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Hodson EM, Knight JF, Willis NS, Craig JC

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[Intervention Review]

Corticosteroid therapy for nephrotic syndrome in children

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ABSTRACT

Background

In nephrotic syndrome protein leaks from the blood to the urine through the glomeruli resulting in hypoproteinaemia and generalised oedema. While the majority of children with nephrotic syndrome respond to corticosteroids, 70% experience a relapsing course. Corticosteroid usage has reduced the mortality rate to around 3%, however they have known serious adverse effects.

Objectives

To determine the benefits and harms of corticosteroid regimens in preventing relapse in children with steroid sensitive nephrotic syndrome (SSNS).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Renal Group Specialised Register, MEDLINE and EMBASE without language restriction, reference lists of articles, abstracts from conference proceedings and contact with known investigators. Date of most recent search: October 2004

Selection criteria

Randomised controlled trials performed in children (three months to 18 years) in their initial or subsequent episode of SSNS, comparing different durations, total doses or other dose strategies using any corticosteroid agent, with outcome data at six months or more.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using a random effects model and results expressed as relative risk (RR) with 95% confidence intervals (CI).Meta-regression was used to explore potential between-study differences due to baseline risk of relapse, study quality and interventions.

Main results

Nineteen trials were identified. Six trials comparing two months of prednisone with three months or more in the first episode showed longer duration significantly reduced the risk of relapse at 12 to 24 months (RR 0.70; 95% CI 0.58 to 0.84). There was an inverse linear relationship between treatment duration and risk of relapse (RR = 1.26 - 0.112 duration; P = 0.03). There was a significant reduction in the number of frequent relapsers and the mean relapse rate/patient/year. Deflazacort was significantly more effective in maintaining remission than prednisone in children who frequently relapsed (RR 0.44; 95% CI 0.25 to 0.78). There were no increases in adverse events.

Authors' conclusions

Children in their first episode of SSNS should be treated for at least three months with an increase in benefit being demonstrated for up to seven months of treatment For a baseline risk for relapse following the first episode of 60% with two months of prednisone, daily prednisone for four weeks followed by alternate-day therapy for six months would reduce the number of children relapsing by 33%. Deflazacort deserves further study for frequent relapsers.

PLAIN LANGUAGE SUMMARY

Corticosteroid drugs for several months after a child has nephrotic syndrome can reduce repeat episodes.

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. Most children who experience this syndrome have repeat episodes. When it is untreated, children can often die from infections. Corticosteroid drugs are used to reduce these infections, but the drugs can also have serious side effects. The review of trials found that using corticosteroids for several months after the first episode has an increasing ability to reduce the risk of relapses, without an increase in serious side effects.

BACKGROUND

Nephrotic syndrome is a condition in which the glomeruli of the kidney leak protein from the blood into the urine. It results in hypoproteinaemia and generalised oedema. In children the incidence of nephrotic syndrome in Europe and North America is 2/100,000 children (Arneil 1961; Schlesinger 1968). The majority of children have minimal change disease, in which changes on light microscopy are minor or absent, and respond to corticosteroid agents. The cause of minimal change nephrotic syndrome is unknown. About 70% of children who respond to corticosteroids experience a relapsing course with recurrent episodes of oedema and proteinuria (Koskimies 1982). Children with untreated nephrotic syndrome are at increased risk of bacterial infection, characteristically resulting in peritonitis, cellulitis or septicaemia, of thromboembolic phenomena and of protein calorie malnutrition. Before antibiotics became available, two thirds of children with nephrotic syndrome died (Arneil 1971). The survivors remitted spontaneously after several months. Mortality rates fell to 35% with the introduction of sulphonamides and penicillin (Arneil 1971).

Corticosteroids have been used to treat childhood nephrotic syndrome since 1950 when large doses of adrenocorticotrophic hormone (ACTH) and cortisone given for two to three weeks were found to induce diuresis with loss of oedema and proteinuria (Arneil 1971). Corticosteroid usage has reduced the mortality rate in childhood nephrotic syndrome to around 3%, with infection remaining the most important cause of death (ISKDC 1984). Of children who present with their first episode of nephrotic syndrome, approximately 95% will achieve remission with corticosteroid therapy (Koskimies 1982). Because of this dramatic before-after evidence, 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. However corticosteroids have known adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and adrenal suppression. Adverse effects are particularly prevalent in those children who relapse frequently and thus require multiple courses of corticosteroids.

The original treatment schedules for childhood nephrotic syndrome were developed in an ad hoc manner. The International Study of Kidney Disease in Children (ISKDC) was established in 1966 and determined by consensus a regimen of daily corticosteroids for four weeks followed by corticosteroids given on three consecutive days out of seven for four weeks (Arneil 1971). Since then many physicians have used regimens involving periods of daily followed by alternate-day or intermittent therapy (three consecutive days out of seven). However the optimal doses and durations of corticosteroid therapy that are most beneficial and least harmful remain to be clarified. Although the management of steroid-sensitive nephrotic syndrome (SSNS) has been reviewed using data from multicentre studies (Bargman 1999; Brodehl 1991), no systematic review has been carried out. The aim of this systematic review is to assess the benefits and harms of corticosteroid therapy in treating children with nephrotic syndrome.

OBJECTIVES

The aim of this review was to assess the benefits and harms of different corticosteroid regimens in children with SSNS. The benefits and harms of therapy were studied in two groups of children:-
1. Children in their initial episode of SSNS
2. Children who experience a relapsing course of SSNS

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs, in which different doses, dose strategies, routes of administration and durations of treatment with prednisone, prednisolone or other corticosteroid are compared in the treatment of SSNS in children, were included.

Types of participants

Inclusion criteria

- Children aged three months to 18 years with SSNS (i.e. oedema free with urine protein = 1+ on dipstick or < 4 mg/m^2/h for three consecutive days while receiving corticosteroid therapy). A renal biopsy diagnosis of minimal change disease was not required for inclusion of the trial.

Exclusion criteria

- Children with SSNS (failure to achieve remission following four weeks or more of prednisone at 60 mg/m^2/day) or congenital nephrotic syndrome.
- Children with other renal or systemic forms of nephrotic syndrome defined on renal biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schönlein nephritis, systemic lupus erythematosus).

Types of interventions

Prednisone, prednisolone or other corticosteroid medication given orally or intravenously.
The aspects of the corticosteroid regimens considered were:-

- Long or short duration compared with standard duration of corticosteroid treatment.
- Total dose of corticosteroid medication given for induction of a remission.
- Comparisons of non-standard durations of corticosteroid therapy. Where possible test regimens were compared with standard regimens (i.e. prednisone or prednisolone given daily for four weeks at a dose of 60 mg/m^2 /d followed by 40 mg/m^2 given for four weeks on alternate days or three consecutive days out of seven days).
- Different corticosteroid agents (e.g. deflazacort) compared with standard agents (e.g. prednisone, prednisolone).
- Intravenous compared with oral route of administration of corticosteroid medication.
- The use of daily, alternate-day or intermittent administration of corticosteroid medication. Intermittent administration refers to the administration of corticosteroids on three consecutive days of seven days.
- Single daily dose compared with divided daily doses of corticosteroid medication.

- Corticosteroid medication given with other agents for the first episode of steroid responsive nephrotic syndrome.

Types of outcome measures

The prevention of relapse in steroid-responsive nephrotic syndrome (SRNS) as measured by:-

- The numbers of children with and without relapse at six months, 12 months and 24 months after completion of treatment.
- The number of children who developed frequently relapsing nephrotic syndrome.
- The number of children who require other immunosuppressive therapy because of steroid toxicity.
- Mean relapse rates per patient.
- Serious adverse events including reduced growth rates, hypertension, cataracts/glaucoma, psychological disorders, infections, thromboses and osteoporosis.
- Cumulative corticosteroid dosage.

Search methods for identification of studies

Relevant trials were obtained from the following sources:-

The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*, Issue 3, 2004) and the Cochrane Renal Group Specialised Register (October 2004).
#1 (Nephrotic and syndrome)
#2 Child
#3 Nephrosis*.ME
#4 Nephrosis-Lipoid*.ME
#5 Nephrotic - Syndrome*.ME
#6 #1 or #3 or #4 or #5
#7 #2 and #6

MEDLINE using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy for nephrotic syndrome in children (see Renal Group Module for details).
MEDLINE Search Strategy (1966 to October 2004):
1. exp nephrotic syndrome/ or nephrotic syndrome.tw.
2. exp nephrosis, lipoid/ or lipoid nephrosis.tw.
3. 1 or 2
4. exp child/ or child$.tw.
5. 3 and 4

EMBASE using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy for nephrotic syndrome in children.
EMBASE Search Strategy (1980 to October 2004):
1. exp nephrotic syndrome/ or nephrotic syndrome.tw.
2. exp steroid/ or steroids.tw
3. 1 and 2

Reference lists of nephrology textbooks, review articles and relevant trials and CD-ROMs and abstract books from nephrology meetings.

Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

The review was undertaken by four reviewers (EH, JK, NW and JC). The titles and abstracts were screened by EH, who discarded studies that were not relevant (i.e. studies of lipid lowering agents) although studies and reviews that could have included relevant data or information on trials were retained initially. Reviewers EH, JK and NW independently assessed abstracts and, if necessary, the full text to determine which studies satisfied the characteristics required for inclusion. Data extraction was carried out by the same reviewers. Where more than one publication of one trial exists, only the publication with the most complete data analysis was included. Studies reported in non-English language journals were translated before assessment. Disagreements were resolved in consultation with JC.

Study quality

The quality of studies to be included were assessed independently by EH, JK and NW, without blinding to authorship, using the criteria of the Cochrane Renal Group adapted from Crowther 1998. Discrepancies were resolved in discussion with JC. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness of follow-up and blinding of participants, investigators and outcome assessment.

1. Allocation concealment
Adequate: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
Unclear: Randomisation stated but no information on method used is available.
Inadequate: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

2. Blinding
Blinding of investigators: Yes/No/not stated
Blinding of participants: Yes/No/not stated
Blinding of outcome assessor: Yes/No/not stated
Blinding of data analysis: Yes/No/not stated
The above were considered not blinded if they knew the treatment group or could identify it in >20% of participants because of side effects of treatment.

3. Intention-to-treat analysis
Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment
Yes: Not specifically reported, but confirmed upon study assessment
No: Not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)
No: Stated but not confirmed upon study assessment
Unclear: Not reported and not clear from study assessment.

4. Completeness of follow-up
Per cent of patients lost to follow up during study.

Statistical analyses

For dichotomous outcomes (relapse or no relapse, side effects) the relative risks (RR) and risk differences (RD) for individual studies were calculated and summary statistics estimated using the random effects model and results compared to those obtained using a fixed effects model. Heterogeneity was analysed with a threshold value of P < 0.1 used for statistical significance. Meta-regression was used to explore potential between-study differences due to study quality or types of interventions used. Where continuous scales of measurement were used to assess the effects of treatment (cumulative steroid therapy, relapse rate), these data were analysed in continuous form as the weighted mean difference (WMD) or standardised mean difference (SMD) if different scales had been used. The time to relapse was not included since many children did not experience relapse so the data would be biased.

RESULTS

Description of studies

The initial literature search (2000) identified 491 studies of which 13 (14 reports) were identified to be RCTs (*see Table of characteristics of included studies*). One trial in abstract form was excluded because of limited outcome data so that 12 trials were included in the systematic review. A further search from 2000 to 2002 identified five additional RCTs (Hiraoka 2000; Jayantha 2002a; Jayantha 2002b; Mattoo 2000; Sharma 2002) including the full publication of the trial (Hiraoka 2000), excluded from the original review because of limited outcome data. Two earlier trials (Leisti 1978; Yoshikawa 1998), which had not been identified in the original search, were also included so that a total of 19 trials were included in this updated review. Two included studies (Jayantha 2002a; Kleinknecht 1982) were published only in abstract form. Additional information was provided by the investigator for two trials (Jayantha 2002a; Jayantha 2002b). A further literature search from 2002-2004 and hand searching of conference proceedings revealed four further RCTs (APN 1999; Hiraoka 2003; Pecoraro 2004; Satomura 2001) of which three were available in abstract form only (APN 1999; Pecoraro 2004; Satomura 2001).

Fifteen trials (APN 1988; APN 1993; APN 1999; Bagga 1999; Hiraoka 2000; Hiraoka 2003; Jayantha 2002a; Kleinknecht 1982; Ksiazek 1995; Norero 1996; Pecoraro 2004; Satomura 2001; Sharma 2002; Ueda 1988; Yoshikawa 1998) evaluated 1292 children in their initial episode of SSNS. In two of these trials (Ksiazek 1995; Pecoraro 2004) a control group was compared with two experimental regimens. Six trials (APN 1993; Bagga 1999; Jayantha 2002a; Ksiazek 1995; Norero 1996; Ueda 1988) compared standard therapy of two months duration (60 mg/m^2/d prednisone for four weeks followed by 40 mg/m^2 on alternate days or on three consecutive days of seven for four weeks) with regimens of at least three months of therapy comprising one to two months of daily and 1.5 - 6 months of alternate-day therapy. From the trial by Ksiazek 1995, data from the standard therapy group and the experimental group treated for 6 months (experimental group 1) were included in the meta-analysis. Norero 1996 excluded those children who became steroid dependent. Four trials (APN 1993; Bagga 1999; Ksiazek 1995; Ueda 1988) comparing long duration therapy with standard duration, stated that duration of follow-up and the time to first relapse was measured from completion of initial therapy (both daily and alternate-day therapy). The other trial (Norero 1996) comparing long duration with standard did not state when the follow-up period commenced in relation to the therapy period. In the sixth trial (Jayantha 2002a), the follow-up period was measured from the end of the period of daily prednisone. Four trials (Hiraoka 2003; Ksiazek 1995; Pecoraro 2004; Sharma 2002) were included in a meta-analysis comparing six months with three months of therapy; from the trial by Ksiazek 1995 data from the experimental groups treated for three months (experimental group 2) and six months (experimental group 1) were included in this analysis. The follow-up period was measured from the completion of the initial course of therapy in three trials (Hiraoka 2003; Ksiazek 1995; Sharma 2002); the time at which the outcome was measured was not reported in the fourth trial (Pecoraro 2004). APN 1988 compared standard therapy with a shorter duration of treatment; the follow-up period was measured from the time of completion of daily prednisone. Kleinknecht 1982 compared five months with one year of therapy; the timing of the follow-up period in relation to the duration of initial therapy was not stated. Hiraoka 2000 and Satomura 2001 compared different total doses of prednisone given over 12 or 8 weeks. Yoshikawa 1998 compared the standard therapy of two months with 4.5 months but both groups received the Chinese herb, Sairei-to. One trial (APN 1999) compared 12 weeks of prednisone plus 8 weeks of cyclosporin with 12 weeks of prednisone only.

Eight trials included 390 children with relapsing SSNS (APN 1981; Broyer 1997; Ekka 1997; Imbasciali 1985; ISKDC 1984; Jayantha 2002b; Leisti 1978; Mattoo 2000). Each study explored different treatment regimens aimed at inducing and/or maintaining remission. In one trial (Jayantha 2002b), children with steroid dependent nephrotic syndrome were excluded. Two trials (Imbasciali 1985; Jayantha 2002b) included children with infrequently and frequently relapsing SSNS.

Risk of bias in included studies

The assessment of study quality is shown in additional Table 1- *Assessment of study quality in trials of steroid therapy in nephrotic syndrome.*

Allocation concealment

Randomisation was adequately concealed in eleven studies (APN 1988; APN 1993; Bagga 1999; Broyer 1997; Hiraoka 2003; Imbasciali 1985; Jayantha 2002a; Jayantha 2002b; Kleinknecht 1982; Sharma 2002; Yoshikawa 1998). In three studies (Jayantha 2002a; Ksiazek 1995; Ueda 1988;) the numbers of children in the treatment and control groups differed markedly and in Ksiazek 1995, it was stated that the parents could influence which treatment group their child was assigned. In Ueda 1988 the calculated total protocol dose (4620 mg/m^2) exceeded the dose administered (3132 ± 417 (SD) mg/m^2) suggesting that the protocol was not adhered to in all patients.

Blinding

Two studies reported blinding of participants and investigators (Broyer 1997; Leisti 1978). No studies reported blinding of outcome for relapse of nephrotic syndrome. However most studies reported this primary outcome measure using the ISKDC's definition of relapse (Abramowicz 1970).

Intention-to-treat analysis

Only four studies were analysed on an intention-to-treat basis (Hiraoka 2000; Hiraoka 2003; Imbasciali 1985; Ksiazek 1995). In eight trials (APN 1981; APN 1988; APN 1993; APN 1999; Bagga 1999; Broyer 1997; ISKDC 1979; Norero 1996) between 2.5% and 26% children with SSNS were excluded after randomisation. In Jayantha 2002b the original analyses excluded patients who became steroid

dependent as they were excluded from the study. In this review, steroid dependent patients could be included in the analyses of RR for relapse at different time points as the numbers of patients excluded due to steroid dependence were provided by the author. Steroid dependent patients could not be included in the analyses of adverse effects, cumulative steroid dose and mean relapse rate/patient/year.

Completeness of follow-up

More than 10% of participants were lost to follow-up in three trials (Bagga 1999; Jayantha 2002a; Jayantha 2002b). In Jayantha 2002a, 11 children were lost to follow-up in the first three months of the seven-month treatment group, while only two children were lost to follow-up from the standard treatment group. In Jayantha 2002b 14 children were lost to follow-up by one year from the standard treatment group and five from the seven-month duration group.

Effects of interventions

Outcome of children in their first episode of SRNS

Seven (APN 1993; Bagga 1999; Hiraoka 2000; Jayantha 2002a; Ksiazek 1995 [experimental group 1 compared with standard group]; Norero 1996; Ueda 1988) involved 481 children, in which the experimental groups received a total calculated induction dose of prednisone of between 2922 to 5235 mg/m^2 administered over three to seven months, while the control groups received two months of therapy (dose 2240 mg/m^2).

- Longer durations and higher doses resulted in significant reductions in relapse rate, the number of relapses/patient/year and the number of children who relapsed frequently (comparison 01, outcomes 01 to 04). No significant heterogeneity was demonstrated for outcome 02 (relapses by 12 to 24 months) but significant heterogeneity existed for outcome 01 (relapses at six months).
- There was no increase in cumulative steroid dose (comparison 01, outcome 05.02).
- Serious adverse events (growth retardation, hypertension, cataracts/glaucoma, psychological disorders, osteoporosis, infections, features of Cushing's Syndrome) were not increased (comparison 01, outcome 06).
- Subgroup analysis showed no difference in response to high dose therapy compared with standard therapy when trials were divided into two groups based methodological quality (adequate versus unclear or inadequate allocation concealment). (comparison 01, outcome 07).

In four studies (Hiraoka 2003; Ksiazek 1995 [experimental group 1 compared with experimental group 2]; Pecoraro 2004 [experimental group 1 compared with control]; Sharma 2002) involving 382 children, six months was compared with three months of therapy.

- The longer duration resulted in significant differences in the risk for relapse at six months (comparison 02, outcome 01.01: RR 0.48, 95% CI 0.35 to 0.64) and 12 months (comparison 02, Outcome 02.01: RR 0.57, 95% CI 0.45 to 0.71).
- The number of children who became frequent relapsers was lower following six months treatment (comparison 02, outcome 01: RR 0.55, 95% CI 0.38 to 0.80) and the mean relapse rate/year was lower (comparison 02, outcome 03: WMD -0.44, 95% CI -82 to -0.07).
- Cumulative steroid dose did not differ between groups (comparison 01, outcome 05.03)
- Adverse effects did not differ between groups (comparison 01, outcome 06).

APN 1988 showed that a total dose and duration less than the standard regimen resulted in a significantly higher relapse rate at six months (comparison 01, outcome 01.01: RR 1.60, 95% CI 1.01 to 2.54) and 12 months (comparison 01, outcome 02.01: RR 1.46, 95% CI 1.01 to 2.12).

Satomura 2001 showed that there was no significant difference in the risk for relapse between a prednisone dose of 2240 mg/m^2 over 12 weeks and 2520 mg/m^2 over eight weeks (comparison 01, outcome 02.04)

Kleinknecht 1982 showed no evidence that the relapse rate was significantly reduced by giving prednisone for one year compared with five months (comparison 02, outcome 01.02 and outcome 02.02).

Yoshikawa 1998 showed no difference in relapse rate at two years or in the number of children who became frequent relapsers between standard therapy (two months) and 4.5 months of prednisone when both groups received the Chinese herb, Sairei-to (comparison 03, outcome 01).

APN 1999 showed that the addition of cyclosporin to 12 weeks of prednisone therapy reduced the risk for relapse at six months (comparison 05, outcome 01: RR 0.33, 95% CI 0.13 to 0.83) but not 12 months (comparison 05, outcome 02). The numbers needing cytotoxic therapy were not significantly different between groups (comparison 05, outcome 03).

Eight studies (APN 1988; APN 1993; Bagga 1999; Hiraoka 2000; Jayantha 2002a; Ksiazek 1995; Norero 1996; Ueda 1988) compared standard therapy (two months) 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 - CER) and the RR for relapse by 12 to 24 months (r^2 = 0.20, P = 0.2) indicating that the RR for relapse by 12 to 24 months was not influenced by the CER.
- Meta-regression showed that the risk of relapse at 12 to 24 months was significantly reduced with increased duration (RR =

1.26 - 0.112 duration; $r^2 = 0.56$, P = 0.03) (Figure 1) and dose (RR = 1.65 dose - 0.00025; $r^2 = 0.70$, P = 0.01) of prednisone (Figure 2).

Figure 1. Correlation between relative risk for relapse (Y axis) and duration of therapy (X axis) showing that relative risk for relapse decrea duration of prednisone therapy.

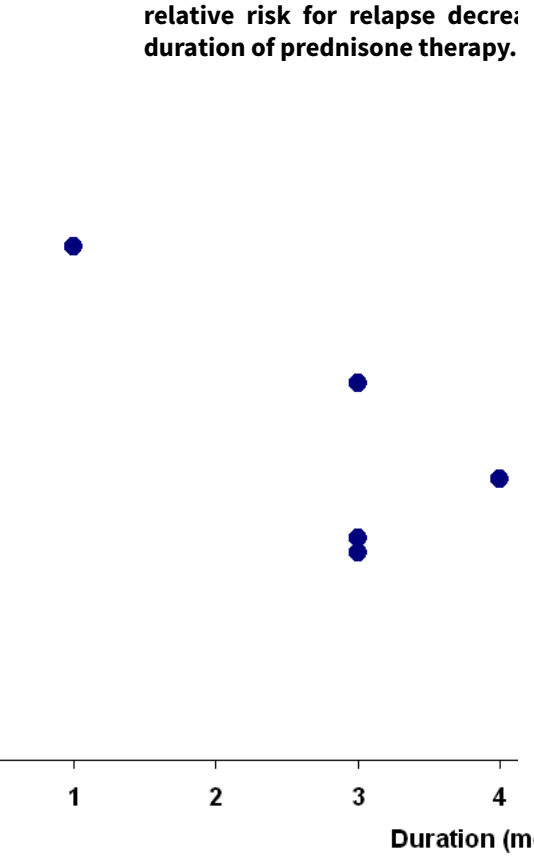
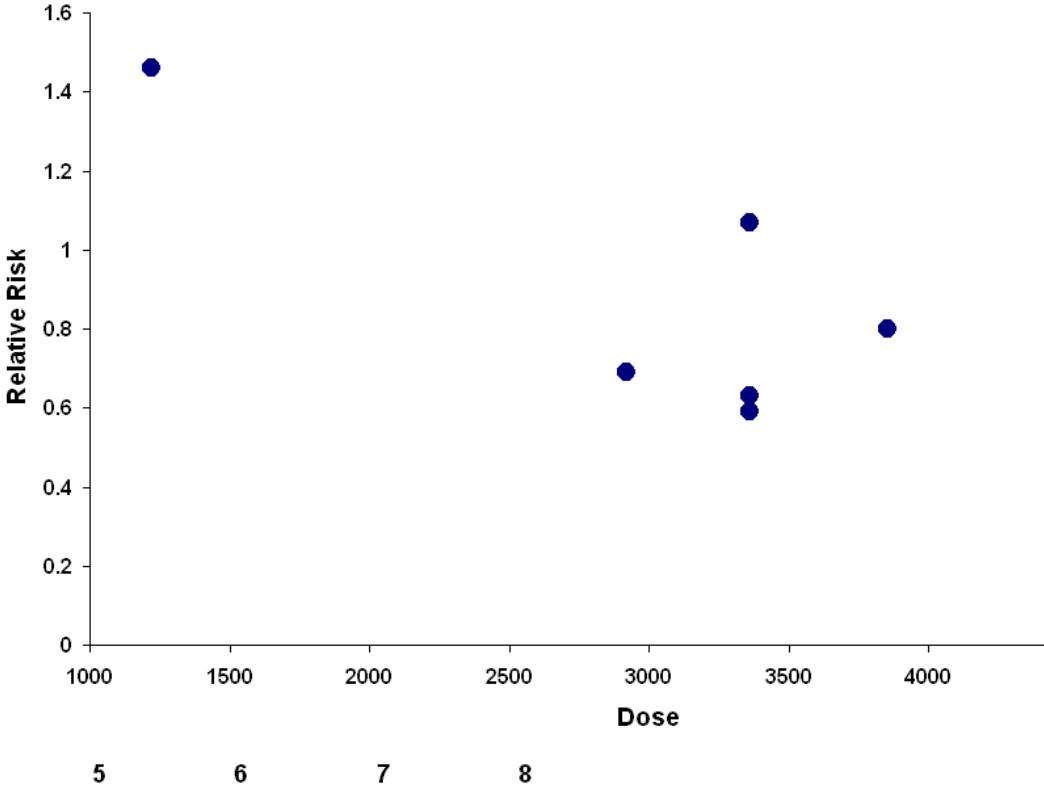


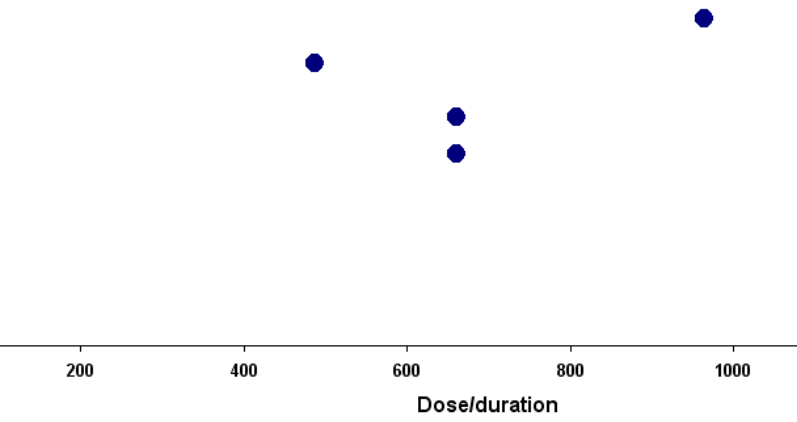
Figure 2. Correlation between relative risk for relapse (Y axis) and total induction dose of prednisone (X axis) showing that the relative risk for relapse falls with increase in dose of prednisone therapy.



- To explore whether duration or dose of prednisone determined the treatment response, the RR for relapse at 12 to 24 months was plotted against the ratio of total dose to duration (mg/m^2/mo) to determine the average monthly dose. This suggested a reduction in risk of relapse was primarily associated with an increase in duration not dose since an increase in dose/month appeared to be associated with increased rather than decreased

RR for relapse (RR = 0.145 + 0.000695 dose/duration; r^2 = 0.34, P = 0.13) (Figure 3).

Figure 3. Reduction in risk of relapse was primarily associated with an increase in duration not dose since an increase in dose/month appeared to be associated with increased rather than decreased RR for relapse.



- However a meta-analysis of two studies where different induction doses were used over the same duration (Hiraoka 2000; Pecoraro 2004) (experimental group 1 compared with experimental group 2) showed that the higher dose significantly reduced the risk of relapse compared with the lower dose (comparison 02, outcome 02.03: RR 0.59, 95% CI 0.42 to 0.84)

Children with relapsing SRNS

Seven studies (APN 1981; Broyer 1997; Ekka 1997; Imbasciali 1985; ISKDC 1979; Jayantha 2002b; Mattoo 2000) included children with relapsing SRNS (comparison 02, outcomes 01 to 06; comparison 03, outcomes 01 to 05; additional Table 2 - *Outcomes of trials in children with relapsing nephrotic syndrome*).

- Alternate-day therapy (APN 1981) was significantly more effective than intermittent therapy in maintaining remission in frequently relapsing children during six months of therapy (comparison 02, outcome 02.01: RR 0.60, 95% CI 0.36 to 1.02) but there was no difference by 12 months (comparison 02, outcome 01.02: RR 1.20, 95% CI 0.93 to 1.55).
- Single daily dosing (Ekka 1997) was as effective as multiple daily dosing in achieving and maintaining remission in children who relapsed frequently (comparison 02, outcome 01.01: RR 1.07, 95% CI 0.77 to 1.50).
- Deflazacort (Broyer 1997) 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 02, outcome 01.04: RR 0.44, 95% CI 0.25 to 0.78).
- Children relapsed significantly less frequently during treatment on daily prednisone compared with intermittent therapy but relapse rates did not differ by nine months after treatment (ISKDC 1979) (comparison 02, outcome 02.02: RR 0.20, 95% CI 0.05 to 0.82).
- Remission rate at one year was not significantly different between children who received intravenous methylprednisolone during induction and those who received oral prednisone only (Imbasciali 1985) (comparison 02, outcome 01.03: RR 1.06, 95% CI 0.75 to 1.53).
- Children with steroid dependent SSNS had significantly fewer relapses if they received daily rather than alternate-day prednisone during upper respiratory tract infections (Mattoo 2000) (comparison 02, outcome 03.04: WMD -3.30, 95% CI -4.03 to -2.57).
- A cross-over study (Leisti 1978) showed that fewer children with post-prednisone adrenocortical suppression relapsed during a six month period if they received partial cortisol substitution with 5 mg of cortisol during remission in comparison with placebo. The data for the patients were combined for each treatment period so the data for the first comparison could not be displayed in a meta-analysis. After three months treatment, 5/13 children (38%) receiving cortisol had relapsed compared with 12/13 receiving placebo (92%) (χ^2 = 4.0, P = 0.05), and at six months 9/13 children receiving cortisol had relapsed compared with 12/13 receiving placebo.
- Significantly fewer children treated with prednisone for seven months relapsed by 6, 12, 24 and 36 months (comparison 03, outcome 01.03: RR 0.60, 95% CI 0.45 to 0.80) compared with standard duration therapy (Jayantha 2002b). The relapse rate/patient/year excluding patients who became steroid dependent was reduced at one, two and three years after treatment (comparison 03; outcome 03.02: WMD -1.79, 95% CI -2.39 to -1.19) and the number of children who developed steroid dependence or relapsed frequently by one year was reduced (comparison 03; outcome 02: RR 0.43, 95% CI 0.19 to 0.95) in the long duration group compared with standard duration. Cumulative steroid dose excluding patients who became steroid dependent during the study was higher at one year in the long treatment group but did not differ at two and three years (comparison 03; outcome 04.02: WMD -1.13, 95% CI -3.08 to -0.82). Hypertension was more common in the long duration group but the difference was not statistically significant (comparison 03; outcome 05.01: RR 2.40, 95% CI 0.86 to 6.73); the number of children with growth failure did not differ between groups.

DISCUSSION

The addition of further RCTs to this systematic review has not changed the main conclusion of the original review:

- Children in their first episode of SSNS should be treated with prednisone for between three and seven months since fewer children suffer relapses within 12 to 24 months without a

demonstrated increase in adverse effects compared with those treated for two months.

- However additional trials indicate a benefit of treating for six months with prednisone compared with three months.

Four (APN 1993; Bagga 1999; Ksiazek 1995; Ueda 1988) of the six studies, which showed a benefit of longer duration over standard duration therapy, reported the number of patients who relapsed at six months and/or 12 to 24 months after completing the full course of initial therapy suggested that the effect of longer duration therapy is not simply due to the reduction in the steroid-free at-risk period. There is a linear relationship between the risk of relapse and the duration of the induction prednisone regimen and between the risk of relapse and the total induction dose of prednisone. Four studies comparing three months treatment with six months treatment confirmed the benefit of prolonged duration of steroid therapy for the first episode of nephrotic syndrome (Hiraoka 2003; Ksiazek 1995; Pecoraro 2004; Sharma 2002). The effect of administering an increased dose over the same duration as the standard dose (2240 mg/m^2) was only examined in one trial, which showed the higher dose was associated with fewer relapses (Hiraoka 2000). Another trial has also examined, in a small number of patients, the effect of different doses given for six months and found that the higher dose was associated with fewer relapses (Pecoraro 2004). A third trial compared two months of therapy with three months of therapy but with a lower total dose; there was no significant difference in the risk for relapse (Satomura 2001). These data suggest that both dose and duration of prednisone are important in reducing the risk for relapse. However examination of the relationship between the risk for relapse and the ratio of dose to duration in trials comparing standard therapy with other regimens suggests that longer duration of treatment is more important than total dose in reducing the risk. The RR of relapse at 12 to 24 months falls by 0.112 (11%) for every month-increase in therapy to seven months. The relationship between the duration of prednisone therapy and the relapse rate when treated for two months is illustrated for different risks of relapse with standard duration therapy in additional Table 3 - *Expected relapse rates in groups of children with different control event rates*. The higher the relapse rate with two months of therapy (CER), the greater the magnitude of the treatment effect expected with increased durations of prednisone therapy. The CER in six studies ranged from 48% to 91% with a mean of 68%. With a relapse rate of 68% in children treated for two months, the event rate would fall by 7.5% for every increase by one month in the duration of therapy. Therefore treatment for six months would reduce the risk of relapse by 30% (4 x 7.5%) to 38% compared with two months. Ideally, clinicians should know the CER 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 regimen for the initial episode of SSNS was originally determined by the ISKDC (Abramowicz 1970). Subsequently, the APN demonstrated that alternate-day therapy (APN 1981) was more effective than intermittent administration in maintaining remission, and that three months of therapy was more effective than two in preventing relapse (APN 1993). These data led to the recommendation that children should receive six weeks of daily prednisone followed by six weeks of alternate-day prednisone (Brodehl 1991). Recently published recommendations (Bargman 1999) 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 RCTs included here.

A single study (Yoshikawa 1998) compared two months therapy with 4.5 months of prednisone therapy and both groups received the Chinese herb Sairei-to for two years. There was no difference in relapse rate at two years with 65% relapsing after two months and 70% relapsing after 4.5 months of prednisone therapy. The authors concluded that the concurrent use of Sairei-to reduced the risk for relapse in both treatment groups, negating the need for a course of prednisone therapy longer than two months. The authors argued this using the results of an earlier study (Yoshikawa 1991) comparing Sairei-to administration with no administration for two years in two groups of children treated with 18 weeks of prednisone. In that study, to which we did not have access, the Sairei-to treated group had fewer relapses (0.25 ± 0.51 relapses/patient) than the untreated group (0.50 ± 0.85 relapses/patient) during the two year study. Further studies are required.

A single study (APN 1999) compared three months of prednisone and eight weeks of cyclosporin with three months of prednisone alone and found a reduced risk for relapse at six months but not 12 months. Further studies are required to determine whether the addition of cyclosporin reduces the risk of relapse sufficiently to justify the risks and costs of therapy.

In children with relapsing SSNS a single small study demonstrated that the synthetic heterocyclic oxazoline glucocorticoid deflazacort (Broyer 1997) 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 demonstrated but the study was underpowered to detect harms. Deflazacort may offer an alternative to prednisone for maintaining remission in children with steroid dependent SRNS. Further RCTs of deflazacort are required to confirm its efficacy. If deflazacort is confirmed to be more effective than prednisone, the benefits and harms of this medication in comparison with non-corticosteroid agents should be examined. A single study (Jayantha 2002b) has demonstrated that children with relapsing SSNS relapse less frequently subsequently if treated with tapering doses of prednisone for seven months compared with the standard ISKDC regimen for relapse (60 mg/m^2/d till urine protein-free for three days followed by 40 mg/m^2 on alternate days for four weeks). Small studies have demonstrated that cortisol substitution in children with post-prednisone adrenal insufficiency, as well as changing from alternate-day to daily prednisone during upper respiratory infection, reduce the number of relapses. Both therapeutic regimens require further examination in RCTs.

Study quality was variable with nine studies (APN 1981; APN 1988; APN 1993; Broyer 1997; Bagga 1999; Hiraoka 2003; Imbasciali 1985; Jayantha 2002a; Sharma 2002) showing adequate allocation concealment. In three (APN 1993; Bagga 1999; Jayantha 2002a) of the six studies included in the meta-analysis comparing standard with long duration treatment allocation concealment was considered adequate. Trials with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30% to 40% (Schulz 1995) and meta-analyses of low quality trials may overestimate the benefit of therapy (Moher 1998). Despite these quality issues, no significant heterogeneity was demonstrated 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 (Egger 1997) 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 appears that durations of therapy up to seven months are associated with reduced risk for relapse compared with two or three months of therapy in the initial treatment of SSNS. No evidence of benefit through prolonging treatment to 12 months was demonstrated in one study (Kleinknecht 1982). Similarly, the efficacy of total induction doses outside the range of doses used in the trials cannot be determined. No increase in harms was demonstrated in the trials. However individual trials were not designed specifically to study harms 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 II statistical error and may not be generalisable to larger groups of children.

AUTHORS' CONCLUSIONS

Implications for practice

- In children in their first episode of SSNS, treatment with prednisone for at least three months results in fewer children relapsing by 12 to 24 months with an increase in benefit being demonstrated for up to seven months of treatment compared with two months therapy. 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 33%.
- In comparison with three months of therapy, six months of therapy results in a reduced risk for relapse without increase in adverse effects.
- The reduction in risk for relapse is associated with both an increase in duration and an increase in dose.
- During daily therapy, prednisone is as effective when administered as a single daily dose compared with divided doses.
- Alternate-day therapy is more effective than intermittent therapy (three consecutive days of seven days) in maintaining remission.
- In relapsing SSNS, long duration of alternate-day prednisone is more effective than the standard duration therapy for relapse originally recommended by the ISKDC.

Implications for research

- Although duration of therapy up to seven months appears more effective than two months therapy in achieving sustained remissions, a further well designed and adequately powered RCT is required to compare daily therapy for four weeks followed by alternate day therapy for six months with two or three months of therapy to confirm this conclusion of the systematic review.
- The optimal way to treat frequently relapsing SSNS with corticosteroids has not been defined. In clinical practice, physicians commonly use prolonged courses of alternate-day prednisone. A further RCT could compare two alternate-day regimens in which the prednisone dose was reduced at different rates in each group.
- Children with SSNS commonly relapse when they develop an intercurrent infection. A further RCT is required to confirm whether additional prednisone at the time of infection can prevent relapse.
- There is evidence that children with SSNS suffer post-prednisone adrenal insufficiency and that this state may predispose to relapse. The efficacy of cortisol substitution in such children should be examined in a further RCT.
- Further studies of the efficacy of Chinese herbs and cyclosporin to reduce relapse rates in children with SSNS should be considered.
- Further studies of deflazacort in comparison with prednisone with larger numbers of patients and longer follow-up periods are required in children with frequently relapsing nephrotic syndrome to confirm its efficacy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

APN 1981

Methods	Country: Northern Europe Recruitment: Multicentre. Renal clinics Randomisation: Sealed envelopes opened locally
Participants	64 children with FRSSNS. Age 2-16 years. 30 expt group 34 control group
Interventions	Expt: prednisone 60mg/m2/day till protein free for 3 + days; then 35mg/m2 on alternate days. Total 6 months. Control: prednisone 60mg/m2/day till protein free for 3+ days; then 40mg/m2 given on 3 consecutive days out of 7. Total 6 months.
Outcomes	No. relapsing during 6 mths of therapy & in subsequent 6 mths. Mean relapse rate during treatment & in subsequent 6 mths.
Notes	Definitions: FRSSNS: 2+ relapses within 6 mth of first response or 4 relapses in any 1 year (ISKDC). Relapse: Urine protein >40mg/m2/hr for 3 consecutive days. (ISKDC) Remission: Urinary protein <4mg/m2/hr for 3 consecutive days. (ISKDC)
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

APN 1981 *(Continued)*

Allocation concealment (selection bias)	High risk	C - Inadequate

APN 1988

Methods	Country: Northern Europe Recruitment: Multicentre. Renal clinics Randomisation: Central but method not stated
Participants	61 children with initial episode SSNS. Age 2-16 yrs. 32 expt group 29 standard group
Interventions	Expt: Prednisone 60mg/m2 daily till urine protein-free for 3 days then 40mg/m2 alternate days till albumin >35g/l. Total about 1 month. Standard: prednisone 60mg/m2/day for 4 weeks & 40mg/m2 alternate days for 4 weeks. Total 2 months.
Outcomes	No. of patients with/without relapse at 6mth & 1 yr after completing daily prednisone. Number (no.) relapses/pt/yr Time to first relapse No.becoming frequent relapsers. No. with serious adverse events.
Notes	Complete one year follow up. Definitions: FRSSNS: ISKDC Relapse: ISKDC Remission: ISKDC and albumin 35g/L. Time to 1st relapse: Cessation of intial daily steroids to onset of 1st relapse.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

APN 1993

Methods	Country: Northern Europe Recruitment: Multicentre. Renal clinics Randomisation: Central office but method not stated
Participants	71 children with initial episode SSNS. Age 2-16 years. 34 expt group 37 standard group
Interventions	Expt: prednisone 60mg/m2/day for 6weeks and 40mg/m2 alternate days for 6 weeks. Total 3 months. Standard: prednisone 60mg/m2/day for 4 weeks and 40mg/m2 alternate days for 4 weeks. Total 2 months.
Outcomes	No. of patients with/without relapse by 6 & 12 mths after completing daily and alternate day prednisone.

APN 1993 *(Continued)*

	No. becoming frequent relapsers. No. of serious adverse events.
Notes	Complete one year follow up. Definitions: FRSSRNS: ISKDC Relapse: ISKDC Remission: ISKDC Time to 1st relapse: cessation of daily & alternate day prednisone to onset of 1st relapse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

APN 1999

Methods	Country: Northern Europe Recruitment: Multicentre. Renal clinics Randomisation: Central office but method not stated
Participants	152 children with initial episode of SSNS. Age NS. 49 excluded (14 steroid resistant, 6 infection or thromboses, 28 loss to FU, protocol violation. Expt: 49; Control: 55.
Interventions	Expt: Cyclosporin 150mg/m2/day for 8 wks. Control: No cyclosporin. Both groups: prednisolone 60mg/m2/d for 6 wks; 40mg/m2 on alt day for 6 wks. Total duration of prednisolone 12 wks.
Outcomes	No. of patients with relapse & mean relapse rate at 6, 12 mths. Median time to relapse. Number needing cytotoxic agents. Adverse effects of cyclosporin.
Notes	Definitions not stated. Abstracts only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bagga 1999

Methods	Country: India Recruitment: Renal clinic Randomisation: Method not stated
Participants	45 children with first episode SSNS. Age 1-12 years. 22 expt group 23 standard group

Bagga 1999 *(Continued)*

Interventions	Expt: prednisolone 2mg/kg/day for 4weeks, 1.5mg/kg/day for 4 weeks then 1.5mg/kg alternate days for 4 weeks, 1mg/kg alternate days for 4 weeks. Total 4 months. Standard: 2mg/kg/day for 4 weeks then 1.5mg/kg/ alternate days for 4 weeks. Total 2 months.
Outcomes	No. of patients with/without relapse by 6 & 12 mths after completing daily and alternate day prednisolone. No. becoming frequent relapsers. Relapse rate/pt/yr; mean time to first relapse. No. of serious adverse events. Cumulative steroid dose.
Notes	Complete one year follow up. Definitions: FRSSNS: 2+ relapses in 6 mths or 3+ within 12 mths of initial epsiode. Relapse: 3+ protein on dipstick for 3 consecutive days. Remission: Nil or trace of protein on dipstick for 3+ consecutive days. Time to 1st relapse: cessation of daily & alternate day prednisone to onset of 1st relapse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Broyer 1997

Methods	Country: France Recruitment: Multicentre. Renal clinics Randomisation: Central using blocks of random numbers
Participants	40 children with SDNS (2+ relapses in 12mths despite alternate day prednisone or within 2mths of stopping this regimen). Mean age 9.2 yrs (expt); 8.5 yrs (control) 20 expt group 20 control group
Interventions	Expt: deflazacort - dose equivalent to prednisone of 60mg/m2/day till in remission for 5 days then 60mg/m2 alternate days for 6 weeks, taper 6-8 weeks then 15-20 mg/m2 alternate days for 1 year. Control: prednisone given as above.
Outcomes	No. relapsing during 1 year of therapy. Mean relapse rate/pt. Serious adverse events.
Notes	6 children in expt group and 5 in control group also received Cyclosporin. Definitions: Relapse: not stated. Remission: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ekka 1997

Methods	Country: India Recruitment: Renal clinic Randomisation: Not stated
Participants	106 children with relapsing SSNS Age 1.3 - 17 years. 52 expt group 54 control group
Interventions	Expt: Prednisolone 2mg/kg/day for 2-4 weeks given as single morning dose & 1.5mg/kg alternate days for 4 weeks. Control: prednisolone 2mg/kg/day for 2-4 weeks given as 3 divided doses & 1.5mg/kg alternate days for 4 weeks.
Outcomes	No. with/without relapse at 9 months. Time to remission. Duration of remission.
Notes	Definitions: Relapse: Urine protein 2+ on dipstick for 3 consecutive days. Remission: Absence of proteinuria for 3 consecutive days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hiraoka 2000

Methods	Country: Japan. Recruitment: Multicentre renal clinics. Randomisation: not stated.
Participants	68 children with initial episode of SSNS. 8 excluded because steroid resistant. Age 1.5-14.4 years. Expt group 30, Control group 30
Interventions	Expt: Prednisolone 60mg/m2/day (max 80mg) for 6 weeks. 40mg/m2 on alternate days for 6 weeks. Total 3 months. Control: Prednisolone 40mg/m2/day (max 60mg) for 6 weeks, 40mg/m2 on alternate days for 6 weeks. Total 3 months.
Outcomes	No. relapsing at 6 mths & 12 mths. No. with frequent relapses. Adverse effects.
Notes	Definitions: Relapse: Urine protein 2+ for 3 days. Remission: Urine protein <4mg/hr/m2 for 3 days or more.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hiraoka 2003

Methods	Country: Japan Recruitment: Multicentre renal clinics. Randomisation: Sealed envelopes.
Participants	73 children with initial episode of SSNS. 3 excluded because steroid resistant. Age: Expt gp 7.6 (4.5) yr. Control gp 7.6 (4.4) yr. Expt gp: 36 evaluated. Cont gp: 34 evaluated.
Interventions	Expt: Prednisolone 60mg/m2/day (max 80mg) for 4 wks; 60mg/m2 (max 80mg) alt days for 4 wks & reducing by 10mg/m2 each mth. Total 28 wks. Control: 60mg/m2/day for 6 wks (max 80mg); 40mg/m2 (max 60mg) on alt days for 6 wks. Total duration 12 wks.
Outcomes	No. relapsing at 6, 12 & 24 mths. No with FRSSNS. Adverse effects.
Notes	Definitions: Relapse: Urine protein 2+ for 3 days. Remission: Urine protein <4mg/hr/m2 for 3 days or more.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Imbasciali 1985

Methods	Country: Italy Recruitment: multicentre. Renal clinics. Randomisation: Table of random numbers
Participants	67 children with either initial episode SSNS or no relapse in previous year. Age 2-14 years. 33 expt group 34 control group
Interventions	Expt: Methylprednisolone 20mg/kg IV for 3 days, prednisone 20mg/m2/day for 4 weeks, 20mg/m2 on alternate days for 4 weeks then 20mg/m2 alternate days for 4 months. Total 6 months. Control: Prednisone 60mg/m2/day for 4 weeks, 40mg/m2 on alternate days for 4 weeks & 20mg/m2 alternate days for 4 months. Total 6 months.
Outcomes	No. with/without relapse during 12-24 mths follow up. Mean relapse rate/pt/yr
Notes	Adults also in study. Some end points not separable for children so not examined. Definitions: Relapse: ISKDC Remission: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement

Imbasciali 1985 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

ISKDC 1979

Methods	Country: USA and Northern Europe. Recruitment: Multicentre. Renal clinics. Randomisation: Not stated.
Participants	64 children with SSNS within 6 months of their initial response to steroid therapy. Age 3 months to 15 years. 32 expt group, 32 control group.
Interventions	Expt: prednisone 60mg/m2/day for 4 weeks & tapered daily dose for 4 weeks. Control: prednisone 60mg/m2/day till remission & 40mg/m2 on 3 consecutive days/7 days.
Outcomes	No. relapsing during treatment and within 12 months. Mean time to next relapse. Mean relapse rate/pt
Notes	Definitions: Relapse: ISKDC Remission: ISKDC Time to relapse: Time from remission to next relapse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Jayantha 2002a

Methods	Country: Sri Lanka Recruitment: Renal clinic. Randomisation: random allocation table
Participants	122 children with initial episode of SSNS. Age 1-11.7 years. Evaluated: 48 expt group (11 lost to FU & 2 excluded), 74 (2 lost to FU after randomisation) control group.
Interventions	Expt: prednisolone 60mg/m2/day for 4 weeks. 60mg/m2 alternate days. Reducing alternate day dose by 10mg/m2 every 4 weeks. Total 7 months. Control: ISKDC regimen-prednisolone 60mg/m2/day for 4 weeks. 40mg/m2 alternate days for 4 weeks. Total 2 months.
Outcomes	No. relapsing by 12 and 24 months. Relapse rate/patient/year. No. with frequent relapses at 1 yr. Cumulative dose of steroid. Adverse effects.
Notes	Abstract and data from author. Definitions: ISKDC - relapse: Proteinuria >/=2+ for 5+ days. Remission:oedema free & urine protein -ve/trace. FRSSNS & SDNS: ISKDC. Data calculated from time of remission.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jayantha 2002a *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Jayantha 2002b

Methods	Country: Sri Lanka. Recruitment: Renal clinic. Randomisation: random allocation table.
Participants	95 children with relapsing SSNS. Patients with SDNS. Age 1-11.1 yrs. Evaluated: 46 expt (34 infrequent relapsers; 2 lost to follow up before 6 mths); 44 control (29 infrequent relapsers; 3 lost to follow up before 6 mths).
Interventions	Expt: prednisolone 60mg/m2/day for 4 weeks. 60mg/m2 alternate days. Reducing alternate day dose by 10mg/m2 every 4 weeks. Total 7 months. Control: ISKDC regimen - Prednisolone 60mg/m2/day till urine protein-free for 3 days. 40mg/m2 alternate days for 4 weeks. Total 2 months.
Outcomes	No. relapsing by 6, 12 and 24 months. Relapse rate/patient/year. No. with frequent relapses, steroid dependence at 1 yr. Cumulative dose of steroid. Adverse effects.
Notes	Abstract and data from author. Definitions: ISKDC-relapse: Proteinuria >/=2+ for 5+ days. Remission:oedema free & urine protein -ve/trace. FRSSNS & SDNS: ISKDC. Data calculated from time of remission.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Kleinknecht 1982

Methods	Country: France Recruitment: Multicentre. Renal clinics Randomisation: Central using blocks of sealed envelopes.
Participants	58 children with initial episode SSNS. Age not stated. 29 expt group, 29 control group.
Interventions	Expt: prednisone 2mg/kg/day for 4 weeks & then tapering dose on alternate days for 12 months. Control: 2mg/kg/day for 4 weeks & then tapering dose alternate days for 5 months.
Outcomes	No. relapsing by 6 months, 12 months & 15 months or more.
Notes	Abstract only. Authors confirmed adequate allocation but unable to supply further study information. Definitions of FRSRNS/relapse /remission/time to 1st relapse not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Kleinknecht 1982 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Ksiazek 1995

Methods	Country: Poland. Recruitment: Renal clinic. Randomisation: Not stated
Participants	184 children with initial episode SSNS. Age 13 months to 11 years. 72 expt group 1, 68 expt group 2, 44 standard group.
Interventions	Expt group 1: Prednisone 1-2 mg/kg/day for 4 weeks, 1mg/kg alternate days for 4 weeks & taper by 25% each month. Total 5 months. Expt group 2: Prednisone 1-2 mg/kg/day for 4 weeks, 1mg/kg alternate days for 4 weeks & taper by 25% per week for 4 weeks. Total 3 months. Standard: Prednisone 4 weeks each of 1-2 mg/kg/day & 1mg/kg on alternate days. Total 2 months.
Outcomes	No. relapsing by 6 months & 2 years after completing daily and alternate day prednisone. Relapse rate/pt/yr.
Notes	Parents could influence treatment group to which child randomised. Unequal numbers in groups. Only expt group 2 used in analyses. Definitions: FRSRNS: ISKDC Relapse: ISKDC Remission: ISKDC Time to 1st relapse: Cessation of daily & alternate day prednisone to onset of 1st remission.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Leisti 1978

Methods	Country: Finland. Recruitment: Renal clinic. Randomisation: not stated.
Participants	13 children with relapsing SSNS and subnormal response to 2 hr ACTH test 1-12 days after completing prednisone. Age 4.7-14.6 years.
Interventions	Expt: 15mg cortisol/day in >/=30kg & 7.5mg/day in <30kg for 6 months or till relapse; Control: placebo for 6 months or till relapse after next relapse treated & post steroid adrenal suppression confirmed. Dose doubled for 3 days when proteinuria or infection developed. Group 2: Placebo followed by cortisol as for Group 1.
Outcomes	No. with relapse during cortisol or placebo at 3 mths & 6mths.
Notes	Crossover study. Data for 2 periods combined. Definitions: Remission and Relapse: ISKDC

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Leisti 1978 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mattoo 2000

Methods	Country: Saudi Arabia. Recruitment: Renal clinic. Randomisation: alternate patients allocated to groups.
Participants	36 children with relapsing SSNS receiving prednisone 0.5mg/kg on alternate days for frequent relapses or following cyclophosphamide. Children who were not compliant or lost to follow up were excluded from the analysis.
Interventions	Expt: Pred given daily (0.5mg/kg) for 5 days during upper respiratory infection. Control: Prednisone at 0.5mg/kg on alternate days continued during infection.
Outcomes	Mean relapse rate/patient during 2 yr follow up.
Notes	Definitions of relapse & remission from ISKDC. Children who were non-compliant or lost to follow up were excluded from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Norero 1996

Methods	Country: Chile Recruitment: Multicentre: Renal clinics Randomisation: Odd and even numbers.
Participants	56 children: initial episode SSNS. Age 6 months to 15 years. 29 expt group. 27 standard group.
Interventions	Expt: Prednisolone 6 weeks each of 60mg/m2/day and 40mg/m2 alternate days. Total 3 months. Standard: Prednisolone 4 weeks each of 60mg/m2/day and 40mg/m2 alternate days. Total 2 months.
Outcomes	No. with relapse by 12 months & 18 months. Mean relapse rate/pt in 18months.
Notes	Children with SDNS (definition : relapse on reducing dose of steroids) were excluded. Renal biopsy showing minimal change disease required for trial entry. Definitions: FRSSNS: 2+ relapses in 6 mths or 3+ in 1 yr. Relapse: Urinary protein 100mg/kg/d or 40mg/m2/hr or urine protein/creatinine ratio > 1 or 3+ on dipstick for > 3 days. Remission: Urine protein <150mg/day for 3 consecutive days. Time to 1st relapse: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement

Norero 1996 *(Continued)*

Allocation concealment (selection bias)	High risk	C - Inadequate

Pecoraro 2004

Methods	Country: Italy. Recruitment: Renal clinic. Randomisation: Alternate pts allocated to each group.
Participants	48 children: Initial episode of SSNS. Age: NS. 16 allocated to each of 3 gps
Interventions	Expt 1 : Prednisone 2mg/kg/d for 6 wks; 2mg/kg on alt days for 6 wks. Reduction by 0.25mg/2 wks. Duration 26 wks. Expt 2: IV methylprednisolone 20mg/kg/dose for 3 days; 1mg/kg/d for 6 wks; 1mg/kg on alt days for 6 wks. Reduce by 0.25mg/2-4 wks. Duration 26 wks. Control: Prednisone 2mg/kg/d for 4 wks; 2mg/kg alt days for 4 wks. Duration 8 wks.
Outcomes	No with relapse at 1 year & 2 years. Adverse effects. Cumulative steroid dose.
Notes	No definitions provided. Abstracts only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Satomura 2001

Methods	Country: Japan Recruitment: Multicentre renal clinics.
Participants	73 children. Initial episode of SSNS. Age: NS. Expt gp 37; control gp 36.
Interventions	Expt: prednisolone 60mg/m2/day for 4wks; 40mg/m2 on alt days for 4 wks. Total 8 wks. Control gp: 40mg/m2/day for 4 wks. 40mg/kg on alt days for 8 wks. Total 12 wks.
Outcomes	No. with relapse at 12 mths. Time to relapse.
Notes	Definitions not stated. Abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

Sharma 2002

Methods	Country: India Recruitment: Renal clinic. Randomisation: random number table
Participants	160 children: initial episode of SSNS. Age 8.9 (6.8 SD) yrs. Evaluated expt 70; control 70.
Interventions	Expt: Prednisolone 60mg/m2/day for 6 wks; 40mg/m2 on alt days for 6 wks; taper by 10mg/m2 each month for 3 mths. (Total 6 mths) Control: As for expt but abrupt cessation at 12 wks (total 3 mths)
Outcomes	No. with relapse by 6, 12 mths. Mean relapse rate. No. frequent relapsers. Cumulative steroid dose. Adverse events.
Notes	Definitions: remission & relapse - ISKDC. FRSSNS: 2+ in 6 mths or 6+ in 18mths. SDNS:ISKDC. Data calculated from end of initial treatment period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ueda 1988

Methods	Country: Japan. Recruitment: Renal clinic. Randomisation: Not stated.
Participants	46 children with first episode SSNS. Mean age 5.6 (3.2) years (expt group) and 7.2 (3.2) years (standard group). 17 expt group. 29 standard group.
Interventions	Expt: Prednisolone 60mg/m2/day for 4 weeks, 60mg/m2 alternate days for 4 weeks & taper by 10mg/m2/mth. Total 7 months. Standard: Prednisolone 60mg/m2/day for 4 weeks and 40mg/m2 on 3 of 7 days for 4 weeks. Total 2 months.
Outcomes	No. relapsing by 6 month & 12 months after completing daily and alternate day prednisolone. Relapse rate/pt/yr.
Notes	Complete one year follow up. Unequal numbers in groups. Definitions: FRSRNS: Any relapse occurring within 2 mths after ceasing prednisone. Relapse:ISKDC Remission: ISKDC Time to relapse: Cessation of initial prednisone treatment to onset of 1st relapse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Yoshikawa 1998

Methods	Country: Japan. Recruitment: Multicentre renal clinics. Randomisation: sealed envelopes
Participants	196 children with first episode of SSNS. 171 evaluated. Mean age 8.0(4.1) yrs in standard & 7.1 (3.7) in expt. groups
Interventions	Expt: Prednisolone 2mg/kg/day for 4 wks, 2mg/kg alt days for 8 wks, 1.5mg/kg alt days for 2 wks, 1mg/kg alt days for 2 wks, 0.5mg/kg alt days for 2 wks. Total 4.5 mths. Standard: Prednisone 2mg/kg/day for 4 wks, 1.3mg/kg alt day for 4 wks. Total 2 mths. Both groups given Chinese herb Sairei-to. > 40kg 8.1g/day, 20-40kg 5.4g/day, <20kg 2.7g/day.
Outcomes	No. relapsing by 2 years. No. of patients with frequent relapses.
Notes	Definitions of relapse & patients with frequent relapses as ISKDC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

SSNS: Steroid sensitive nephrotic syndrome
FRSSNS: Frequently relapsing steroid sensitive nephrotic syndrome
SDNS: Steroid dependent nephrotic syndrome
ISKDC: International Study of Kidney Disease in Children

DATA AND ANALYSES

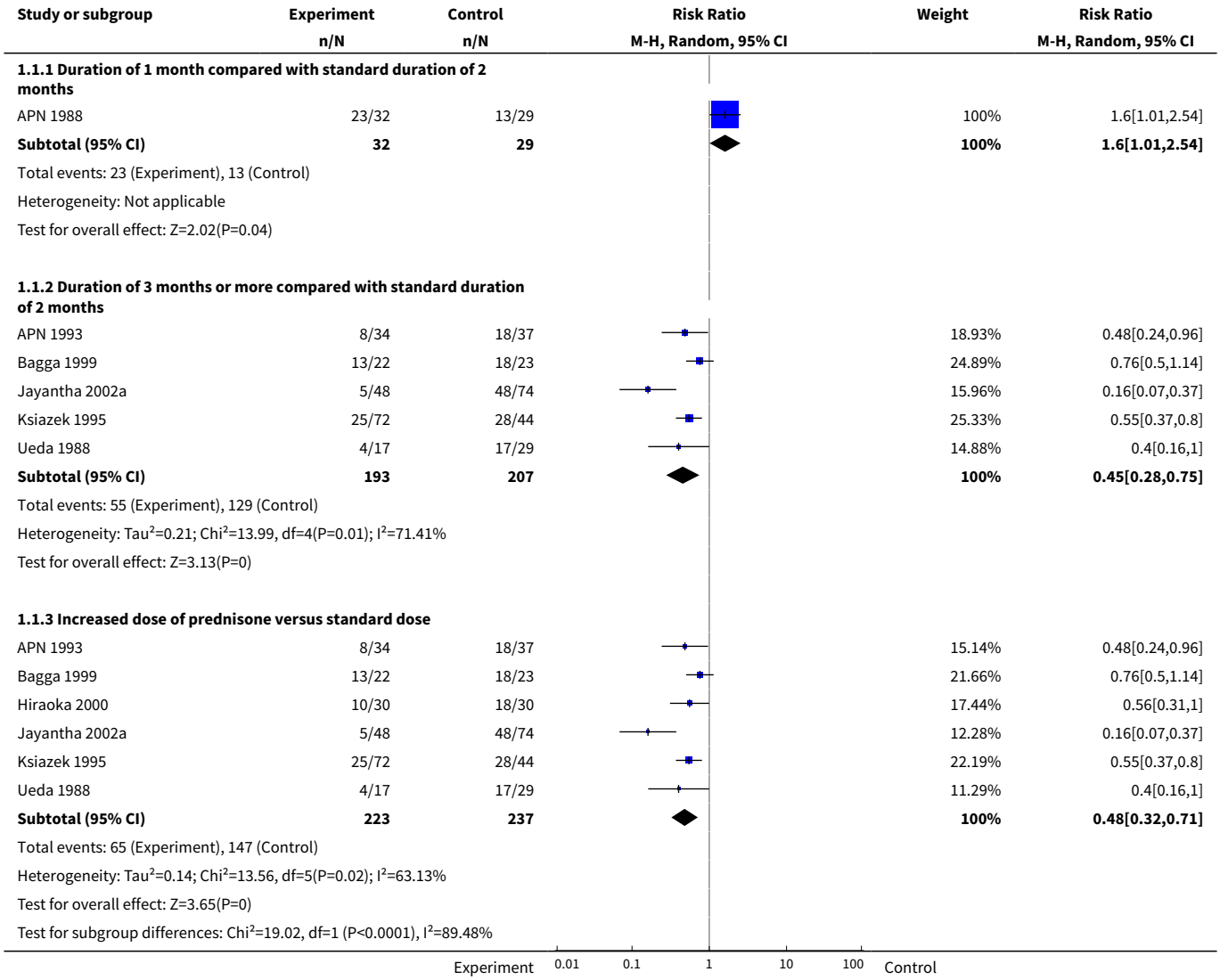
Comparison 1. Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing by 6 months	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Duration of 1 month compared with standard duration of 2 months	1	61	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.01, 2.54]
1.2 Duration of 3 months or more compared with standard duration of 2 months	5	400	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.28, 0.75]
1.3 Increased dose of prednisone versus standard dose	6	460	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.32, 0.71]
2 Number of children relapsing by 12 -24 months	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Duration of 1 month compared with standard duration of 2 months	1	60	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.01, 2.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Duration of 3 months or more compared with standard duration of 2 months	6	422	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
2.3 Increased dose of prednisone versus standard dose	7	481	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.56, 0.80]
2.4 12 weeks (2240mg/m2) compared with 8 weeks (2520mg/m2)	1	73	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.84, 1.85]
3 Mean relapse rate/patient/year	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Duration of three months or more compared with standard duration of 2 months	4	295	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.29, -0.00]
4 Number with frequent relapses	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Duration of 1 month compared with standard duration of 2 months	1	61	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.85, 2.59]
4.2 Duration of 3 months or more compared with standard duration of 2 months	6	452	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.46, 0.84]
4.3 Increased dose of prednisone versus standard dose (2240mg/m2)	7	512	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.48, 0.84]
5 Cumulative steroid dose in gm/square metre	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Duration of 1 month compared with standard duration of 2 months	1	61	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.28, -0.68]
5.2 Duration of three months or more compared with standard duration of 2 months	3	245	Mean Difference (IV, Random, 95% CI)	0.71 [-0.67, 2.09]
6 Adverse events: increased prednisone dose compared with standard duration	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Psychological disorders	4	293	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.66, 9.06]
6.2 Hypertension	7	526	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.60, 4.28]
6.3 Opthalmological disorders	6	460	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.15, 4.42]
6.4 Retarded growth	4	354	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.18]
6.5 Cushing's syndrome	4	292	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.78, 1.96]
6.6 Infections	2	172	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.17]
6.7 Osteoporosis	3	233	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.06, 3.38]

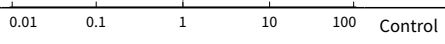
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Subgroup analysis: Relapse at 12-24 months according to adequacy of allocation concealment	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Adequate allocation concealment	3	204	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.51, 0.87]
9.2 Unclear or inadequate allocation concealment	4	277	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.55, 0.90]

Analysis 1.1. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 1 Number of children relapsing by 6 months.



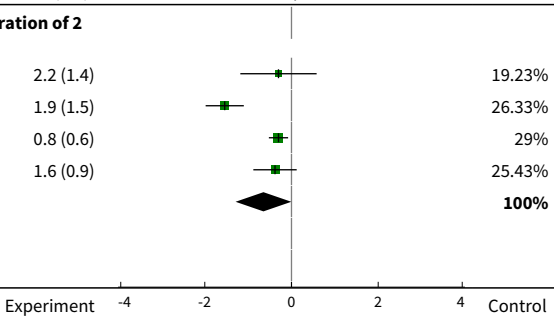
Analysis 1.2. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 2 Number of children relapsing by 12 -24 months.

Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Duration of 1 month compared with standard duration of 2 months					
APN 1988	25/31	16/29		100%	1.46[1.01,2.12]
Subtotal (95% CI)	**31**	**29**		**100%**	**1.46[1.01,2.12]**
Total events: 25 (Experiment), 16 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.01(P=0.04)					
1.2.2 Duration of 3 months or more compared with standard duration of 2 months					
APN 1993	13/34	24/37		12.05%	0.59[0.36,0.96]
Bagga 1999	16/22	21/23		27.69%	0.8[0.6,1.06]
Jayantha 2002a	16/35	43/53		17.95%	0.56[0.38,0.83]
Ksiazek 1995	36/72	32/44		26.65%	0.69[0.51,0.92]
Norero 1996	15/29	13/27		10.6%	1.07[0.63,1.82]
Ueda 1988	5/17	18/29		5.06%	0.47[0.22,1.04]
Subtotal (95% CI)	**209**	**213**		**100%**	**0.7[0.58,0.84]**
Total events: 101 (Experiment), 151 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=6.23, df=5(P=0.28); I^2=19.8%					
Test for overall effect: Z=3.85(P=0)					
1.2.3 Increased dose of prednisone versus standard dose					
APN 1993	13/34	24/37		10.62%	0.59[0.36,0.96]
Bagga 1999	16/22	21/23		22.83%	0.8[0.6,1.06]
Hiraoka 2000	15/30	23/29		14.33%	0.63[0.42,0.94]
Jayantha 2002a	16/35	48/53		16.16%	0.5[0.35,0.73]
Ksiazek 1995	36/72	32/44		22.07%	0.69[0.51,0.92]
Norero 1996	15/29	13/27		9.4%	1.07[0.63,1.82]
Ueda 1988	5/17	18/29		4.6%	0.47[0.22,1.04]
Subtotal (95% CI)	**239**	**242**		**100%**	**0.67[0.56,0.8]**
Total events: 116 (Experiment), 179 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=8.1, df=6(P=0.23); I^2=25.97%					
Test for overall effect: Z=4.38(P<0.0001)					
1.2.4 12 weeks (2240mg/m2) compared with 8 weeks (2520mg/m2)					
Satomura 2001	23/36	19/37		100%	1.24[0.84,1.85]
Subtotal (95% CI)	**36**	**37**		**100%**	**1.24[0.84,1.85]**
Total events: 23 (Experiment), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi^2=20.35, df=1 (P=0), I^2=85.26%					



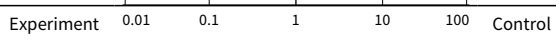
Analysis 1.3. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 3 Mean relapse rate/patient/year.

Study or subgroup	Experiment N	Experiment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 Duration of three months or more compared with standard duration of 2 months							
Bagga 1999	22	1.9 (1.6)	23	2.2 (1.4)		19.23%	-0.3[-1.18,0.58]
Jayantha 2002a	35	0.4 (0.5)	53	1.9 (1.5)		26.33%	-1.54[-1.98,-1.1]
Ksiazek 1995	72	0.5 (0.6)	44	0.8 (0.6)		29%	-0.3[-0.52,-0.08]
Ueda 1988	17	1.3 (0.8)	29	1.6 (0.9)		25.43%	-0.38[-0.88,0.12]
Subtotal ***	**146**		**149**			**100%**	**-0.65[-1.29,-0]**
Heterogeneity: Tau²=0.36; Chi²=24.93, df=3(P<0.0001); I²=87.97%							
Test for overall effect: Z=1.97(P=0.05)							



Analysis 1.4. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 4 Number with frequent relapses.

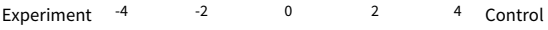
Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Duration of 1 month compared with standard duration of 2 months					
APN 1988	18/32	11/29		100%	1.48[0.85,2.59]
Subtotal (95% CI)	**32**	**29**		**100%**	**1.48[0.85,2.59]**
Total events: 18 (Experiment), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.39(P=0.17)					
1.4.2 Duration of 3 months or more compared with standard duration of 2 months					
APN 1993	6/34	12/37		11.91%	0.54[0.23,1.29]
Bagga 1999	7/22	8/23		12.89%	0.91[0.4,2.1]
Jayantha 2002a	8/48	26/70		17.97%	0.45[0.22,0.91]
Ksiazek 1995	25/72	21/44		45.21%	0.73[0.47,1.13]
Norero 1996	3/29	4/27		4.51%	0.7[0.17,2.84]
Ueda 1988	3/17	15/29		7.52%	0.34[0.12,1.01]
Subtotal (95% CI)	**222**	**230**		**100%**	**0.63[0.46,0.84]**
Total events: 52 (Experiment), 86 (Control)					
Heterogeneity: Tau²=0; Chi²=3.56, df=5(P=0.61); I²=0%					
Test for overall effect: Z=3.09(P=0)					
1.4.3 Increased dose of prednisone versus standard dose (2240mg/m2)					
APN 1993	6/34	12/37		10.01%	0.54[0.23,1.29]
Bagga 1999	7/22	8/23		10.83%	0.91[0.4,2.1]
Hiraoka 2000	9/30	13/30		15.97%	0.69[0.35,1.37]
Jayantha 2002a	8/48	26/70		15.1%	0.45[0.22,0.91]
Ksiazek 1995	25/72	21/44		37.99%	0.73[0.47,1.13]
Norero 1996	3/29	4/27		3.79%	0.7[0.17,2.84]
Ueda 1988	3/17	15/29		6.32%	0.34[0.12,1.01]
Subtotal (95% CI)	**252**	**260**		**100%**	**0.64[0.48,0.84]**
Total events: 61 (Experiment), 99 (Control)					
Heterogeneity: Tau²=0; Chi²=3.62, df=6(P=0.73); I²=0%					



Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=3.25(P=0)					
Test for subgroup differences: Chi²=8, df=1 (P=0.02), I²=75%					

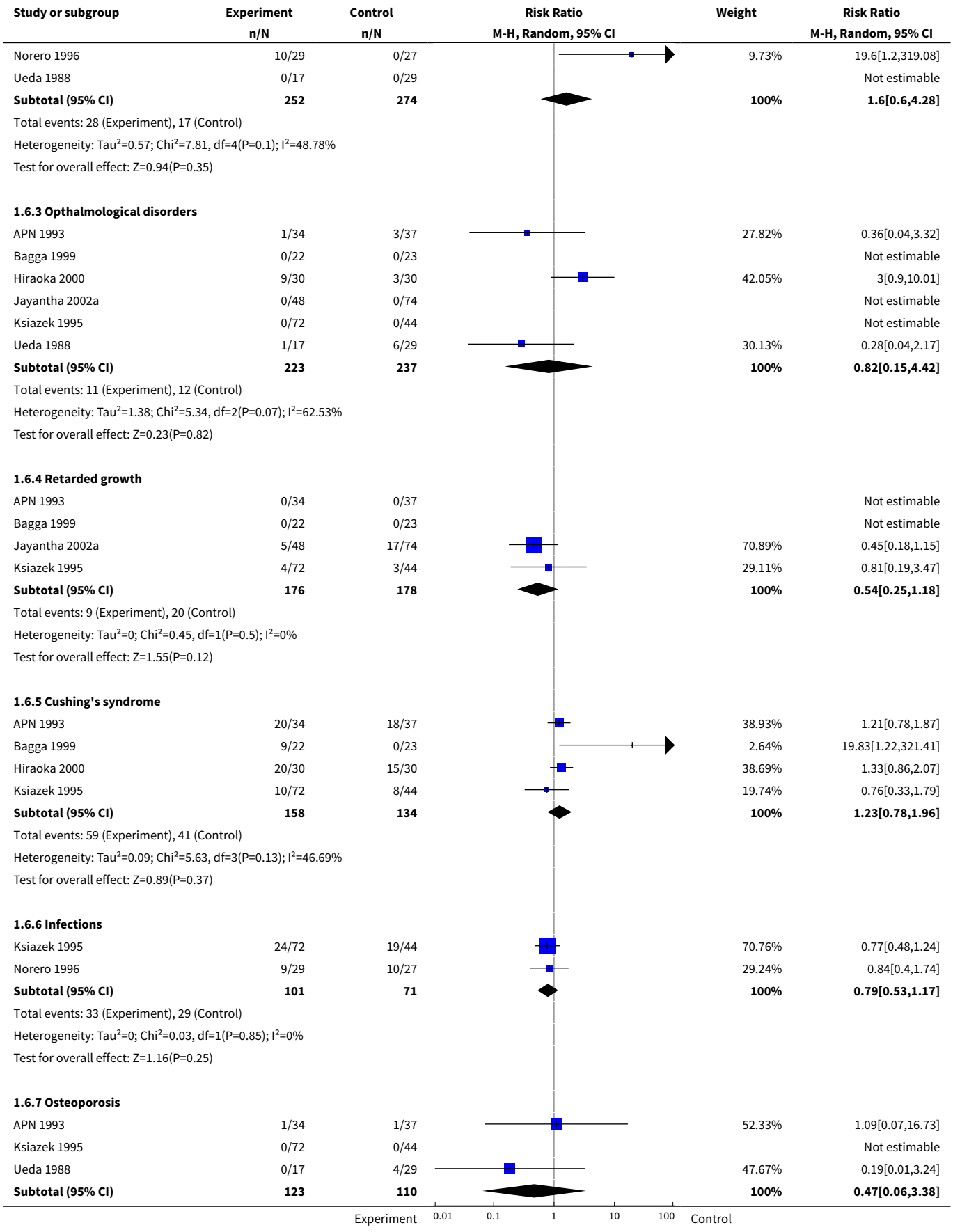
Analysis 1.5. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 5 Cumulative steroid dose in gm/square metre.

Study or subgroup	Experiment N	Experiment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Duration of 1 month compared with standard duration of 2 months							
APN 1988	32	1.2 (0.7)	29	2.2 (0.5)		100%	-0.98[-1.28,-0.68]
Subtotal ***	**32**		**29**			**100%**	**-0.98[-1.28,-0.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.48(P<0.0001)							
1.5.2 Duration of three months or more compared with standard duration of 2 months							
Bagga 1999	22	6.5 (2.6)	23	5.2 (2.7)		33.34%	1.26[-0.27,2.79]
Jayantha 2002a	32	7.1 (2.9)	52	5.7 (2.5)		39.32%	1.45[0.24,2.66]
Ksiazek 1995	72	5.6 (4.4)	44	6.6 (5.4)		27.34%	-1.02[-2.91,0.87]
Subtotal ***	**126**		**119**			**100%**	**0.71[-0.67,2.09]**
Heterogeneity: Tau²=0.89; Chi²=4.96, df=2(P=0.08); I²=59.72%							
Test for overall effect: Z=1.01(P=0.31)							
Test for subgroup differences: Chi²=5.5, df=1 (P=0.02), I²=81.8%							

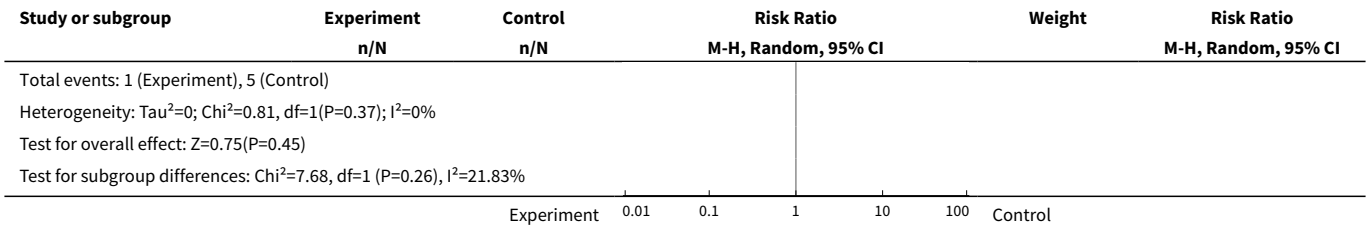


Analysis 1.6. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 6 Adverse events: increased prednisone dose compared with standard duration.

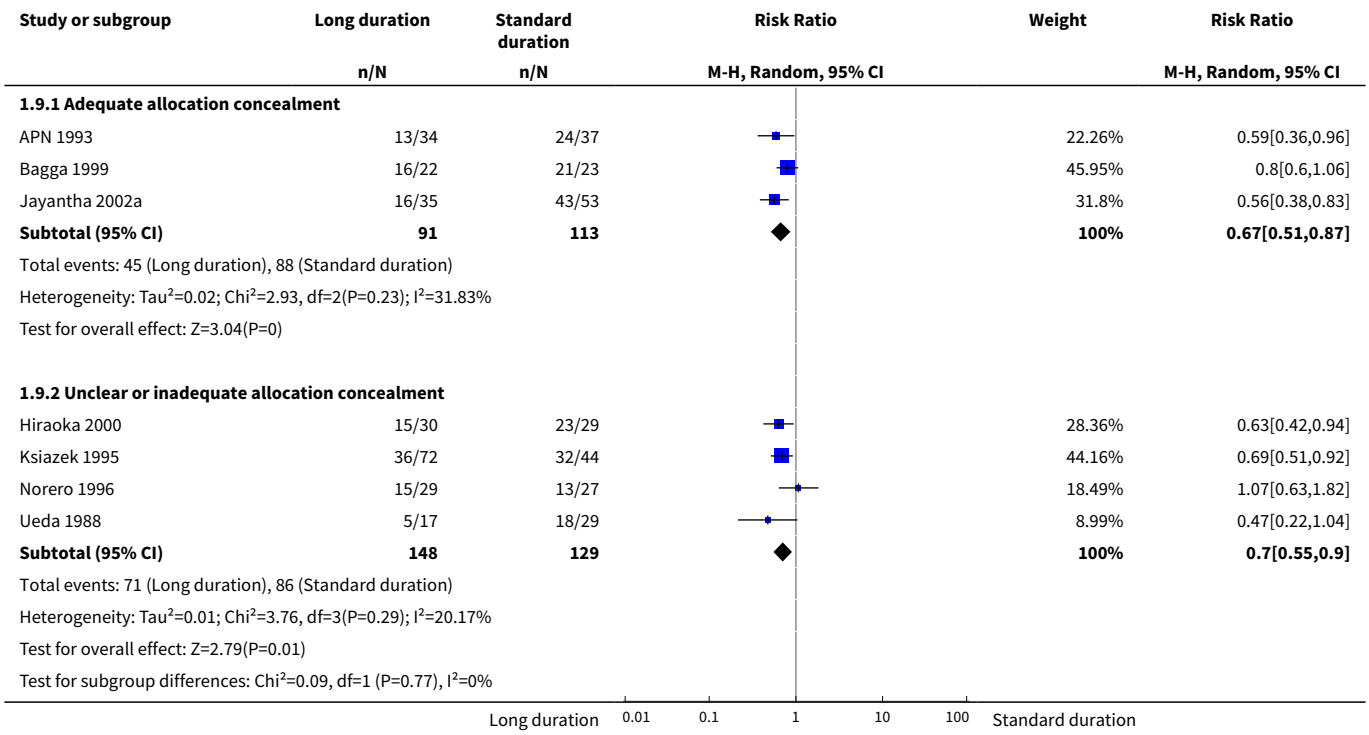
Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Psychological disorders					
APN 1993	4/34	2/37		64.62%	2.18[0.43,11.13]
Hiraoka 2000	3/30	1/30		35.38%	3[0.33,27.23]
Ksiazek 1995	0/72	0/44			Not estimable
Ueda 1988	0/17	0/29			Not estimable
Subtotal (95% CI)	**153**	**140**		**100%**	**2.44[0.66,9.06]**
Total events: 7 (Experiment), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.82); I²=0%					
Test for overall effect: Z=1.33(P=0.18)					
1.6.2 Hypertension					
APN 1993	0/34	0/37			Not estimable
Bagga 1999	3/22	0/23		9.12%	7.3[0.4,133.75]
Hiraoka 2000	4/30	3/40		23.11%	1.78[0.43,7.36]
Jayantha 2002a	5/48	9/74		29.91%	0.86[0.31,2.4]
Ksiazek 1995	6/72	5/44		28.13%	0.73[0.24,2.26]



Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Norero 1996	10/29	0/27		9.73%	19.6[1.2,319.08]
Ueda 1988	0/17	0/29			Not estimable
Subtotal (95% CI)	**252**	**274**		**100%**	**1.6[0.6,4.28]**
Total events: 28 (Experiment), 17 (Control)					
Heterogeneity: Tau^2=0.57; Chi^2=7.81, df=4(P=0.1); I^2=48.78%					
Test for overall effect: Z=0.94(P=0.35)					
1.6.3 Opthalmological disorders					
APN 1993	1/34	3/37		27.82%	0.36[0.04,3.32]
Bagga 1999	0/22	0/23			Not estimable
Hiraoka 2000	9/30	3/30		42.05%	3[0.9,10.01]
Jayantha 2002a	0/48	0/74			Not estimable
Ksiazek 1995	0/72	0/44			Not estimable
Ueda 1988	1/17	6/29		30.13%	0.28[0.04,2.17]
Subtotal (95% CI)	**223**	**237**		**100%**	**0.82[0.15,4.42]**
Total events: 11 (Experiment), 12 (Control)					
Heterogeneity: Tau^2=1.38; Chi^2=5.34, df=2(P=0.07); I^2=62.53%					
Test for overall effect: Z=0.23(P=0.82)					
1.6.4 Retarded growth					
APN 1993	0/34	0/37			Not estimable
Bagga 1999	0/22	0/23			Not estimable
Jayantha 2002a	5/48	17/74		70.89%	0.45[0.18,1.15]
Ksiazek 1995	4/72	3/44		29.11%	0.81[0.19,3.47]
Subtotal (95% CI)	**176**	**178**		**100%**	**0.54[0.25,1.18]**
Total events: 9 (Experiment), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.45, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=1.55(P=0.12)					
1.6.5 Cushing's syndrome					
APN 1993	20/34	18/37		38.93%	1.21[0.78,1.87]
Bagga 1999	9/22	0/23		2.64%	19.83[1.22,321.41]
Hiraoka 2000	20/30	15/30		38.69%	1.33[0.86,2.07]
Ksiazek 1995	10/72	8/44		19.74%	0.76[0.33,1.79]
Subtotal (95% CI)	**158**	**134**		**100%**	**1.23[0.78,1.96]**
Total events: 59 (Experiment), 41 (Control)					
Heterogeneity: Tau^2=0.09; Chi^2=5.63, df=3(P=0.13); I^2=46.69%					
Test for overall effect: Z=0.89(P=0.37)					
1.6.6 Infections					
Ksiazek 1995	24/72	19/44		70.76%	0.77[0.48,1.24]
Norero 1996	9/29	10/27		29.24%	0.84[0.4,1.74]
Subtotal (95% CI)	**101**	**71**		**100%**	**0.79[0.53,1.17]**
Total events: 33 (Experiment), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=1.16(P=0.25)					
1.6.7 Osteoporosis					
APN 1993	1/34	1/37		52.33%	1.09[0.07,16.73]
Ksiazek 1995	0/72	0/44			Not estimable
Ueda 1988	0/17	4/29		47.67%	0.19[0.01,3.24]
Subtotal (95% CI)	**123**	**110**		**100%**	**0.47[0.06,3.38]**



Analysis 1.9. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 9 Subgroup analysis: Relapse at 12-24 months according to adequacy of allocation concealment.



Comparison 2. Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing by 6 months	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Duration of 6 months compared with 3 months	3	350	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.35, 0.64]
1.2 Duration of 12 months compared with 5 months	1	58	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.32, 3.09]

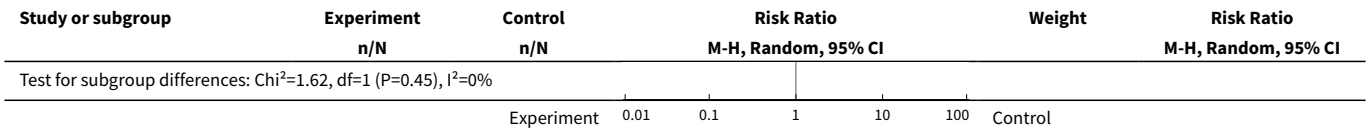
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of children relapsing by 12 -24 months	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Duration of 6 months compared with 3 months	4	382	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.45, 0.71]
2.2 Duration of 12 months compared with 5 months	1	58	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.13]
2.3 High dose versus low dose given for same duration	2	91	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.84]
3 Mean relapse rate/patient/year	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Duration of 6 months compared with 3 months	2	280	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.82, -0.07]
4 Number with frequent relapses	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Duration of 6 months compared with 3 months	3	350	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.39, 0.80]
5 Cumulative steroid dose in gm/square metre	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.3 Duration of 6 months compared with 3 months	2	280	Mean Difference (IV, Random, 95% CI)	-1.55 [-3.00, 1.90]
6 Adverse events: Duration of 6 months compared with 3 months	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Hypertension	3	349	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.65, 2.16]
6.2 Opthalmological	3	335	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.14, 1.08]
6.3 Infections	2	280	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.62]
6.4 Cushing's syndrome	3	349	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.39, 1.59]
6.5 Gastrointestinal bleeding	1	140	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.26, 8.70]
6.6 Addisonian crisis	1	140	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.39]
6.7 Psychological disorders	2	209	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.45]
6.8 Growth	1	140	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.29, 5.42]
6.9 Osteoporosis	1	140	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 1 Number of children relapsing by 6 months.

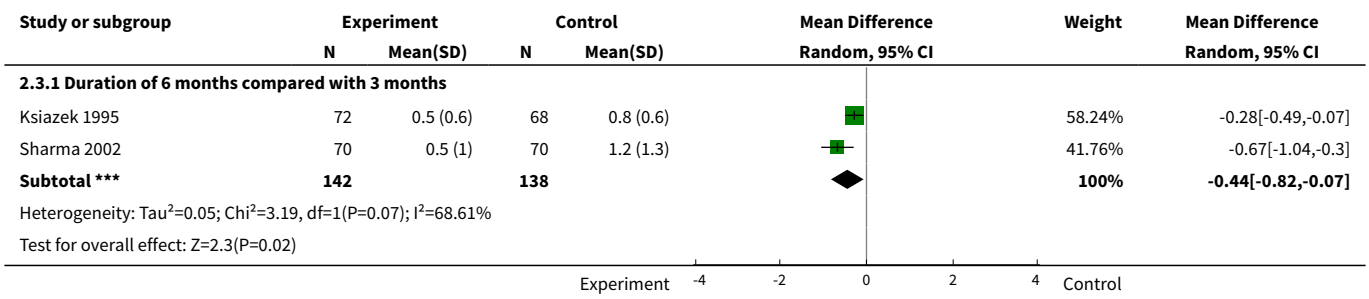
Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Duration of 6 months compared with 3 months					
Hiraoka 2003	4/36	10/34		7.62%	0.38[0.13,1.09]
Ksiazek 1995	25/72	46/68		67.36%	0.51[0.36,0.73]
Sharma 2002	12/70	29/70		25.02%	0.41[0.23,0.74]
Subtotal (95% CI)	**178**	**172**		**100%**	**0.48[0.35,0.64]**
Total events: 41 (Experiment), 85 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=2(P=0.74); I^2=0%					
Test for overall effect: Z=4.98(P<0.0001)					
2.1.2 Duration of 12 months compared with 5 months					
Kleinknecht 1982	5/29	5/29		100%	1[0.32,3.09]
Subtotal (95% CI)	**29**	**29**		**100%**	**1[0.32,3.09]**
Total events: 5 (Experiment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21), I^2=36.2%					

Analysis 2.2. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 2 Number of children relapsing by 12 -24 months.

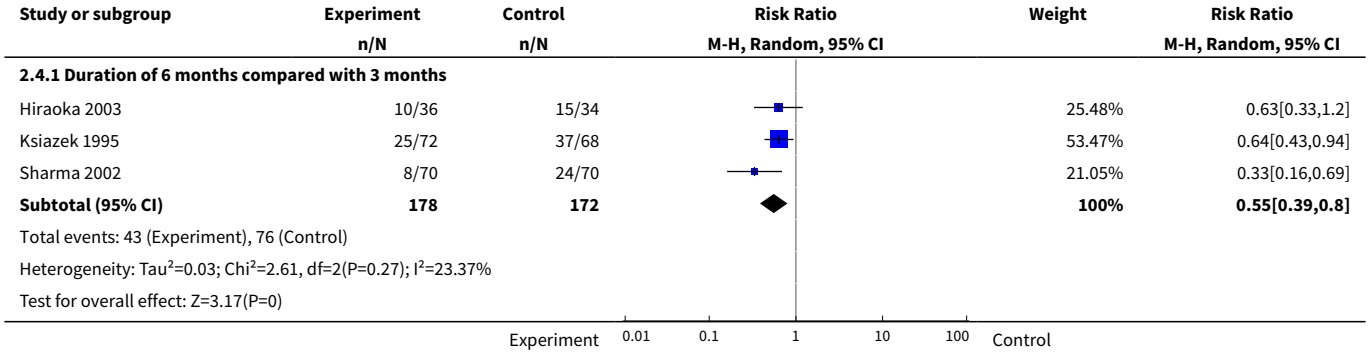
Study or subgroup	Experiment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Duration of 6 months compared with 3 months					
Hiraoka 2003	15/36	21/34		19.6%	0.67[0.42,1.08]
Ksiazek 1995	36/72	54/68		48.66%	0.63[0.49,0.82]
Pecoraro 2004	6/16	12/16		9.66%	0.5[0.25,1]
Sharma 2002	18/70	44/70		22.07%	0.41[0.26,0.63]
Subtotal (95% CI)	**194**	**188**		**100%**	**0.57[0.45,0.71]**
Total events: 75 (Experiment), 131 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=3.56, df=3(P=0.31); I^2=15.76%					
Test for overall effect: Z=4.98(P<0.0001)					
2.2.2 Duration of 12 months compared with 5 months					
Kleinknecht 1982	16/29	21/29		100%	0.76[0.51,1.13]
Subtotal (95% CI)	**29**	**29**		**100%**	**0.76[0.51,1.13]**
Total events: 16 (Experiment), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
2.2.3 High dose versus low dose given for same duration					
Hiraoka 2000	15/30	23/29		74.7%	0.63[0.42,0.94]
Pecoraro 2004	6/16	12/16		25.3%	0.5[0.25,1]
Subtotal (95% CI)	**46**	**45**		**100%**	**0.59[0.42,0.84]**
Total events: 21 (Experiment), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=2.92(P=0)					



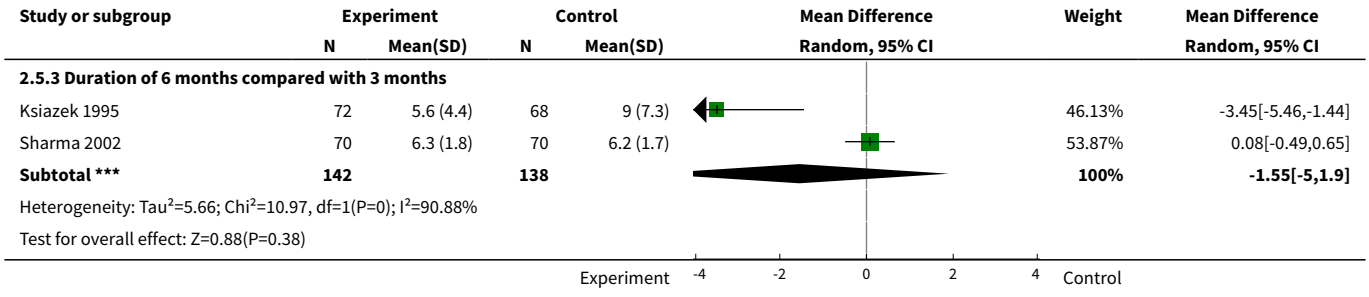
Analysis 2.3. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 3 Mean relapse rate/patient/year.



Analysis 2.4. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 4 Number with frequent relapses.

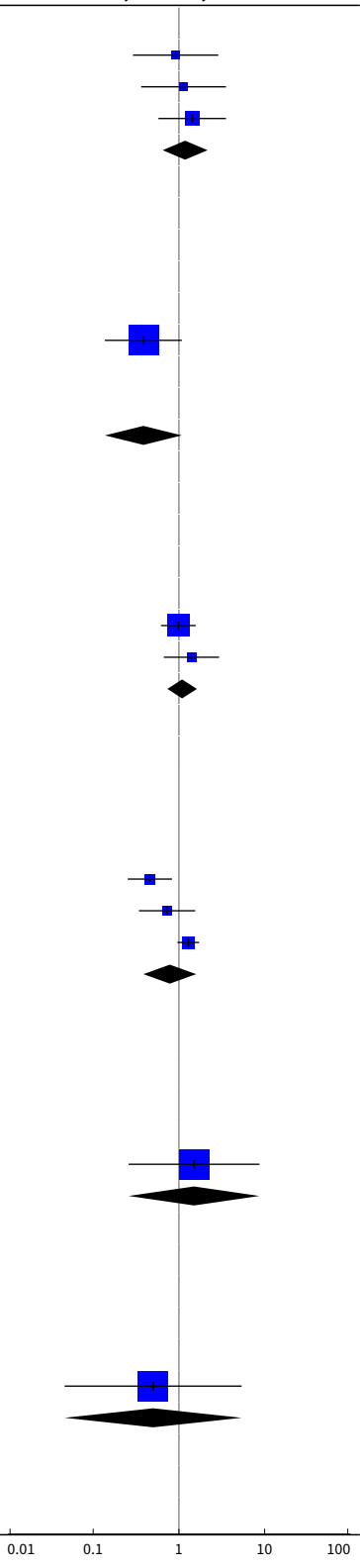


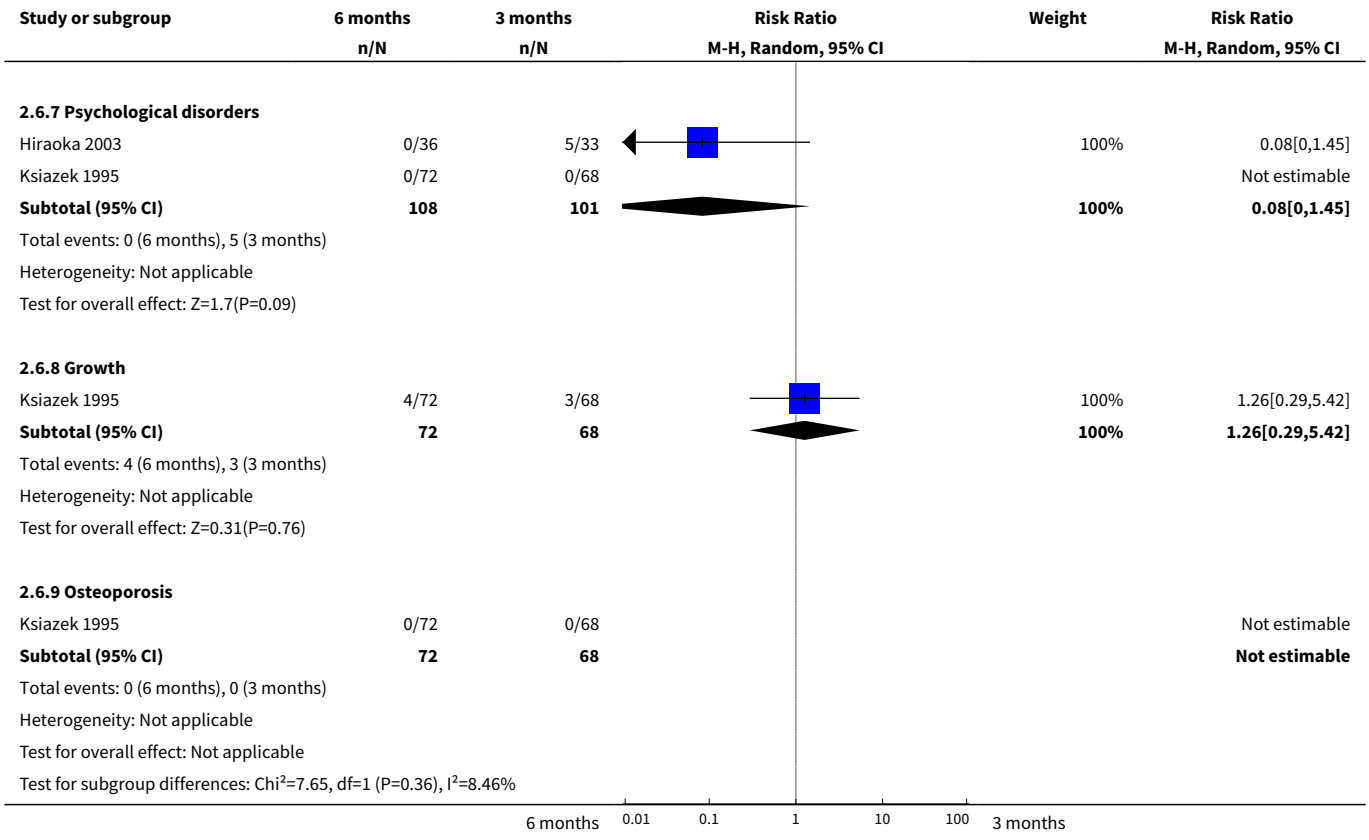
Analysis 2.5. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 5 Cumulative steroid dose in gm/square metre.



Analysis 2.6. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: comparisons of 3 months or more of steroids, Outcome 6 Adverse events: Duration of 6 months compared with 3 months.

Study or subgroup	6 months n/N	3 months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Hypertension					
Hiraoka 2003	5/36	5/33		27.72%	0.92[0.29,2.88]
Ksiazek 1995	6/72	5/68		28.04%	1.13[0.36,3.54]
Sharma 2002	10/70	7/70		44.24%	1.43[0.58,3.54]
Subtotal (95% CI)	**178**	**171**		**100%**	**1.18[0.65,2.16]**
Total events: 21 (6 months), 17 (3 months)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
2.6.2 Opthalmological					
Hiraoka 2003	4/28	10/27		100%	0.39[0.14,1.08]
Ksiazek 1995	0/72	0/68			Not estimable
Sharma 2002	0/70	0/70			Not estimable
Subtotal (95% CI)	**170**	**165**		**100%**	**0.39[0.14,1.08]**
Total events: 4 (6 months), 10 (3 months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.81(P=0.07)					
2.6.3 Infections					
Ksiazek 1995	24/72	23/68		71.64%	0.99[0.62,1.57]
Sharma 2002	14/70	10/70		28.36%	1.4[0.67,2.94]
Subtotal (95% CI)	**142**	**138**		**100%**	**1.09[0.73,1.62]**
Total events: 38 (6 months), 33 (3 months)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					
2.6.4 Cushing's syndrome					
Hiraoka 2003	10/36	20/33		32.4%	0.46[0.25,0.83]
Ksiazek 1995	10/72	13/68		28.42%	0.73[0.34,1.55]
Sharma 2002	45/70	35/70		39.18%	1.29[0.96,1.72]
Subtotal (95% CI)	**178**	**171**		**100%**	**0.78[0.39,1.59]**
Total events: 65 (6 months), 68 (3 months)					
Heterogeneity: Tau^2=0.31; Chi^2=10.6, df=2(P=0); I^2=81.13%					
Test for overall effect: Z=0.68(P=0.5)					
2.6.5 Gastrointestinal bleeding					
Sharma 2002	3/70	2/70		100%	1.5[0.26,8.7]
Subtotal (95% CI)	**70**	**70**		**100%**	**1.5[0.26,8.7]**
Total events: 3 (6 months), 2 (3 months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
2.6.6 Addisonian crisis					
Sharma 2002	1/70	2/70		100%	0.5[0.05,5.39]
Subtotal (95% CI)	**70**	**70**		**100%**	**0.5[0.05,5.39]**
Total events: 1 (6 months), 2 (3 months)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					

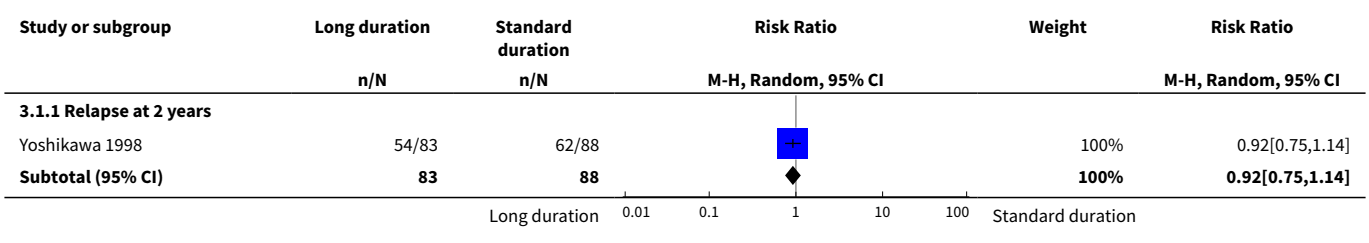


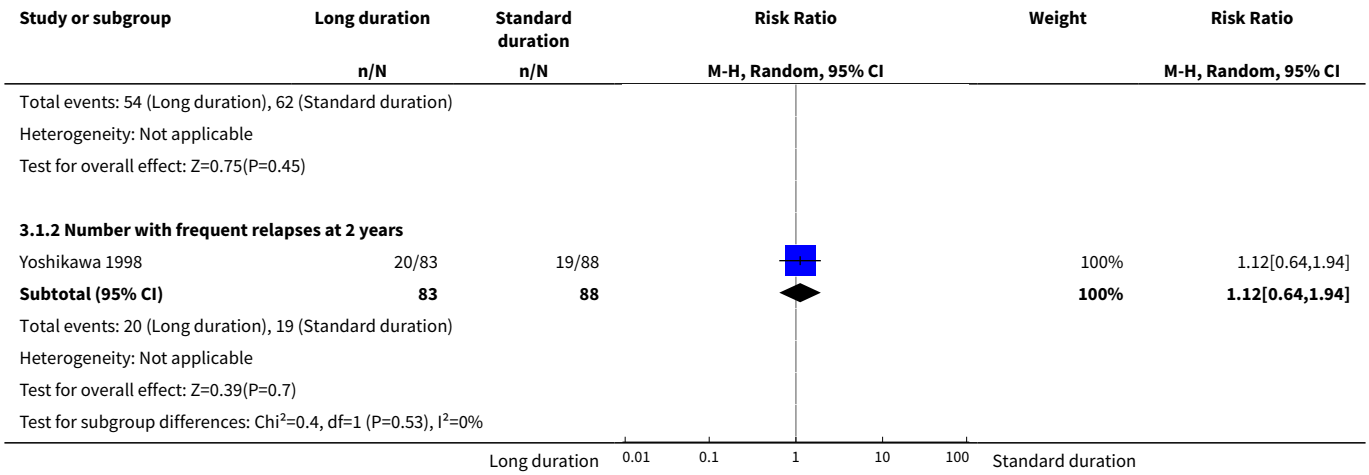


Comparison 3. Steroid therapy and Sairei-to in first episode of nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Long prednisone & Sairei-to versus standard prednisone & Sairei-to	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Relapse at 2 years	1	171	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.14]
1.2 Number with frequent relapses at 2 years	1	171	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.64, 1.94]

Analysis 3.1. Comparison 3 Steroid therapy and Sairei-to in first episode of nephrotic syndrome, Outcome 1 Long prednisone & Sairei-to versus standard prednisone & Sairei-to.

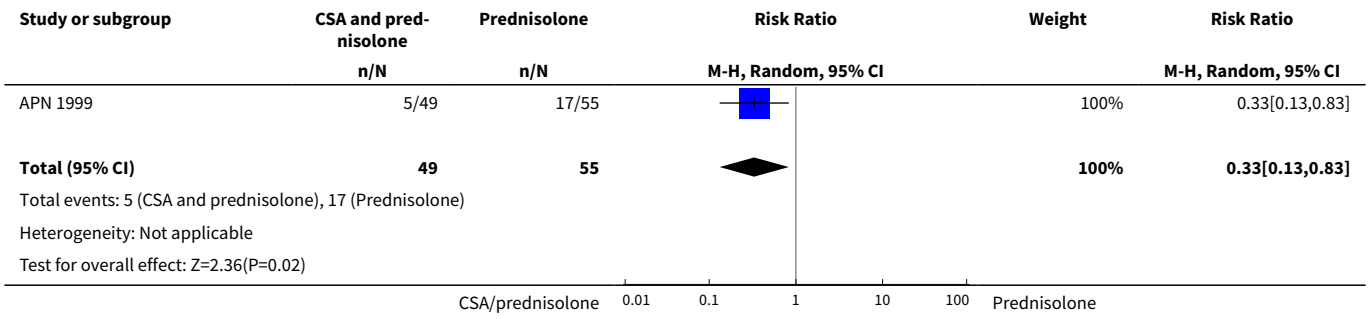




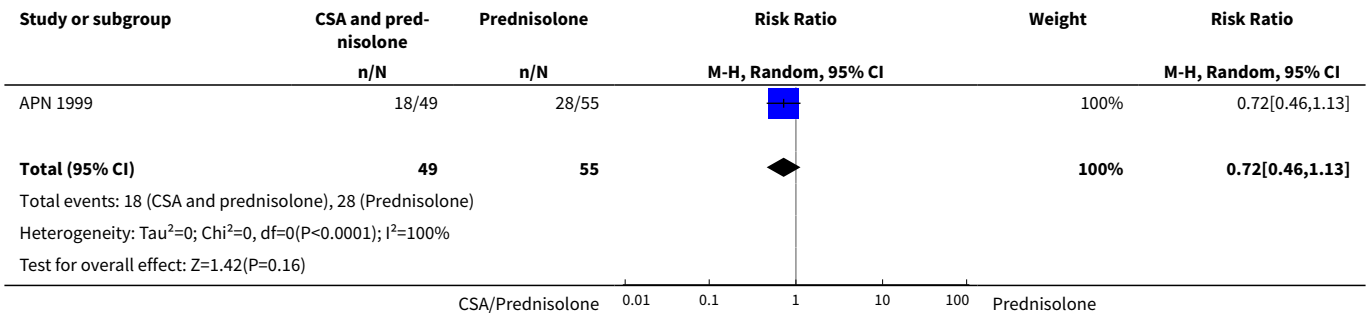
Comparison 4. Cyclosporin and steroid therapy in first episode of childhood nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Relapse by 6 months	1	104	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.13, 0.83]
2 Relapse by 12 months	1	104	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.46, 1.13]
3 Number needing cytotoxic agents	1	104	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.23]

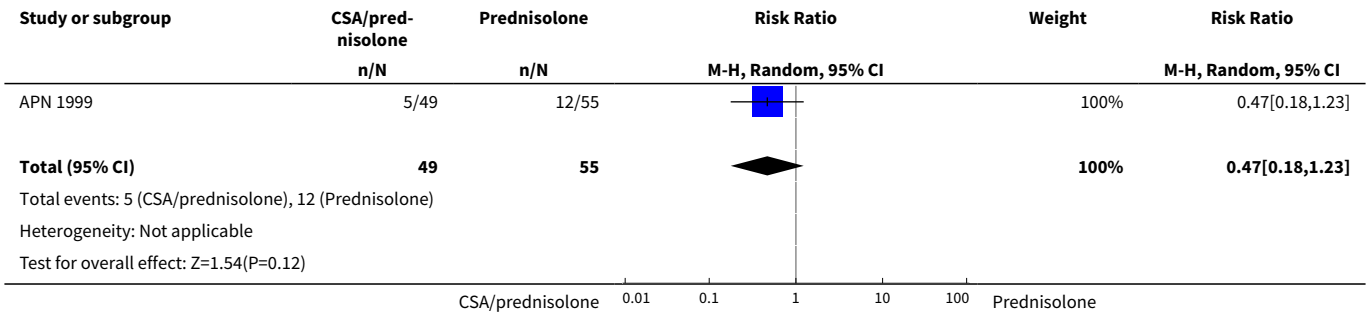
Analysis 4.1. Comparison 4 Cyclosporin and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 1 Relapse by 6 months.



Analysis 4.2. Comparison 4 Cyclosporin and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 2 Relapse by 12 months.



Analysis 4.3. Comparison 4 Cyclosporin and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 3 Number needing cytotoxic agents.



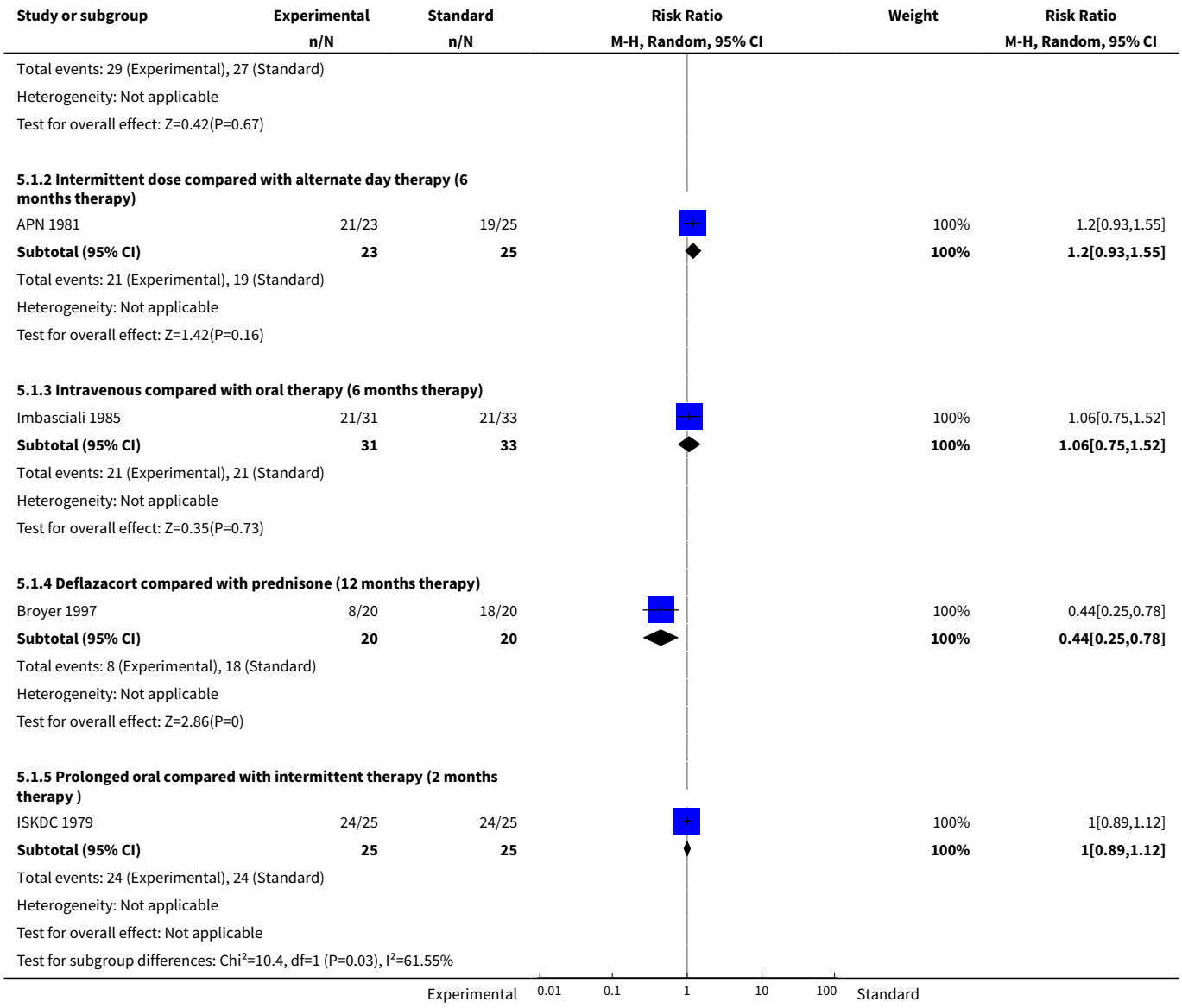
Comparison 5. Steroid therapy in relapse of nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children with further relapses by 9 - 12 months	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Single dose compared with divided dose therapy (2 months therapy)	1	94	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.77, 1.50]
1.2 Intermittent dose compared with alternate day therapy (6 months therapy)	1	48	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.93, 1.55]
1.3 Intravenous compared with oral therapy (6 months therapy)	1	64	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.52]
1.4 Deflazacort compared with prednisone (12 months therapy)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.25, 0.78]
1.5 Prolonged oral compared with intermittent therapy (2 months therapy)	1	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.89, 1.12]

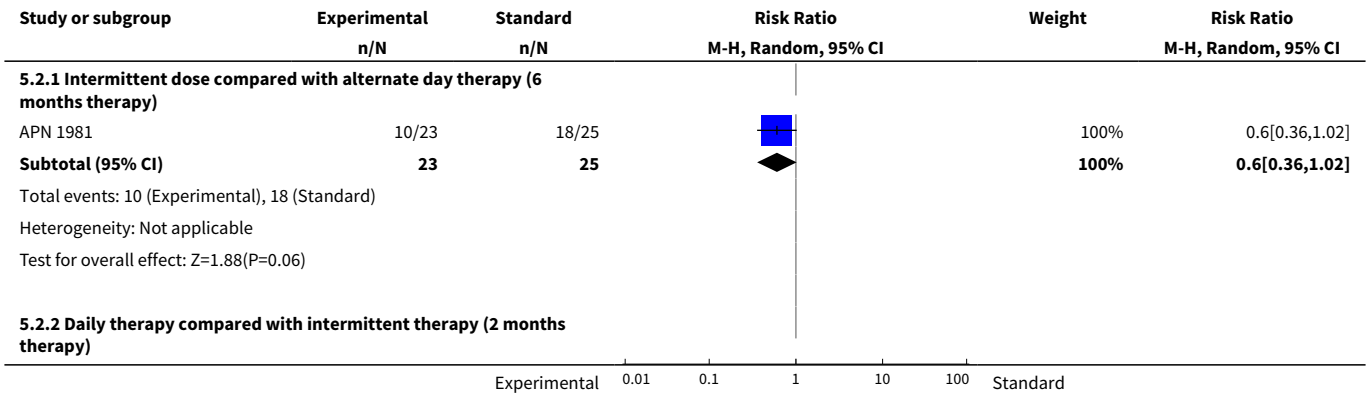
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of children relapsing during therapy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Intermittent dose compared with alternate day therapy (6 months therapy)	1	48	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.02]
2.2 Daily therapy compared with intermittent therapy (2 months therapy)	1	50	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.05, 0.82]
3 Mean relapse rate/patient/year	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Single dose compared with divided dose therapy (2 months therapy)	1	94	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.64, 0.24]
3.2 Daily therapy compared with intermittent therapy (2 months therapy)	1	50	Mean Difference (IV, Random, 95% CI)	0.54 [-0.50, 1.58]
3.3 Deflazacort compared with prednisone (12 months therapy)	1	40	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.77, -1.03]
3.4 Increased prednisone for URTI	1	36	Mean Difference (IV, Random, 95% CI)	-3.3 [-4.03, -2.57]
4 Mean time to relapse	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Single dose compared with divided dose therapy (2 months therapy)	1	94	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.64, 1.04]
4.2 Daily therapy compared with intermittent therapy (2 months therapy)	1	50	Mean Difference (IV, Random, 95% CI)	1.79 [0.90, 2.68]
5 Cumulative steroid dose in gm/square metre	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Single dose compared with divided dose therapy (2 months therapy)	1	94	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.68, 0.58]
6 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Single dose compared with divided dose therapy (2 months duration)	1	94	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.18, 1.82]

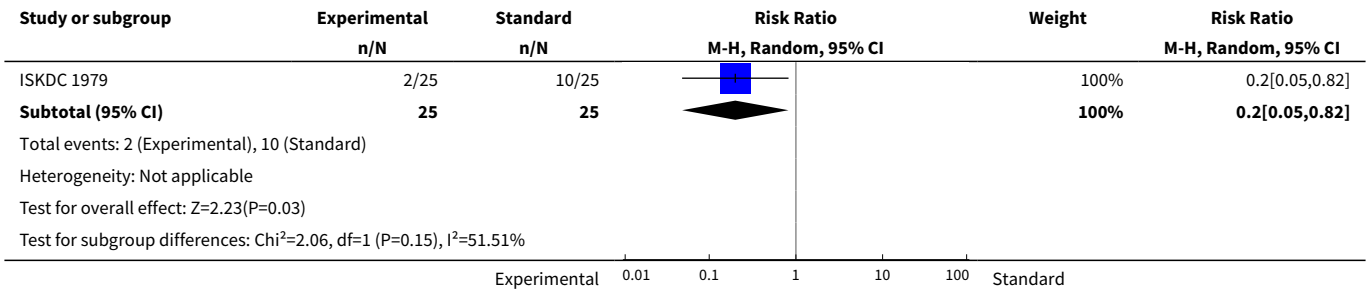
Analysis 5.1. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 1 Number of children with further relapses by 9 - 12 months.

Study or subgroup	Experimental n/N	Standard n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Single dose compared with divided dose therapy (2 months therapy)					
Ekka 1997	29/47	27/47		100%	1.07[0.77,1.5]
Subtotal (95% CI)	**47**	**47**		**100%**	**1.07[0.77,1.5]**

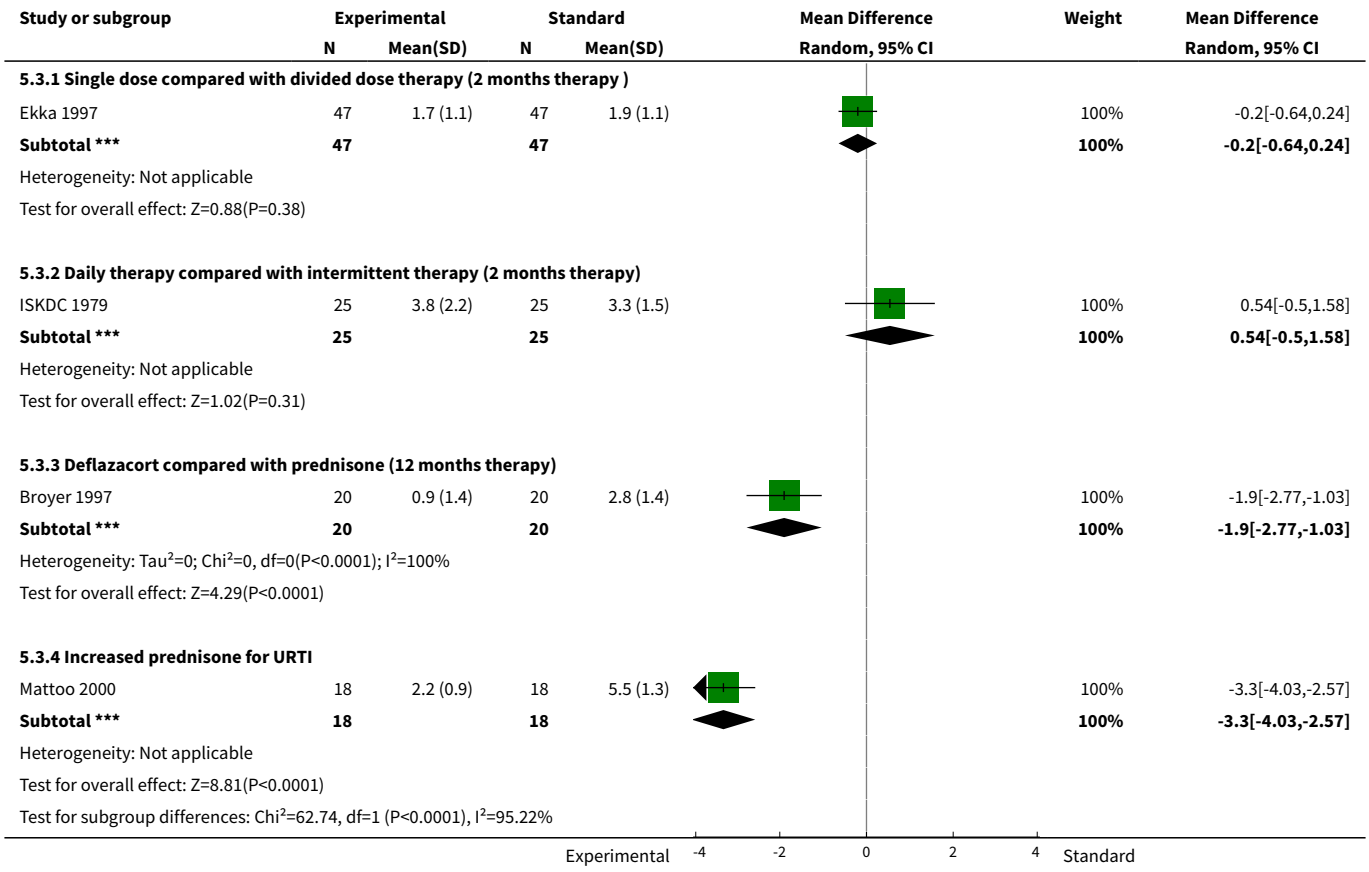


Analysis 5.2. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 2 Number of children relapsing during therapy.

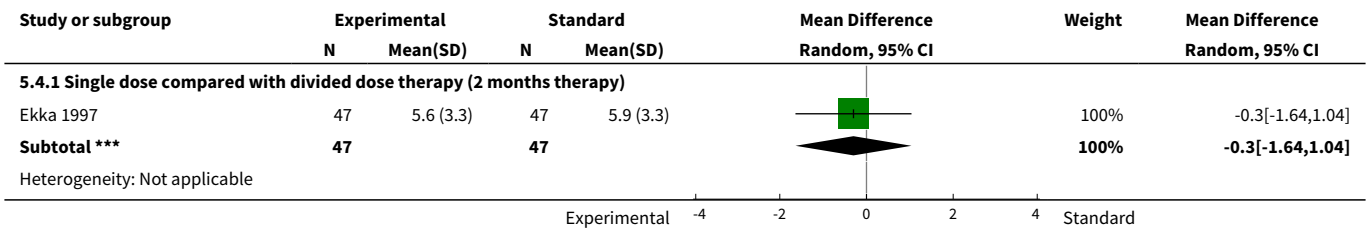


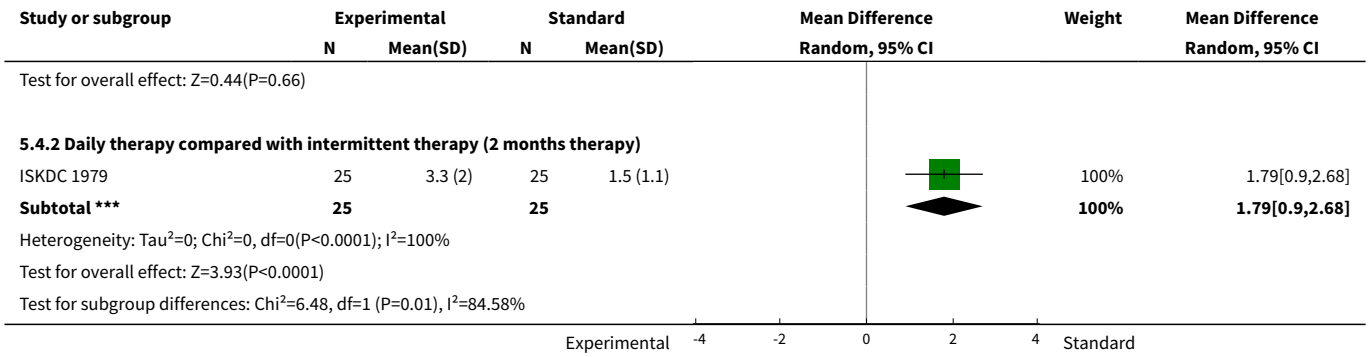


Analysis 5.3. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 3 Mean relapse rate/patient/year.

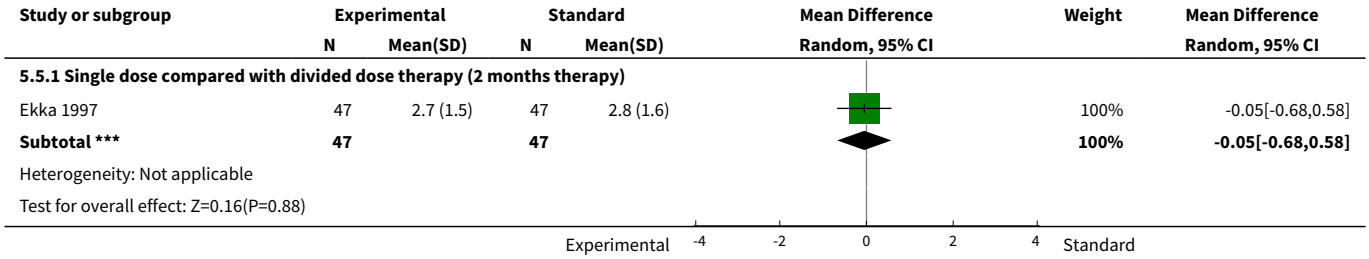


Analysis 5.4. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 4 Mean time to relapse.

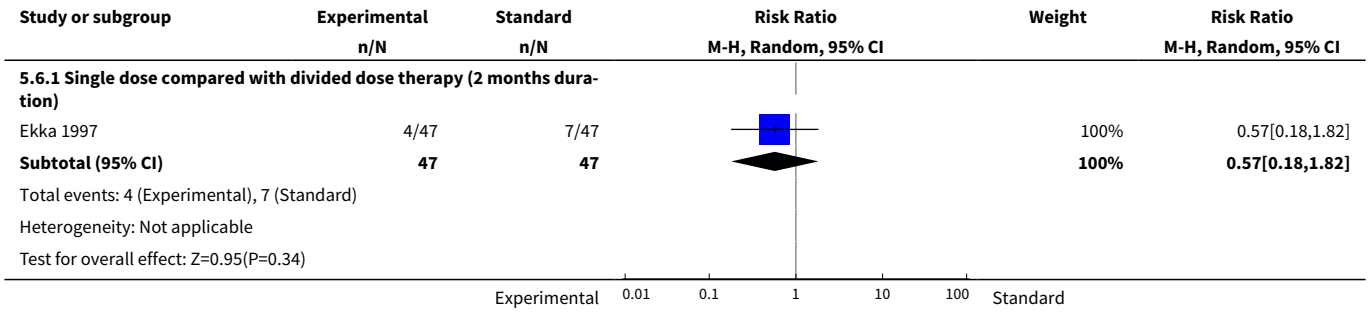




Analysis 5.5. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 5 Cumulative steroid dose in gm/square metre.



Analysis 5.6. Comparison 5 Steroid therapy in relapse of nephrotic syndrome, Outcome 6 Serious adverse events.



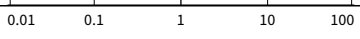
Comparison 6. Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapses	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Relapse by 6 months	1	90	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.25]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 Relapse by 12 months	1	76	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.29, 0.65]
1.3 Relapse by 2 years	1	64	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.45, 0.80]
1.4 Relapse by 3 years	1	53	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.90]
2 Number with frequently relapsing or steroid dependent NS	1	72	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.95]
3 Relapse rate/patient/year	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Relapse rate at 1 year	1	72	Mean Difference (IV, Random, 95% CI)	-1.78 [-2.30, -1.26]
3.2 Relapse rate at 2 years	1	56	Mean Difference (IV, Random, 95% CI)	-1.79 [-2.39, -1.19]
3.3 Relapse rate at 3 years	1	41	Mean Difference (IV, Random, 95% CI)	-1.74 [-2.39, -1.09]
4 Cumulative steroid dose in gm/kg	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 After one year	1	72	Mean Difference (IV, Random, 95% CI)	0.59 [0.02, 1.16]
4.2 After two years	1	56	Mean Difference (IV, Random, 95% CI)	-0.32 [-1.52, 0.88]
4.3 After three years	1	41	Mean Difference (IV, Random, 95% CI)	-1.13 [-3.08, 0.82]
5 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Number with hypertension	1	72	Risk Ratio (M-H, Random, 95% CI)	2.4 [0.86, 6.73]
5.2 Number with growth failure	1	72	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.62, 2.50]

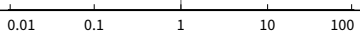
Analysis 6.1. Comparison 6 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 1 Number with relapses.

Study or subgroup	Long duration n/N	Standard duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Relapse by 6 months					
Jayantha 2002b	1/44	29/46		100%	0.04[0.01,0.25]
Subtotal (95% CI)	**44**	**46**		**100%**	**0.04[0.01,0.25]**
Total events: 1 (Long duration), 29 (Standard duration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.34(P=0)					
6.1.2 Relapse by 12 months					
Jayantha 2002b	16/42	30/34		100%	0.43[0.29,0.65]
Subtotal (95% CI)	**42**	**34**		**100%**	**0.43[0.29,0.65]**
Total events: 16 (Long duration), 30 (Standard duration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.07(P<0.0001)					
6.1.3 Relapse by 2 years					
Jayantha 2002b	21/36	27/28		100%	0.6[0.45,0.8]
Subtotal (95% CI)	**36**	**28**		**100%**	**0.6[0.45,0.8]**
Total events: 21 (Long duration), 27 (Standard duration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.46(P=0)					
6.1.4 Relapse by 3 years					
Jayantha 2002b	21/30	23/23		100%	0.71[0.56,0.9]
Subtotal (95% CI)	**30**	**23**		**100%**	**0.71[0.56,0.9]**
Total events: 21 (Long duration), 23 (Standard duration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.8(P=0.01)					
Test for subgroup differences: Chi^2=12.35, df=1 (P=0.01), I^2=75.7%					



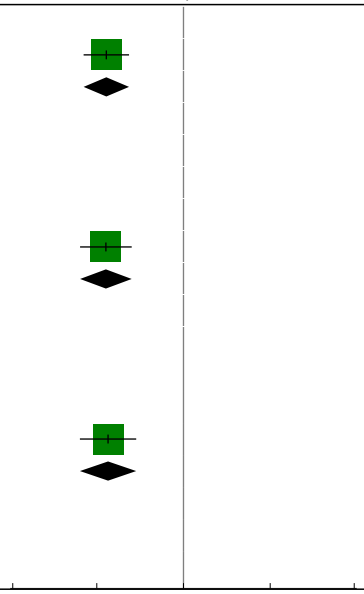
Analysis 6.2. Comparison 6 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 2 Number with frequently relapsing or steroid dependent NS.

Study or subgroup	Long duration n/N	Standard duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jayantha 2002b	7/40	13/32		100%	0.43[0.19,0.95]
Total (95% CI)	**40**	**32**		**100%**	**0.43[0.19,0.95]**
Total events: 7 (Long duration), 13 (Standard duration)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.08(P=0.04)					



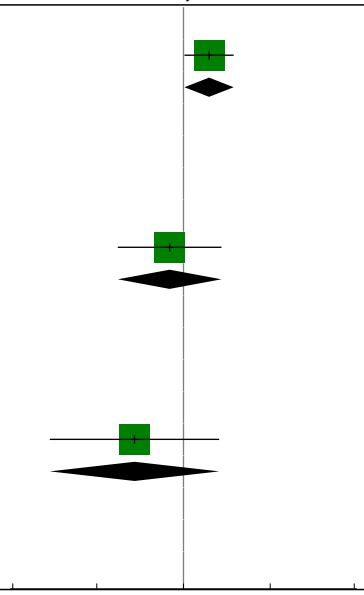
Analysis 6.3. Comparison 6 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 3 Relapse rate/patient/year.

Study or subgroup	Long duration N	Long duration Mean(SD)	Standard duration N	Standard duration Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.3.1 Relapse rate at 1 year							
Jayantha 2002b	40	0.4 (0.5)	32	2.1 (1.5)		100%	-1.78[-2.3,-1.26]
Subtotal ***	**40**		**32**			**100%**	**-1.78[-2.3,-1.26]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=6.66(P<0.0001)							
6.3.2 Relapse rate at 2 years							
Jayantha 2002b	33	0.4 (0.4)	23	2.2 (1.4)		100%	-1.79[-2.39,-1.19]
Subtotal ***	**33**		**23**			**100%**	**-1.79[-2.39,-1.19]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=5.89(P<0.0001)							
6.3.3 Relapse rate at 3 years							
Jayantha 2002b	25	0.4 (0.4)	16	2.2 (1.3)		100%	-1.74[-2.39,-1.09]
Subtotal ***	**25**		**16**			**100%**	**-1.74[-2.39,-1.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.25(P<0.0001)							
Test for subgroup differences: Chi²=0.01, df=1 (P=0.99), I²=0%							

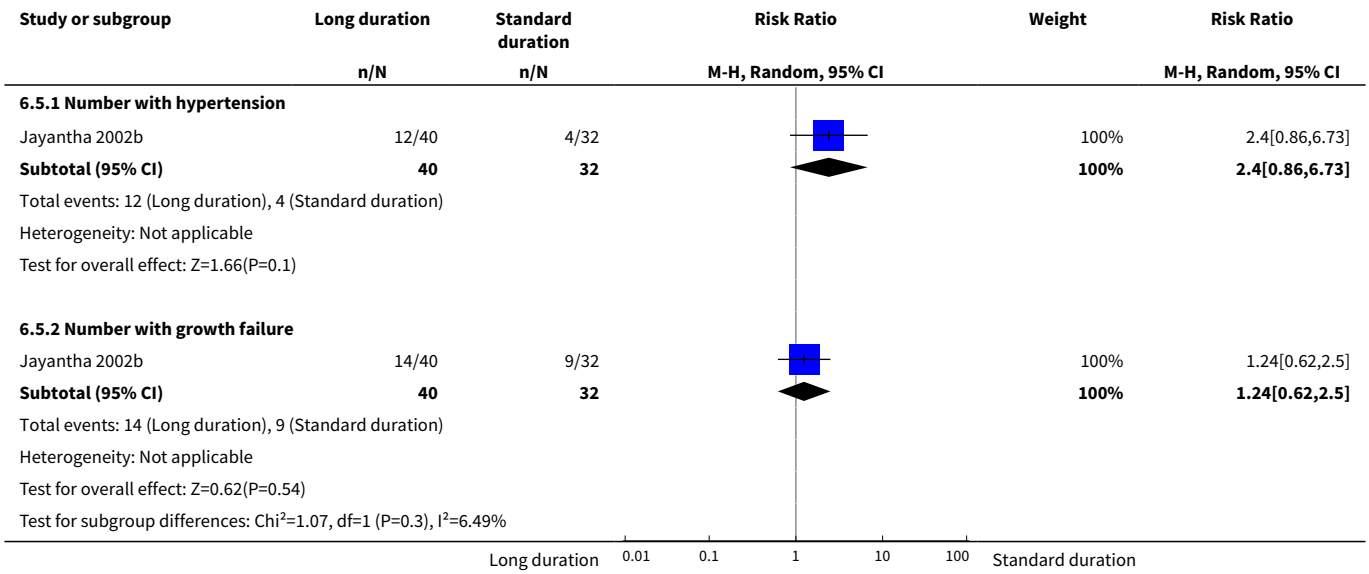


Analysis 6.4. Comparison 6 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 4 Cumulative steroid dose in gm/kg.

Study or subgroup	Long duration N	Long duration Mean(SD)	Standard duration N	Standard duration Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.4.1 After one year							
Jayantha 2002b	40	3.3 (1.2)	32	2.7 (1.3)		100%	0.59[0.02,1.16]
Subtotal ***	**40**		**32**			**100%**	**0.59[0.02,1.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.04(P=0.04)							
6.4.2 After two years							
Jayantha 2002b	33	4.3 (2)	23	4.6 (2.4)		100%	-0.32[-1.52,0.88]
Subtotal ***	**33**		**23**			**100%**	**-0.32[-1.52,0.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.52(P=0.6)							
6.4.3 After three years							
Jayantha 2002b	25	5.3 (2.8)	16	6.4 (3.3)		100%	-1.13[-3.08,0.82]
Subtotal ***	**25**		**16**			**100%**	**-1.13[-3.08,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
Test for subgroup differences: Chi²=4.09, df=1 (P=0.13), I²=51.05%							



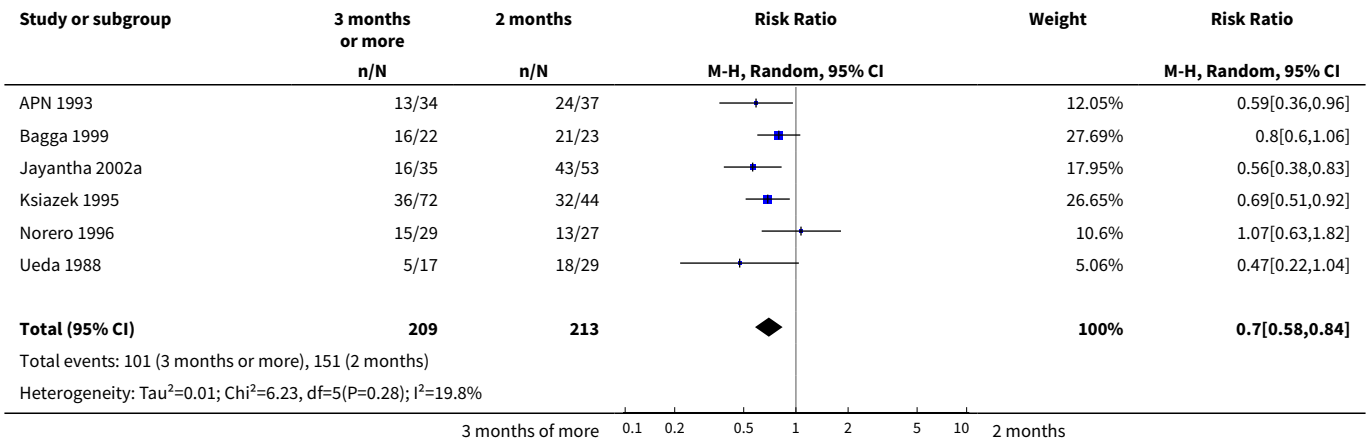
Analysis 6.5. Comparison 6 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 5 Adverse effects.

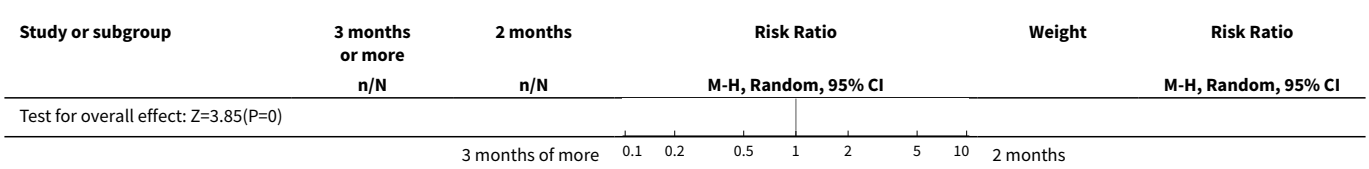


Comparison 7. Steroid therapy in first episode of childhood nephrotic syndrome

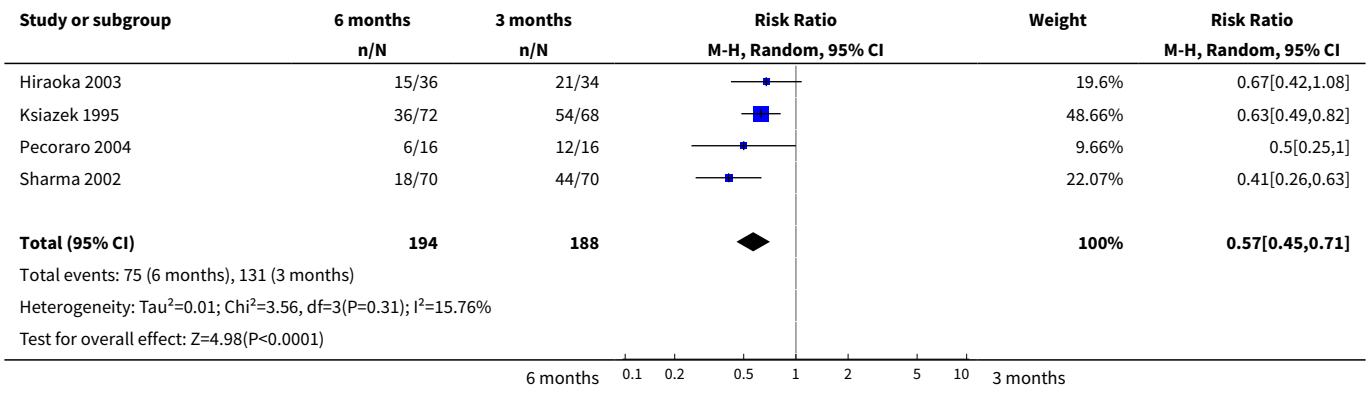
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing by 12-24 months after 3 months or more of prednisone compared with 2 months	6	422	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
2 Number of children relapsing after 6 months of predisone therapy compared with 3 months	4	382	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.45, 0.71]

Analysis 7.1. Comparison 7 Steroid therapy in first episode of childhood nephrotic syndrome, Outcome 1 Number of children relapsing by 12-24 months after 3 months or more of prednisone compared with 2 months.





Analysis 7.2. Comparison 7 Steroid therapy in first episode of childhood nephrotic syndrome, Outcome 2 Number of children relapsing after 6 months of predisone therapy compared with 3 months.



ADDITIONAL TABLES

Table 1. Assessment of study quality in trials of steroid therapy in nephrotic syndrome

	Study ID	Allocation concealment	Intention-to-treat analysis	Completeness of follow-up	Blinding of investigators & participants	Blinding of outcome assessment
Initial episode of nephrotic syndrome	Kleinknecht 1982	Adequate	Unclear	0% lost to follow up at 1 year	No blinding	Not stated
	APN 1988	Adequate	No; 11.6% of 69 with SSNS withdrawn after randomisation	1.6% lost to follow up at 1 year	No blinding	Not stated
	Ueda 1988	Inadequate	Unclear	0% lost to follow up at 1 year	No blinding	Not stated
	APN 1993	adequate	No; 7.8% of 61 with SSNS withdrawn after randomisation	0% lost to follow up at 2 year	No blinding	Not stated
	Ksiazek 1995	Inadequate	Yes	0% lost to follow up at 1 year	No blinding	Not stated

Table 1. Assessment of study quality in trials of steroid therapy in nephrotic syndrome *(Continued)*

	Norero 1996	Inadequate	No; 26% of 82 with SSNS withdrawn after randomisation excluded	0% lost to follow up at 1.5 years	No blinding	Not stated
	Bagga 1999	Adequate	No: 4% of 47 with SSNS withdrawn after randomisation	0% lost to follow up at 1 year	No blinding	Not stated
Relapse of nephrotic syndrome	ISKDC 1979	Unclear	No; 17% of 64 withdrawn after randomisation	5.5% lost to follow up at 6-9 months	No blinding	Not stated
	APN 1981	Inadequate	No; 25% of 64 withdrawn after randomisation	0% lost to follow up at 1 year excluded	No blinding	Not stated
	Imbasciali 1985	Adequate	Yes	0% lost to follow up at 12-24 months	No blinding	Not stated
	Ekka 1997	Unclear	Unclear	10% lost to follow up at 9 months	No blinding	Not stated
	Broyer 1997	Adequate	No; 2.5% withdrawn after randomisation	2.5% lost to follow up at 1 year	Both	Not stated
Additional studies (2002)	Hiraoka 2000	Unclear	Yes	1.6% lost to follow up at 2 years	No blinding	Not stated
	Jayantha 2002a	Adequate	No	11% lost to follow up in initial 3-6 months & excluded from analysis	No blinding	No blinding
	Leisti 1978	Unclear	Unclear	0% lost to follow up	Both	Not stated
	Mattoo 2000	Inadequate	No	Children lost to follow up were excluded from analysis	No blinding	Not stated
	Yoshikawa 1998	Adequate	Unclear	7.7% of 196 did not complete 2 year follow up & excluded from analysis	No blinding	Not stated
	Jayantha 2002b	Adequate	No	20% of 95 lost to follow up at 1 year	No blinding	Not stated
	Sharma 2002	Adequate	No	4% of 156 lost to follow up	No blinding	Not stated
Additional studies (2004)	Hiraoka 2003	Adequate	Yes	3% of 70 SSNS lost to follow up	No blinding	Not stated
	APN VIII 1999	Unclear	No; 25% of 138 with SSNS withdrawn after randomisation	0% lost to follow up	No blinding	Not stated

Table 1. Assessment of study quality in trials of steroid therapy in nephrotic syndrome *(Continued)*

	Pecoraro 2003	Inade-quate	No	Unclear	No blinding	Not stated
	Satomura 2001	Unclear	No	Unclear	No blinding	Not stated

Table 2. Outcomes of trials in children with relapsing nephrotic syndrome

Study ID	Relapse on thera-py RR (95% CI)	Relapse by 9 months RR (95% CI)	Relapse by 12 months RR (95% CI)	Mean relapse rate WMD (95% CI)	Comparison of steroid regimens
ISKDC 1979	0.20 (0.05 to 0.82)	1.00 (0.89 to 1.12)		0.54 (-0.50 to 1.58)	Daily versus intermittent
APN 1981	0.60 (0.36 to 1.02)		1.20 (0.93 to 1.55)	-0.20 (-0.65 to 0.25)	Alternate day versu intermittent
Imbasciali 1985			1.06 (0.75 to 1.52)		IV & oral versu oral
Ekka 1997		1.07 (0.77 to 1.50)			Daily versus divided dose
Broyer 1997			0.44 (0.25 to 0.78)	-1.90 (-2.77 to -1.03)	Deflazacort versus prednisone
Mattoo 2000				-3.30 (-4.03 to -2.57)	Daily versus alternate-day in URTI
Jayantha 2002b			0.43 (0.29 to 0.65)	-1.78 (-2.30 to -1.26)	7 months therapy versus standard ISKDC regimen for relapse

Table 3. Expected relapse rates in groups of children with different control event rates

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%	9%	35%
60%	7%	25%
40%	4%	20%

Table 3. Expected relapse rates in groups of children with different control event rates *(Continued)*

20%	2%	10%
10%	1%	5%

WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 4, 2000

Date	Event	Description
27 October 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Elisabeth Hodson: Study selection, quality appraisal, data extraction, data analysis, writing review, updating review.
John Knight: Study selection, quality appraisal, data extraction
Narelle Willis: Literature search, obtaining articles, organising translation, data extraction, data analysis, data display, updating review.
Jonathan Craig: Data analysis, writing review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Kidney Foundation, Australia.
- National Health and Medical Research Council, Australia.
- Commonwealth Department of Health and Aging, Australia.

NOTES

28 November 2002
Inclusion of five additional trials
Updating of sections on Description of studies, Methodological Quality, Results, Discussion, Implications for clinical practice and Implications for research
Additions to Table of Included Studies
Updating of Additional Tables
Above carried out to incorporate findings of additional trials

In addition alterations in criteria for quality assessment according to the Cochrane Renal Group guidelines

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Drug Administration Schedule; Glucocorticoids [adverse effects] [therapeutic use]; Nephrotic Syndrome [*drug therapy]; Prednisone [therapeutic use]; Pregnenediones [therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Respiratory Tract Infections [drug therapy] [virology]; Secondary Prevention; Virus Diseases [drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant