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Chapter 6: Idiopathic focal segmental glomerulosclerosis in adults

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INTRODUCTION

This chapter makes treatment recommendations for adults with biopsy-proven, idiopathic FSGS. The cost implications for global application of this guideline are addressed in Chapter 2.

6.1: Initial evaluation of FSGS

6.1.1: Undertake thorough evaluation to exclude secondary forms of FSGS. (*Not Graded*)

6.1.2: Do not routinely perform genetic testing. (*Not Graded*)

BACKGROUND

The classical description of FSGS includes segmental increase of mesangial matrix with obliteration of the capillaries, sclerosis, hyalinosis, foam cells, and segmental scarring, and adhesion between the glomerular tuft and Bowman's capsule. A recently proposed pathology classification has pointed to the existence of nonsclerotic forms of FSGS.[152] There has been a marked increase in the number of known underlying causes for the lesion of FSGS over the last 10–20 years. Perhaps a consequence of this has been that the incidence, the age of onset, and the clinical presentation have also dramatically altered over this timeframe. FSGS is now one of the most common patterns of glomerular injury encountered in human kidney biopsies,[153,154] and it is the most common cause of proteinuria in the African-American and US Hispanic populations.

RATIONALE

- FSGS should be classified as idiopathic (primary) FSGS or secondary FSGS. This is not merely semantic, but has therapeutic implications. Idiopathic FSGS is defined by exclusion of any other identifiable cause of secondary FSGS.[155] Secondary causes of FSGS are listed in Table 9, and should be evaluated by detailed examination of the patient, including medical history, physical examination, family history, kidney imaging, and kidney pathology, including electron micoscopy studies.[156]
- There are no good data to support genetic testing in adults with FSGS, even in cases of steroid resistance. In the absence of a family history of FSGS, mutations of *NPHS1* (nephrin), *NPHS2* (podocin), *alpha-actinin-4*, *CD2AP*, and *TRPC-6* are detected in only 0–3% of adults with FSGS.[105,157–163] In addition, some patients with a genetic abnormality have responded to therapy, suggesting that the results of genetic analysis should not change treatment decisions.
- African-Americans with FSGS are likely to have mutations in the apolipoprotein L1 (*APOL1*) gene.[164] Most patients will present with non-nephrotic proteinuria. The therapeutic implications of this mutation are currently unknown, so this guideline does not suggest routine testing for *APOL1* mutations.

6.2: Initial treatment of FSGS

6.2.1: We recommend that corticosteroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with clinical features of the nephrotic syndrome. (*1C*)

6.2.2: We suggest prednisone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (*2C*)

6.2.3: We suggest the initial high dose of corticosteroids be given for a minimum of 4 weeks; continue high-dose corticosteroids up to a maximum of 16 weeks, as tolerated, or until complete remission has been achieved, whichever is earlier. (*2D*)

6.2.4: We suggest corticosteroids be tapered slowly over a period of 6 months after achieving complete remission. (*2D*)

6.2.5: We suggest CNIs be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis). (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

BACKGROUND

Patients with FSGS and persistent proteinuria are at increased risk of progressive CKD and its accompanying cardiovascular morbidity and mortality. Risks are dependent on the level of proteinuria and kidney function.

The potential benefit of therapy includes disease cure, control, and/or slowing the progression to ESRD. In FSGS,

Table 9 | Causes of FSGS

Idiopathic (primary) FSGS

Secondary FSGS

1. Familial
   a. Mutations in α-*actinin 4*
   b. Mutations in *NPHS1* (nephrin)
   c. Mutations in *NPHS2* (podocin)
   d. Mutations in *WT-1*
   e. Mutations in *TRPC6*
   f. Mutations in *SCARB2* (LIMP2)
   g. Mutations in *INF2* (formin)
   h. Mutations in CD2-associated protein
   i. Mitochondrial cytopathies

2. Virus associated
   a. HIV-associated nephropathy
   b. Parvovirus B19

3. Medication
   a. Heroin-nephropathy
   b. Interferon-α
   c. Lithium
   d. Pamidronate/alendronate
   e. Anabolic steroids

4. Adaptive structural-functional responses likely mediated by glomerular hypertrophy or hyperfiltration
   4.1 Reduced kidney mass
      a. Oligomeganephronia
      b. Unilateral kidney agenesis
      c. Kidney dysplasia
      d. Cortical necrosis
      e. Reflux nephropathy
      f. Surgical kidney ablation
      g. Chronic allograft nephropathy
      h. Any advanced kidney disease with reduction in functioning nephrons
   4.2 Initially normal kidney mass
      a. Diabetes mellitus
      b. Hypertension
      c. Obesity
      d. Cyanotic congenital heart disease
      e. Sickle cell anemia

5. Malignancy (lymphoma)

6. Nonspecific pattern of FSGS caused by kidney scarring in glomerular disease
   a. Focal proliferative glomerulonephritis (IgAN, LN, pauci-immune focal necrotizing and crescentic GN)
   b. Hereditary nephritis (Alport syndrome)
   c. Membranous glomerulopathy
   d. Thrombotic microangiopathy

FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HIV, Human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; LN, lupus nephritis. Adapted from Deegens JK, Steenbergen EJ, Wetzels JF. Review on diagnosis and treatment of focal segmental glomerulosclerosis. *Neth J Med* 2008; 66: 3–12 with permission from Van Zuiden Communications B.V.;[155] accessed http://www.njmonline.nl/getpdf.php?t=a&id=10000260.

outcome parameters can be divided into kidney and proteinuric events. Disease cure and control are defined primarily by changes in proteinuria (see Table 10).

In most cases of idiopathic FSGS, the natural history of the disease is prolonged, with even complete remitters having a relapse rate of up to 40%. Those with partial remissions still have a risk of slowly progressive loss of kidney function. There is also a significant minority with no response to therapy; hence, the potential benefits of treatment must be constantly weighed against the risks of the chosen immunosuppressive therapy.[13]

Prognosis in patients with idiopathic FSGS is predicted by the severity and persistence of proteinuria. Patients with non-nephrotic proteinuria have a good prognosis, with kidney survival rates of more than 95% after a mean follow-up of 6.5 to 9.3 years,[165–167] even in older studies when few patients, if any, were treated with RAS blockade. The conclusion still seems to be valid, since a very recent study concluded that even partial remission (reduction to non-nephrotic range proteinuria) was associated with significant improvement in kidney survival (80% vs. 40%) compared to no remission.[103]

Many observational studies have demonstrated that remission of proteinuria, whether spontaneous or induced by therapy, is associated with a good outcome.[103,168–171] Many studies have shown, in univariate and multivariate analyses, that development of a remission was associated with prednisone treatment.[103,172–174]

The natural history of primary FSGS with nephrotic syndrome is quite variable. Important predictors are the magnitude of proteinuria, the level of kidney function, and the amount of tubulo-interstitial injury.[101,165,175] Resistance to corticosteroids and immunosuppressive therapy is now considered the strongest predictor of ESRD.[166,176] Prognosis is poor in patients who do not achieve remission, with 5-year kidney survival averaging 65% (60–90%) and 10-year kidney survival 30% (25–56%).[165–167,177]

RATIONALE

- Most patients that progress have persistent nephrotic-range proteinuria; patients with non-nephrotic proteinuria are at low risk for progressive kidney failure and ESRD.
- Those with sustained non-nephrotic proteinuria are at increased risk of cardiovascular morbidity and mortality. Those risks should be managed, including treatment of proteinuria with RAS blockade and control of blood pressure.
- There is low-quality evidence to recommend corticosteroid or immunosuppressive therapy in primary FSGS when accompanied by nephrotic syndrome.
- There is no evidence to suggest corticosteroid or immunosuppressive therapy in secondary FSGS.

RAS Blockade and Blood Pressure Control

Optimal conservative management of patients with FSGS should follow guidelines for patients with persistent proteinuria (see Chapter 2). RAS blockade should be routine; however, it may be delayed in nephrotic syndrome to see if there is a response to initial corticosteroid therapy. This is particularly relevant if the nephrotic syndrome is severe, since the risk of developing AKI due to hypoperfusion and acute tubular necrosis (ATN) is increased in this setting.[148,178]

Table 10 | Definitions of nephrotic syndrome in adults with FSGS

Classification	Definition
Complete remission	Reduction of proteinuria to <0.3 g/d or <300 mg/g (<30 mg/mmol), urine creatinine and normal serum creatinine and serum albumin >3.5 g/dl (35 g/l)
Partial remission[a]	Reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]), urine creatinine and stable serum creatinine (change in creatinine $<25\%$) or Reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]), urine creatinine and a decrease $>50\%$ from baseline, and stable serum creatinine (change in creatinine $<25\%$)
Relapse	Proteinuria >3.5 g/d or >3500 mg/g (>350 mg/mmol) urine creatinine after complete remission has been obtained
Frequent relapse	Not defined in adults
Steroid-dependent	Two relapses during or within 2 weeks of completing steroid therapy
Steroid-resistant	Persistence of proteinuria despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >4 months

FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate.
[a]Both definitions of partial remission have been used in the literature.

Corticosteroids

Corticosteroid therapy should only be considered for patients with idiopathic FSGS associated with nephrotic syndrome. There are no data to support treatment with corticosteroids in patients without nephrotic-range proteinuria and, although there are no RCTs, there are numerous observational studies to support the use of corticosteroids in FSGS when associated with nephrotic-range proteinuria.

Prior to 1985, idiopathic FSGS was considered a steroid-resistant disease with poor outcome.[165] In contrast, observational studies conducted after 1985 have reported better outcomes and suggested that this improvement in response was associated with a higher initial dose and longer duration of treatment with corticosteroids.

Treatment routines have varied with durations from 4 to 24 months, and prednisone dosing from 0.3 to 1.5 mg/kg/d, reported complete remission rates range from 28% to 74%, and partial remission rates from 0% to 50%. The average time to complete remission is 3–4 months, with a range up to 8 months.[166,168,169,171]

The timing of prednisone therapy initiation has been debated. Spontaneous remissions do occur, with reported rates varying from 5% to 23%. Spontaneous remissions are more likely to occur in patients with tip lesions, with preserved kidney function, and lower grades of proteinuria.[179] In such patients, prednisone treatment could be delayed to see if spontaneous remission occurs with RAS blockade and other conservative approaches, but no studies have investigated this approach, or systematically analyzed its risks and benefits.

In the absence of any evidence specific for FSGS, we suggest that the guidelines for adult MCD are used to direct further therapy in steroid-responsive primary FSGS (see Chapter 5).

There is no evidence to support the use of corticosteroids in secondary FSGS and, in current practice, such patients are not treated with immunosuppressive therapy.[180]

Other Immunosuppressive Agents

Adult patients may tolerate poorly the sustained corticosteroid regimen recommended for primary FSGS, but there are no RCTs to support the use of alternative immunosuppressive agents as first-line therapy.

A retrospective observational study compared high-dose oral prednisone (1 mg/kg/d) for at least 4 months and tapering thereafter, with low-dose prednisone (0.5 mg/kg/d) in combination with cyclosporine (3 mg/kg/d initial dose, tapering to 50 mg/d) or azathioprine (2 mg/kg/d initial dose, tapering to 0.5 mg/kg/d). Average duration of treatment was 20 months. Low-dose prednisone was given to 16 patients with obesity, bone disease, or mild diabetes. Remission rates were comparable; 63% for prednisone ($n=9$), 80% for prednisone plus azathioprine ($n=6$), and 86% for prednisone plus cyclosporine ($n=10$).[172] Another study used tacrolimus as initial therapy in six patients and noted a remission in all.[181]

A randomized study in adult patients with FSGS and persistent nephrotic syndrome after 6 months of RAS blockade compared MMF (2 g/d for 6 months) plus low-dose prednisone (0.5 mg/kg/d for 8–12 weeks) to high-dose prednisone (1 mg/kg/d for 12–24 weeks, followed by tapering over 8 weeks). Similar remission rates were observed in the two regimens, 71% (12/17 patients) vs. 69% (11/16 patients).[111] These limited data suggest that patients who do not tolerate prolonged high-dose prednisone might benefit from alternative immunosuppressive agents, alone or in combination with a lower dose of prednisone. A CNI is favored in view of the evidence derived from studies in patients with steroid-resistant FSGS (see below).

6.3: Treatment for relapse

6.3.1: We suggest that a relapse of nephrotic syndrome is treated as per the recommendations for relapsing MCD in adults (see Chapters 5.1 and 5.2). (*2D*)

RATIONALE

- There is very low–quality evidence to guide treatment of relapses in steroid-responsive FSGS. We suggest that the guidelines for relapsing MCD are followed (see Chapter 5.2).

6.4: Treatment for steroid-resistant FSGS

6.4.1: For steroid-resistant FSGS, we suggest that cyclosporine at 3–5 mg/kg/d in divided doses be given for at least 4–6 months. (*2B*)

6.4.2: If there is a partial or complete remission, we suggest continuing cyclosporine treatment for at least 12 months, followed by a slow taper. (*2D*)

6.4.3: We suggest that patients with steroid-resistant FSGS, who do not tolerate cyclosporine, be treated with a combination of mycophenolate mofetil and high-dose dexamethasone. (*2C*)

Table 11 | Treatment schedules

Drug and dosing scheme
Initial treatment
*Prednisone**
1 mg/kg/d in patients (up to a maximum of 80 mg/d) or alternate-day prednisone 2 mg/kg (up to 120 mg) for at least 4 weeks and for a maximum of 4 months; in case of a complete remission, taper prednisone: e.g., reduce dose by 10 mg per 2 weeks down to 0.15 mg/kg/d, then taper dose every 2–4 weeks by 2.5 mg. In SR FSGS patients, taper off prednisone over 6 weeks.
Therapy for SR FSGS
Cyclosporine
3–5 mg/kg/d: in two divided doses (initial target levels 125–175 ng/ml [104–146 nmol/l]); in case of a remission continue treatment for 1 year then try to slowly taper cyclosporine: reduce cyclosporine dose by 25% every 2 months. If no remission by 6 months, discontinue cyclosporine treatment.
Or
Tacrolimus
0.1–0.2 mg/kg/d in two divided doses (initial target levels 5–10 ng/ml [6–12 nmol/l]); in case of remission see advice for cyclosporine.
And
Prednisone
0.15 mg/kg/d for 4–6 months, then taper off over 4–8 weeks.

FSGS, Focal segmental glomerulosclerosis; SR, steroid-resistant.

BACKGROUND

There is no agreement in the literature regarding the duration of prednisone therapy that defines steroid-resistance. Some authors advise the use of alternative immunosuppressive therapy after only 4–8 weeks of prednisone, whereas others define resistance as persistent nephrotic syndrome after 4 months prednisone in a dose of 1 mg/kg/d.[144,170,182,183] We suggest that prednisone be given for 4 months before defining resistance to therapy.

RATIONALE

Cyclosporine is effective in inducing remission of proteinuria in patients with steroid-resistant FSGS. Remissions can develop slowly, and may take 3–6 months after start of therapy.

- A partial remission provides a substantial outcome benefit.
- Relapses are very frequent after withdrawal of cyclosporine. More prolonged treatment may lead to more persistent remissions. Relapses occur frequently when using cyclosporine for a 6-month period. A longer duration of therapy and slow tapering strategy in cyclosporine-responsive patients can be used in FSGS (Table 11) similar to that advised in adults with MCD.
- There is limited evidence to support the efficacy of other regimens in patients with steroid-resistant proteinuria.

CNIs

Two RCTs have shown that cyclosporine is more effective than no treatment in inducing remission of proteinuria in FSGS with SRNS.[110,184,185] In one of the two studies, cyclosporine was combined with low-dose prednisone. These are summarized in Online Suppl Tables 14–16. Remission in the two studies occurred in 60% and 69%, but relapse after cyclosporine withdrawal occurred in 69% and 61%, respectively. An additional benefit to cyclosporine treatment was an attenuated deterioration of kidney function in one study, with doubling of SCr in 25% of treated vs. 52% of control patients. An additional, but low-quality, controlled trial (Online Suppl Tables 14–16) as well as various uncontrolled studies have confirmed that treatment with cyclosporine reduces proteinuria in patients with FSGS.[141,186–189] These observational studies reported remission rates of 10–75%. The variation in reported remission rates may depend on the definition of steroid resistance, the prior use of alkylating agents, and the concomitant use of low-dose prednisone. Remissions usually develop within 2–3 months, but may take longer (4–6 months). All studies report high relapse rates (60–80%). Patients who respond within 6 months to cyclosporine can sometimes be maintained for periods of years without untoward effects on kidney function; however, deterioration of kidney function may occur, even if proteinuria has remitted.[188] Deterioration of kidney function is more likely in patients who use high-dose cyclosporine (>5.5 mg/kg/d), in patients with pre-existing reduced GFR (<60 ml/min per 1.73 m^2) and pre-existent tubulointerstitial fibrosis.[144]

There are no RCTs using tacrolimus. Uncontrolled studies suggest that tacrolimus may be an alternative to cyclosporine.[181,190] Segarra *et al.*[190] treated 25 patients with cyclosporine-resistant or cyclosporine-dependent FSGS. Tacrolimus was used in a dose of 0.15 mg/kg/d and targeted to trough levels of 5–10 μg/l; there was a 100% remission rate in the cyclosporine-dependent patients, 100% in patients who had developed resistance to cyclosporine, and 62% in patients with resistance to the initial treatment with cyclosporine. These limited observational studies suggest tacrolimus may be an alternative in patients intolerant of cyclosporine.

Other Immunosuppressive Agents

A recent RCT compared cyclosporine to the combination of MMF and high-dose dexamethasone in children and young adults with steroid-resistant FSGS.[111] There was no statistically significant difference in remission rates. The study was largely underpowered, and inferiority of the MMF regimen could not be excluded. Case reports and small observational studies have reported response to alkylating agents, sirolimus, and rituximab, but there is insufficient evidence to support the use of any of these agents in patients with steroid-resistant FSGS.

RESEARCH RECOMMENDATIONS

- An RCT is needed of corticosteroid therapy at presentation compared to delayed corticosteroid therapy.
- An RCT is needed to evaluate the comparative efficacy of CNIs, alkylating agents, and MMF in steroid-resistant FSGS.
- Validation studies are needed on the most recent classification of FSGS[152] to test its reproducibility, impact on outcome, and capacity to predict response to corticosteroids and immunosuppressive agents.

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SUPPLEMENTARY MATERIAL

Supplementary Table 14: Evidence profile of studies examining p.o. Cyc plus steroid vs. steroid in steroid-resistant nephrotic syndrome and/or FSGS in children.

Supplementary Table 15: Summary table of studies examining p.o. Cyc plus steroid vs. steroid in children with SRNS or FSGS (categorical outcomes).

Supplementary Table 16: Summary table of studies examining p.o. Cyc plus steroid vs. steroid in children with SRNS or FSGS (continuous outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php