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REVIEW

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Evidence-based management of steroid-sensitive nephrotic syndrome

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Abstract Using data from systematic reviews and randomised controlled trials, the evidence for managing steroid sensitive nephrotic syndrome (SSNS) is reviewed. In the initial episode, increased duration (3–7 months) of prednisone compared with 2 months significantly reduced the risk for relapse at 12–24 months [relative risk (RR) 0.70; 95% confidence intervals (CI) 0.58–0.84] without increase in adverse effects. Six months of prednisone was significantly more effective than 3 months (RR 0.57; 95% CI 0.45–0.71). Higher prednisone doses given for the same duration reduced the risk of relapse (RR 0.59; 95% CI 0.42–0.84) suggesting that both dose and duration of prednisone therapy lead to prolonged remission. In relapsing SSNS prolonged prednisone treatment, daily prednisone during infections, oral or intravenous cyclophosphamide, chlorambucil, levamisole and cyclosporin significantly reduced the risk of relapse. Comparative effects of these options remain uncertain because of the absence of head-to-head trials, but existing trial evidence is strongest for cyclophosphamide and cyclosporin. Further adequately powered multinational trials are required to determine the optimum induction dose and duration of prednisone in the initial episode of SSNS and to determine the relative efficacies of immunosuppressive agents and the efficacy of newer agents, including mycophenolate and tacrolimus, in relapsing SSNS.

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Introduction

Idiopathic nephrotic syndrome is an uncommon condition in children with an incidence of 1–2 per 100,000 children aged below 16 years [1, 2]. The International Study of Kidney Disease in Childhood (ISKDC) determined the histopathological, clinical and laboratory characteristics of nephrotic syndrome in children [3]. Overall 87% of 521 children had idiopathic nephrotic syndrome with renal biopsy appearances of minimal change nephrotic syndrome (MCNS) in 76%. There is a close correlation between MCNS and response to steroids with 93% of children becoming free of proteinuria with 8 weeks of therapy [4]. Patients with other renal pathologies [5] may also achieve complete remission with steroids. Response to steroids is associated with a good long-term prognosis for renal function.

The long-term prognosis for most children with steroid-sensitive nephrotic syndrome (SSNS) is for resolution of their disease and maintenance of normal renal function. Approximately 80% of children with SSNS will relapse one or more times. Of those, 50% relapse frequently or become steroid dependent [6, 7]. The frequency of relapses decreases with time with 50–70% of children being relapse-free at 5 years and about 85% relapse-free at 10 years [6, 7]. Early relapse after initial treatment and short duration of remission increase the risk for subsequent relapse [8, 9]. Patients with frequent relapses during childhood are more likely to have disease persisting into adulthood [10].

Management of SSNS aims to induce and maintain complete remission without serious adverse effects of therapy. Steroid therapy is the primary therapy used to induce and maintain remission. Alkylating agents (cyclophosphamide, chlorambucil), cyclosporin and levamisole are commonly used to achieve prolonged periods of remission in children with frequently relapsing or steroid-

dependent SSNS. The aim of this review is to evaluate the benefits and harms of currently used treatment regimens for the initial and subsequent episodes of SSNS.

What is the best evidence?

The best evidence for determining whether an intervention does more harm than good comes from randomised controlled trials (RCTs) or from systematic reviews of RCTs. Combining results from RCTs in systematic reviews provides an explicit method by which we can test whether the benefits and harms of interventions are constant across groups of patients or whether they vary. In addition, it may allow the efficacy of therapy to be demonstrated, when this is not evident from individual underpowered trials. In this review evidence from such studies will be considered primarily and evidence from lower grades of evidence only included where RCT evidence is not available. Specialised search strategies of major databases (including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials) are used to identify RCTs in all languages for inclusion in a systematic review. Additional RCTs are identified by searching conference proceedings. The inclusion of all relevant RCTs is crucial to avoid bias in determining the efficacy of therapy since RCTs with negative results are less likely to be published. Where appropriate, results of trials are combined in meta-analyses, in which dichotomous data for individual trials may be expressed as relative risk (RR) or risk difference (RD) with 95% confidence intervals (CI) and a summary estimate RR or RD calculated. By convention, a summary estimate RR or RD with the upper limit of CI below one (the line of no effect) indicates that experimental therapy is more effective than control and/or reduces the incidence of an adverse effect. A summary estimate with its 95% CI crossing one indicate that no significant difference between therapies has been demonstrated.

Treatment of the first episode of SSNS

The ISKDC agreed on standard steroid regimens for the first episode of SSNS [11]. At presentation children received prednisone 60 mg/m^2/day (maximum dose 80 mg) in divided doses for 4 weeks followed by 40 mg/m^2/day (maximum 60 mg/day) in divided doses on 3 consecutive days out of 7 days for 4 weeks. Subsequent RCTs demonstrated that alternate day prednisone was more effective in maintaining remission than prednisone given on 3 consecutive days out of 7 days [12] and that there was no significant difference in the risk for relapse between single daily and divided doses of prednisone [13]. For reasons of ease of administration and compliance, a single daily dose is clearly the preferred option during daily therapy.

The ISDKC regimen is associated with a high relapse rate so that the efficacy of longer durations of steroids have been investigated in several RCTs, which have been combined in a systematic review [14, 15]. Treatment with prednisone for 3–7 months (administered daily for 4–8 weeks at 60 mg/m^2/day and then on alternate days) compared with 2 months of therapy reduced the risk for relapse by 30% at 12–24 months (six trials; 422 patients; RR 0.70, 95% CI 0.58-0.84) (Fig. 1a) with a significant reduction in the number of children who relapsed frequently (RR 0.63, 95% CI 0.46-0.84). There were no significant differences in risks for adverse effects (Table 1). Other trials [14] have demonstrated that steroid therapy for 6 months significantly reduced the risk for relapse compared with 3 months (4 trials; 382 children; RR 0.57; 95% CI 0.45-0.71) (Fig. 1b). No additional benefit was demonstrated in one trial of treatment for 12 months compared with 5 months [16]. Duration of prednisone less than 2 months [17] was less effective than the standard regimen (one trial; 60 patients; RR 1.46, 95% CI 1.01–2.12). These data provide evidence that prolonged steroid therapy (5–7 months) should be given to reduce the risk for relapse following the first episode of SSNS.

Is dose or duration of steroid therapy important?

Increased duration of steroid therapy results in increased total dose of steroid therapy making the effects of duration and dose difficult to separate. Plotting the RR for relapse against the ratio of dose/duration suggested that duration was more important than dose [14]. However, two RCTs [18, 19] have compared different total doses of prednisone administered for the same duration (3 or 6 months). A meta-analysis of these studies showed that the risk of relapse was reduced by 40% with higher doses of steroids (RR 0.59; 95% CI 0.42–0.84) suggesting that both increased dose of steroids and prolonged duration are important in reducing the risk of relapse.

Applicability to individual patient care

There is an inverse linear relationship between the risk for relapse and duration or total doses of induction therapy, suggesting an increase in benefit with treatment up to 7 months (Fig. 2). If 100% of children relapsed, the RR for relapse would fall by 11% per month for every 1 month increase in duration of therapy above 2 months (Table 2). Using the average relapse rate of 70% in children included in RCTs and treated for 2 months, the number of children relapsing by 12–24 months would fall by 7.7% for every increase by 1 month in the duration of therapy so that treatment for 6 months would reduce the risk of relapse by 31% (4×7.7%) to 39%.

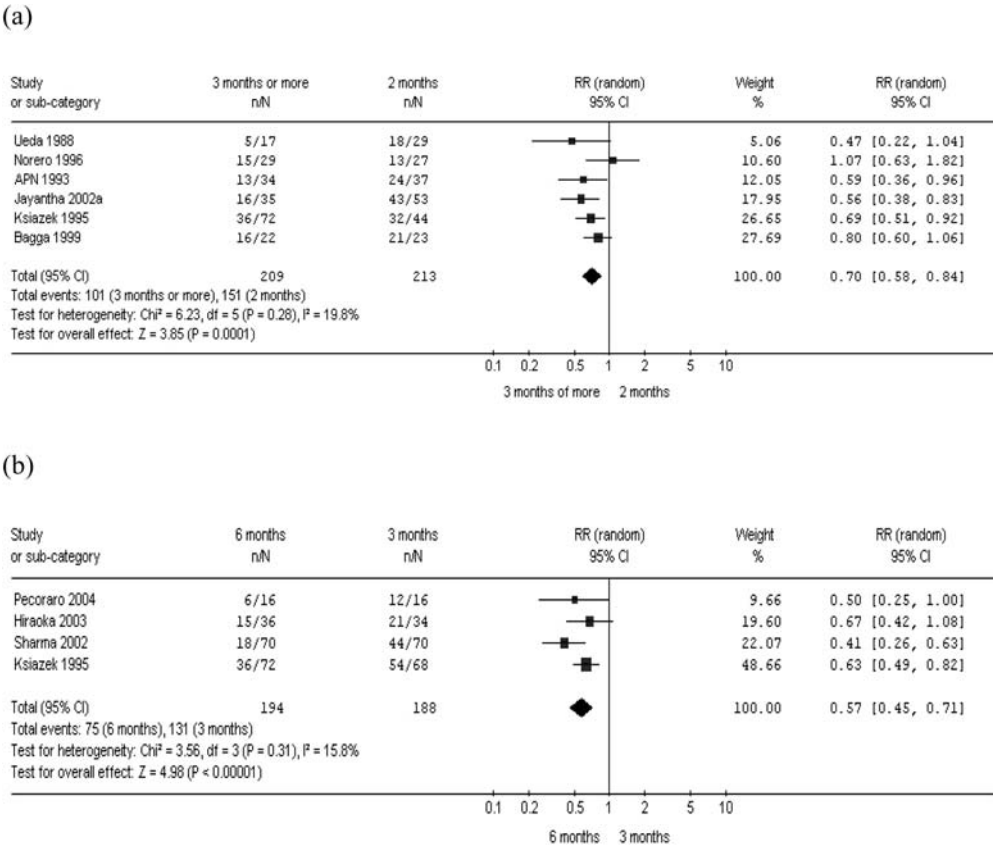

Fig. 1 Meta-analyses of the relative risk (95% confidence intervals) for relapse of nephrotic syndrome by 12–24 months in (**a**) six trials comparing prolonged prednisone therapy (3–7 months) with 2-month therapy and in (**b**) four trials comparing 6 with 3 months of prednisone therapy in children with the first episode of steroid-sensitive nephrotic syndrome. Results are shown ordered by trial weights. The test statistic Z indicates that increased duration of prednisone is significantly more effective in reducing the number of children who relapse compared with 2 months of prednisone (reproduced from Hodson et al. [14, 15] from the Cochrane Library with permission from John Wiley & Sons Ltd.)

Table 1 Adverse effects of steroids with treatment by 12–24 months of the first episode of steroid-sensitive nephrotic syndrome for 3–7 months compared with 2 months or total induction dose of 2,240 mg/m^2 (reproduced from the Cochrane Library with permission from John Wiley & Sons Ltd.)

Adverse effects	No. of trials	Patient no.	Risk difference (95% confidence intervals)
Hypertension	7	526	0.05 (–0.03 to 0.06)
Opthalmological disorders	6	460	0.00 (–0.04 to 0.12)
Growth retardation	4	354	–0.02 (–0.08 to 0.04)
Psychological disorders	4	293	0.01 (–0.03 to 0.06)
Cushing's syndrome	4	292	0.15 (–0.06 to 0.36)
Osteoporosis	3	233	–0.02 (–0.09 to 0.05)
Severe infections	2	172	–0.08 (–0.23 to 0.06)

Alternative regimens in the first episode of SSNS

The Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) has demonstrated a reduction in RR for relapse with cyclosporin (150 mg/m^2/day for 8 weeks) and prednisone compared with prednisone alone at 6 months (104 children; RR 0.33; 95% CI 0.13–0.83), but not at 1 or 2 years [14, 20]. The cumulative prednisone dose after 2 years was slightly but not significantly less in the cyclosporin-treated group, and no significant elevations in blood pressure or falls in glomerular filtration rate (GFR) were documented. The Chinese herb, Sairei-to, may be effective as a steroid sparing agent [14, 21]. Further trials are required before these regimens can be recommended for the initial episode of SSNS.

Treatment of frequently relapsing and steroid dependent SSNS

Steroid therapy

There are few data on steroid regimens for frequently relapsing and steroid-dependent SSNS. The ISKDC proposed that relapsing SSNS should be treated with daily prednisone (60 mg/m^2/day) till the child had been in remission for 3 days followed by 4 weeks of prednisone given on 3 consecutive days out of 7. More recently, alternate day therapy has been preferred [12]. Important trial data are listed below.

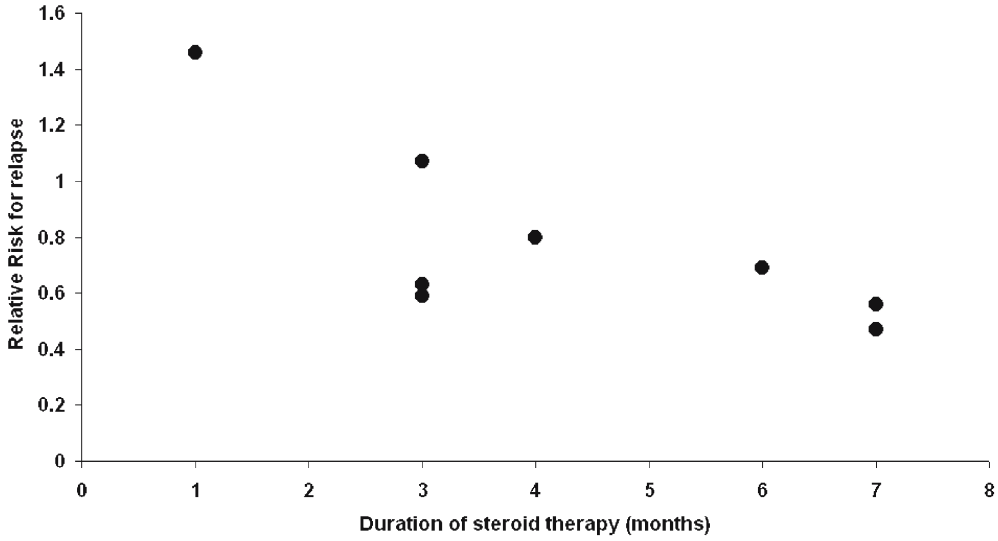

Fig. 2 Relationship between the risk of relapse (relative risk) by 12–24 months and the duration of prednisone given to children in the first episode of steroid-responsive nephrotic syndrome. Regression equation for duration of prednisone treatment: RR=1.26–0.11 duration; r^2=0.56 (reproduced from Hodson et al. [14, 15] from the Cochrane Library with permission from John Wiley & Sons Ltd.)

Table 2 Expected relapse rates by 12–24 months after the first episode of steroid-sensitive nephrotic syndrome in populations of children at different risks of relapse after 2 months of prednisone (reproduced from the Cochrane Library with permission from John Wiley & Sons Ltd.)

Relapse rate with 2 months of therapy	Reduction in relapse rate for each extra month* above 2 months' therapy	Reduction in relapse rate with 4 months extra therapy	Relapse rate with 6 months of therapy
100%	11%	44%	56%
70%	7.7%	31%	39%
50%	5.5%	22%	28%

* Regression equation for duration of prednisone treatment: relative risk =1.26–0.11 duration

Additional steroid therapy during intercurrent infections

Children commonly relapse when they have infections. Children with steroid-dependent SSNS had significantly fewer relapses during 2 years follow-up if they received daily rather than alternate-day prednisone during upper respiratory tract infections (36 children; mean difference –3.30; 95% CI –4.03 to –2.57) [14, 22].

Long duration regimens for relapsing SSNS

The risk of relapse at 1 year (76 children; RR 0.43; 95% CI 0.29–0.65) and at 2 years (64 children; RR 0.60; 95% CI 0.45–0.80) and the number of children with frequently relapsing or steroid-dependent SSNS (72 children; RR 0.43; 95% CI 0.20–0.95) were significantly reduced if children are treated for 7 months compared with the modified ISKDC regimen for relapsing patients [14, 23].

Deflazacort

Deflazacort [14, 15, 24] significantly reduced the number of children with steroid-dependent SSNS who relapsed during therapy (40 children; RR 0.44; 95% CI 0.25–0.78), without significant differences in side effects.

Pulse intravenous methylprednisolone

The number with relapse at 1 year was not significantly different (RR 1.06; 95% CI 0.75–1.52) when intravenous methylprednisolone (three doses of 20 mg/kg) followed by oral prednisone for 5 months was compared with oral prednisone for 6 months [14, 15, 25].

Non-steroid therapies

Alkylating agents

Both oral cyclophosphamide (2–3 mg/kg/day) and chlorambucil (0.2 mg/kg/day) administered for 8 weeks significantly reduce the risk of relapse in frequently relapsing SSNS (Table 3) [26, 27]. In a single comparison trial, cyclophosphamide and chlorambucil were equally effective [26, 27, 28]. The efficacy of cyclophosphamide administered for 12 weeks was not significantly different from 8 weeks [26, 27, 29] in an RCT though a study comparing treated patients with historical controls had suggested a benefit of treating for 12 weeks [30]. A recent trial [27, 31] has demonstrated that intravenous cyclophosphamide (500 mg/m^2/dose for 6 monthly doses) was more effective than oral cyclophosphamide (2 mg/kg/day for 12 weeks) in reducing the risk for relapse at 6 months

Table 3 Comparisons of efficacy and adverse effects of interventions for steroid-sensitive nephrotic syndrome

First episode of steroid-sensitive nephrotic syndrome				
Interventions	No. of trials	No. of patients	Relative risk (95% confidence intervals)	Risk difference (95% confidence intervals) of serious adverse effects[a]
Steroids for 3–7 months vs. 2 months	6	422	0.70 (0.58–0.84)[a]	Hypertension 0.05 (–0.02–0.12) Ophthalmologic 0.00 (–0.04–0.03)
Steroids for 6 months vs. 3 months	4	382	0.57 (0.45–0.71)[a]	Hypertension 0.02 (–0.05–0.08) Ophthalmologic –0.02 (–0.09–0.05)
Frequently relapsing or steroid-dependent steroid-sensitive nephrotic syndrome				
Interventions	No. of trials	No. of patients	Relative risk (95% confidence intervals)	% treated with non-steroid agent with serious adverse effects
Cyclophosphamide vs. steroids	3	102	0.44 (0.26–0.73)[b]	Infections 1.5%[c] Seizures 0%[c] Cystitis 2.2%[c]
Chlorambucil vs. steroids	2	32	0.13 (0.03–0.57)[b]	Infections 6.3%[c] Seizures 3.4%[c] Cystitis 0%[c]
Cyclosporin vs. alkylating agents	2	95	1.10 (0.68-1.80)[b]	Hypertension 4%[b] Reduced renal function 9%[b]

[a] Data from Hodson el al. [14, 15]. [b] Data from Durkan et al. [26, 27]. [c]Data from Latta et al. [32]

Table 4 Adverse effects of alkylating agents in children with steroid-sensitive nephrotic syndrome (reproduced from Latta et al. [31] with permission from Springer Publishing)

Adverse effect		Cyclophosphamide		Chlorambucil	
		Total assessed	No. (%) with outcome	Total assessed	No. (%) with outcome
Deaths	Patients	866	7 (0.8%)	625	7 (1.1%)
Malignancies	Patients	866	2 (0.2%)	534	3 (0.6%)
Seizures	Patients	866	0 (0%)	266	9 (3.4%)
Infections	Courses	609	9 (1.5%)	552	35 (6.3%)
Hemorrhagic cystitis	Courses	762	22 (2.2%)	552	0 (0%)
Leucopenia	Courses	619	210 (32.4%)	456	151 (33%)
Thrombocytopenia	Courses	214	5 (2.1%)	408	24 (5.9%)
Hair loss	Courses	736	131 (17.8%)	237	5 (2.1%)

(RR 0.56; 95% CI 0.33–0.92), but not 2 years. Adverse effects did not differ between groups except that the children treated intravenously suffered fewer serious infections during treatment.

Adverse effects with alkylating agents are frequent and may be severe. In a systematic review Latta et al. [32] examined adverse effects from 38 reports, concerning 866 children receiving 906 courses of cyclophosphamide and 638 children receiving 671 courses of chlorambucil for frequently relapsing SSNS (Table 4). The authors concluded that chlorambucil in the recommended dosage was potentially more toxic than cyclophosphamide based on a higher risk of infections, malignancies and seizures. However, this conclusion was not based on comparative data from RCTs so differences in patient populations cannot be excluded. Gonadal toxicity with alkylating agents is more likely in boys than girls. In SSNS there is a dose-dependent relationship between the number of patients with sperm counts $<10^6$/ml and the cumulative dose of cyclophosphamide. The threshold cumulative dose for safe use remains uncertain because of individual reports of oligospermia in boys receiving less than 200 mg/kg. These data suggest that single courses of cyclophosphamide exceeding 12 weeks (2 mg/kg/day; cumulative dose 168 mg/kg), and second courses should be avoided if possible. There were few data on chlorambucil and the margin between effective treatment and a dose toxic to the male gonad may be smaller with chlorambucil than cyclophosphamide.

Cyclosporin

Single trials [26, 27, 33, 34] have demonstrated no significant difference in efficacy during treatment between cyclosporin and cyclophosphamide (55 children; RR 1.07; 95% CI 0.48–2.35) or cyclosporin and chlorambucil (40 children; RR 0.82; 95% CI 0.44–1.53). The majority of children treated with cyclosporin relapse when therapy is ceased. Adverse effects are significant with 4% of children developing hypertension, 9% reduced renal function, 28% gum hypertrophy and 34% hirsutism [26]. A retrospective study has shown that the administration of ketoconazole with cyclosporin as a cyclosporine-sparing agent reduced the number of children with renal impairment, increased the likelihood of withdrawing steroids and reduced the cost of therapy [35].

Levamisole

In three trials levamisole significantly reduced the risk for relapse in comparison with prednisone alone (three trials; 137 patients; RR 0.60; 95% CI 0.45–0.79) [27], but was ineffective in a fourth trial (48 patients; RR 1.18; 95% CI 0.96–1.46) [36]. Among the 3 trials [36, 37, 38], which enrolled frequently relapsing and/or steroid-dependent patients, the difference in efficacy may be related to the total dose administered (35 mg/m^2/month [37, 38] versus 20 mg/m^2/month [36]) and to the dose frequency (alternate day [37, 38] versus 2 consecutive days out of 7 days [36]). No trials have compared levamisole with other non-steroid agents. In a retrospective analysis of children with frequently relapsing or steroid-dependent SSNS, the mean number of relapses was reduced to an equivalent extent by levamisole treatment given for 6 months or more or cyclophosphamide given for 8–12 weeks [39]. Adverse effects of levamisole are uncommon, but include leucopenia, gastrointestinal effects and occasionally vasculitis [40, 41]. Unfortunately, the current manufacturers of levamisole have decided to cease its production.

Other agents

In RCTs, no significant reduction in the risk for relapse has been demonstrated with azathioprine [26], mizoribine [42], intravenous immunoglobulin [43] or sodium cromoglycate [44]. Mycophenolate mofetil [45, 46], tacrolimus [47], vincristine [48] and the ACE inhibitor, captopril [49], have been shown to reduce the risk of relapse in uncontrolled studies.

Conclusions

Information from meta-analyses of RCTs on the efficacy of interventions for steroid-sensitive nephrotic syndrome compared with the risks of some serious adverse effects is shown in Table 3. In children in their initial episode of SSNS, we know that the following therapies are likely to be more beneficial than harmful: 3 to 7 months of steroid therapy compared with 2 months and 6 months of steroid therapy compared with 3 months.

These data indicate that prolonged courses of steroid therapy should be administered in the first episode of SSNS to reduce the risk of early relapse and that this regimen, by reducing relapses, may result in a net reduction in steroid exposure compared with shorter courses.

In children with frequently relapsing and steroid-dependent SSNS, we know that the following therapies are likely to be beneficial: oral cyclophosphamide (2 mg/kg/day) for 8 weeks; oral chlorambucil (0.2 mg/kg/day) for 8 weeks; cyclosporin 6 mg/kg/day.

Though efficacy does not differ between cyclophosphamide and chlorambucil, serious adverse effects appear to be more common with chlorambucil, suggesting that cyclophosphamide should be used rather than chlorambucil (Tables 3, 4). Cyclosporin is as effective as alkylating agents during therapy, but has significant side effects (Table 3). These data suggest that either cyclophosphamide or cyclosporin may be used as the first non-steroid agent in children with relapsing SSNS with the choice based on treatment duration, side effect profile and availability.

In children with their first episode of SSNS, we need more information on the optimal duration and/or total dose of steroid therapy in terms of benefits and harms, the relative contributions of steroid duration and dose to efficacy and whether cyclosporin with 3 months of steroid therapy would be more effective and less toxic than 6 months of steroids. In children with frequently relapsing and steroid-dependent SSNS, we need more information on the efficacy of levamisole in frequently relapsing and steroid-dependent SSNS, the relative efficacies of alkylating agents, cyclosporin and levamisole in frequently relapsing and steroid-dependent SSNS, the relative efficacy of medications in steroid-dependent compared with frequently relapsing SSNS, the efficacy of mycophenolate compared with steroids alone or other non-steroid agents, the efficacy of tacrolimus compared with other non-steroid agents and the efficacy of angiotensin-converting enzyme inhibitors in comparison with steroids or non-steroid medications.

Paediatric nephrologists need further information on how to manage their patients from adequately powered randomised controlled trials. Since SSNS is a relatively rare condition in many countries, adequately powered international multicentre trials, such as the planned double-blind, placebo-controlled trial of levamisole [50], are required to answer these important questions.

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