM study (Gauckler et al, 2025)

Second-generation anti-CD20 monoclonal antibodies, such as obinutuzumab, may achieve more sustained B-cell depletion. However, their efficacy in steroid-resistant disease remains modest (approximately 50%). Emerging approaches, including chimeric antigen receptor (CAR) T-cell therapies, aim to achieve deeper B-cell depletion, although their role in podocytopathies has yet to be defined. Also, the role of apheresis-based interventions remains limited. Low-density lipoprotein (LDL) apheresis has been proposed in native kidney disease, although supporting evidence is low, whereas plasma exchange or immunoadsorption are primarily used in cases of recurrent disease after transplantation. These strategies may evolve with the broader availability of disease-specific biomarkers such as anti-nephrin antibodies. At the same time, several emerging therapies are under investigation and may further expand treatment options in the near future.

Clinical considerations and patient burden

The clinical burden of podocytopathies should not be underestimated. These conditions impose significant physical and psychosocial strain, often compounded by the adverse effects of prolonged immunosuppressive therapy. A patient-centred approach remains essential. Accurate classification of FSGS is critical, as it directly informs treatment decisions. In clinical practice, distinguishing primary from secondary or genetic forms remains challenging.

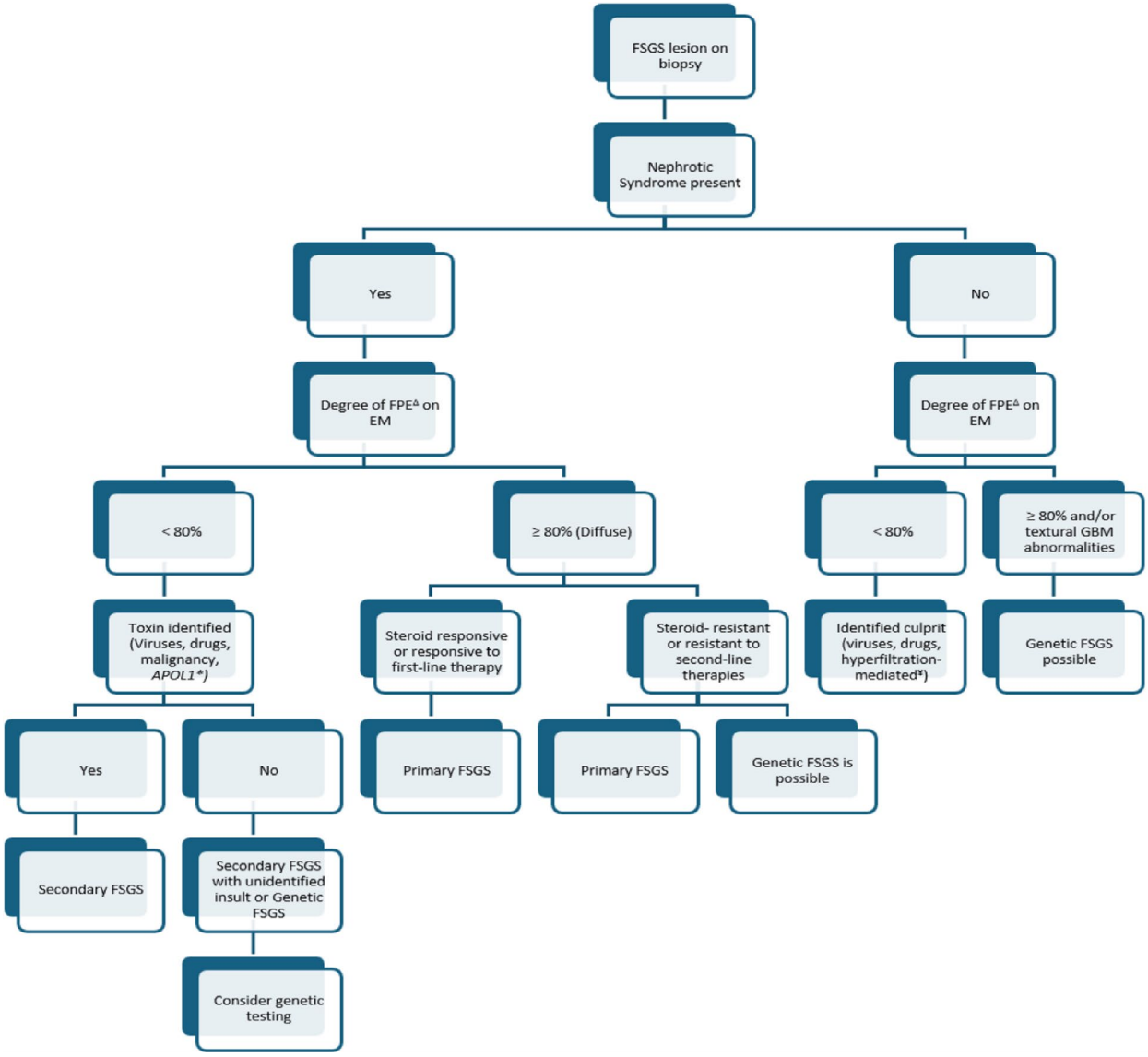


Figure 5.
Algorithm to differentiate primary, secondary, and genetic FSGS based on clinical presentation and electron microscopy findings (Navarro-Torres et al, 2025)

The presence of nephrotic syndrome is a key initial discriminator. In patients without nephrotic syndrome, even with significant proteinuria, preserved serum albumin suggests a non-primary process. In such cases, electron microscopy may be informative: extensive foot process effacement (≥80%) favours a genetic form, whereas more limited effacement suggests secondary disease. In patients with nephrotic syndrome, the degree of foot process effacement and response to therapy are particularly informative. Diffuse effacement, together with response to steroids or calcineurin inhibitors, supports a diagnosis of primary FSGS. In contrast, resistance to therapy raises the possibility of a genetic form, although primary disease cannot be excluded. Lower degrees of effacement are more consistent with secondary or genetic causes, but overlaps exist.

As diagnostic tools evolve, particularly with the development of anti-nephrin and other anti-slit diaphragm antibody testing, current approaches are likely to be refined.

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KEY POINTS

1 MCD and FSGS are histological patterns of podocyte injury grouped as podocytopathies. FSGS is the second most common cause of primary nephrotic syndrome in adults, whereas MCD accounts for 10–15% of adult nephrotic syndrome cases.

2 The presence of nephrotic syndrome, steroid responsiveness, and the degree of foot process effacement can help differentiate primary, secondary, and genetic FSGS.

3 Evidence supports a role for immune mechanisms in primary FSGS pathogenesis, particularly involving autoimmune responses against slit diaphragm proteins such as nephrin.

4 While immunosuppressive therapy is central to treatment, supportive care remains an essential component of management.

5 Glucocorticoids are first-line therapy. Calcineurin inhibitors are effective in both steroid-dependent and steroid-resistant disease, while anti-CD20 agents are mainly beneficial in steroid-dependent cases. Response to steroids remains a key determinant of prognosis.

Written by Jasna Trbojevic-Stankovic.
The speaker reviewed and approved the content.

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Further readings

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