Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials

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Abstract

***Aims*—To determine the benefits and toxicity of different corticosteroid regimes in preventing relapse in steroid responsive nephrotic syndrome.**

***Design*—Meta-analysis of randomised controlled trials.**

***Subjects*—Twelve trials involving 868 children aged 3 months to 18 years.**

***Main outcome measure*—Frequency of relapse.**

***Results*—A meta-analysis of five trials, which compared two months of prednisone with three months or more in the first episode, showed that the longer duration significantly reduced the risk of relapse at 12–24 months (relative risk 0.73; 95% confidence interval 0.60 to 0.89) without an increase in adverse events. There was an inverse linear relation (relative risk 1.382 (SE 0.215) − 0.133 (SE 0.048) duration; r^2 = 0.66; p = 0.05) between the duration of treatment and risk of relapse.**

***Conclusions*—Children in their first episode of steroid responsive nephrotic syndrome should be treated with prednisone for at least three months, with an increase in benefit being shown for up to seven months of treatment.**

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Keywords: nephrotic syndrome; corticosteroid therapy; systematic review; meta-analysis

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Corticosteroid therapy has been used in childhood nephrotic syndrome since the 1950s. Of children who present with their first episode, the majority of children have minimal change disease and 90–95% will respond to steroid therapy.[1 2] With steroid therapy, mortality has fallen from 35%[3] to 3%[4] because of a reduction in serious infections. Because of this dramatic before–after evidence that corticosteroids improve the outcome of nephrotic syndrome, oral corticosteroids are the first line treatment of a child presenting with idiopathic nephrotic syndrome. No properly controlled prospective trials of corticosteroids compared to placebo were carried out.

Nephrotic syndrome is a potentially chronic disease with about 70% of patients suffering a relapsing course and being at risk of the adverse effects of steroid treatment. A standard prednisone regimen developed by the International Study of Kidney Disease in Children (ISKDC)[5] and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[6] for the initial attack is widely used. This consists of daily prednisone for four weeks followed by intermittent prednisone[5] (three consecutive days out of seven) or alternate day prednisone[6] for four weeks.

Using data from several multicentre studies, it has been recommended[7 8] that the dose and duration of corticosteroid therapy should exceed that used in the standard regime. However, the optimal dose and duration of prednisone or other steroid agent that is most beneficial in maintaining remission and associated with least toxicity is not clear. The aim of this study is to assess the benefits and harms of corticosteroid therapy in the management of childhood nephrotic syndrome by conducting a systematic review and meta-analysis of randomised controlled trials. The information will assist clinicians in their decision making and identify to researchers questions that remain to be answered.

Methods

SEARCH STRATEGIES

Randomised and quasi-randomised trials of corticosteroid agents in steroid responsive nephrotic syndrome (SRNS) were identified from Medline (1966 to July 1998), Embase (1988 to July 1998), and the Cochrane Controlled Trials Register (Cochrane Library Issue 2, 1998). The databases were searched using optimally sensitive strategies for the identification of randomised controlled trials developed for the Cochrane Collaboration,[9 10] combined with text words and subject headings for nephrotic syndrome, lipoid nephrosis, child, and steroid. Reference lists of review articles, relevant trials, nephrology textbooks, and proceedings of scientific meetings were also searched. Investigators known to be active in the field were also contacted to seek information about any unpublished trials.

INCLUSION CRITERIA

Titles were screened by one reviewer (EH), who retained articles in which children with SRNS were treated with corticosteroid agents only. Abstracts were reviewed independently for study eligibility by two reviewers (EH, JK). Studies were selected if they were randomised or quasi-randomised trials, if they involved children aged 3 months to 18 years in their initial or subsequent episode of SRNS,[11] if they compared different durations, total doses, or other dose strategies of prednisone or other corticosteroid agent, and if follow up data for six months or more were available. Studies involving children with steroid resistant nephrotic syndrome, congenital nephrotic syndrome, or nephrotic syndrome associated with other glomerulonephritides were excluded.

Table 1 Characteristics of trials of corticosteroid therapy in children in their first episode of steroid responsive nephrotic syndrome

Authors, year, country	*Patients (controls)*	*Patients (expt)* *	*Experiment intervention dose*	*Duration*	*Control intervention dose*	*Duration*
Kleinknecht *et al*[18], 1982, France	29	29	Prednisone 2 mg/kg/day for 4 weeks and taper alternate days	1 year	Prednisone 2 mg/kg/day for 4 weeks and taper alternate days	5 months
APN[19]†, 1988, North Europe	29	32	Prednisone 60 mg/m^2/day till urine protein free for 3 days and 40 mg/m^2 alternate days till albumin >35 g/l	1 month (average)	Prednisone 60 mg/m^2/day for 4 weeks and 40 mg/m^2 alternate days for 4 weeks	2 months
Ueda *et al*[20], 1988, Japan	29	17	Prednisolone 60 mg/m^2/day for 4 weeks, 60 mg/m^2 alternate days for 4 weeks and taper by 10 mg/m^2/mth to zero	7 months	Prednisolone 60 mg/m^2/day for 4 weeks and 40 mg/m^2 on 3 of 7 days for 4 weeks	2 months
APN[21], 1993, North Europe	37	34	Prednisone—6 weeks each of 60 mg/m^2/day and 40 mg/m^2 alternate days	3 months	Prednisone—4 weeks each of 60 mg/m^2/day and 40 mg/m^2 alternate days	2 months
Ksiazek and Wyszynska[22], 1995, Poland	44	68‡	Prednisone 1–2 mg/kg/day for 4 weeks, 1 mg/kg alternate days for 4 weeks and taper by 25% per week for 4 weeks	3 months	Prednisone 4 weeks each of 1–2 mg/kg/day and 1 mg/kg on alternate days	2 months
		72‡	Prednisone 1–2 mg/kg/day for 4 weeks, 1 mg/kg alternate days for 4 weeks and taper by 25% each month	6 months		
Norero *et al*[23], 1996, Chile	27	29	Prednisolone—6 weeks each of 60 mg/m^2/day and 40 mg/m^2 alternate days	3 months	Prednisolone—4 weeks each of 60 mg/m^2/day and 40 mg/m^2 alternate days	2 months
Bagga *et al*[24], 1999, India	23	22	Prednisone—4 weeks each of 2 mg/kg/day, 1.5 mg/kg/day, 1.5 mg/kg alternate days, 1 mg/kg alternate days	4 months	Prednisone—4 weeks each of 2 mg/kg/day and 1.5 mg/kg alternate days	2 months

*Experimental group.
†Arbeitsgemeinschaft für Pädiatrische Nephrologie.
‡Experimental groups 1 and 2 in study by Ksiazek and Wyszynska.[22]

Table 2 Characteristics and aims of trials of corticosteroid therapy in children with relapsing steroid responsive nephrotic syndrome

Authors, year, country	*Study aim*	*Participants*	*Experimental intervention*	*Control intervention*
ISKDC[25]*, 1979, USA, Canada, Europe	Comparison of daily with intermittent therapy to maintain remission	64 children with frequently relapsing nephrotic syndrome; 32 experimental, 32 control	Prednisone 60 mg/m^2/day for 4 weeks, then tapered daily dose for 4 weeks	Prednisone 60 mg/m^2/day till remission, 40 mg/m^2 on 3 days of 7 for 4 weeks
APN[16]†, 1981, North Europe	Comparison of alternate day with intermittent therapy to maintain remission	64 children with frequently relapsing nephrotic syndrome; 30 experimental, 34 control	Prednisone 60 mg/m^2/day till remission, 35 mg/m^2 on alternate days. Total 6 months	Prednisone 60 mg/m^2/day till remission, 40 mg/m^2 on 3 days out of 7. Total 6 months
Imbasciali *et al*[26], 1985, Italy	Comparison of IV and oral steroid to induce and maintain remission	67 children with either initial episode or no relapse in previous year; 33 experimental, 34 control	Methylprednisone 20 mg/kg IV for 3 days, prednisone 20 mg/m^2/day for 4 weeks, 20 mg/m^2 and 10 mg/m^2 alternate days for 4 weeks, 20 mg/m^2 alternate days for 4 months	Prednisone 60 mg/m^2/day for 4 weeks, 40 mg/m^2 on alternate days for 4 weeks, 20 mg/m^2 alternate days for 4 months
Ekka *et al*[27], 1997, India	Comparison of daily with divided dose to induce and maintain remission	106 children in relapse; 52 experimental, 54 control	Prednisolone 2 mg/kg/day for 2 or 4 weeks as single morning dose, 1.5 mg/kg alternate days for 4 weeks	Prednisolone 2 mg/kg/day for 2 or 4 weeks in 3 divided doses, 1.5 mg/kg alternate days for 4 weeks
Broyer *et al*[28], 1997, France	Comparison of deflazacort and prednisone to induce and maintain remission	40 children with steroid dependent nephrotic syndrome; 20 experimental , 20 control	Deflazacort equal to prednisone 60 mg/m^2/day to remission, 60 mg/m^2 alternate days for 6 weeks, 15–20 mg/m^2 alternate days. Total 1 year	Prednisone 60 mg/m^2/day to remission, 60 mg/m^2 alternate days for 6 weeks, 15–20 mg/m^2 alternate days. Total 1 year

*International Study of Kidney Disease in Children.
†Arbeitsgemeinschaft für Pädiatrische Nephrologie.

Table 3 Assessment of study quality in trials of corticosteroid therapy in children with steroid responsive nephrotic syndrome

Episode of nephrotic syndrome	*Author and year*	*Allocation concealment*	*Intention to treat analysis*	*Completeness of follow up**	*Blinding of outcome assessment*
Initial	Kleinknecht *et al*, 1982[18]	Adequate	No	E	No blinding
	APN, 1988[19]	Adequate	No	A	No blinding
	Ueda *et al*, 1988[20]	Inadequate	No	A	No blinding
	APN, 1993[21]	Adequate	No	A	No blinding
	Ksiazek and Wyszynska, 1995[22]	Inadequate	Yes	A	No blinding
	Norero *et al*, 1996[23]	Inadequate	No	A	No blinding
	Bagga *et al*, 1999[24]	Unclear	No	A	No blinding
Relapse	ISKDC, 1979[25]	Unclear	No	D	No blinding
	APN, 1981[16]	Inadequate	No	D	No blinding
	Imbasciali *et al*, 1985[26]	Adequate	Yes	A	No blinding
	Ekka *et al*, 1997[27]	Unclear	No	C	No blinding
	Broyer *et al*, 1997[28]	Adequate	Yes	B	Double blind

*Completeness of follow up: A, <3% excluded; B, 3–9% excluded; C, 10–19.9% excluded; D, 20% or more excluded; E, unclear.
APN, Arbeitsgemeinschaft für Pädiatrische Nephrologie.
ISKDC, International Study of Kidney Disease in Children.

Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial existed, only the publication with the most complete data was included.

QUALITY ASSESSMENT

The quality of studies was assessed by two reviewers (EH, JK) without blinding to authorship using the method of Crowther and Henderson-Smart.[12] Discrepancies were resolved in discussion with a third reviewer (JC). The quality items assessed were allocation concealment, intention to treat analysis, completeness of follow up, and blinding of outcome assessment because these are known to influence the true treatment effect.[13]

DATA EXTRACTION

Data extraction was carried out independently by two reviewers (EH, JK). Disagreements were resolved in consultation with a third reviewer (JC). The standard steroid regime advocated by ISKDC[5] and APN[6] was compared with other regimes where possible. The primary outcome measure was the prevention of relapse as measured by the number of children with and without relapse at six months or more of the study. Secondary outcome measures sought were the number who developed frequently relapsing nephrotic syndrome,[5] mean relapse rate per patient, mean length of time to next relapse, cumulative corticosteroid dosage, and adverse events (reduced growth rate, hypertension, cataracts, glaucoma, psychological disorders, infections, thromboses, osteoporosis).

STATISTICAL METHODS

For dichotomous outcomes the relative risks (RR), risk differences (RD), and number needed to treat (NNT) for individual studies were calculated and summary effect measures calculated in RevMan[14] using the random effects model. The random effects model takes into account the between study variability as well as the within study variability. A fixed effects model was also used to test for the robustness of the analysis and outliers. Heterogeneity was analysed using the χ^2 test with an α of 0.1 used for statistical significance. Weighted mean differences (WMD) were calculated from pooled data for continuous scales of measurement. To ensure independence in trials with two or more experimental arms, only one experimental arm could be included in the analyses. As we wished to examine a wide range of doses and durations of therapy, we chose to include the experimental group with the longest duration of treatment when trials had more than one experimental arm. Examination of the effects of study quality, patient type (initial episode, relapsing), and different interventions was attempted by subgroup analysis. To determine whether RR was constant across studies or whether it varied depending on plausible effect modifiers such as dose and duration of treatment and the risk of relapse in the control group (control event rate), meta-regression was performed.[15] For the analyses, the total dose of prednisone administered for induction of the first remission was calculated from the treatment protocol described.

Results

TRIAL CHARACTERISTICS

Of the 491 studies identified, 14 were identified by full text review to be randomised controlled trials. Two articles[6 16] were duplicate publications, so the article containing the most information[16] was included. One trial[17] in abstract form only was excluded as follow up data were only available to three months. One study[18] was available in abstract form only. Additional information on the results was not available from the investigators. Thus 12 trials involving 868 children were evaluated. Table 1 shows the characteristics of the seven trials[18–24] in children in their initial episode of SRNS. Five trials[20–24] compared standard therapy (60 mg/m^2/day prednisone for four weeks followed by 40 mg/m^2 on alternate days or on three con-

Table 4 Meta-analysis of five trials in children in their first episode of steroid responsive nephrotic syndrome, comparing three months or more of prednisone with two months therapy

	Number of trials	*RR (95% CI)†*	*RD (95% CI)†*	*NNT (95% CI)†*	*WMD (95% CI)*
Relapse by 6 months[20–24]	4	0.59 (0.46, 0.76)	−0.27 (−0.38, −0.16)	4 (2, 6)	
Relapse by 12–24 months[20–24]	5	0.73 (0.60, 0.89)	−0.20 (−0.31, −0.10)	5 (3, 10)	
No. frequent relapsers[20–24]	5	0.67 (0.48, 0.93)	−0.13 (−0.22, −0.03)	8 (5, 33)	
Mean relapse rate/pt/y[20 23 24]	3				−0.31 (−0.51, −0.12)
Mean time to relapse (weeks)[20 24]	2				1.50 (−0.75, 3.75)
Serious adverse events*[20–24]	5	0.89 (0.56, 1.41)	−0.01 (−0.12, 0.09)		
Number with infections[22 23]	2	0.79 (0.53, 1.18)	−0.09 (−0.23, 0.06)		
Cumulative steroid dose[23 24]	2				192 (−2038, 2421)

*Hypertension, psychological disorders, cataracts, glaucoma, reduced growth rate, thromboses, osteoporosis.
†Only the experimental treatment arm of six months duration from the trial of Ksiazek and Wyszynski[22] has been included.
RR, relative risk; RD, risk difference; NNT, number needed to treat; WMD, weighted mean difference.

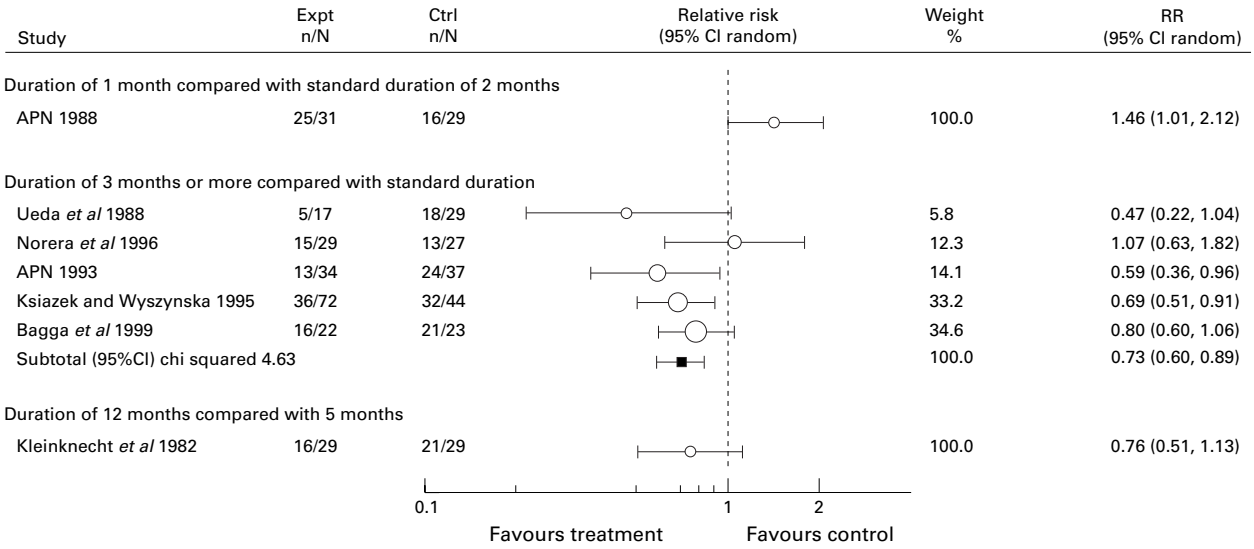

Figure 1 Meta-analysis of the relative risk (95% CI) for relapse of nephrotic syndrome by 12–24 months in five trials (334 patients) of corticosteroid therapy in children with their first episode of nephrotic syndrome. Results are ordered by trial weights. Only the experimental arm of six months duration from Ksiazek and Wyszynski[22] has been included. Also shown are the relative risks for relapse in the two other studies of corticosteroid therapy in children with their first episode of nephrotic syndrome.

secutive days out of seven for two months), with regimes of at least three months of therapy comprising 1–2 months of daily and 1.5–6 months of alternate day therapy. In one of these trials[22] standard therapy was compared with two experimental regimes. The outcomes from the experimental group treated for six months were included in the analyses. One of these trials[22] excluded those children who became steroid dependent. One trial[19] compared standard therapy with a shorter duration of treatment and one trial[18] compared five months with one year of therapy. Table 2 shows the aims and characteristics of five trials[16 25–28] in children with relapsing SRNS. Each study explored different treatment regimes aimed at inducing and/or maintaining remission.

STUDY QUALITY

Table 3 shows the assessment of study quality. Randomisation was adequately concealed in five studies. In two studies[20 22] the numbers of children in the treatment and control groups differed considerably, and in the Polish study[22] it was stated that the parents could influence which treatment group their child was assigned to. In the Japanese study[20] the calculated total protocol dose (4620 mg/m^2) exceeded the dose administered (3132 (SD 417) mg/m^2) suggesting that the protocol was not adhered to in all patients. Only three studies were analysed on an intention to treat basis.[22 26 28] Fewer than 10% of participants were excluded in seven studies.[19–24 26] Only one study[28] reported that outcome assessment was blinded. However, most studies reported the primary outcome measure using the ISKDC's definition of relapse.[5]

OUTCOME OF CHILDREN IN THEIR FIRST EPISODE OF SRNS

Meta-analysis of the five studies[20–24] involving 334 children, in which the experimental groups received a total calculated induction dose of prednisone of between 2922 and 4620 mg/m^2 administered over three to seven months, showed that the longer durations and higher doses resulted in significant reductions in relapse rate, the number of relapses per patient per year, and the number of children who relapsed frequently (table 4, fig 1). There was no increase in serious adverse events, infections, or cumulative steroid dose reported. No significant heterogeneity was shown (fig 1). Only one[21] of the five studies showed adequate allocation concealment, so subgroup analysis based on study quality was not possible. A single study[20] showed that a total dose and duration less than the standard regime resulted in a significantly higher relapse rate at 12 months (RR 1.46; 95% confidence interval (CI) 1.01 to 2.12) and a shorter time to first relapse (WMD −3.00; 95% CI −4.94 to −1.06). A further single trial[18] showed no evidence that the relapse rate was significantly reduced by giving prednisone for one year compared with five months (RR 0.76; 95% CI 0.51 to 1.13).

In the six studies[19–24] comparing standard therapy with other doses and durations of therapy, there was no significant association between the rate of relapse in the control groups treated for only two months (control event rate) and the relative risk for relapse at 12–24 months (r^2 = 0.18, p = 0.4). Combining these six studies (fig 2) showed that the risk of relapse was significantly reduced with increased duration (RR = 1.382 (SE 0.215) − 0.133 duration (SE 0.048); r^2 = 0.66; p = 0.05) and dose (RR 1.701 (SE 0.292) − 0.000264 dose (SE 8.630^{E-05}); r^2 = 0.70; p = 0.04) of prednisone. To explore whether duration or dose of prednisone determined the treatment response, we plotted the ratio of total dose to duration against relative risk (RR) to determine the average monthly dose (fig 3). This suggested that a reduction in risk of relapse was primarily associated with an increase in duration not dose, as an increase in

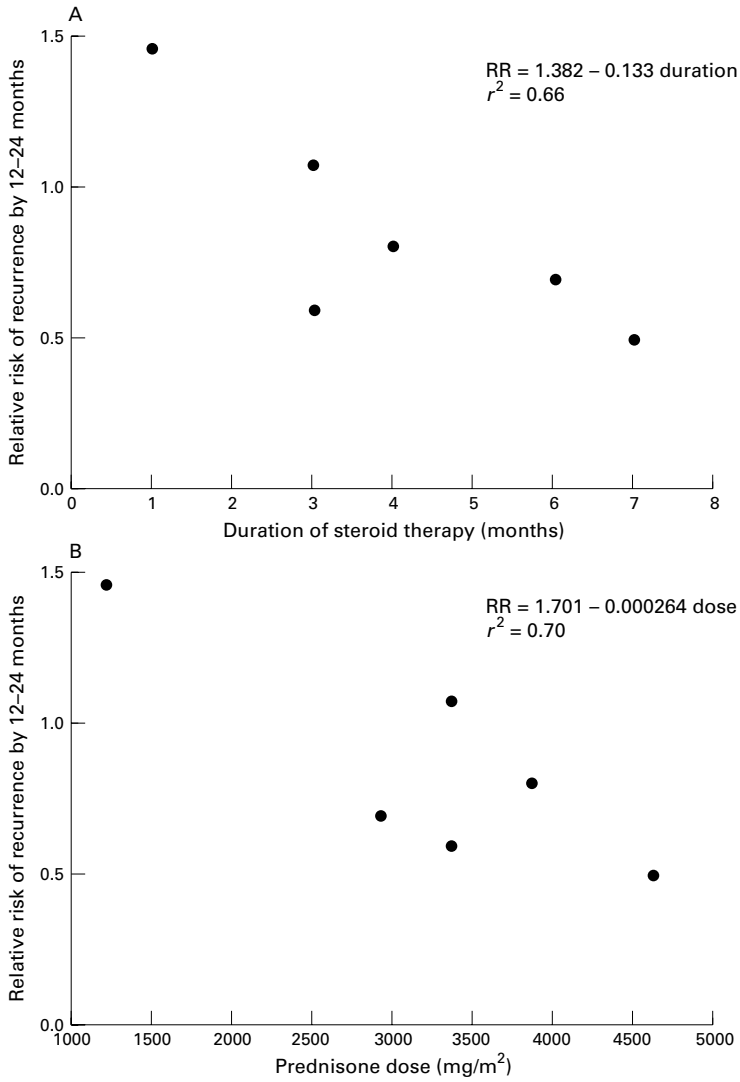

Figure 2 Relation between the risk of relapse by 12–24 months and the duration and dose of prednisone given to children in the first episode of steroid responsive nephrotic syndrome (six trials; 394 patients). Only the experimental arm of six months duration from Ksiazek and Wyszynski[22] has been included.

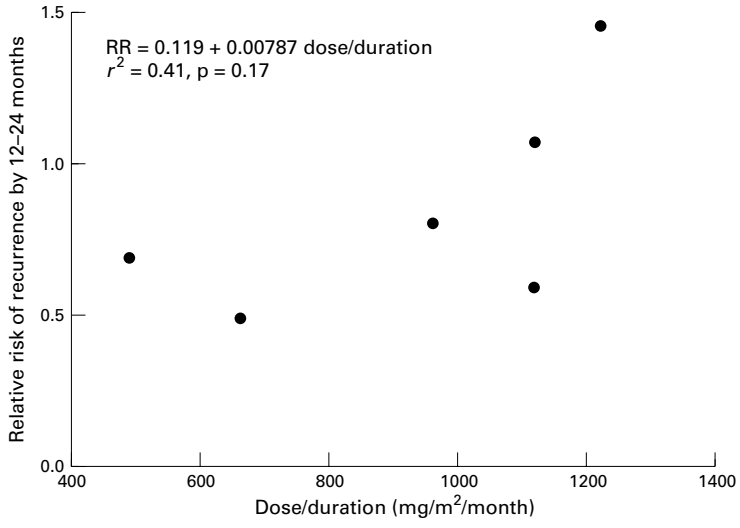

Figure 3 Relation between the risk of relapse by 12–24 months and the ratio of total dose to duration of treatment in children in the first episode of steroid responsive nephrotic syndrome (six trials; 394 patients). Only the experimental arm of six months duration from Ksiazek and Wyszynski[22] has been included.

dose per month appeared to be associated with increased rather than decreased relative risk for relapse.

CHILDREN WITH RELAPSING SRNS

Tables 2 and 5 show the characteristics and results of the studies[16 25–28] in children with relapsing SRNS. Alternate day therapy[16] was significantly more effective than intermittent therapy in maintaining remission in frequently relapsing children during six months of therapy but there was no difference by 12 months. Single daily dosing[27] was as effective as multiple daily dosing in achieving and maintaining remission in children who relapsed frequently. Deflazacort[28] significantly reduced the number of children who relapsed during therapy and reduced the relapse rate among those who relapsed without significant differences in side effects. Comparison of therapeutic interventions used in children with their first episode of nephrotic syndrome with those used in children with relapsing nephrotic syndrome was not possible as no studies compared the same interventions in these different patient groups.

Discussion

Treatment of children in their first episode of SRNS with prednisone for between three and seven months compared with two months results in fewer children experiencing relapses within 12–24 months without a notable increase in adverse effects. In addition there is a linear dose–response relation between the risk of relapse and the duration and total induction dose of prednisone.

Examination of the relation between the risk for relapse and the ratio of dose to duration suggests that longer duration of treatment is more important than total dose in reducing the risk. The relative risk of relapse at 12–24 months falls by 0.133 (13%) for every month increase in therapy to seven months (fig 2). Table 6 illustrates the relation between the duration of prednisone therapy and the relapse rate when treated for two months. The higher the relapse rate with two months of therapy (control event rate), the greater the magnitude of the treatment effect expected with increased durations of prednisone therapy. The control event rate in six studies ranged from 48% to 91% with a mean of 66%. With relapse rate of 66% in children treated for two months, the event rate would fall by 9% for every increase by one month in the duration of therapy so that treatment for six months would reduce the risk of relapse by 36% ($4 \times 9\%$) to 30% compared with two months. Ideally clinicians should know the control event rate in their local population so that they can determine how much increasing the duration of therapy will improve the outcome among their patients.

The treatment regime for the initial episode of SRNS was originally determined by the ISKDC.[5] Subsequently the APN showed that alternate day therapy[6] was more effective that intermittent administration in maintaining remission and that three months of therapy was more effective than two in preventing relapse.[21] These data led to the recommendation that

Table 5 Outcome of five trials of corticosteroid therapy in children with relapsing steroid responsive nephrotic syndrome

Author, year	*Relapse on therapy, RR (95% CI)*	*Relapse by 9 months, RR (95% CI)*	*Relapse by 12 months, RR (95% CI)*	*Mean relapse rate during study, WMD (95% CI)*
ISKDC, 1979[25]	0.20 (0.05, 0.82)	1.00 (0.89, 1.12)		0.54 (−0.50, 1.58)
APN, 1981[16]	0.60 (0.36, 1.02)		1.20 (0.93, 1.55)	−0.20 (−0.65, 0.25)
Imbasciali *et al*, 1985[26]			1.06 (0.75, 1.52)	
Ekka *et al*, 1997[27]		1.07 (0.77, 1.50)		
Broyer *et al*, 1997[28]			0.44 (0.25, 0.78)	−1.90 (−2.77, −1.03)

RR, relative risk; WMD, weighted mean difference.
ISKDC, International Study of Kidney Disease in Children.
APN, Arbeitsgemeinschaft für Pädiatrische Nephrologie.

Table 6 Expected relapse rates of nephrotic syndrome in different groups of children at different risk of relapse after two months of prednisone

Relapse rate when treated for 2 months (%)	*Reduction in relapse rate for each additional 1month* of therapy above 2 months (%)*	*Relapse rate if treated for an additional 5 months (total 7 months) (%)*
80	11	25
60	8	20
40	5	15
20	3	5
10	1	5

*Regression equation for duration of prednisone treatment: RR = 1.38 − 0.133 duration.

children should receive six weeks of daily prednisone followed by six weeks of alternate day prednisone.[7] Recently published recommendations[8] for initial treatment of nephrotic syndrome in children state that daily prednisone should be used for four to six weeks, followed by alternate day therapy for four to six weeks. However, neither of the authors based their conclusions on a systematic review and meta-analysis of the randomised trials included here.

In children with relapsing SRNS a single small study showed that the synthetic heterocyclic oxazoline glucocorticoid deflazacort[28] maintained 66% more children with steroid dependent SRNS in remission during treatment in comparison with prednisone given in an equivalent dose. No significant increase in adverse events was shown but the study was underpowered to detect adverse events. Deflazacort may offer an alternative to prednisone for maintaining remission in children with steroid dependent SRNS. Further randomised controlled trials of deflazacort are required to confirm its efficacy. If deflazacort is confirmed to be more effective than prednisone, the benefits and toxicity of this medication in comparison with non-corticosteroid agents should be examined.

Study quality was generally poor with only five studies[18 19 21 26 28] showing adequate allocation concealment. In only one[21] of the five studies included in the meta-analysis was allocation concealment considered adequate. Trials with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30–40%[13] and meta-analyses of low quality trials may overestimate the benefit of therapy.[29] Despite these quality issues, no significant heterogeneity was shown and there was a consistent reduction in the number of children experiencing relapse with the longer duration of treatment.

Publication bias resulting from the exclusion of some unpublished trials cannot be totally excluded. Publication bias[30] may result in an overestimate of treatment efficacy if the unpublished trials show no treatment effect. Formal testing using funnel plots or regression analysis was not possible because of the small number of studies. Responses from four senior investigators active in the field did not reveal any unpublished studies.

From the data, it was not possible to determine whether durations of treatment exceeding seven months would result in further reductions in the risk for relapse. No evidence of benefit through prolonging treatment to 12 months was shown in one study.[18] Similarly the efficacy of total induction doses outside the range of doses used in the trials cannot be determined. No increase in toxicity was shown in the trials. However, individual trials were not designed specifically to study toxicity and so were underpowered for the detection of side effects of corticosteroids. Thus the low reported incidence of side effects with prolonged duration of corticosteroids could be explained by a type 2 statistical error and may not be generalisable to larger groups of children.

From this meta-analysis of randomised controlled trials it can be concluded that children in their first episode of nephrotic syndrome should be treated for at least three months, with an increase in benefit being shown for up to seven months of treatment. In a population with a baseline risk for relapse of 60% with two months of prednisone, daily prednisone for four weeks followed by alternate day therapy for six months would be expected to reduce the number of children experiencing a relapse by about 40%.

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