Chapter 3: Steroid-sensitive 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 respond to corticosteroid therapy by achieving complete remission (SSNS). The cost implications for global application of this guideline are addressed in Chapter 2. This chapter does not apply to children under 1 year of age in whom nephrotic syndrome is often associated with gene mutations and with histologies other than MCD.

3.1: Treatment of the initial episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (*1B*)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m^2/d or 2 mg/kg/d to a maximum 60 mg/d. (*1D*)

3.1.1.2: We recommend that daily oral prednisone be given for 4–6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2–5 months with tapering of the dose. (*1B*)

*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

Nephrotic syndrome affects 1–3 per 100,000 children below 16 years of age.[14] Eighty percent of children respond to corticosteroid therapy.[14] A kidney biopsy diagnosis is not required routinely at presentation because the International Study of Kidney Disease in Children (ISKDC) demonstrated that, while 93% of children with MCD responded to corticosteroids, 25–50% of children with mesangial proliferative glomerulonephritis (MPGN) or FSGS also responded to corticosteroids.[15] The majority of children who relapse continue to respond completely to corticosteroids throughout their subsequent course, and the long-term prognosis, including maintenance of normal kidney function, is good.[16–18] In contrast, without treatment, nephrotic syndrome in children is associated with high risk of death, particularly from bacterial infection. Before the use of corticosteroids and antibiotics, 40% of children died, with half of these deaths being from infection.[19] A recent study reports only one death (0.7%) associated with nephrotic syndrome among 138 children with SSNS presenting between 1970 and 2003.[20]

The definitions used for nephrotic syndrome, complete remission, initial responder, initial and late steroid non-responders (steroid resistance), infrequent relapses, frequent relapses and steroid dependence are listed in Table 1. The likelihood of initial corticosteroid unresponsiveness is increased with increasing age at presentation,[14] in African and African-American children,[21] and in children with kidney pathologies other than MCD.[15] The likelihood of late resistance to corticosteroids is associated with a shorter interval to the first relapse, and relapsing during the initial course of corticosteroid therapy.[22]

RATIONALE

- There is moderate-quality evidence that administering prednisone for three months reduces the risk of relapse in children with the first episode of SSNS, with an increase in benefit seen with up to 6 months of treatment.
- There is moderate-quality evidence that corticosteroid therapy should be given as a single daily dose for at least 4 weeks, followed by alternate-day therapy for 2–5 months.
- The initial dose regimen of corticosteroid therapy is based on recommendations from the ISKDC, and has not been defined in RCTs.

Corticosteroid Use in the First Episode of SSNS in Children

With corticosteroid therapy, 80–90% of patients with childhood nephrotic syndrome achieve complete remission.[14,17] However, 80–90% of these children have one or more relapses[17,18] following the 2-month steroid regimen proposed by the ISKDC[23] and adapted by Arbeitsgemeinschaft für Pädiatrische Nephrologie.[24] Therefore, RCTs have evaluated the benefits of increased duration of therapy for the initial episode of SSNS. A meta-analysis[25] of six RCTs (422 children) demonstrated that the risk of relapse at 12–24 months was reduced by 30% (risk ratio of relapse 0.70; 95% confidence intervals [CI] 0.58–0.84) with 3 months or more of corticosteroid therapy compared to 2 months. There was

Table 1 | Definitions of nephrotic syndrome in children

Classification	Definition
Nephrotic syndrome	Edema, uPCR $\geqslant$2000 mg/g ($\geqslant$200 mg/mmol), or $\geqslant$300 mg/dl, or 3+ protein on urine dipstick, hypoalbuminaemia $\leqslant$2.5 g/dl ($\leqslant$25 g/l)
Complete remission	uPCR $<$200 mg/g ($<$20 mg/mmol) or $<$1+ of protein on urine dipstick for 3 consecutive days
Partial remission	Proteinuria reduction of 50% or greater from the presenting value and absolute uPCR between 200 and 2000 mg/g (20–200 mg/mmol)
No remission	Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR $>$2000 mg/g ($>$200 mg/mmol)
Initial responder	Attainment of complete remission within initial 4 weeks of corticosteroid therapy
Initial nonresponder/ steroid resistance	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
Relapse	uPCR $\geqslant$2000 mg/g ($\geqslant$200 mg/mmol) or $\geqslant$3+ protein on urine dipstick for 3 consecutive days
Infrequent relapse	One relapse within 6 months of initial response, or one to three relapses in any 12-month period
Frequent relapse	Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy
Late nonresponder	Persistent proteinuria during 4 or more weeks of corticosteroids following one or more remissions

uPCR, urine protein:creatinine ratio.

an inverse linear relationship between duration of treatment and risk of relapse seen when prednisone was given for up to 6 months (risk ratio = 1.26 –0.112 duration; $r^2 = 0.56$, $P = 0.03$).[25] Also a meta-analysis[25] of four RCTs (382 children) identified that treatment for 6 months significantly reduced the risk of relapse at 12–24 months compared to 3 months (RR 0.57; 95% CI 0.45–0.71). No significant differences in the incidence of adverse effects between treatment groups were demonstrated. However, individual trials were not designed specifically to study harm, and so were underpowered for the detection of side-effects of corticosteroids.[25]

There are no RCTs examining different initial doses of corticosteroid for the first episode of childhood nephrotic syndrome. A dose of prednisone 60 mg/m^2/d was recommended empirically by the ISKDC in 1979; this is roughly equivalent to 2 mg/kg. Although theoretical studies indicate that dosing for body weight results in a lower total dose compared to dosing for surface area, there are no data on whether this is of clinical relevance, so either method of calculating prednisone dose may be utilized.[26] Two RCTs have demonstrated that the mean time to remission did not differ significantly when daily corticosteroid therapy was given as a single daily dose compared to divided doses (weighted mean difference 0.04 days; 95% CI −0.98–1.06).[25]

The majority (94%) of children respond to corticosteroids within 4 weeks of daily prednisone therapy.[27] To reduce the risk of relapse, prednisone should be given daily for at least 4 weeks in the initial episode of nephrotic syndrome. In an RCT, the risk of relapse was significantly higher at 6 months and 12 months when prednisone was given for 1 month compared to 2 months (RR 1.46; 95% CI 1.01–2.12 at 12 months).[28] Prednisone should be given on alternate days after 4 weeks of daily treatment rather than on 3 consecutive days out of 7 days, based on an RCT that showed the former had a lower risk of relapse.[29] Alternate-day (rather than daily) prednisone is suggested to maintain remission, because linear growth is less affected.[30] Although widely used particularly in France,[31] there is no evidence to support the administration of high-dose i.v. methylprednisolone to a child with nephrotic syndrome, who has not achieved remission after 4 weeks of daily corticosteroids, before labeling that child as steroid-resistant.

3.2: Treatment of relapsing SSNS with corticosteroids

3.2.1: Corticosteroid therapy for children with infrequent relapses of SSNS:

3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (*2D*)

3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (*2C*)

3.2.2: Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:

3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)

3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)

3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)

3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)

BACKGROUND

Children with nephrotic syndrome who respond to corticosteroids have an 80–90% chance of having one or more relapses.[17,18] Half of those that relapse have infrequent relapses and can be managed with short courses of prednisone. The remaining children have FR or SD SSNS.[17,18] The risks of a child developing frequent relapses or becoming steroid-dependent are increased with shorter time to first relapse,[32] the number of relapses in the first 6 months after initial treatment,[15,18] younger age at the initial episode,[33,34] in boys,[34] prolonged time to first remission,[31,35] infection at first relapse,[32] and hematuria in first episode.[35] The most consistent indicator for a frequently relapsing course is early relapse after initial treatment. Studies have not assessed whether the other factors are independent risk factors for predicting frequent relapses or steroid dependence. Children with FR or SD SSNS, and children whose first episode of SSNS occurred at a young age, have a longer duration of relapsing or SD nephrotic syndrome compared to children with infrequent relapses or older age of onset.[16,33] Corticosteroids are needed to achieve remission, and low doses given on alternate days may maintain remission in patients with FR SSNS without recourse to corticosteroid-sparing agents. Low-dose daily or alternate-day corticosteroids may still be required to maintain remission in SD SSNS, despite receiving corticosteroid-sparing agents.

RATIONALE

- In children with infrequent relapses of SSNS, corticosteroid therapy regimens are based on empirical recommendations from the ISKDC and an RCT in children with FR SSNS.
- In children with FR and SD SSNS, there is low-quality evidence that increasing the duration of corticosteroid therapy increases the duration of remission.
- In children with SD SSNS, there is low-quality evidence that changing children from alternate-day to daily corticosteroids at onset of upper respiratory infections reduced the risk of relapse.
- In children with FR and SD SSNS, there is very low–quality evidence that low-dose alternate-day or daily corticosteroid therapy reduces the risk of relapse.

Corticosteroid Use in Relapses in Children with Infrequent Relapses of SSNS

There are no RCTs examining relapse regimens with corticosteroids in infrequently relapsing SSNS. In children with frequently relapsing SSNS, the ISKDC demonstrated that the number of relapses in the 7 months after treatment did not differ significantly between children treated with 8 weeks of daily prednisone compared to daily prednisone till remission followed by 4 weeks of prednisone given on 3 consecutive days out of 7 days (further relapse by 9 months RR 1.07; 95% CI 0.77–1.50).[25] Based on these data we suggest that children with infrequently relapsing SSNS should receive daily corticosteroids only until remission followed by four weeks of alternate day prednisone.

Corticosteroid Therapy in Frequently Relapsing (FR) and Steroid-Dependent (SD) SSNS in Children

Approximately 40% of children with SSNS have FR or SD SSNS. A single RCT in children with relapsing nephrotic syndrome demonstrated that the risk of relapse at 12 and 24 months was significantly reduced with prednisone treatment for 7 months compared to 2 months of therapy.[25] These data, and the data on prednisone duration in the initial episode of SSNS, suggest that it is reasonable to treat a child with FR or SD SSNS with longer corticosteroid regimens than those suggested for children who relapse infrequently. Three RCTs have demonstrated that daily prednisone dose during upper respiratory tract and other infections reduced the risk for relapse in children with SD SSNS.[25,36,37]

To maintain remission in children with SD SSNS, prednisone may be given on alternate days in the lowest dose possible to maintain remission. An observational study demonstrated that low-dose alternate-day prednisone (mean dose 0.48 mg/kg on alternate days) reduced the risk of relapse in FR SSNS compared to historical controls.[38] Guidelines from the British Association of Paediatric Nephrology recommend that children with SD SSNS receive 0.1–0.5 mg/kg on alternate days for at least 3–6 months before tapering.[39] Guidelines from the Indian Paediatric Nephrology Group recommend that the prednisone dose be tapered to 0.5–0.7 mg/kg on alternate days or lower, and continued for 9–18 months with careful monitoring of corticosteroid toxicity.[40] A nonrandomized comparator study indicated that low-dose daily prednisone (0.25 mg/kg) was more effective in maintaining remission compared to historical controls not treated with low-dose prednisone with a reduction in relapse rate from 2.25 per patient per year to 0.5 per patient per year.[41]

3.3: Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.1: We recommend that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (*1B*)

3.3.2: We recommend that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (*1B*) We suggest that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (*2C*)

3.3.2.1: We suggest that cyclophosphamide (2 mg/kg/d) be given for 8–12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)

3.3.2.2: We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (*2D*)

3.3.2.3: We suggest that chlorambucil (0.1–0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)

3.3.2.4: We suggest that second courses of alkylating agents not be given. (*2D*)

3.3.3: We recommend that levamisole be given as a corticosteroid-sparing agent. (*1B*)

3.3.3.1: We suggest that levamisole be given at a dose of 2.5 mg/kg on alternate days (*2B*) for at least 12 months (*2C*) as most children will relapse when levamisole is stopped.

3.3.4: We recommend that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (*1C*)

3.3.4.1: We suggest that cyclosporine be administered at a dose of 4–5 mg/kg/d (starting dose) in two divided doses. (*2C*)

3.3.4.2: We suggest that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (*2D*)

3.3.4.3: Monitor CNI levels during therapy to limit toxicity. (*Not Graded*)

3.3.4.4: We suggest that CNIs be given for at least 12 months, as most children will relapse when CNIs are stopped. (*2C*)

3.3.5: We suggest that MMF be given as a corticosteroid-sparing agent. (*2C*)

3.3.5.1: We suggest that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (*2C*)

3.3.6: We suggest that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (*2C*)

3.3.7: We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*2C*)

3.3.8: We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*1B*)

BACKGROUND

About half of the children with SSNS who relapse will have FR or SD SSNS.[17,18] The long-term prognosis for most children with SSNS is for complete resolution of their disease over time and maintenance of normal kidney function. Therefore limiting the long-term adverse effects of treatment is an important objective. Children with FR or SD SSNS require prolonged corticosteroid therapy, which is associated with significant adverse effects. including impaired linear growth, behavioral changes, obesity, Cushing's syndrome, hypertension, ophthalmological disorders, impaired glucose tolerance, and reduced bone mineral density. Adverse effects may persist into adult life in young people, who continue to relapse after puberty.[42] To reduce the risk of corticosteroid-related adverse effects, children with FR or SD SSNS may require other agents, including alkylating agents (cyclophosphamide, chlorambucil) and CNI (cyclosporine, tacrolimus). Adverse effects of these agents include increased risk of infection and reduced fertility (alkylating agents)[42,43] and kidney dysfunction and hypertension (CNI).[44] CNIs and MMF are much more expensive than the other agents, and this may limit access to them in many countries.

RATIONALE

In children with FR and SD SSNS:

- There is moderate-quality evidence to support the use of alkylating agents (cyclophosphamide, chlorambucil), levamisole, and CNI (cyclosporine, tacrolimus).
- There is low-quality evidence to support the use of mycophenolate mofetil (MMF).
- There is very low–quality evidence to support the efficacy of rituximab.
- There is moderate-quality evidence to demonstrate that mizoribine and azathioprine are not effective.

Children with FR or SD SSNS often continue to relapse into adolescence or adulthood, and require prednisone in variable doses for long periods of time to achieve and maintain remission. Patients successfully treated with corticosteroid-sparing therapy have improved growth rates, reduced body mass index, reduction of Cushingoid features, and improvement in other corticosteroid-related adverse effects.[45–48] In all cases when contemplating corticosteroid-sparing therapy, the adverse effects of such therapy must be assessed against the benefits, in terms of reducing both the relapse rate and adverse effects of corticosteroids.

Fourteen RCTs in children have compared cyclophosphamide (three trials), chlorambucil (two trials), levamisole (six trials), mizoribine (one trial), and azathioprine (two trials) to placebo, no specific treatment, or prednisone in children with FR and/or SD SSNS. Trials either did not differentiate between FR and SD SSNS, or included only SD SSNS patients. Cyclophosphamide, chlorambucil, and levamisole reduced the risk of relapse during short term follow up (6–12 months) by more than 50% (Table 2). Two RCTs demonstrated no significant differences in the risk of relapse

Table 2 | Meta-analyses of RCTs of corticosteroid-sparing agents in children with FR or SD SSNS

Agent	*N* of RCTs	*N* of patients	Risk ratio of relapse (95% CI)	Time of outcome (months)	Relative risk reduction
Cyclophosphamide[a]	3	102	0.44 (0.26,0.73)	6–12	56%
Chlorambucil[b]	2	32	0.13 (0.03,0.57)	12	87%
Levamisole[c,d]	5	269	0.43 (0.27,0.68)	4–12	57%
Mizoribine[e]	1	197	Relapse rate ratio[f] 0.81 (0.61, 1.05)	18	Not significant
Azathioprine[g]	2	60	0.90 (0.59,1.38)	6	Not significant

CI, confidence interval; FR, frequently relapsing; RCT, randomized controlled trial; SD, steroid-dependent; SSNS, steroid-sensitive nephrotic syndrome.
[a]Cyclophosphamide and prednisone vs. prednisone.
[b]Chlorambucil and prednisone vs. prednisone, or vs. placebo and prednisone.
[c]Levamisole and prednisone vs. placebo and prednisone, levamisole and prednisone vs. prednisone, levamisole vs. prednisone, Levamisole vs. no specific therapy.
[d]One trial using much lower dose of levamisole was excluded (see text).
[e]Mizoribine and prednisone vs. placebo and prednisone.
[f]Relapse risk ratio = [Total number of relapses ÷ observation period in treatment group] ÷ [Total number of relapses ÷ observation period in control group].
[g]Azathioprine and prednisone vs. placebo and prednisone, azathioprine and prednisone vs. prednisone.
Data from Hodson *et al.*[49]

between cyclosporine and cyclophosphamide, or between cyclosporine and chlorambucil during cyclosporine treatment. RCTs have identified no significant differences in the risk for relapse between levamisole and i.v. cyclophosphamide, and between oral cyclophosphamide and oral chlorambucil.[49]

Alkylating Agents

Alkylating agents (cyclophosphamide, chlorambucil) may result in prolonged remission off all therapy, though they may have significant adverse effects. In RCTs with 6–12 months of follow-up, alkylating agents reduced the risk of relapse compared to prednisone, placebo, or no specific treatment by about 65% (RR 0.34; 95% CI 0.18–0.63)[49] (Table 2). In a systematic review of observational studies and RCTs, alkylating agents in FR SSNS resulted in remission rates of 72% after 2 years but sustained in only 36% after 5 years. These agents were less effective in SD SSNS with remission rates of 40% and 24% after 2 and 5 years, respectively.[43] Patients younger than 3 years at onset of SSNS[50] and those commencing cyclophosphamide before 3.8 years[51] were less likely to achieve long-term remission with cyclophosphamide, while children aged over 7.5 years were more likely to achieve long-term remission.[51] Eight weeks of cyclophosphamide therapy was significantly more effective in reducing the risk for relapse compared to 2 weeks (Table 3). In SD SSNS patients, there was no significant difference in the risk of relapse between 8 and 12 weeks of cyclophosphamide therapy in one RCT (Table 3). However, the Arbeitsgemeinschaft für Pädiatrische Nephrologie concluded that 12 weeks of cyclophosphamide was more effective compared to historical controls treated for 8 weeks.[52] Cyclophosphamide is associated with hemorrhagic cystitis but this rarely occurs at the doses used. Nevertheless, where possible, cyclophosphamide should be administered when the child is in remission, with a good urine output, and can receive a high fluid intake. The i.v. route may be considered where nonadherence to therapy is likely. Two RCTs found no significant difference in the risk of relapse between oral and i.v. cyclophosphamide at 12–24 months follow-up. However, at 6 months, significantly more children treated with monthly pulses of i.v. cyclophosphamide for 6 months were in remission, compared to oral treatment for 8–12 weeks (Table 3; Online Suppl Tables 1–3). Studies have demonstrated the efficacy of chlorambucil at doses of 0.1–0.2 mg/kg/d given for 8 weeks (cumulative dose 11.2 mg/kg) (Table 2). Higher doses did not increase efficacy and resulted in increased risks, particularly of hematological and infectious adverse effects.[53]

It is suggested that second courses of alkylating agents not be given. Gonadal toxicity with alkylating agents is well documented, with males more affected than females. There is a dose-dependent relationship between the total dose of cyclophosphamide and probability of sperm counts below 10^6/ml. A "safe" dose of cyclophosphamide remains unclear, but a maximum cumulative dose of 168 mg/kg (2 mg/kg/d for 12 weeks) in boys is below the total dose ($>$200–300 mg/kg) at which azoospermia has generally been reported.[43,54] There are fewer data available on chlorambucil, but studies in patients treated for lymphoma found that azoospermia was associated with total doses of 10–17 mg/kg, suggesting that the margin between efficacy and toxicity is narrow for chlorambucil.[55] Studies have reported a higher risk of malignancy following chlorambucil use compared to cyclophosphamide.[43]

Levamisole

Five of six RCTs have demonstrated a significant reduction in the risk for relapse during levamisole treatment compared to prednisone, placebo, or no specific treatment[49] (Table 2). In four of these five RCTs that involved children with FR or SD SSNS, levamisole was given at a dose of 2.5 mg/kg on alternate days. In the sixth trial, a smaller dose (2.5 mg/kg of levamisole on 2 consecutive days per week) did not reduce the risk of relapse compared to placebo.[56] Most children relapse when levamisole was discontinued. Observational studies have documented a more prolonged reduction in relapse frequency when it is used for 12–24 months.[57–59] Adverse effects of levamisole are uncommon and minor, with mild leucopenia and gastrointest-

Table 3 | RCTs comparing corticosteroid-sparing agents in FR and SD SSNS

Agents	*N* of RCTs	*N* of patients	Risk ratio of relapse (95% CI)	Time of outcome (months)	Conclusion
Cyclophosphamide 8 wk vs. 2 wk	1	29	0.25 (0.07, 0.92)	12	8 wk significantly more effective
Cyclophosphamide 8 wk vs. 12 wk	1	73	0.98 (0.74, 1.28)	24	No significant difference
Cyclophosphamide 8 wk vs. chlorambucil 8 wk	1	50	1.15 (0.69, 1.94),	12	No significant difference
i.v. vs. oral cyclophosphamide	2	83	0.99 (0.76, 1.29)	12–24	No significant difference
Cyclophosphamide vs. cyclosporine	1	55	1.07 (0.48, 2.35)	9	No significant difference during therapy
Chlorambucil vs. cyclosporine	1	40	0.82 (0.44, 1.53)	6	No significant difference during therapy
i.v. cyclophosphamide vs. levamisole	1	40	1.00 (0.7, 1.43)	12	No significant difference
Mycophenolate vs. cyclosporine	1	24	5.0 (0.68, 36.66)	12	No significant difference (small numbers)
Cyclosporine 5 mg/kg vs. 2.5 mg/kg	1	44	Hazard ratio 0.37 (0.18, 0.79)	24	Higher dose significantly more effective

CI, confidence interval; FR, frequently relapsing; RCT, randomized controlled trial; SD, steroid-dependent; SSNS, steroid-sensitive nephrotic syndrome.
Data from Hodson *et al.*[49]

inal upsets described. Rare cases of cutaneous vasculitis have been described with levamisole therapy.[60] Levamisole is unavailable in many countries.

CNIs

Two RCTs have demonstrated no significant differences in the risk of relapse between cyclosporine during treatment and cyclophosphamide or chlorambucil during treatment.[61,62] However, cyclosporine has a higher relapse rate compared to alkylating agents when assessed at 12–24 months after treatment. An RCT from Japan reported that 50% of 49 children treated with cyclosporine relapsed compared to 70% of 59 children treated with placebo during the 24 weeks of therapy.[63] In observational studies, cyclosporine maintains remission in 60–90% of children with SD SSNS, who had relapsed after alkylating-agent therapy.[64–66] However, in children with SD SSNS due to biopsy-proven MCD, only 40% remained in remission after 2 years of therapy and all relapsed within a median of 26 days when cyclosporine was discontinued.[65] Most studies have used cyclosporine at 3–6 mg/kg/d in two divided doses targeting 12-hour trough levels of 80–150 ng/ml [67–125 nmol/l] with maintenance of lower levels after a child has been in stable remission for 3–6 months, aiming to minimize cyclosporine nephrotoxicity. In an RCT the sustained remission rate was significantly higher in children maintaining a 12-hour cyclosporine trough level of 60–80 ng/ml [50–67 nmol/l] (mean dose 4.7 mg/kg/d) compared to children treated with 2.5 mg/kg/d (Table 3, Online Suppl Tables 6–7).[67] Limited data suggest peak (C2) levels rather than trough (C0) levels can be used for monitoring.[68]

Tacrolimus has not been studied in RCTs in children with SSNS. Tacrolimus is widely used in North America in children with FR and SD SSNS, because of the cosmetic side effects of cyclosporine. There are few data to support its use, though its efficacy would appear to be similar to that of cyclosporine based on an observational study in SD SSNS.[69] The tacrolimus dose is adjusted to maintain the 12-hour trough levels in the range of 5–10 ng/ml [6–12 nmol/l] initially based on data from kidney transplant studies.

The principal side-effects of cyclosporine are kidney dysfunction, hypertension, gum hypertrophy, and hypertrichosis. Hypertension and kidney dysfunction are reported in 5–10% of children.[49,64,66] Hypertrichosis and gum hypertrophy develop in 70% and 30%, respectively, in children treated with cyclosporine for more than 1 year.[64] Tacrolimus also causes kidney dysfunction and hypertension, but significantly less hypertrichosis; tacrolimus-associated diabetes mellitus has been described in children with nephrotic syndrome.[70]

In children receiving cyclosporine for 12 months or more, tubulointerstitial lesions on kidney biopsy are reported in 30–40% of cases. This increases to 80% after 4 or more years of treatment.[71] Cyclosporine-associated arteriopathy is uncommon. The duration of safe therapy is controversial, with some authors suggesting that CNI therapy should be restricted to 2 years,[71] while others have suggested that longer courses of cyclosporine can be tolerated.[72]

Coadministration of ketoconazole with cyclosporine in children with SD SSNS resulted in a 48% reduction in mean dose of cyclosporine, equivalent to a net cost saving of 38% with no reduction in efficacy, in a nonrandomized comparator study.[73] This approach to therapy has been suggested in order to help offset the costs of this drug class.

MMF

To date, all studies of mycophenolic acid prodrugs in nephrotic syndrome have used MMF. In a small RCT, five of 12 children treated for 1 year with MMF relapsed compared to one of 12 treated with cyclosporine. Although this difference was not statistically significant, the patient numbers were too small to determine the relative efficacies of MMF and cyclosporine (Table 3, Online Suppl Tables 4–5).[74] GFR remained stable during MMF treatment but fell during cyclosporine treatment. In a prospective study of 33 children (26 with FR SSNS) treated with MMF for 6 months, 24 (75%) children remained in remission during therapy, with 12 remaining relapse-free for 6 months after the drug was ceased; eight of these 12 patients continued in remission during 18–30 months of follow-up.[75] In a retrospective study

Table 4 | Advantages and disadvantages of corticosteroid-sparing agents as first agent for use in FR or SD SSNS

Agent	Advantages	Disadvantages
Cyclophosphamide	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious short- and long-term adverse effects Only one course should be given
Chlorambucil	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious adverse effects Only one course should be given Not approved for SSNS in some countries
Levamisole	Few adverse effects Generally inexpensive	Continued treatment required to maintain remission Limited availability Not approved for SSNS in some countries
Cyclosporine	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Cosmetic side-effects
Tacrolimus	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Risk of diabetes mellitus Not approved for SSNS in some countries
Mycophenolate mofetil	Prolonged remissions in some children with FR and SD SSNS Few adverse effects	Continued treatment often required to maintain remission Probably less effective than CNIs Expensive Not approved for SSNS in some countries

FR, frequently relapsing; SD, steroid-dependent; SSNS, steroid-sensitive nephrotic syndrome.

of SD SSNS in 42 children, who were treated for at least 6 months, mean reduction in relapse rate was 3.8 per year.[76] MMF was generally well tolerated, with small numbers of children developing leucopenia and abdominal pain. In observational studies, MMF has been used for up to 45 months and has been well tolerated.[76] In most studies, MMF has been given in a dose of 1200 mg/m^2/d or about 30 mg/kg/d in two divided doses. MMF has been used with cyclosporine in children with poorly controlled SD SSNS and has allowed reduction in cyclosporine dose.[77] Mycophenolate sodium may be an alternative if MMF is not tolerated because of adverse effects, but there are no data to support its use in nephrotic syndrome. In pediatric kidney transplant patients on cyclosporine, a single-dose pharmacokinetic study has demonstrated that 450 mg/m^2 mycophenolate sodium and 600 mg/m^2 of MMF provide similar mycophenolic acid exposure.[78] Recruitment has commenced for an RCT comparing MMF to cyclophosphamide (ClinicalTrials.gov identifier NCT01092962).

Choice of First Agent for FR or SD SSNS

There are no data from RCTs to determine which corticosteroid-sparing agent should be used as the first agent in a child with FR or SD SSNS. In Table 4, the advantages and disadvantages of alkylating agents, levamisole, CNIs, and MMF are presented. This table should help in the decision-making of the clinician and families in determining which agent a child with FR or SD SSNS should receive as their first corticosteroid-sparing agent.

Rituximab in SD SSNS

The place of rituximab in treatment of SD SSNS remains to be established. A single open-labeled RCT enrolling 54 children with SD SSNS dependent on prednisone and CNIs found that rituximab reduced the rate of relapse at 3 months significantly (18.5% and 48.1% in experimental and control arms, respectively) and increased the probability of being free of prednisone and CNI treatment.[79] These data confirm the results of case series that have reported prolonged remissions in 80% of children following rituximab, an anti CD20 monoclonal antibody, with doses of 375 mg/m^2 per dose given for up to four weekly doses.[80,81] Rituximab caused acute reactions, such as fever, vomiting and diarrhea, skin rash, and bronchospasm in about one-third of patients in one series.[81] Other reported serious side effects include *Pneumocystis jiroveci* pneumonia and pulmonary fibrosis.[80,82] Patient recruitment has commenced for an RCT comparing rituximab to placebo in cyclosporine-dependent SD SSNS (Clinicaltrials.gov identifier NCT 01268033).

Other Medications

Mizoribine is widely used as a corticosteroid-sparing agent in Japan. A single RCT (197 patients) demonstrated that the relapse rate (measured as the ratio of the total number of relapses/duration of observation in the mizoribine-treated group and placebo group) did not differ significantly between treatment and placebo groups (relapse-rate ratio 0.81; 95% CI 0.61–1.05)[63] (Table 2).

It is recommended that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS, since two RCTs have demonstrated no significant difference in the risk of relapse between azathioprine and placebo (RR 0.90; 95% CI 0.59–1.38)[49] (Table 2).

3.4: Indication for kidney biopsy

3.4.1: Indications for kidney biopsy in children with SSNS are (*Not Graded*):

- **late failure to respond following initial response to corticosteroids;**
- **a high index of suspicion for a different underlying pathology;**
- **decreasing kidney function in children receiving CNIs.**

RATIONALE

Kidney biopsy is indicated in children with nephrotic syndrome who fail to respond to corticosteroids after one or more remissions (late nonresponder) to determine kidney pathology. There is no fixed upper age limit for treating children with nephrotic syndrome without prior kidney biopsy, particularly in Northern Europe and India where 40–50% adolescents have MCD.[14,83,84] However, in populations with a much higher prevalence of FSGS and other pathologies, particularly African or African-American populations, it is reasonable to consider biopsy at the time of onset of nephrotic syndrome diagnosis before treatment.[85] While it is sometimes recommended that children with SSNS should undergo annual kidney biopsy if CNI therapy is continued beyond 2 years,[71] there are no data to determine whether the benefits of regular biopsies exceed the harm. Biopsies should be considered in children with deteriorating kidney function, when this persists after CNI doses are reduced. Routine biopsies of children with FR or SD SSNS before using corticosteroid-sparing therapy are not indicated. Studies show that the most important predictor for kidney survival in childhood nephrotic syndrome is not kidney pathology, but the achievement and maintenance of remission following any therapy.[86]

3.5: Immunizations in children with SSNS

3.5.1: To reduce the risk of serious infections in children with SSNS (*Not Graded*):

- **Give pneumococcal vaccination to the children.**
- **Give influenza vaccination annually to the children and their household contacts.**
- **Defer vaccination with live vaccines until prednisone dose is below either 1 mg/kg daily (< 20 mg/d) or 2 mg/kg on alternate days (< 40 mg on alternate days).**
- **Live vaccines are contraindicated in children receiving corticosteroid-sparing immunosuppressive agents.**
- **Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.**
- **Following close contact with Varicella infection, give nonimmune children on immunosuppressive agents varicella zoster immune globulin, if available.**

RATIONALE

Children with nephrotic syndrome are at increased risk of invasive pneumococcal disease[87] and should receive pneumococcal immunization with the heptavalent conjugate vaccine (7vPCV) and the 23-valent polysaccharide vaccine (23vPPV) according to local recommendations for initial immunization and repeat immunization. Adequacy of response to the 7vPCV vaccine has not been studied in children with nephrotic syndrome. Serological response to 23vPPV was not different in children with active nephrotic syndrome on high-dose prednisone (60 mg/m^2/d) compared to children who received the vaccine while on low-dose alternate day prednisone.[88] In most patients, antibody levels persisted for at least 36 months.[89] Children with SSNS and their household contacts should receive annual influenza vaccination.[90,91]

Live Vaccines

Live vaccines (measles, mumps, rubella, varicella, rotavirus) are contraindicated in children on immunosuppressive or cytotoxic agents[90,91] and should be deferred until:

- Prednisone dose is below 1 mg/kg/d (below 20 mg/d) or below 2 mg/kg on alternate days (below 40 mg on alternate days).
- The child has been off cytotoxic agents (cyclophosphamide, chlorambucil) for more than 3 months.
- The child has been off other immunosuppressive agents (CNIs, levamisole, MMF) for more than 1 month.

Healthy siblings and household contacts of children with impaired immunity should be vaccinated with measles, mumps, rubella, varicella, and rotavirus vaccines (where indicated) to prevent them from infecting children with impaired immunity.[90] However, immunosuppressed children should avoid direct exposure to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.

Varicella Immunization

Varicella infection may lead to life-threatening disease in children receiving immunosuppressive medications. Varicella immunization is safe and effective in children with nephrotic

syndrome, including children on low-dose alternate-day prednisone.[12]

- Children with SSNS, who are not receiving immunosuppressive or cytotoxic agents other than low-dose daily or alternate-day prednisone, should be offered varicella immunization if nonimmune.[90,91]
- Families of nonimmune children with SSNS, who are receiving immunosuppressive agents, should be asked to contact their physician as soon as possible if the child comes into close contact with another child with chicken pox, or an adult with herpes zoster, so that the child can receive zoster immune globulin (if available) within 72 hours of exposure.[90]
- Aciclovir or valaciclovir should be administered to immunosuppressed children at the onset of chicken pox lesions.

RESEARCH RECOMMENDATIONS

Further information from RCTs is required:

- To determine the relative efficacies of alkylating agents, levamisole, MMF, CNIs in FR and SD SSNS.
- To determine the relative benefits and adverse effects of cyclosporine and tacrolimus in FR and SD SSNS.
- To determine the additional benefits and risks of mycophenolic acid when added to CNIs in SD SSNS.
- To determine the additional benefits and risks of rituximab in comparison or in addition to other corticosteroid-sparing agents in SD SSNS.

DISCLAIMER

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Evidence profile of studies examining IV vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome.

Supplementary Table 2: Existing systematic review on IV vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome.

Supplementary Table 3: Summary tables of studies examining IV vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome (categorical outcomes).

Supplementary Table 4: Summary table of RCT examining MMF vs. CsA in frequently relapsing nephrotic syndrome in children (categorical outcomes).

Supplementary Table 5: Summary table of RCT examining MMF vs. CsA in frequently relapsing nephrotic syndrome in children (continuous outcomes).

Supplementary Table 6: Summary table of RCT examining low vs. fixed dose CsA treatment in children with frequently relapsing nephrotic syndrome (categorical outcomes).

Supplementary Table 7: Summary table of RCT examining low vs. fixed dose CsA treatment in children with frequently relapsing 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