

Chapter 4: Steroid-resistant nephrotic syndrome in children

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INTRODUCTION

This chapter makes treatment recommendations for children aged 1 to 18 years with nephrotic syndrome, who do not achieve a complete remission with corticosteroid therapy, i.e., SRNS. This chapter does not apply to children with SRNS under 1 year of age, nor to SRNS due to histologic patterns of glomerular injury other than MCD, MPGN, or FSGS. The cost implications for global application of this guideline are addressed in Chapter 2.

4.1: Evaluation of children with SRNS

4.1.1: We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (2D)

4.1.2: The following are required to evaluate the child with SRNS (Not Graded):

- a diagnostic kidney biopsy;
- evaluation of kidney function by GFR or eGFR;
- quantitation of urine protein excretion.

BACKGROUND

SRNS generally, and FSGS specifically, is associated with a 50% risk for ESRD within 5 years of diagnosis if patients do not achieve a partial or complete remission.⁸⁶ Persistent nephrotic syndrome is associated with poor patient-reported quality of life, thromboembolic events, hypertension, peritonitis and other serious infections, persistent dyslipidemia, and death.^{92–95} Children reaching ESRD have a greatly reduced life expectancy, 19 years on average following initiation of dialysis, and approximately 40 years following transplantation.⁹⁶

The cumulative burden of ongoing disease-related complications must be measured against potential medication-associated toxicities due to corticosteroids and other immunosuppressive agents. These issues are discussed in Chapter 3, SSNS and in Chapter 1, Introduction.

The potential benefit of therapy includes disease cure, control of nephrotic syndrome, and/or or slowing the progression to ESRD. There are times when the nephrologist, with the child's family or caregivers, will have to accept that a point of futility has been reached, characterized by unremitting and progressive loss of kidney function, resistance to multiple drug therapies, or concern for cumulative drug-associated toxicities.

RATIONALE

- Management of children with SRNS requires confirmation of resistance to corticosteroids, usually defined by unresponsiveness to oral prednisone or prednisolone* for a minimum of 8 weeks.
- Kidney biopsy is necessary to exclude secondary causes of nephrotic syndrome, and assess the extent of interstitial and glomerular fibrosis.
- Kidney function, measured by eGFR, at presentation and its deterioration over time is associated with the long-term risk for kidney failure.
- Quantification of proteinuria is essential, since this provides the comparison for subsequent treatment responsiveness.

*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.

Steroid Resistance

The minimum requirement of corticosteroid exposure to define resistance remains unclear. Variations in the definition of SRNS create difficulties in comparing therapeutic trials. Based upon the International Study of Kidney Disease in Children (ISKDC), 95% of children with SSNS will demonstrate resolution of proteinuria with 4 weeks of daily corticosteroid therapy and 100% after an additional 3 weeks of alternate-day therapy.²⁷ Subsequent studies have reported additional remissions after an extended exposure to steroids in low-dose prednisone control arms within RCTs and after high doses of i.v. or oral corticosteroids in observational studies.^{97,98} It is not clear if these late responses are due to the extended corticosteroid exposure, a late effect of prior therapy, or natural history of the disease. Consequently, we have elected to utilize one of the commonly used definitions of resistance, i.e., a minimum exposure of 8 weeks of prednisone 2 mg/kg/d or 60 mg/m²/d for 4 weeks followed by 1.5 mg/kg or 40 mg/m² per dose alternate-day for 4 weeks.⁹⁹ At this point, steroid resistance dictates the requirement for kidney biopsy to define the histopathology. Steroids may be continued for an additional 4 weeks, totaling 12 weeks, while awaiting histopathology results.

Kidney Biopsy

A kidney biopsy in the evaluation of SRNS is recommended. This evaluation—including light microscopy,

immunofluorescence, and electron microscopy—may indicate disorders that also result in the clinical features of the nephrotic syndrome, e.g., immunoglobulin A nephropathy (IgAN) or LN. The therapy is subsequently dictated by the underlying diagnosis. (See Chapters 10 and 12 for IgAN and LN, respectively.) Alternately, it may show pathologic lesions of FSGS or, despite steroid resistance, still show MCD. In Chapter 2 it was noted that 20 glomeruli are needed in a biopsy to confidently exclude lesions that are affecting only 5% of them; hence, there is a possibility of missing an FSGS lesion in many routine biopsies containing fewer than this number. The kidney biopsy will also provide information regarding the degree of interstitial and glomerular fibrosis, which will be utilized in the assessment of prognosis of children with SRNS. Results of the biopsy are also often used to explain to both patient and family why there has not been a response to therapy, and that the prognosis is likely to be substantially altered from the initial one.

Laboratory Assessment

Kidney function should be measured at the time a diagnosis of SRNS is made to inform prognosis and assessment of response to subsequent therapy. Despite the inaccuracies in eGFR determination in the presence of nephrotic syndrome, kidney function at the time of diagnosis is a predictor of the long-term risk for kidney failure. Proteinuria should be quantified by uPCR to allow subsequent treatment response to be defined as partial, complete, or no remission (Table 1, Chapter 3).^{86,100–103} The uPCR should be measured in a first morning void to prevent variation based upon orthostatic effects.¹⁰⁴ Measurements of 24-hour urine protein may also be used but such collections are impractical in young children who are not toilet-trained. Observational studies of patients with FSGS demonstrate a 5-year kidney survival of 90% in patients with a complete remission following any single or combination of tested therapies.^{86,103} Partial remission has been associated with an intermediate 5-year kidney survival of 80% in adults, although these data are not available for children.¹⁰³ Absence of remission predicts a 5-year kidney survival of approximately 50%.^{86,100,103}

Many genetic mutations have been identified in subjects with SRNS and FSGS. In children with SRNS over 1 year of age, podocin mutations have been reported in 0–30%. The significant variation in the prevalence of SRNS-associated mutations is exemplified by the absence of podocin mutations in an African-American cohort of 18 children with FSGS¹⁰⁵ and the findings of a 28% prevalence of podocin mutations in a European cohort of 25 children published by the same group of investigators.¹⁰⁶ Routine evaluation for genetic mutations is not recommended in this guideline due to the variable availability of genetic testing, significant cost, low to absent prevalence observed in some populations, and the lack of systematic studies of treatment response and prognosis relative to specific genetic polymorphisms.

4.2: Treatment recommendations for SRNS

4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (1B)

4.2.1.1: We suggest that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (2C)

4.2.1.2: We suggest CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (2C)

4.2.1.3: We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (2D)

4.2.2: We recommend treatment with ACE-I or ARBs for children with SRNS. (1B)

4.2.3: In children who fail to achieve remission with CNI therapy:

4.2.3.1: We suggest that mycophenolate mofetil (2D), high-dose corticosteroids (2D), or a combination of these agents (2D) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.

4.2.3.2: We suggest that cyclophosphamide not be given to children with SRNS. (2B)

4.2.4: In patients with a relapse of nephrotic syndrome after complete remission, we suggest that therapy be restarted using any one of the following options: (2C)

- oral corticosteroids (2D);
- return to previous successful immunosuppressive agent (2D);
- an alternative immunosuppressive agent to minimize potential cumulative toxicity (2D).

BACKGROUND

The risk for kidney failure in patients with persistent nephrotic syndrome provides the rationale for utilizing an alternate therapy once steroid resistance has been established.

Both cyclosporine and corticosteroids have a direct effect on the podocyte cytoskeleton,¹⁰⁷ in addition to their immunomodulating properties, indicating these agents may have multiple beneficial mechanisms of action in nephrotic syndrome.

RATIONALE

- There is moderate-quality evidence that cyclosporine induces complete or partial remission in a majority of children with SRNS.
- There is low-quality evidence that tacrolimus has a similar impact on proteinuria control and may improve adherence to treatment, based upon lower risk for hypertrichosis and gingival hyperplasia compared to cyclosporine.

- There is moderate-quality evidence that treatment with renin-angiotensin system (RAS) blockade is associated with a reduction in proteinuria.
- The risk for kidney failure is significantly greater for patients who fail to achieve a partial or complete remission with any single or combination therapy.

CNI Therapy

Cyclosporine has been most widely studied for treatment of SRNS. In three RCTs with 49 patients, 26 treated with cyclosporine and 23 with placebo or control therapy¹⁰⁸⁻¹¹⁰ (Table 5), cyclosporine resulted in a complete remission in 31% and partial remission in 38% during 6 months of therapy. The 69% cumulative complete and partial remission was significantly better than the 0-16% remission in the control arms of these randomized studies. In a single RCT of 138 children and adults comparing cyclosporine (N=72) to mycophenolate combined with high-dose oral dexamethasone (N=66), cyclosporine resulted in a 19.4% complete remission and 26.4% partial remission during 12 months of therapy.¹¹¹ Based upon case series, complete and partial remissions are less common in the presence of nephrotic syndrome associated with podocin mutations. However, remissions have been reported, and suggest that a trial of CNI therapy may induce at least a partial remission even in these patients.¹¹²

Tacrolimus has been compared to cyclosporine in one study with 41 total participants¹¹³ and showed no significant difference in control of proteinuria. In this trial, the frequency of nephrotoxicity, hypertension, and diabetes mellitus were not different between cyclosporine and tacrolimus. The only difference in these agents was in the side-effect profile of hypertrichosis (95% vs. 0%, P < 0.001) and gingival hyperplasia (60% vs. 5%, P < 0.001) cyclosporine vs. tacrolimus, respectively, which may significantly impact adherence to treatment recommendations.

The optimal duration of CNI therapy is unknown. Published RCTs in children have utilized 6- and 12-month treatment phases. Reduction in proteinuria has been documented to occur in 4.4 ± 1.8 weeks,¹⁰⁹ with median times to complete and partial remission of 8 and 12 weeks.¹¹³ Relapse

in up to 70% of those responding to CNI therapy has been documented after discontinuation of 6- and 12-month courses of therapy. Extension of therapy beyond 12 months to prevent relapse is common practice; however, the impact of this approach on relapse risk, long-term kidney function, and risk for nephrotoxicity has not been established. Drug level monitoring is common but optimal levels are unknown for SRNS.

No studies have evaluated cyclosporine alone vs. cyclosporine with low-dose prednisone. Consequently, the necessity of corticosteroids as an adjunct to CNI for SRNS is unknown. A low-dose corticosteroid is recommended here to be consistent with the majority of clinical trials. Tapering of the dose to the lowest level that maintains remission is recommended.

The impact of podocyte-altering genetic polymorphisms on response to immunomodulating therapy has been reported in small genetic SRNS cohort studies with response ranging from 7% to 80% of cohorts (ranging between 4 and 34 subjects).¹¹² No RCTs of SRNS have evaluated the impact of underlying genetic polymorphisms.¹¹⁴

RAS Blockade

RAS blockade in addition to CNI therapy is recommended to reduce proteinuria in SRNS. Two RCTs demonstrated a reduction in proteinuria with ACE-I therapy using enalapril¹¹⁵ and fosinopril.¹¹⁶ A dose-response reduction of proteinuria has been observed: a 33% reduction in proteinuria with a 0.2 mg/kg dose of enalapril, and a 52% reduction in proteinuria with a 0.6 mg/kg dose of enalapril.¹¹⁵

Epidemiologic evidence from retrospective cohort studies in adults and children with FSGS^{99,103} has demonstrated the risk for kidney failure is significantly greater for patients who fail to achieve a partial or complete remission of proteinuria. There are only two published RCTs that provide evidence of the combination of cyclosporine and RAS blockade in SRNS.

ALTERNATIVE THERAPIES TO CNIs

High-dose corticosteroids. There is very low-quality evidence that extended courses of oral or i.v. corticosteroids, following a traditional initial steroid regimen, may increase

Table 5 | CNI trials in SRNS

Author	N	Intervention	Control	Treatment duration (months)	Remission: complete or partial	RR for remission	Conclusion
Lieberman 1996 ¹⁰⁹	24	Cyclosporine	Placebo	6	12 (100%) vs. 2 (17%)	5.48 (1.95-15.44)	Remission cyclosporine > placebo
Ponticelli 1993 ¹¹⁰	17 ^a	Cyclosporine	Supportive therapy	12 ^b	6 (60%) vs. 0 (0%)	9.45 (0.62-1.51)	Remission cyclosporine > control
Garin 1988 ¹⁰⁸	8	Cyclosporine	None	2	0 (0%) vs. 0 (0%)	0 (0.0-0.0)	No significant difference
Choudhry 2009 ¹¹³	41	Tacrolimus + prednisone	Cyclosporine + prednisone	12	18 (86%) vs. 15 (75%)	1.14 (0.84-1.55)	No significant difference
Gipson 2011 ¹¹¹	138	Cyclosporine	MMF + Dexamethasone	12	33 (45.8%) vs. 22 (33%)	1.35 (0.90-2.10)	No significant difference

CNI, calcineurin inhibitor; SRNS, steroid-resistant nephrotic syndrome; RR, relative risk.

^aChildren.

^bSix months full dose followed by taper 25% every 2 months.

Table 6 | Remission in corticosteroid-treated control arms of SRNS randomized trials

Trial	Treatment	Remission outcome	Events	Total N	Response (%)
ISKDC 1974 ⁹⁷	Prednisone	Complete	6	13	46.2
Tarshish 1996 ⁹⁸	Prednisone	Complete or partial	12	21	57.1
Prednisone response		Complete or partial	18	34	52.9
Lieberman 1996 ¹⁰⁹	Placebo	Partial	2	12	16.7
Ponticelli 1993 ¹¹⁰	No Steroids	Complete or partial	0	7	0.0
Garin 1988 ¹⁰⁸	Placebo	Complete	0	4	0.0
No prednisone response		Complete or partial	2	23	8.7

ISKDC, International Study of Kidney Disease in Children; SRNS, steroid-resistant nephrotic syndrome.

Table 7 | Cytotoxic therapy in SRNS

Author	N	Intervention	Control	Remission complete or partial	RR for remission	Conclusion
ISKDC 1974 ⁹⁷	31	Cyclophosphamide p.o. + prednisone 3 mo	Prednisone 3 mo	10 (56%) vs. 6 (46%)	1.20 (0.59–2.47)	ND
Tarshish 1996 ⁹⁸	53	Cyclophosphamide po x 3 mo + prednisone 12 mo q.o.d.	Prednisone 12 mo q.o.d.	16 (50%) vs. 12 (57%)	0.88 (0.53–1.45)	ND

ISKDC, International Study of Kidney Disease in Children; ND, not determined; p.o., orally; q.o.d., every other day; SRNS, steroid-resistant nephrotic syndrome.

the likelihood of remission. In one study, children with SRNS, defined as resistant to 4 weeks daily and 4 weeks alternate day prednisone, received i.v. corticosteroids (methylprednisolone or dexamethasone) for 6 doses combined with oral prednisone, and the short-term outcome was assessed at the end of a 2-week regimen. Because only a minority of those randomized to methylprednisolone actually received that agent, the study is of very low quality. The remaining patients were treated with dexamethasone. Of the 81 subjects treated, 78 were evaluated in the results. The corticosteroid pulse therapy induced a 34% complete remission and 13% partial remission with no significant difference between methylprednisolone and dexamethasone treatment groups.¹¹⁷ The remission response rates from low-dose corticosteroids in small randomized studies in SRNS are summarized in Table 6, and suggest that up to 53% of patients with SRNS achieve remission with extended steroid therapy; 0–17% (mean 8%) achieve remission with no additional therapy.

MMF. A single RCT evaluated MMF in combination with oral dexamethasone vs. cyclosporine. Patients in the MMF arm of this trial had a 33% combined complete and partial remission rate with 12 months of therapy. The study did not demonstrate a significant difference between the treatment arms (see Table 5).¹¹¹ Similarly, observational studies involving children with SRNS who were treated for a minimum of 6 months with mycophenolate demonstrated a complete remission rate from 23% to 62%, a partial remission rate of 25% to 37% and no remission in 8% to 40%.^{116,118}

Cytotoxic agents. There is moderate evidence to suggest that cytotoxic agents in children with SRNS should not be

used, based upon two randomized controlled trials that show no evidence of benefit of these agents combined with prednisone, compared to corticosteroids alone. The evidence is of moderate quality due to the small sample size (Table 7).^{97,98} In the ISKDC trial, there was no significant difference in achieving a complete remission with cyclophosphamide therapy plus corticosteroids compared to corticosteroids alone with 10/18 vs. 6/13 achieving complete remission in the combined-therapy group vs. corticosteroids alone group and an increase in adverse events.¹¹⁹ Although imprecision may affect this risk estimate, the RR and CI are centered around 1. In the Tarshish trial comparing cyclophosphamide plus corticosteroids vs. corticosteroids alone, there was also no evidence of benefit with the addition of cyclophosphamide, i.e., 16/32 with combination vs. 12/21 monotherapy ($P = NS$). One additional randomized trial compared cyclophosphamide ($N = 17$) to cyclosporine ($N = 15$). The study was halted at week 12 according to predefined stopping rules, due to the significant difference between the combined complete and partial remission rates of 60% in cyclosporine group and 17% in the cyclophosphamide group ($P < 0.05$).¹²⁰ At the present time, the potential harm from cytotoxic agents—including serious infections, increased risk for late onset malignancy, reduced fertility, hemorrhagic cystitis, and alopecia—far exceeds any evidence of benefit (Online Suppl Table 14).⁴³

Rituximab. Rituximab is not recommended as a treatment option for SRNS due to the lack of RCTs and risk for serious adverse events, which may persist long after the discontinuation of the therapy.⁸² Although this may be a promising agent, prospective randomized studies are required.

Relapsing Disease

In SRNS patients with relapse after complete remission, we suggest that immunosuppressant therapy be reinstated. This recommendation is based upon the concern that uncontrolled SRNS is likely to lead both to complications from the persistent nephrotic state as well as a high risk for kidney failure. We have no evidence in the literature to support a specific treatment choice. Options are provided without prioritization, and include oral corticosteroids, a return to the previously effective immunosuppressant agent, or the selection of an alternate immunosuppressant agent to avoid potential toxicity. Assessment of risk vs. benefit needs reassessment and becomes more relevant with each relapse.

RESEARCH RECOMMENDATIONS

- RCTs are needed in resistant nephrotic syndrome comparing CNIs to alternate immunosuppressive and nonimmunosuppressive agents.
- Investigation of treatment options is needed for patients with nephrotic syndrome associated with genetic mutations.
- RCTs are needed examining rituximab therapy for SRNS.

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SUPPLEMENTARY MATERIAL

Supplementary Table 8: Evidence profile of RCTs examining CsA vs. placebo in steroid-resistant nephrotic syndrome in children.

Supplementary Table 9: Meta-analyses and systematic reviews on steroid-resistant nephrotic syndrome in children.

Supplementary Table 10: Evidence profile of studies examining CsA vs. Cyc treatment in children with steroid-resistant nephrotic syndrome.

Supplementary Table 11: Summary table of studies examining CsA vs. Cyc treatment in children with steroid-resistant nephrotic syndrome (categorical outcomes).

Supplementary Table 12: Evidence profile of RCTs examining ACE-I treatment for steroid-resistant nephrotic syndrome in children.

Supplementary Table 13: Summary table of RCTs examining ACE treatment for steroid-resistant nephrotic syndrome in children (continuous outcomes).

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 Table 17: Summary table RCTs examining IV vs. p.o. Cyc treatment in children with steroid-resistant nephrotic syndrome (continuous outcomes).

Supplementary Table 18: Summary table of RCT examining TAC vs. CsA treatment in children with steroid-resistant nephrotic syndrome (categorical outcomes).

Supplementary Table 19: Summary table of RCT examining TAC vs. CsA treatment in children with steroid-resistant nephrotic syndrome (continuous outcomes).

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