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Corticosteroid therapy for nephrotic syndrome in children (Review)

Hahn D, Hodson EM, 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 most children with nephrotic syndrome respond to corticosteroids, 80% experience a relapsing course. Corticosteroids have reduced the mortality rate to around 3%. However corticosteroids have well recognised potentially serious adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and behavioural disturbances. This is an update of a review first published in 2000 and updated in 2003, 2005 and 2007.

Objectives

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

Search methods

We searched the Cochrane Renal Group's Specialised Register to 26 February 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) 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.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data. Results were expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI).

Main results

Ten new studies were identified so a total of 34 studies (3033 total participants) were included in the 2015 review update. The risk of bias attributes were frequently poorly performed. Low risk of bias was reported in 18 studies for sequence generation, 16 studies for allocation concealment, seven for performance and detection bias, 15 for incomplete reporting and 16 for selective reporting. Three months or more of prednisone significantly reduced the risk of frequently relapsing nephrotic syndrome (FRNS) (6 studies, 582 children: RR 0.68, 95% CI 0.47 to 1.00) and of relapse by 12 to 24 months (8 studies, 741 children: RR 0.80, 95% CI 0.64 to 1.00) compared with two months. Five or six months of prednisone significantly reduced the risk of relapse (7 studies, 763 children: RR 0.62, 95% CI 0.45 to 0.85) but not FRNS (5 studies,

591 children: RR 0.78, 95% CI 0.50 to 1.22) compared with three months. However there was significant heterogeneity in the analyses. Subgroup analysis stratified by risk of bias for allocation concealment showed that the risk for FRNS did not differ significantly between two or three months of prednisone and three to six months among studies at low risk of bias but was significantly reduced in extended duration studies compared with two or three months in studies at high risk or unclear risk of bias. There were no significant differences in the risk of adverse effects between extended duration and two or three months of prednisone. Four studies found that in children with FRNS, daily prednisone during viral infections compared with alternate-day prednisone or no treatment significantly reduced the rate of relapse.

Authors' conclusions

In this 2015 update the addition of three well-designed studies has changed the conclusion of this review. Studies of long versus shorter duration of corticosteroids have heterogeneous treatment effects, with the older high risk of bias studies tending to over-estimate the effect of longer course therapy, compared with more recently published low risk of bias studies. Among studies at low risk of bias, there was no significant difference in the risk for FRNS between prednisone given for two or three months and longer durations or total dose of therapy indicating that there is no benefit of increasing the duration of prednisone beyond two or three months in the initial episode of SSNS.

The risk of relapse in children with FRNS is reduced by the administration of daily prednisone at onset of an upper respiratory tract or viral infection. Three additional studies have increased the evidence supporting this conclusion. This management strategy may be considered for children with FRNS. A paucity of data on prednisone use in relapsing nephrotic syndrome remains. In particular there are no data from RCTs evaluating the efficacy and safety of prolonged courses of low dose alternate-day prednisone although this management strategy is recommended in current guidelines.

PLAIN LANGUAGE SUMMARY

Corticosteroid therapy for children with nephrotic syndrome

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. When it is untreated, children can often die from infections. Most children, with nephrotic syndrome, respond to corticosteroid drugs (prednisone, prednisolone) reducing the risk of serious infection. However they usually have repeat episodes, which are often triggered by viral infections. Corticosteroid drugs can have serious side effects.

We looked at evidence from 34 studies enrolling 3033 children. Fourteen of 21 studies, in children with their first episode of nephrotic syndrome, evaluated prednisone for two or three months compared with longer durations. Thirteen studies evaluated different corticosteroid regimens in children with frequently relapsing disease (FRNS). Studies were of variable methodological quality with only about half of the studies at low risk of bias.

Among studies of long versus shorter duration of prednisone, older studies at high or unclear risk of bias tended to over-estimate the effect of longer course therapy compared with new studies at low risk of bias. Studies at low risk of bias found no significant differences in the risk of relapse or the development of FRNS between prednisone given for three to six months compared with two or three months. Therefore there is no benefit of increasing the duration of prednisone beyond two or three months in the initial episode of SSNS.

Based on four studies in children with frequently relapsing nephrotic syndrome, prednisone given for five to seven days at the onset of a viral infection reduces the risk of relapse.

This review updates information previously published in 2000, 2003, 2005 and 2007. The addition of three new studies evaluating different durations of prednisone in the first episode of nephrotic syndrome has changed the conclusions expressed in previous versions of this review

Summary of findings for the main comparison. Steroid therapy in first episode of nephrotic syndrome: three months of more versus two months for nephrotic syndrome in children

Steroid therapy in first episode of nephrotic syndrome: 3 months of more versus 2 months for nephrotic syndrome in children

Patient or population: patients with nephrotic syndrome in children
Settings:
Intervention: steroid therapy in first episode of nephrotic syndrome: 3 months of more versus 2 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroid therapy in first episode of nephrotic syndrome: 3 months of more compared with 2 months				
Number with frequent relapses by 12 to 24 months	**Study population**		**RR 0.68** (0.47 to 1)	582 (6)	⊕⊕⊝⊝ **low**[1,2]	
	358 per 1000	**243 per 1000** (168 to 358)				
	Moderate					
	359 per 1000	**244 per 1000** (169 to 359)				
Number of children relapsing by 12 to 24 months	**Study population**		**RR 0.8** (0.64 to 1)	741 (8)	⊕⊕⊝⊝ **low**[1,2]	
	668 per 1000	**535 per 1000** (428 to 668)				
	Moderate					
	647 per 1000	**518 per 1000** (414 to 647)				

Number with frequent relapses by 12 to 24 months stratified by risk of bias for allocation concealment: low risk of bias for allocation concealment	**Study population**		**RR 0.92** (0.69 to 1.23)	362 (3)	⊕⊕⊕⊕ **high**
	359 per 1000	**330 per 1000** (247 to 441)			
	Moderate				
	348 per 1000	**320 per 1000** (240 to 428)			
Number with frequent relapses by 12 to 24 months stratified by risk of bias for allocation concealment: unclear or high risk of bias for allocation bias	**Study population**		**RR 0.45** (0.26 to 0.77)	220 (3)	⊕⊕⊕⊝ **moderate**[1]
	357 per 1000	**161 per 1000** (93 to 275)			
	Moderate				
	371 per 1000	**167 per 1000** (96 to 286)			
Adverse events: psychological disorders	**Study population**		**RR 2.18** (0.43 to 11.13)	233 (3)	⊕⊕⊝⊝ **low**[1,3]
	18 per 1000	**40 per 1000** (8 to 202)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Adverse events: hypertension	**Study population**		**RR 1.79** (0.47 to 6.86)	456 (6)	⊕⊕⊕⊝ **moderate**[1]
	60 per 1000	**107 per 1000** (28 to 410)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Adverse events: eye complications	**Study population**		**RR 0.32** (0.07 to 1.42)	400 (5)	⊕⊕⊕⊝ **moderate**[1]
	43 per 1000	**14 per 1000**			

	(3 to 62)
Moderate	
0 per 1000	**0 per 1000** (0 to 0)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Some studies at high or unclear risk of bias
[2] Significant heterogeneity between studies
[3] Few studies included in analysis

Summary of findings 2. Steroid therapy in first episode of nephrotic syndrome: five or six months versus three months for nephrotic syndrome in children

Steroid therapy in first episode of nephrotic syndrome: 5 to 6 months versus 3 months for nephrotic syndrome in children

Patient or population: patients with nephrotic syndrome in children
Settings:
Intervention: steroid therapy in first episode of nephrotic syndrome: 5 to 6 months versus 3 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroid therapy in first episode of nephrotic syndrome: 5 to 6 months verus 3 months				
Number with frequent relapses by 12 to 24 months	**Study population**		**RR 0.78** (0.5 to 1.22)	591 (5)	⊕⊕⊝⊝ **low**[1]	
	363 per 1000	**283 per 1000**				

		(182 to 443)			
	Moderate				
	393 per 1000	**307 per 1000** (196 to 479)			
Number of children relapsing by 12 to 24 months	**Study population**		**RR 0.62** (0.45 to 0.85)	763 (7)	⊕⊕⊝⊝ **low**[1,2]
	694 per 1000	**430 per 1000** (312 to 590)			
	Moderate				
	703 per 1000	**436 per 1000** (316 to 598)			
Subgroup analysis by risk of bias for number with frequent relapses: low risk of bias for allocation concealment	**Study population**		**RR 1** (0.74 to 1.34)	377 (3)	⊕⊕⊕⊕ **high**
	438 per 1000	**438 per 1000** (324 to 587)			
	Moderate				
	441 per 1000	**441 per 1000** (326 to 591)			
Subgroup analysis by risk of bias for number with frequent relapses: Unclear or high risk of bias for allocation concealment	**Study population**		**RR 0.36** (0.18 to 0.72)	214 (2)	⊕⊕⊕⊝ **moderate**[2]
	234 per 1000	**84 per 1000** (42 to 168)			
	Moderate				
	185 per 1000	**67 per 1000** (33 to 133)			
Adverse events: hypertension	**Study population**		**RR 1.37** (0.91 to 2.05)	636 (5)	⊕⊕⊕⊝ **moderate**[2]
	111 per 1000	**153 per 1000** (101 to 229)			
	Moderate				

	114 per 1000	**156 per 1000** (104 to 234)			
Adverse events: eye complications	**Study population**		**RR 0.46** (0.18 to 1.17)	614 (5 studies)	⊕⊕⊕⊖ **moderate**[2]
	36 per 1000	**17 per 1000** (6 to 42)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Adverse events: cushingoid appearance	**Study population**		**RR 0.92** (0.62 to 1.36)	646 (5)	⊕⊕⊕⊖ **moderate**[2]
	365 per 1000	**336 per 1000** (226 to 496)			
	Moderate				
	386 per 1000	**355 per 1000** (239 to 525)			
Adverse events: psychological disorders	**Study population**		**RR 0.38** (0.03 to 4.39)	389 (3)	⊕⊕⊖⊖ **low**[2,3]
	48 per 1000	**18 per 1000** (1 to 209)			
	Moderate				
	46 per 1000	**17 per 1000** (1 to 202)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 Significant heterogeneity between studies
2 Some studies at high or unclear risk of bias
3 Few studies included in analyses

BACKGROUND

Description of the condition

Nephrotic syndrome is a well-recognised chronic illness in childhood. The characteristic features, including oedema, proteinuria and hypoalbuminaemia, result from alterations of the perm-selectivity barrier of the glomerular capillary wall. The reported incidence is 2 to 7/100,000 children, with a prevalence of 16/100,000 (Eddy 2003). Recent prospective studies revealed an incidence of 1.15 to 2.1/100,000 children/year (El Bakkali 2011).The incidence of nephrotic syndrome is higher in Asian (McKinney 2001), African-American (Srivastava 1999) and Arab children (Elzouki 1984). Most children have minimal change disease, in which changes on light microscopy are minor or absent, and respond to corticosteroid agents. Despite the overall incidence of childhood nephrotic syndrome remaining relatively stable over the last three decades, the histological pattern appears to be changing with an increase in the incidence of focal and segmental glomerulosclerosis (FSGS), even after adjustment for biopsy practices (Bonilla-Felix 1999; Gulati 1999; Srivastava 1999). The histological variant and response to immunosuppressive treatment may be related to ethnicity (Eddy 2003). Steroid-sensitive nephrotic syndrome (SSNS) is less common in African and African-American children, and in South Africa 7.2% of 236 African children had SSNS compared with 62% of 286 Indian children (Bhimma 1997). The pathogenesis of SSNS remains unknown but appears to be related to abnormalities in T-cell and B-cell regulation. About 80% of children who respond to corticosteroids experience a relapsing course with recurrent episodes of oedema and proteinuria (Koskimies 1982; Tarshish 1997). The complications of nephrotic syndrome are related to effects of the disease itself, and adverse effects related to corticosteroid therapy and corticosteroid sparing agents. Children with nephrotic syndrome, which is resistant to therapy, 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) and fell further with the use of corticosteroid medications.

Description of the intervention

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 80% 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 and no randomised controlled prospective studies of corticosteroids compared to placebo were carried out. The achievement of remission with corticosteroid therapy determines long term prognosis for kidney function irrespective of kidney histology (Niaudet 2009). However corticosteroids have known adverse effects. Major complications related to prolonged corticosteroid use in nephrotic syndrome include growth impairment, particularly with steroid therapy administered daily (Hyams 1988), cataracts (Ng 2001) and excessive weight gain or obesity (Rüth 2005).Two recent studies (Mishra 2010; Neuhaus 2010) highlight the impact of psychological and behavioural abnormalities related to corticosteroid therapy. Anxiety, depression, emotional lability, aggressive behaviour and attention problems had already developed with completion of 12 weeks of therapy (Mishra 2010). Neuhaus 2010 demonstrated family background, particularly maternal distress, reduced quality of life and psychosocial adjustment. Adverse effects are particularly prevalent in those children who relapse frequently and thus require multiple courses of corticosteroids.

How the intervention might work

The pharmacology and pharmacodynamics of corticosteroids in SSNS are not fully understood (Mehls 2011). It is widely believed the main effect is through the regulation of nuclear gene expression via the cytosolic glucocorticoid receptor, which activates genes for anti-inflammatory cytokines and suppresses genes for pro-inflammatory cytokines. Glucocorticoids are lipid soluble and can easily pass through cell membranes. This process takes several hours. More recently research had identified corticosteroid effects, which are independent of nuclear gene transcription and occur earlier. At high glucocorticoid doses, suppression of T-cell function occurs. Corticosteroids also act directly to stabilise the podocyte cytoskeleton.

Why it is important to do this review

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 and several randomised controlled trials (RCTs) have investigated different durations and total corticosteroid therapy doses in an effort to delineate the optimal doses and durations of corticosteroid therapy that are most beneficial and least harmful. These have been evaluated in previous versions of this systematic review. However despite these data there remains no consensus on the most appropriate corticosteroid regimen to achieve and maintain remission with the least adverse effects. Therefore the 2015 update of this review has been undertaken to identify further RCTs, which compare different corticosteroid regimens in the initial episode of SSNS and in relapsing disease.

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 RCTs and quasi-RCTs, in which different doses, dose strategies, routes of administration and durations of treatment with prednisone, prednisolone or other corticosteroid agent 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. become oedema free with urine protein ≤ 1+ on dipstick, urinary protein/creatinine ratio ≤ 20 mg/mmol or ≤ 4 mg/m^2/h for three consecutive days while receiving corticosteroid therapy). A kidney biopsy diagnosis of minimal change disease was not required for inclusion of the study.

- Children with initial episode of SSNS
- Children with relapsing SSNS

Exclusion criteria

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

Types of interventions

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

- Shorter duration compared with two months of corticosteroid treatment
- Longer durations compared with two or three months of corticosteroid treatment
- Comparisons of different doses of corticosteroid medication given for induction of a remission
- Comparisons of other regimens of corticosteroid therapy
- Different corticosteroid agents (e.g. deflazacort, methylprednisolone) compared with standard agents (e.g. prednisone, prednisolone)
- Comparisons 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

Primary outcomes

1. The numbers of children with and without relapse at six months, 12 months and 24 months after completion of treatment.
2. The number of children who developed frequently relapsing nephrotic syndrome.

Secondary outcomes

1. The number of children who required other immunosuppressive therapy because of steroid toxicity
2. Mean relapse rates/patient
3. Serious adverse events including reduced growth rates, hypertension, cataracts/glaucoma, psychological disorders, infections, thromboses and osteoporosis
4. Cumulative corticosteroid dosage

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register up to 26 February 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies and CD-ROMs and abstract books from nephrology meetings.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Conference proceedings of meetings of the International Pediatric Nephrology Association and European Society for Paediatric Nephrology.

Data collection and analysis

Selection of studies

The initial review was undertaken by four authors. The titles and abstracts were screened by two authors 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 studies were retained initially. Three authors independently assessed abstracts, and if necessary the full text, to determine which studies satisfied the characteristics required for inclusion. The 2003, 2005 and 2007 updates were undertaken by three authors (EH, NW, JC).

This 2015 update was undertaken by four authors (DH, EH, NW, JC). Potentially relevant studies were initially determined by two authors from titles and abstracts. Full text articles of potentially eligible articles were reviewed for eligibility by two authors.

Data extraction and management

Data extraction and assessment of risk of bias were performed by two authors using standardised data extraction forms. Studies in languages other than English were translated before data extraction. Where more than one report of a study was identified, data were extracted from all reports. Where there were discrepancies between reports, data from the primary source was used. Study authors were contacted for additional information about studies where possible.

Assessment of risk of bias in included studies

For this update, the following items were assessed during the risk of bias assessment tool (Higgins 2011).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (relapse or no relapse, side effects) the risk ratio (RR) 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. Where continuous scales of measurement were used to assess the effects of treatment (cumulative steroid therapy, relapse rate), these data were analysed as the mean difference (MD) 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.

Unit of analysis issues

Data from cross-over studies were included in the meta-analyses if separate data for the first part of the study were available. Otherwise results of cross-over studies were reported in the text only.

Dealing with missing data

We aimed to analyse available data in meta-analyses using ITT data. However, where ITT data were not provided, or additional information could not be obtained from authors, available published data were used in the analyses.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test with N-1 degrees of freedom and an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

The search strategy used aimed to reduce publication bias caused by lack of publication of studies with negative results. Where there were several publications on the same study, all reports were reviewed to ensure that all details of methods and results were included to reduce the risk of selective outcome reporting bias.

Data synthesis

Data were combined using random effects model for dichotomous and continuous data.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to investigate between study differences based on risk of bias, differences between definitions of FRNS and different durations of treatment in the experimental group in studies comparing two months with three or more months of prednisone.

Sensitivity analysis

Where a single study differed considerably from the other studies in the meta-analysis, this study was temporarily excluded to determine whether its removal altered the results of the meta-analysis.

RESULTS

Description of studies

Results of the search

Search results are shown in Figure 1.

Figure 1. Study flow diagram.

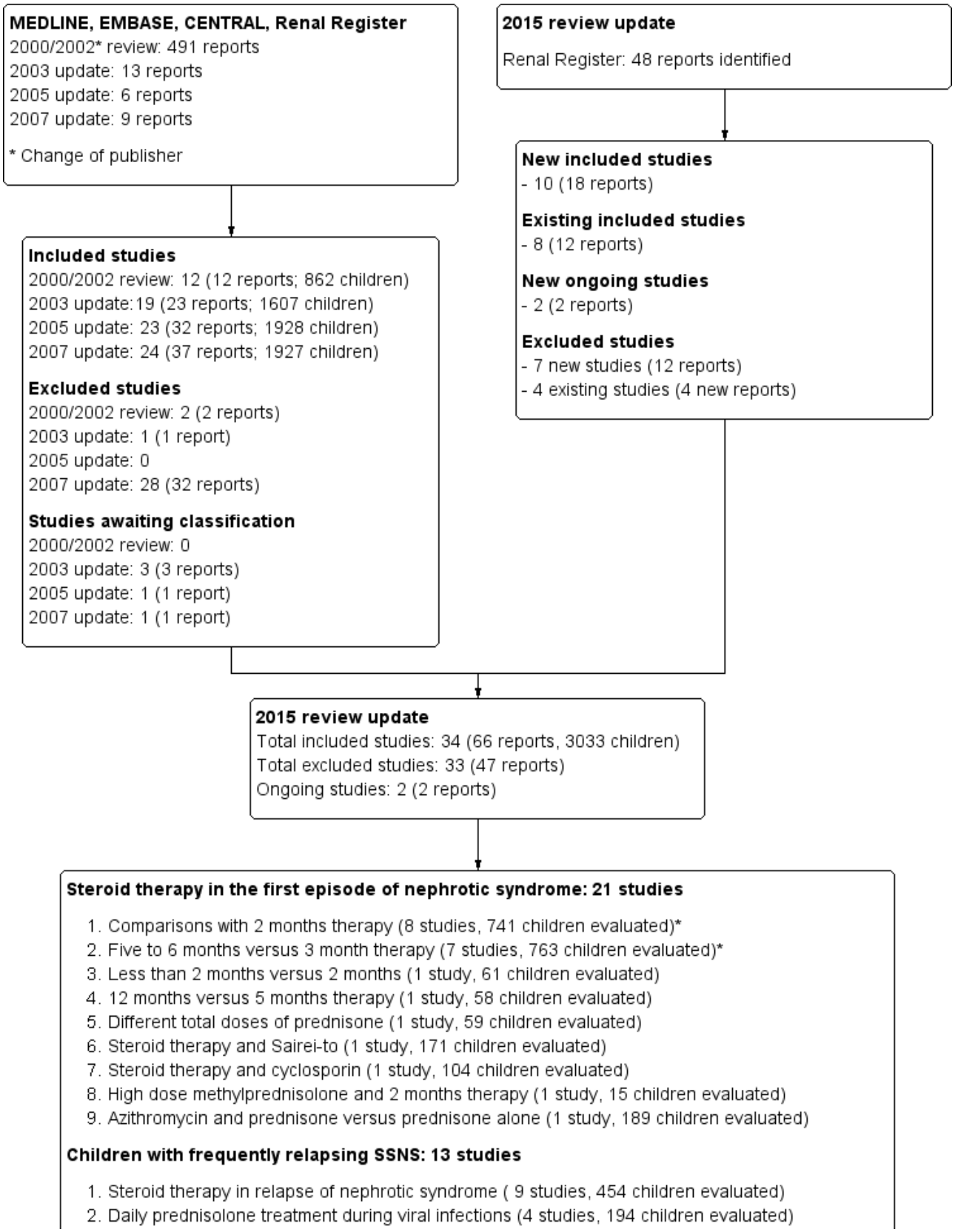


Figure 1. (Continued)

1. Steroid therapy in relapse of nephrotic syndrome (9 studies, 454 children evaluated)
2. Daily prednisolone treatment during viral infections (4 studies, 194 children evaluated)

* One study had children in each comparison group

For this latest update our search (to 26 February 2015) identified 48 potentially relevant reports. Of these, nine new studies (16 reports) (Abeyagunawardena 2008; Abeyagunawardena 2014; Gulati 2009; Liern 2008; Mishra 2012; Sinha 2014; Teeninga 2013; Yoshikawa 2014; Zhang 2014) were included. One study awaiting assessment (Mocan 1999) was also included. Our search also identified two studies that are underway; no results were yet available to include in our analysis (PREDNOS Study 2013, PREDNOS 2 Study 2014). We also found 12 reports of nine previously included studies (APN 1988; APN 1993; Bagga 1999; Broyer 1997; Ekka 1997; Hiraoka 2000; Norero 1996; Pecoraro 2003; Yoshikawa 1998). This update includes 34 studies (66 reports) that involved a total of 3033 participants.

For the search results of our previous reviews please see (Hodson 2002; Hodson 2003; Hodson 2005; Hodson 2007).

Included studies

The 34 included studies were divided into groups according to comparisons of corticosteroid regimens. Most studies used prednisone or prednisolone. For ease of reading, the term "prednisone" has been used in the text for both medications.

Prednisone treatment in first episode of nephrotic syndrome

Three months or more versus two months of therapy (741 evaluated children)

Seven studies (APN 1993; Bagga 1999; Jayantha 2002a; Ksiazek 1995; Norero 1996; Satomura 2001; Ueda 1988; Yoshikawa 2014) compared therapies of two months duration with regimens of three months or more. In all of these studies except Satomura 2001, increased duration of treatment resulted in increased total prednisone dose compared with the control group. Satomura 2001 compared three months of treatment with two months weeks using the same total dose of prednisone in each group. In Ksiazek 1995, which compared three different regimens, data from the two month therapy group and the experimental group treated for six months (experimental group 1) were included in the meta-analysis. Norero 1996 excluded those children who became steroid dependent.

Five to six months versus three months of therapy (763 evaluated children)

Seven studies (Hiraoka 2003; Ksiazek 1995; Mishra 2012, Pecoraro 2003; Sharma 2000; Sinha 2014; Teeninga 2013) compared five or six months of prednisone with three months of therapy. In all studies except Teeninga 2013, increased duration of prednisone resulted in increased total prednisone dose compared with the control group. Teeninga 2013 compared three months with six months therapy, using the same total dose of prednisone in both groups. From 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. Pecoraro 2003 had three groups - a control group treated for three months and two experimental groups treated for six months with different total doses of prednisone. Only the control group and treatment group 1 were included in the meta-analysis.

Less than two months versus two months of therapy (61 evaluated children)

APN 1988 compared less than the two month of prednisone with two months.

12 months versus five months of therapy (58 evaluated children)

Kleinknecht 1982 compared five months of prednisone with one year of therapy; the timing of the follow-up period in relation to the duration of initial therapy was not stated.

Different total doses of prednisone (59 evaluated children)

Hiraoka 2000 compared different total doses of prednisone given for three months.

Prednisone and Sairei-to therapy (171 evaluated children)

Yoshikawa 1998 compared two months of prednisone with 4.5 months but both groups received the Chinese herb, Sairei-to. The assumption was made that the effect of the herb would be the same in both treatment groups. However because this assumption may not be correct, this study was considered separately from other studies comparing different durations of prednisone.

Prednisone and cyclosporin therapy (104 evaluated children)

APN 1999 compared three months of prednisone plus two months of cyclosporin with three months of prednisone only.

High dose oral methylprednisolone therapy (15 evaluated children)

Mocan 1999 compared high dose oral methylprednisolone given over two weeks with six months of prednisone therapy.

Prednisone and azithromycin therapy (211 evaluated children)

Zhang 2014 compared the addition of azithromycin to prednisone with prednisone alone at initiation of therapy in the first episode of nephrotic syndrome.

Relapsing nephrotic syndrome

Daily prednisone treatment during viral infections (194 evaluated children)

Three studies (Abeyagunawardena 2008; Gulati 2009; Mattoo 2000) compared daily with alternate-day prednisone to prevent relapse during viral infections in children with SSNS receiving alternate-day prednisone. One study (Abeyagunawardena 2014) compared daily prednisone with placebo to prevent relapse during upper respiratory tract infections in children with SSNS off prednisone.

Relapsing nephrotic syndrome: other interventions (454 evaluated children)

Nine studies investigated relapsing SSNS (APN 1981; Broyer 1997; Ekka 1997; Imbasciati 1985; ISKDC 1984; Jayantha 2002b; Leisti 1978; Li 1994; Liern 2008). Ekka 1997 and Li 1994 compared single daily with three times/day dosage of prednisone. The remaining studies explored different treatment regimens aimed at

inducing remission, maintaining remission or both. Jayantha 2002b excluded children with steroid dependent nephrotic syndrome. Imbasciati 1985 and Jayantha 2002b included children with infrequently and frequently relapsing SSNS.

Excluded studies

In total, we excluded 34 studies (66 reports) after full text assessment for this review. Of the 34 excluded studies, five were not RCTs and 29 were RCTs involving non-corticosteroid interventions in children with SSNS.

Risk of bias in included studies

Risk of bias assessments were performed using Cochrane's risk of bias assessment tool (Appendix 2). Summaries of risk of bias assessments are shown in Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

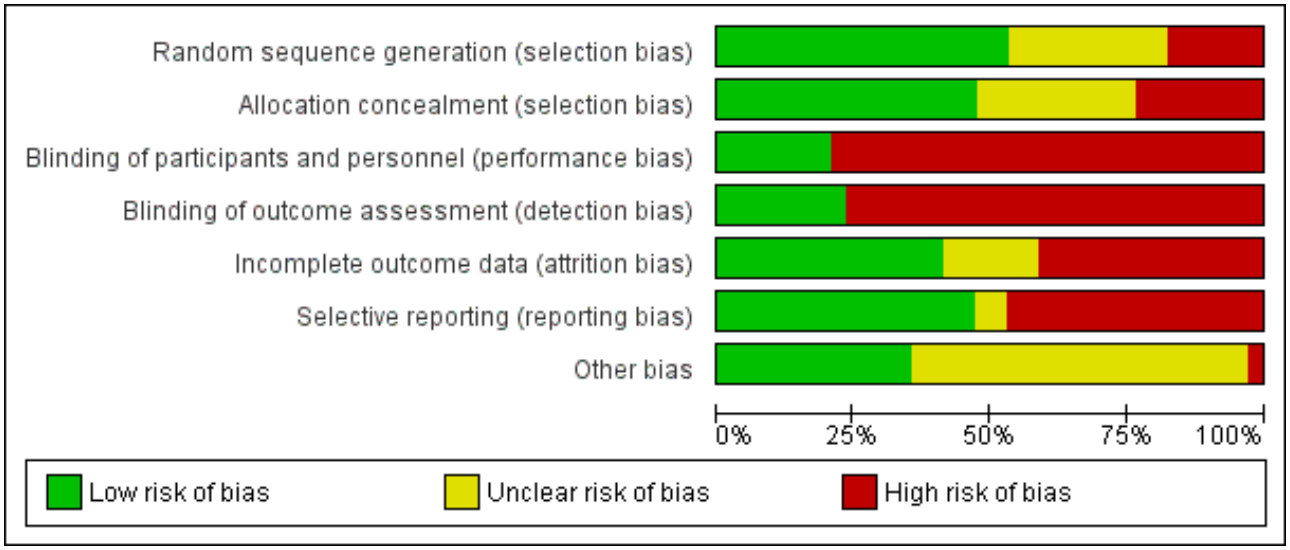


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

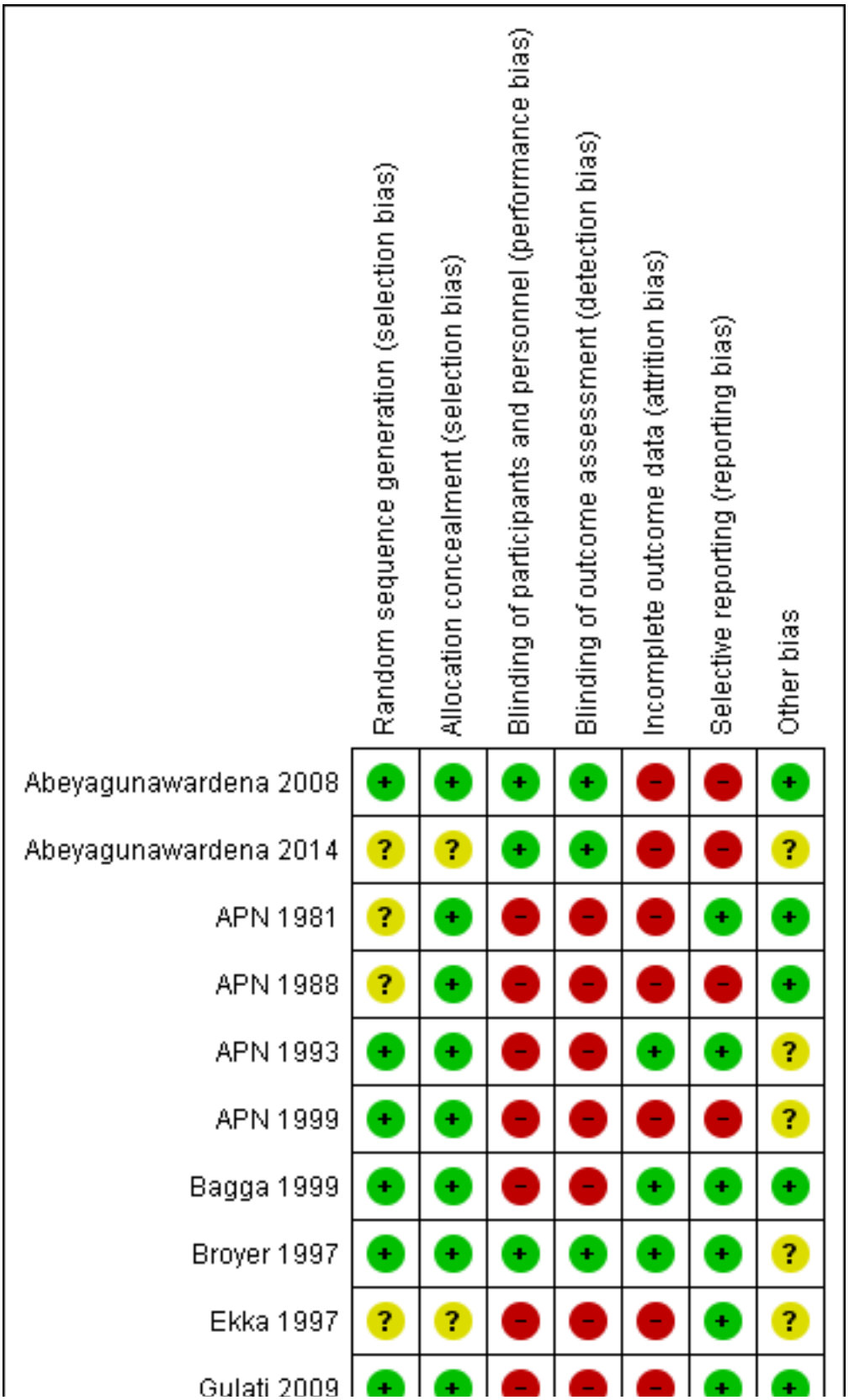
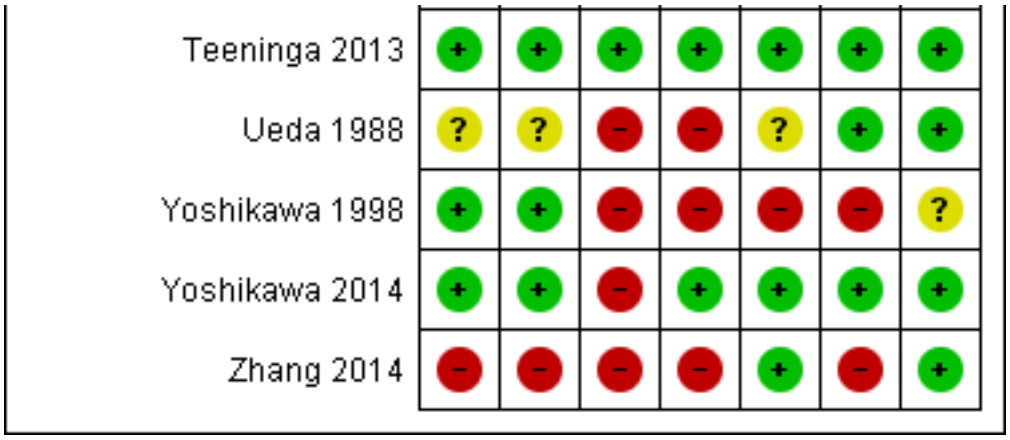


Figure 3. (Continued)

Figure 3. (Continued)



Allocation

Sequence generation was considered to be at low risk of bias in 18 studies (Abeyagunawardena 2008; APN 1993; APN 1999; Bagga 1999; Broyer 1997; Gulati 2009; Hiraoka 2003; Imbasciati 1985; Jayantha 2002a; Jayantha 2002b; Kleinknecht 1982; Liern 2008; Mishra 2012; Sharma 2000; Sinha 2014; Teeninga 2013; Yoshikawa 1998; Yoshikawa 2014), and high risk in six studies (Li 1994; Mattoo 2000; Mocan 1999, Pecoraro 2003; Satomura 2001; Zhang 2014). Sequence generation methods was assessed as unclear in the remaining 10 studies.

Allocation concealment was considered to be at low risk of bias in 16 studies (Abeyagunawardena 2008; APN 1981; APN 1988; APN 1993; APN 1999; Broyer 1997; Gulati 2009; Hiraoka 2003; Imbasciati 1985; Kleinknecht 1982; Liern 2008; Sinha 2014; Teeninga 2013; Yoshikawa 1998; Yoshikawa 2014) and at high risk of bias in eight studies (Ksiazek 1995; Li 1994; Mattoo 2000; Mocan 1999; Norero 1996; Pecoraro 2003; Satomura 2001; Zhang 2014). Ksiazek 1995 stated that parents could influence which treatment group their child was assigned. Allocation concealment methods was assessed as unclear in the remaining 10 studies.

Blinding

Seven studies were considered to be at low risk of performance and detection bias because they were placebo controlled studies (Abeyagunawardena 2008; Abeyagunawardena 2014; Broyer 1997; Leisti 1978; Liern 2008; Sinha 2014; Teeninga 2013). Yoshikawa 2014 was an open-label study but at low risk of detection bias. The remainder were at high risk of both performance and detection bias. Most studies reported the primary outcome of relapse using the ISKDC definition of relapse (ISKDC 1970).

Incomplete outcome data

We assessed 14 studies to be at low risk of attrition bias because they reported fewer than 10% of participants lost to follow-up or excluded from analysis (APN 1993; Bagga 1999; Broyer 1997; Hiraoka 2000; Hiraoka 2003; Imbasciati 1985; Ksiazek 1995; Leisti 1978; Mattoo 2000; Mishra 2012; Sinha 2014; Teeninga 2013; Yoshikawa 2014; Zhang 2014). Fourteen studies considered at high risk of attrition bias because more than 10% of participants were lost to follow-up or excluded from the analysis (Abeyagunawardena 2008; Abeyagunawardena 2014; APN 1981; APN 1988; APN 1999; Ekka 1997; Gulati 2009; ISKDC 1979; Jayantha 2002a; Jayantha 2002b; Mocan 1999; Norero 1996; Sharma 2000; Yoshikawa 1998). The remaining six studies were considered to be unclear risk of attrition bias.

Selective reporting

Studies were deemed to be at risk of reporting bias if outcome data did not include one or more outcomes of frequently relapsing nephrotic syndrome, relapse rate and adverse events. Studies were also considered to be at high risk of bias if data were provided in a format, which could not be entered into the meta-analyses. Cross-over studies were considered to be at high risk of bias if data from the first and second parts of the study were not separable. Sixteen studies were at low risk of reporting bias (APN 1981; APN 1993; Bagga 1999; Broyer 1997; Ekka 1997; Gulati 2009; Hiraoka 2000; Hiraoka 2003; Imbasciati 1985; Jayantha 2002a; Norero 1996; Sharma 2000; Sinha 2014; Teeninga 2013; Ueda 1988; Yoshikawa 2014). There were 16 studies at high risk of selective reporting bias (Abeyagunawardena 2008; Abeyagunawardena 2014; APN 1988; APN 1999; ISKDC 1979; Jayantha 2002b; Kleinknecht 1982; Ksiazek 1995; Leisti 1978; Li 1994; Liern 2008; Mattoo 2000; Mocan 1999; Pecoraro 2003; Yoshikawa 1998; Zhang 2014). Mishra 2012 and Satomura 2001 were assessed to be at unclear risk of selective reporting bias

Other potential sources of bias

Twelve studies were considered at low risk of potential bias as they were funded educational or philanthropic organisations (Abeyagunawardena 2008; APN 1981; APN 1988; Bagga 1999; Gulati 2009; Leisti 1978; Norero 1996; Sinha 2014; Teeninga 2013; Ueda 1988; Yoshikawa 2014; Zhang 2014). One study was considered to be at high risk of bias as it was funded by industry and no full-text publication has been identified 10 years after the first conference abstract (Pecoraro 2003). The remaining 21 studies were deemed unclear of other risk of bias as no information on funding sources was provided.

In Ueda 1988 the calculated total protocol dose (4620 mg/m^2) exceeded the dose administered (3132 ± 417 mg/m^2) suggesting that the protocol was not adhered to in all patients. In three studies (Jayantha 2002a; Ksiazek 1995; Ueda 1988) the numbers of children in the treatment and control groups differed markedly.

Effects of interventions

See: **Summary of findings for the main comparison** Steroid therapy in first episode of nephrotic syndrome: three months of more versus two months for nephrotic syndrome in children; **Summary of findings 2** Steroid therapy in first episode of nephrotic syndrome: five or six months versus three months for nephrotic syndrome in children

Outcome of children in their first episode of SSNS

Three months or more versus two months therapy

The risk of frequently relapsing nephrotic syndrome (FRNS) was significantly lower with prolonged duration of prednisone compared with two months (Analysis 1.1 (6 studies, 582 children): RR 0.68, 95% CI 0.47 to 1.00; I^2 = 36%).

The number of children relapsing by 12 to 24 months and the mean relapse rate/patient/year were significantly lower with prolonged duration of prednisone compared with two months (Analysis 1.2 (8 studies, 741 children): RR 0.80, 95% CI 0.64 to 1.00; I^2 = 66%); Analysis 1.3 (4 studies, 295 children): MD -0.65, 95% CI -1.29 to -0.00; I^2 = 88%). Cumulative prednisone dose did not differ significantly between groups (Analysis 1.4 (3 studies, 245 children): MD 0.71 g/m^2, 95% CI -0.67 to 2.09; I^2 = 60%).

There was medium to high levels of heterogeneity between studies in all analyses.

The heterogeneity was not explained by inclusion/exclusion of patients with steroid-dependent disease, different durations of prednisone (three months versus more than three months) or different definitions of FRNS (ISKDC definition compared with other definitions) (Analysis 1.5).

Subgroup analysis based on risk of bias components (allocation concealment, attrition bias) indicated that there was no significant difference in the risk of FRNS in studies at low risk of bias for allocation concealment (Analysis 1.6.1 (3 studies, 362 children): RR 0.92, 95% CI 0.69 to 1.23; I^2 = 0%). In contrast the risk of FRNS was significantly increased in studies at high or unclear risk of bias for allocation concealment (Analysis 1.6.2 (3 studies, 220 children): RR 0.45, 95% CI 0.26 to 0.77; I^2 = 0%). The data for attrition bias are identical and are not shown. Thus heterogeneity between studies was explained by differences in risk of bias between studies.

Serious adverse events (growth retardation, hypertension, cataracts/glaucoma, psychological disorders, osteoporosis, infections, features of Cushing's Syndrome) were not significantly different between regimens (Analysis 1.7). In Yoshikawa 2014, results were reported as events not patients and are not included in the meta-analyses. The authors reported that frequency and severity of adverse events were similar in both groups.

Five or six months versus three months therapy

There was no significant difference in the risk of FRNS between prednisone treatment for five or six months compared with three months (Analysis 2.1 (5 studies, 591 children): RR 0.78, 95% CI 0.50 to 1.22; I^2 = 67%).

Prednisone given for five to six months significantly reduced the risk of relapse by 12 to 24 months compared with three months (Analysis 2.2 (7 studies, 763 children): RR 0.62, 95% CI 0.45 to 0.85; I^2 = 83%) and the mean relapse rate/patient/year was significantly reduced (Analysis 2.3 (3 studies, 460 children): MD -0.39, 95% CI -0.64 to -0.14; I^2 = 40%). Cumulative prednisone dose did not differ significantly between groups (Analysis 2.4 (3 studies, 460 children): MD -0.47, 95% CI -1.67 to 0.73; I^2 = 85%).

There was medium to high levels of heterogeneity among studies in all analyses.

The heterogeneity was not explained by inclusion/exclusion of patients with steroid dependent disease or different definitions of FRNS (ISKDC definition compared with other definitions) (Analysis 2.5).

Subgroup analysis of the risk for FRNS was performed based on risk of bias for allocation concealment, blinding (performance/detection bias) and attrition. There was no significant difference in the risk of FRNS in studies at low risk of bias for allocation concealment (Analysis 2.6.1 (3 studies, 377 children): RR 1.00, 95% CI 0.74 to 1.34; I^2 = 35%). In contrast the risk of FRNS was significantly increased in studies at high or unclear risk of bias for allocation concealment (Analysis 2.6.2 (2 studies, 14 children): RR 0.36, 95% CI 0.18 to 0.72; I^2 = 0%). Similarly there was no significant difference in the risk of FRNS in studies at low risk of performance/detection bias or attrition bias (Analysis 2.7.1; Analysis 2.8.1) while there was a significant reduction in the risk of FRNS in studies at unclear or high risk of performance/detection bias or attrition bias (Analysis 2.7.2; Analysis 2.8.2). Thus heterogeneity between studies was explained by differences in risk of bias among studies.

Adverse effects did not differ significantly between groups (Analysis 2.9).

One month versus two months therapy

APN 1988 showed that prednisone duration less than the two month regimen resulted in a significantly higher relapse rate at six and 12 months (Analysis 3.1 (1 study, 61 children): RR 1.60, 95% CI 1.01 to 2.54; Analysis 3.2 (1 study, 60 children): RR 1.46, 95% CI 1.01 to 2.12). There was no significant differences in the risk for FRNS (Analysis 3.3) and the cumulative prednisone dose (Analysis 3.4).

Five months versus 12 months therapy

Kleinknecht 1982 showed no evidence that the relapse rate was significantly reduced by giving prednisone for one year compared with five months (Analysis 4.1).

Different total doses of prednisone

Hiraoka 2000 used different total prednisone doses in each group with both groups receiving treatment for three months. The number of children relapsing by 12 months was significantly reduced in children treated with the higher dose (Analysis 5.1 (1 study, 59 children): RR 0.63, 95% CI 0.42 to 0.94). However there was no significant difference in the risk for FRNS (Analysis 5.2 (1 study, 60 children): RR 0.69, 95% CI 0.35 to 1.37). Adverse effects did not differ between groups (Analysis 5.3).

Two month steroid therapy and Sairei-to compared with 4.5 months prednisone and Sairei-to

Yoshikawa 1998 showed no significant difference in relapse rate at two years or in the number of children who relapsed frequently between two months and four and a half months of prednisone

when both groups received the Chinese herb, Sairei-to (Analysis 6.1).

Three month steroid therapy and cyclosporin compared with 3 months prednisone

APN 1999 showed that the addition of cyclosporin to 12 weeks of prednisone therapy reduced the risk for relapse at six months (Analysis 7.1 (1 study, 104 children): RR 0.33, 95% CI 0.33 to 0.83) and at 12 months (Analysis 7.2 (1 study, 104 children): RR 0.72, 95% CI 0.46 to 1.13). The numbers needing cytotoxic therapy were not significantly different between groups (Analysis 7.3 (1 study, 104 children): RR 0.47, 95% CI 0.18 to 1.23). The median time of cumulative sustained remission after completing initial therapy was 22.8 months (95% CI 11.6 to 34) in the cyclosporin/prednisone group and 12.5 months (95% CI 5.9 to 19.1) in the prednisone only group. There was a delay in the time to relapse at six and 12 months but there were no differences at 18 and 24 months. The mean relapse rates/patient at six and 12 months of 0.12 and 0.63 in the cyclosporin/prednisone group were significantly lower than those in the prednisone-only group (0.57 and 1.03) but there was no difference at 18 and 24 months after therapy. Serum creatinine did not differ at the end of follow-up (Analysis 7.4). Temporary hirsutism and gum hypertrophy were seen in 60% and 9% of children given cyclosporin. Psychological disturbances occurred in 27% of cyclosporin-treated patients compared with 14% of patients treated with prednisone alone. Mean systolic and diastolic blood pressures were increased by 10 mmHg and 8 mmHg respectively during cyclosporin therapy.

High dose oral methylprednisolone

Mocan 1999 showed no significant difference in the time to relapse and the relapse rate at one year in patients receiving high dose oral methylprednisolone given over two weeks versus six months of prednisone therapy (Analysis 8.1 (1 study, 15 children): MD -8.10, 95% CI -30.51 to 14.31); Analysis 8.2 (1 study, 15 children): MD 0.00, 95% CI -0.27 to 0.27). However the mean time to remission was significantly shorter in the methylprednisolone group (Analysis 8.3 (1 study, 15 children): MD -7.70, 95% CI -13.24 to -2.16).

Azithromycin and prednisone versus prednisone alone

Zhang 2014 found no significant difference in the risk of relapse by six months between prednisone with azithromycin and prednisone alone (Analysis 9.1).

Outcome of children with frequently relapsing SSNS

Daily prednisone treatment during viral infections

Abeyagunawardena 2008 demonstrated in a cross-over study that daily prednisone administered during an infection significantly reduced the risk of relapse compared with continuing alternate-day prednisone (Analysis 10.1 (1 study, 40 children): RR 0.49, 95% CI 0.18 to 1.30; first part of study).

Gulati 2009 reported a significant reduction in infection related relapses per patient year (Analysis 10.2.1 (1 study, 95 children): MD -0.70, 95% CI -0.87 to -0.53) and in the total number of relapses/patient-year (Analysis 10.2.2 (1 study, 95 children): MD -0.90, 95% CI -1.08 to -0.72) in children receiving daily prednisone during infections compared with alternate daily prednisone.

Mattoo 2000 showed a significant reduction in the total relapse episodes/patient at two years (Analysis 10.3 (1 study, 36 participants): MD -3.30, 95% CI -4.03 to -2.57) in children receiving daily prednisone during infections compared with alternate-day prednisone.

Abeyagunawardena 2014 found in a cross-over study that children with SSNS off prednisone for at least three months had fewer relapses when administered prednisone for five days at the onset of upper respiratory tract infection (URTI) compared with placebo (11 relapses in 113 URTI versus 25 relapses in 101 URTI; P = 0.014). 65.5% of children in the prednisone group had no relapses compared with 40.6% in the placebo group.

Other comparisons of prednisone usage

Nine studies included children with relapsing SSNS (APN 1981; Broyer 1997; Ekka 1997; Imbasciati 1985; ISKDC 1979; Jayantha 2002b; Leisti 1978; Li 1994; Liern 2008) (Table 1).

Alternate-day therapy (APN 1981) was more effective than intermittent therapy in maintaining remission in frequently relapsing children during six months of therapy (Analysis 11.1.1: RR 0.60, 95% CI 0.36 to 1.02) but there was no difference by 12 months (Analysis 11.2.1: RR 1.20, 95% CI 0.93 to 1.55).

Single daily dosing (Ekka 1997) was as effective as multiple daily dosing in maintaining remission in children who relapsed frequently (Analysis 11.2.1: RR 1.07, 95% CI 0.77 to 1.50) with no significant difference in the mean relapse rate/patient (Analysis 11.3.1 (94 children): MD -0.20, 95% CI -0.64 to 0.24). The time to remission did not differ between single and multiple daily dosing patient groups (Analysis 11.6 (2 studies, 138 children): MD 0.04 days, 95% CI -0.98 to 1.06; I^2 = 0%). Serious side effects including hypertension were less common in the single daily dose patients compared with divided dose patients (Analysis 11.7 (2 studies, 138 children): RR 0.41; 95% CI 0.18 to 0.91; I^2 = 0%). In one study, cushingoid features and obesity were less common in the single daily dose group (Li 1994).

Deflazacort (Broyer 1997) significantly reduced the number of children who relapsed during therapy (Analysis 11.2.4 (40 children): RR 0.44, 95% CI 0.25 to 0.78) and reduced the relapse rate among those who relapsed (Analysis 11.3.3 (40 children): MD -1.90, 95% CI -2.77 to -1.03) without significant differences in side effects.

The mean time to relapse in a cross-over study (Liern 2008), comparing alternate-day methylprednisolone with an equivalent dose of deflazacort after the first relapse, was longer in deflazacort treated patients (105 ± 4.19 days) compared with those treated with methylprednisolone (85 ± 3.8 days). There was no differences in the mean time to remission.

Children (ISKDC 1979) relapsed significantly less frequently during treatment on daily prednisone compared with intermittent therapy (Analysis 11.1.2 (50 children): RR 0.20, 95% CI 0.05 to 0.82) but the numbers with relapse (Analysis 11.2.5 (50 children): RR 1.00, 95% CI 0.89 to 1.12) and the mean relapse rate/patient did not differ by nine months after treatment (Analysis 11.3.2 (50 children): MD 0.54, 95% CI -0.50 to 1.58). During treatment the mean time to relapse was significantly longer in children treated with daily prednisone (Analysis 11.4.2 (50 children): MD 1.79, 95% CI 0.90 to 2.68).

Remission rate at one year was not significantly different between children who received intravenous methylprednisolone during induction and those who received oral prednisone only (Imbasciati 1985) (Analysis 11.2.3 (64 children): RR 1.06, 95% CI 0.75 to 1.53) but the total dose of oral prednisone administered was higher in the control group than in the group receiving intravenous prednisone.

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%) ($Chi^2 = 4.0$, 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 six months (Analysis 12.1.1 (90 children): RR 0.04, 95% CI 0.01 to 0.25), 12 months (Analysis 12.1,2 (76 children): RR 0.43 95% CI 0.29 to 0.65), two years (Analysis 12.1.3 (64 children): RR 0.60, 95% CI 0.45 to 0.80) and three years (Analysis 12.1.4 (53 children) RR 0.71, 95% CI 0.56 to 0.90) compared with standard duration therapy (Jayantha 2002b). The relapse rate/patient/year excluding patients who became steroid dependent was reduced at one (Analysis 12.2.1 (72 children): MD-1.78, 95% CI -2.30 to -1.26), two (Analysis 12.2.2 (56 children): MD -1.79, 95% CI -2.39 to -1.19) and three years (Analysis 12.2.3 (41 children): MD-1.74, 95% CI -2.39 to -1.09) after treatment and the number of children who developed steroid dependence or relapsed frequently by one year was reduced (Analysis 12.3 (72 children): 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 (Analysis 12.4.1 (72 children): MD 0.59 g/kg, 95% CI 0.02 to 1.16) in the long treatment group but did not differ at two (Analysis 12.4.2 (56 children): MD -0.32 g/kg, 95% CI -1.52 to 0.88) and three years (Analysis 12.4.3: MD -1.13 g//kg, 95% CI -3.08 to -0.82). Hypertension was more common in the long duration group but the difference was not statistically significant (Analysis 12.5.1 (72 children): RR 2.40, 95% CI 0.86 to 6.73); the number of children with growth failure did not differ between groups (Analysis 12.5.2 (72 children): RR 1.24, 95% CI 0.62 to 2.50).

DISCUSSION

Summary of main results

We added 10 studies to this 2015 update to bring the total number of included studies to 34 enrolling 3033 children. Analysis of data from three studies has led to the new conclusion that in studies at low risk of bias, there is no significant difference in the risk for FRNS between two and three months of prednisone and more than three months of prednisone in the initial episode of SSNS. Data from three other studies increased the evidence base to support administering prednisone or increasing the dose during URTI to reduce the risk of relapse in children with FRNS.

Prednisone in the first episode of SSNS

Our initial review in 2000 demonstrated that prednisone administered for three months or more significantly reduced the risk of relapse by 12 to 24 months and of FRNS compared with two months in the initial episode of SSNS. Increasing the duration of prednisone up to seven months increased the benefit obtained. It was unclear whether the increase in benefit was related to increased duration or increased dose though indirect analyses suggested that duration was more important than dose. However it was also noted that some included studies in the analyses were at unclear or high risk of bias. In the 2003 and 2005 updates, additional studies were identified which reported that six months of prednisone significantly reduced the risk of relapse compared with three months. In clinical practice, paediatric nephrologists tended to use increasing durations of prednisone in the initial episode of nephrotic syndrome though considerable variation existed between physicians reflecting in part the poor quality of the evidence from randomised studies (MacHardy 2009; Samuel 2013).

This 2015 update included three large, well designed studies (Sinha 2014; Teeninga 2013; Yoshikawa 2014) comparing different durations of prednisone. In Teeninga 2013 children received the same total dose of prednisone administered over three or six months, however children included in Sinha 2014 and Yoshikawa 2014 received a higher total dose of prednisone in the six months treatment group compared with the shorter treatment group. Inclusion of these studies in meta-analyses showed that the risk of relapse by 12 to 24 months and of FRNS continued to favour extended duration of prednisone except for the analysis of FRNS in the comparison of five to six months with three months of prednisone. However there was considerable heterogeneity between studies with I^2 results varying between 36% and 83%. Subgroup analysis stratified for the risk of bias domains showed that studies at low risk of bias for allocation concealment, attrition bias and performance/detection bias found no significant differences in the risk of relapse by 12 to 24 months or FRNS between two to three months of prednisone and three to seven months. Studies at high risk of bias on the other hand showed significant benefits of increasing treatment duration. Therefore studies of long versus shorter duration corticosteroids have heterogeneous treatment effects, with the older high risk of bias studies tending to over-estimate the effect of longer course therapy, compared with more recently published low risk of bias studies. Among studies at low risk of bias, there was no significant difference in the risk for FRNS between prednisone given for two to three months and longer durations or total dose of therapy indicating that there is no benefit of increasing the duration of prednisone beyond two to three months in the initial episode of SSNS. A study comparing two months with four months of prednisone is currently underway in Europe (PREDNOS Study 2013).

Prednisone in relapsing SSNS

Daily prednisone during viral infections compared with alternate-day prednisone therapy reduced the rate of relapse. Three additional larger studies of improved methodological quality have increased the power of this analysis so that this management may be considered for children with frequently relapsing SSNS, who are already receiving alternate-day prednisone. Preliminary data from a fourth study suggests that daily prednisone during URTI reduces the risk of relapse in children not receiving prednisone. A further

study addressing this question is currently underway in Europe (PREDNOS 2 Study 2014).

Overall completeness and applicability of evidence

This review includes studies evaluating corticosteroid therapy and nephrotic syndrome, with the majority of studies focusing on therapy for the initial presentation of nephrotic syndrome. Three additional well designed studies involving 562 children has led to the change in conclusions for this review so that the optimum duration of prednisone is suggested to be two or three months of prednisone in the initial episode of SSNS rather than longer durations as argued in previous versions of this review.

There remain few data on the treatment of relapsing nephrotic syndrome with prednisone. In particular there are no studies addressing the use of long term alternate-day corticosteroid therapy to maintain remission in children with frequently relapsing nephrotic syndrome although this management is widely recommended in guidelines (KDIGO 2012).

Adverse effects of medications were either not reported or there was limited reporting in studies. Among 16 studies evaluating increased duration or dose in the initial episode of SSNS, hypertension, ophthalmological disorders and Cushing's syndrome were reported in 12, 11 and eight studies respectively. Prednisone therapy is known to be associated with significant behavioural and psychological adverse effects (Mishra 2010; Neuhaus 2010). However only seven of these studies reported this outcome and no studies reported data on quality of life for the child or their family. Adverse effects of medications were reported in more detail in the three well designed studies published in 2013 and 2014 (Sinha 2014; Teeninga 2013; Yoshikawa 2014).

The studies included the major ethnic groups, but there are few separable data for African-American or African children. These groups of children, who are known to have a higher incidence of initial and late steroid-resistant nephrotic syndrome (Kim 2005; Gipson 2011), may show different responses in studies of increased dose or duration of prednisone.

Quality of the evidence

Of the 34 studies included, only 18 (53%) and 16 studies (47%) revealed adequate random sequence generation and allocation concealment respectively. In part this may be due to suboptimal reporting of these parameters in earlier studies. However some studies published recently failed to provide adequate information on these parameters. Blinding of participants, investigators and outcome assessors was only reported in seven (21%) studies. Studies without blinding were considered at high risk of bias because knowledge of treatment groups could influence both patient management and reporting of remission and relapse by urinalyses. Both attrition bias (incomplete reporting of outcome data) and reporting bias (selective outcome reporting) were at low risk of bias in fewer than 50% of studies. Studies with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30% to 40% (Schulz 1995) and meta-analyses of low quality studies may overestimate the benefit of therapy (Moher 1998). Addition of recently published well designed studies resulted in significant heterogeneity in the primary efficacy outcomes (relapse, FRNS) in studies assessing the duration of prednisone for the initial episode of SSNS. Subgroup analyses of these studies demonstrated that older studies at higher risk of bias overestimated the benefit of increased duration of prednisone while newer studies at low risk of bias found no significant benefit of prolonging prednisone beyond two to three months in the initial episode of nephrotic syndrome resulting in changed conclusions for this review.

In summary of finding tables (Summary of findings for the main comparison; Summary of findings 2) for comparisons of two months with three months or more, and of three months with five or six months in the first episode of SSNS, the overall quality of studies was considered low for efficacy outcomes because of a high risk of bias in some studies and heterogeneity between studies. When studies with the outcome of FRNS were separated into subgroups according to risk of bias for allocation concealment, the quality of the evidence was considered high for studies at low risk of allocation concealment and moderate for studies at high or uncertain risk of bias of allocation concealment. The quality of studies for the adverse effects was considered moderate or low because of inclusion of some poor quality studies and few included studies.

Only 15/34 studies were included in the summary of findings tables and all compared treatment regimens in the first episode of nephrotic syndrome. The remaining studies were single studies or data could not be included in the meta-analyses.

Potential biases in the review process

A detailed search using the Cochrane Renal Group's Specialised Register was completed in February 2015. The Renal Register contains conference abstracts as well as published studies and there is no language restriction. This minimised the risk that eligible studies were omitted, although more recently published eligible studies and eligible studies in some congress proceedings not searched could have been missed. There were 10 (29%) included studies that were only available in abstract form with limited information on study methods and outcomes. Failure to include these studies could result in overestimation of treatment effect since it is known that negative studies are less likely to be published or may be published later than positive studies (Hopewell 2007). Alternately, some authors have argued that inclusion of these studies could result in overestimation of treatment effect through selective outcome reporting and incomplete reporting of the number of patients completing follow-up (Egger 2001).

Many studies were small and had incomplete information on study methods and results and further results particularly of older studies could not be obtained despite contacting authors. Of the 34 included studies 19 were published in 2000 or earlier - before the CONSORT checklist first published in 1996 would be likely to influence study methodology and reporting (Moher 2001).

This was an extensive review; each step was completed independently by at least two authors thus minimising risks of errors in determining study eligibility, data extraction and risk of bias assessment and data synthesis.

Agreements and disagreements with other studies or reviews

New studies at low risk of bias included in this review indicate that there is no significant benefit of treating children for more than two to three months in the initial episode of SSNS. The KDIGO 2012

and other country based guidelines (Gipson 2009; Haute Autorité de Santé 2008; IPNG-IAP 2008) recommend treatment with three months or more of prednisone for the initial episode of SSNS.

In support of the KDIGO guidelines (KDIGO 2012), this review identified four studies showing that increasing prednisone administration from alternate-day to daily or giving prednisone to children not on prednisone at the onset of an intercurrent viral infection reduces the risk of relapse.

This review did not identify any RCTs evaluating the use of prolonged courses of alternate-day prednisone to reduce the risk for relapse in children with frequently relapsing nephrotic syndrome although guidelines (Gipson 2009; Haute Autorité de Santé 2008; IPNG-IAP 2008; KDIGO 2012) have recommended this practice.

The listed guidelines and narrative reviews (Greenbaum 2012) emphasise the use of non-corticosteroid immunosuppressive medications in children with frequently relapsing or steroid dependent disease. These medications are the subject of another Cochrane systematic review (Pravitsitthikul 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Prolongation of prednisolone therapy beyond two to three months in the initial episode of SSNS does not reduce the risk of relapse in studies at low risk of bias whether the same total dose of prednisone is used for short and long durations or whether the total dose of prednisone is increased with longer durations of treatment. The results of a further well designed study evaluating different durations and therefore total doses of prednisone are awaited (PREDNOS Study 2013).

Daily prednisone therapy during an upper respiratory infection or other infection reduces the risk of relapse compared with continuing alternate-day prednisone or no prednisone.

During daily therapy, prednisone is as effective when administered as a single daily dose compared with divided doses.

Implications for research

We now know that administering prednisone over six months rather than two or three months does not reduce the risk of relapse or of developing frequently relapsing disease. However all studies evaluating the duration of prednisolone have used similar daily and alternate daily doses of prednisolone based on the empirical regimens established by ISDKC and Arbeitsgemeinschaft für Pädiatrische Nephrologie in the 1970s and 1980s so we still do not know whether the same results could be obtained with lower total doses of prednisolone.

Adverse events including hypertension, ophthalmological disorders and behavioural or psychological effects are poorly reported. Recently published studies have provided additional information on adverse effects. The results of the PREDNOS Study 2013 comparing eight weeks with 16 weeks of prednisone will include a detailed assessment of the behavioural effects of prednisone.

Further RCTs are required to evaluate different durations of alternate-day prednisone regimens in children with frequently relapsing SSNS as prolonged alternate-day prednisone is recommended in current guidelines although there are no RCT data to support this recommendation.

Four RCTs from emerging countries have shown that daily prednisone administered during an intercurrent infection reduces the risk of relapse. A further well designed RCT is currently assessing this intervention in European children, where the pattern of intercurrent infections may be different (PREDNOS 2 Study 2014).

There is some 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 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. Studies including the use of ACTH in comparison with prednisone may also be of benefit.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abeyagunawardena 2008

Methods	• Study design: cross-over RCT • Time frame: July 2003 to January 2005. Study continued until 40 children had 2 URTIs • Duration of follow-up: until child had 2 URTI
Participants	• Country: Sri Lanka • Setting: single tertiary referral centre • Inclusion criteria: children aged 1 to 16 y with FRNS receiving maintenance low dose (0.1 to 0.6 mg/kg) alternate-day oral prednisolone • Number: 40 • Median age (range): 5.3 years (1.5 to 13.2) • Sex (M/F): 29/11 • Exclusion criteria: glucocorticoid related side effects; frequent relapses requiring steroid sparing agents, did not have two viral infections within study period, sustained remission with disease stability
Interventions	Treatment group • Prednisolone 5 mg daily for 7 days at onset of viral infection Control group • Placebo daily for 7 days Randomised at onset of URTI to receive one of the interventions. At next URTI received alternate therapy
Outcomes	• Number relapsing during 6 months of therapy and in subsequent 6 months • Mean relapse rate during treatment and in subsequent 6 months
Notes	• Definitions * FRNS: 2+ relapses within 6 months of first response or 4 relapses in any 1 year (ISKDC definition) * Relapse: urine protein excretion 3+ or more on urinalysis for 3 consecutive days in patient who had previously been in remission * Remission: urinary protein excretion negative or trace on urinalysis for 3 consecutive days * URTI: presence of 3 or more of the following criteria - cough, runny nose, sore throat, lethargy, body aches and fever

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated, sealed envelopes, sequential patients
Allocation concealment (selection bias)	Low risk	Randomly allocated, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and parents blinded to contents of containers
Blinding of outcome assessment (detection bias)	Low risk	Investigators and parents blinded to contents of containers

Abeyagunawardena 2008 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	8/48 excluded from study (17%) for need for additional immunosuppression (4), no second viral infection (3), number without further relapses (1)
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded; no mention of adverse events
Other bias	Low risk	The study appears to be free of other source of bias

Abeyagunawardena 2014

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Country: Sri Lanka • Setting: tertiary referral university centre • Inclusion criteria: children with FRNS off prednisone for 3 months • Number: 48 • Mean age ± SD (years): treatment group (12.0 ± 2.4); control group (10.0 ± 2.9) • Sex: not reported • Exclusion criteria: children with SSNS receiving alternate-day prednisone
Interventions	Treatment group • Prednisolone 0.5 mg/kg/d for 5 days at start of each URTI for 12 months and then crossed over to control group Control group • Placebo for 5 days at start of each URTI for 12 months and then crossed over to treatment group
Outcomes	• Number of relapses associated with URTI in each year
Notes	• Abstract only • Definitions of SDNS, URTI and relapse not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised
Allocation concealment (selection bias)	Unclear risk	Said to be randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo administered to control group

Abeyagunawardena 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo administered to control group
Incomplete outcome data (attrition bias) All outcomes	High risk	15/48 (31%) did not complete both parts of the 2 year cross-over study
Selective reporting (reporting bias)	High risk	No report of adverse effects; cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses
Other bias	Unclear risk	Abstract only; no information provided

APN 1981

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 12 months
Participants	• Country: northern Europe • Setting: multicentre, renal clinics • Inclusion criteria: children with FRNS • Number (analysed/randomised): treatment group 1 (23/30); treatment group 2 (25/34) • Mean age ± SD (months): treatment group 1 (88.5 ± 33.0); treatment group 2 (101.3 ± 35.1) • Sex (M/F): treatment group 1 (15/8); treatment group 2 (18/7) • Exclusion criteria: not reported
Interventions	Treatment group 1 (alternate) • Prednisone: 60 mg/m^2/d till protein free for 3+ days; then 35 mg/m^2 on alternate days • Total duration: 6 months Treatment group 2 • Prednisone: 60 mg/m^2/d till protein free for 3+ days; then 40 mg/m^2 given on 3/7 consecutive days • Total duration: 6 months
Outcomes	• Number relapsing during 6 months of therapy and in subsequent 6 months • Mean relapse rate during treatment and in subsequent 6 months
Notes	• Definitions * FRNS: 2+ relapses within 6 months of first response or 4 relapses in any 1 year (ISKDC definition) * Relapse: urine protein > 40 mg/m^2/h for 3 consecutive days (ISKDC) * Remission: urinary protein < 4 mg/m^2/h for 3 consecutive days (ISKDC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Low risk	Sealed envelopes provided to each centre. "One opened when patient qualified to enter the study"

APN 1981 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding no mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	16/64 withdrawn: steroid toxicity (8); incorrect treatment or uncooperative parents (6); late non-response (1); one patient unaccounted for in the text
Selective reporting (reporting bias)	Low risk	Recorded the review's pre-specified outcomes (number with relapse, frequency of relapses, adverse events)
Other bias	Low risk	Supported by grants from the VW Foundation

APN 1988

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 2 years
Participants	• Country: northern Europe • Setting: multicentre, renal clinics • Inclusion criteria: children with initial episode SSNS • Number: treatment group 1 (32); treatment group 2 (29) • Age range: 2 to 16 years • Sex (M/F): not reported • Exclusion criteria: parents. previous treatment with corticosteroids or immunosuppressive agents; any contraindications to corticosteroid therapy
Interventions	Treatment group 1 (4weeks) • Prednisone: 60 mg/m^2/d till urine protein-free for 3 days then 40 mg/m^2 on alternate days till albumin > 35 g/L • Total duration: about 1 month Treatment group 2 (8 weeks) • Prednisone 60 mg/m^2/d for 4 weeks and then 40 mg/m^2 on alternate days for 4 weeks • Total duration: 2 months
Outcomes	• Number of patients with/without relapse at 6 months and 1 year after completing daily prednisone • Number relapses/patient/y • Time to first relapse • Number becoming frequent relapsing patients • Number with serious adverse events
Notes	• Complete one year follow-up

APN 1988 *(Continued)*

- Definitions
  - * FRNS using ISKDC definition
  - * Relapse: ISKDC definition
  - * Remission: ISKDC definition with albumin ≥ 35 g/L

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Low risk	"Central random allocation" reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	"77 patients were initially recruited into the trial, but 16 had to be removed at an early stage due to steroid resistance (8), or early deviations from the treatment protocol (8)" "34 patients completed the study for the full 2 years. Data for the other 27 patients were included for the period that they remained in the study protocol. Of the 27, 5 patients of the short-course group and 4 from the standard group were removed when they required other immunosuppressive agents; 2 patients from each group left the country during the course of the study; 7 children from the short-course group, and 3 from the standard group, were lost to follow-up due to failure of continuous parental cooperation; and late treatment faults were observed in 3 cases after short-course treatment, and in 1 patient after standard therapy. The full course was completed by 15 patients receiving the short course and by 19 receiving standard treatment."
Selective reporting (reporting bias)	High risk	Did not report all the review's pre-specified outcomes. No report on number of FRNS
Other bias	Low risk	Supported by grants from the VW Foundation

APN 1993

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 2 years
Participants	• Country: northern Europe • Setting: multicentre, renal clinics • Inclusion criteria: children with initial episode SSNS • Number: treatment group 1 (34); treatment group 2 (37) • Median age, range (years): treatment group 1 (3.9, 1.5 to 8); treatment group 2 (4.4, 1.5 to 14)

APN 1993 *(Continued)*

	• Sex (M/F): not reported • Exclusion criteria: previous treatment with corticosteroids or immunosuppressive agents; contraindications to corticosteroid therapy
Interventions	Treatment group 1 (3 months) • Prednisone: 60 mg/m^2/d for 6 weeks and then 40 mg/m^2 on alternate days for 6 weeks • Total duration: 3 months Treatment group 2 (2 months) • Prednisone: 60 mg/m^2/d for 4 weeks and then 40 mg/m^2 on alternate days for 4 weeks • Total duration: 2 months
Outcomes	• Number of patients with/without relapse by 6 and 12 months after completing daily and alternate-day prednisone • Number becoming frequent relapsers • Number of serious adverse events
Notes	• Complete one year follow-up • Definitions * FRNS: ISKDC definition * Relapse: ISKDC definition * Remission: ISKDC definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central random allocation
Allocation concealment (selection bias)	Low risk	Central random allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	7.7% excluded for protocol violation. This proportion of missing outcomes are not sufficient to impact results
Selective reporting (reporting bias)	Low risk	Reported the review's pre-specified outcomes
Other bias	Unclear risk	Insufficient information to assess

APN 1999

Methods	• Study design: parallel RCT

APN 1999 *(Continued)*

	• Time frame: NS • Follow-up period: 2 years
Participants	• Country: northern Europe • Setting: multicentre tertiary services • Inclusion criteria: children aged 1 to 16 y; first episode of SSNS (albumin < 25 g/L, proteinuria > 40 mg/kg/h); GFR > 68 mL/min/1.73 m^2 • Number (analysed/randomised): treatment group 1 (49/62); treatment group 2 (55/65) • Mean age ± SD (years): treatment group 1 (5.1 ± 2.8); treatment group 2 (5.6 ± 3.2) • Sex (M/F): not reported • Exclusion criteria: SRNS; post infectious glomerulonephritis; secondary nephrotic syndrome; no previous steroids/immunosuppressives, no contraindication to these

Interventions	Treatment group 1
	• CSA: 150 mg/m^2/d for 8 weeks; dose altered to achieve levels 80 to 150 ng/mL
	• Prednisone: 60 mg/m^2/d for 6 weeks; 40 mg/m^2 on alternate days for 6 weeks
	  * Total duration: 12 weeks
	Treatment group 2
	• Prednisone 60 mg/m^2/d for 6 weeks; 40 mg/m^2 on alternate days for 6 weeks
	  * Total duration 12 weeks

Outcomes	• Number of patients with relapse and mean relapse rate at 6, 12 months • Median time to relapse • Number needing cytotoxic agents • Adverse effects of CSA • ISKDC and APN definitions of remission/relapse used • Cumulative steroid dose • Adverse effects
Notes	• Stop or end point/s: need for CPA treatment • Additional data requested from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Co-ordinating centre, centrally allocated
Allocation concealment (selection bias)	Low risk	Centrally allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	152 randomised, 25 withdrew consent (127 entered study)

APN 1999 *(Continued)*

		CSA/prednisone group: 13/62 (17%) excluded (SRNS (7), Infection (3), thrombosis (2), protocol deviation (1)) Prednisone group: 10/65 (15%) excluded (infection (1), SRNS (7), protocol deviation (1), unstated (1))
Selective reporting (reporting bias)	High risk	Not all of review's pre-specified outcomes have been reported. No report on number of frequently relapsing nephrotic syndrome (FRNS). Adverse events and outcomes in reported in percentages
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Bagga 1999

Methods	• Study design: parallel RCT • Time frame: September 1992 to June 1995 • Follow-up: minimum of 1 year from completion of initial therapy
Participants	• Country: India • Setting: renal clinic • Inclusion criteria: children aged 1 to 12 y with first episode SSNS • Number (analysed/randomised): treatment group 1 (22/24); treatment group 2 (23/27) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: received corticosteroids or immunosuppressive agents; showing features of an underlying systemic disease (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura, amyloidosis, vasculitis, and hereditary glomerular diseases); haematuria (> 5 red cells/high-power field of a centrifuged specimen); persistent hypertension (blood pressure more than the 95th percentile for height for age on three or more occasions); CrCl < 80 mL/min/1.73 m^2
Interventions	Treatment group 1 (4 months) • Prednisolone: 2 mg/kg/d for 4 weeks, 1.5 mg/kg/d for 4 weeks then 1.5 mg/kg alternate days for 4 weeks, 1 mg/kg alternate days for 4 weeks • Total duration: 4 months Treatment group 2 (2 months) • Prednisolone: 2 mg/kg/d for 4 weeks then 1.5 mg/kg on alternate days for 4 weeks • Total 2 months
Outcomes	• Number of patients with/without relapse by 6 and 12 months after completing daily and alternate-day prednisolone • Number becoming frequent relapsers • Relapse rate/patient/year; mean time to first relapse • Number of serious adverse events • Cumulative steroid dose

Notes	• Complete one year follow-up
	• Definitions
	  * FRNS: 2+ relapses in 6 months or 3+ within 12 months of initial episode
	  * Relapse: 3+ protein on dipstick for 3 consecutive days
	  * Remission: nil or trace of protein on dipstick for 3+ consecutive days

Bagga 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Information from author that sequence generation was random
Allocation concealment (selection bias)	Low risk	Information from author that allocation occurred after child had entered study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal/lost to follow-up: 6/51; steroid resistance (4); poor compliance (2)
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported
Other bias	Low risk	Research grant from the All India Institute of Medical Sciences, New Delhi, India. The study appears to be free of other source of bias

Broyer 1997

Methods	• Study design: parallel RCT • Time period: not reported • Follow-up: 1 year
Participants	• Country: France • Setting: multicentre, renal clinics • Inclusion criteria: children with SDNS (2+ relapses in 12 months despite alternate-day prednisone or within 2 months of stopping this regimen). • Number: treatment group 1 (20); treatment group 2 (20) • Mean age ± SD (years): treatment group 1 (9.2 ± 2.7); treatment group 2 (8.5 ± 4) • Sex (M/F): treatment group 1 (15/5); treatment group 2 (17/3) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Deflazacort: dose equivalent to prednisone of 60 mg/m^2/d till in remission for 5 days then 60 mg/m^2 on alternate days for 6 weeks, taper 6 to 8 weeks then 15 to 20 mg/m^2 on alternate days for 1 year Treatment group 2 • Prednisone given as above
Outcomes	• Number relapsing during 1 year of therapy • Mean relapse rate/patient

Broyer 1997 *(Continued)*

	• Serious adverse events

Notes	• Six children in treatment group and 5 in control group also received cyclosporin
	• Definitions
	  * Relapse: not reported
	  * Remission: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Blocks of 10 packages containing equal numbers of each intervention in order determined by random code"
Allocation concealment (selection bias)	Low risk	"Block randomisation and sealed packages, lots of 10"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured. "Medication in identical bottles and identical tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured. "Blinded until end of study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal/lost to follow-up: 2/40 (loss to follow-up (1); protocol treatment deviation (1))
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported (cannot report on SDNS, as all remained on steroids as per protocol).
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Ekka 1997

Methods	• Study design: parallel RCT • Time frame: December 1993 to June 1995 • Follow-up: 9 months
Participants	• Country: India • Setting: renal clinic • Inclusion criteria: children aged 1.3 to 17 y with relapsing SSNS • Number (analysed/randomised): treatment group 1 (47/52); treatment group 2 (48/54) • Mean age ± SD (years): treatment group 1 (5.6 ± 2.8); treatment group 2 (6.6 ± 3.4) • Sex (M/F): treatment group 1 (32/15); treatment group 2 (31/16) • Exclusion criteria: received corticosteroids or other immunosuppressive drugs for treatment of the current relapse; steroid resistance or dependence
Interventions	Treatment group 1 (single dose) • Prednisolone: 2 mg/kg/d for 2 to 4 weeks given as single morning dose and then 1.5 mg/kg on alternate days for 4 weeks

Ekka 1997 *(Continued)*

	Treatment group 2 (divided dose) • Prednisolone: 2 mg/kg/d for 2 to 4 weeks given as 3 divided doses and then 1.5 mg/kg on alternate days for 4 weeks
Outcomes	• Number 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
Random sequence generation (selection bias)	Unclear risk	"Randomised " - insufficient information about sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal/lost to follow-up: 12/106; did not report for follow-up (11); steroid resistant (1)
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Gulati 2009

Methods	• Study design: parallel RCT • Time frame: September 2006 to October 2009 • Duration of follow-up: 24 months
Participants	• Country: India • Setting: single tertiary centre • Inclusion criteria: children aged 1 to 16 y with FRNS, eligible for prednisone therapy ± levamisole; levamisole given to those requiring > 1 mg/kg prednisolone on alternate days, who had ≥ 1 feature of steroid toxicity • Number (analysed/randomised): treatment group 1 (49/50); treatment group 2 (46/50) • Mean age ± SD (months): treatment group 1 (78.5 ± 35.6); treatment group 2 (81.7 ± 38.7) • Sex (M/F): treatment group 1 (35/15); treatment group 2 (32/18)

Gulati 2009 *(Continued)*

	• Exclusion criteria: impaired renal function (SCr > 1.2 mg/dl), immunosuppressives other than oral prednisone in preceding 6 months; steroid threshold > 1 mg/kg on alternate days to maintain remission with more than one feature of steroid toxicity, e.g. cataracts; BMI > 95th percentile for age; stage 2 hypertension
Interventions	Treatment group 1 • Existing prednisolone alternate-day dose increased to a daily dose for 7 days at onset of viral infection Treatment group 2 • Prednisolone continued at same alternate-day dose at onset of viral infection
Outcomes	• Rates of infection-associated relapses expressed as episodes/patient year • Total number of relapses/patient-year • Frequency and types of infection • Cumulative dose of prednisone received in both groups
Notes	• Definitions * FRNS: at least 2 relapses in 6 months, or > 3 relapses in 12 months * Viral infection: one or more of fever, rhinorrhoea or cough, diarrhoea * Infection related relapse: presence of 3+ to 4+ proteinuria for 3 consecutive days occurring in the week after 7 days of onset of an infective illness * Remission: trace/negative protein for 3 consecutive days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation. "randomised by stratified randomisation" on basis of therapy with or without levamisole
Allocation concealment (selection bias)	Low risk	"allocation was concealed with opaque sealed envelopes opened at inclusion"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	11/100 (11%) patients excluded or lost to follow-up; lost to follow-up (5), discontinued treatment (6)
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported
Other bias	Low risk	Funded by the Indian Council of Medical Research. CTRI/2008/091/000245

Hiraoka 2000

Methods	• Study design: parallel RCT

Hiraoka 2000 *(Continued)*

	• Time frame: December 1993 to August 1996 • Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre, renal clinics • Inclusion criteria: children with initial episode of SSNS. Eight excluded because steroid resistant • Number (analysed/randomised): treatment group 1 (30/34); treatment group 2 (29/34) • Mean age ± SD (years): treatment group 1 (6.4 ± 3.4); treatment group 2 (7.1 ± 4.0) • Sex (M/F): treatment group 1 (21/13); treatment group 2 (21/13) • Exclusion criteria: not reported
Interventions	Treatment group 1 (high dose) • Prednisolone: 60 mg/m^2/d (max 80 mg) for 6 weeks, 40 mg/m^2 on alternate days for 6 weeks • Total duration: 3 months Treatment group 2 (standard) • Prednisolone: 40 mg/m^2/d (max 60 mg) for 6 weeks, 40 mg/m^2 on alternate days for 6 weeks • Total duration: 3 months
Outcomes	• Number relapsing at 6 months and 12 months • Number with frequent relapses • Adverse effects
Notes	• Definitions * Relapse: Urine protein 2+ for 3 days. * Remission: Urine protein < 4 mg/h/m^2 for 3 days or more

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated " - insufficient information about sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data Withdrawal/lost to follow-up: 8/68 excluded for steroid resistance
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Hiraoka 2003

Methods	• Study design: parallel RCT • Time frame: August 1996 and May 1999 • Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre renal clinics • Inclusion criteria: children with initial episode of SSNS • Number (analysed/randomised): treatment group 1 (36/38); treatment group 2 (34/35) • Mean age ± SD (years): treatment group 1 (7.6 ± 4.5); treatment group 2 (7.4 ± 4.4) • Sex (M/F): treatment group 1 (25/13); treatment group 2 (22/13) • Exclusion criteria: not reported
Interventions	Treatment group 1 (long duration) • Prednisolone: 60 mg/m^2/d (max 80 mg) for 4 weeks; 60 mg/m^2 (max 80 mg) on alternate days for 4 weeks and reducing by 10 mg/m^2 each month • Total duration: 28 weeks • Total calculated dose: 4620 mg/m^2 Treatment group 2 (standard duration) • Prednisolone: 60 mg/m^2/d for 6 weeks (max 80 mg); 40 mg/m^2 (max 60 mg) on alternate days for 6 weeks • Total duration: 12 weeks • Total calculated dose: 3360 mg/m^2
Outcomes	• Number relapsing at 6, 12 and 24 months • Number with FRNS • Adverse effects

Notes	• Definitions
	  * Relapse: urine protein 2+ for 3 days
	  * Remission: urine protein < 4 mg/h/m^2 for 3 days or more

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated" - sealed envelopes
Allocation concealment (selection bias)	Low risk	"Simple randomisation using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding

Hiraoka 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal/ lost to follow-up: 3/73; steroid resistance (3)
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Imbasciati 1985

Methods	• Study design: parallel RCT • Time frame: June 1980 to June 1983 • Follow-up: 12 to 24 months
Participants	• Country: Italy • Setting: multicentre, renal clinics • Inclusion criteria: children aged 2 to 14 y with either initial episode SSNS or no relapse in previous year • Number (analysed/randomised): treatment group 1 (33/44); treatment group 2 (34/45) • Median age, range (years): treatment group 1 (9, 2 to 54); treatment group 2 (8, 2 to 56) • Sex (M/F): treatment group 1 (29/15); treatment group 2 (31/14) • Exclusion criteria: evidence of underlying systemic disease, neoplasia, viral hepatitis, or exposure to drugs or toxic agents known to induce the nephrotic syndrome; treated with steroids or cytotoxic agents within one year before admission
Interventions	Treatment group 1 • Methylprednisolone: 20 mg/kg IV for 3 days, prednisone 20 mg/m^2/d for 4 weeks, 20 mg/m^2 on alternate days for 4 weeks then 20 mg/m^2 on alternate days for 4 months • Total duration: 6 months Treatment group 2 • Prednisone: 60 mg/m^2/d for 4 weeks, 40 mg/m^2 on alternate days for 4 weeks and 20 mg/m^2 on alternate days for 4 months • Total duration: 6 months
Outcomes	• Number with/without relapse during 12-24 months follow-up • Mean relapse rate/patient/year

Notes	• Adults also in study. Some end points not separated for children so not examined
	• Definitions
	  * Relapse: ISKDC
	  * Remission: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned from a table with random numbers"
Allocation concealment (selection bias)	Low risk	Central randomisation centre

Imbasciati 1985 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. All 89 randomised patients followed for 12-24 months
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

ISKDC 1979

Methods	• Study design: parallel RCT • Time frame: 20 September 1973 to 26 August 1976 • Follow-up: at least 8 months
Participants	• Country: USA and Northern Europe • Setting: multicentre, renal clinics • Inclusion criteria: children aged 3 mo to 15 y with SSNS within 6 months of their initial response to steroid therapy • Number (analysed/randomised): treatment group 1 (28/32); treatment group 2 (26/32) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: proteinuria ≤ 40 mg/h/m^2; hypoalbuminaemia ≥ 2.5 g/dL at the onset of their disease; prior treatment with steroids or other cytotoxic immunosuppressant agents; evidence of underlying systemic disease or exposure to agents associated with the nephrotic syndrome
Interventions	Treatment group • Prednisone: 60 mg/m^2/d for 4 weeks and tapered daily dose for 4 weeks Control group • Prednisone: 60 mg/m^2/d till remission and 40 mg/m^2 on 3/7 consecutive days
Outcomes	• Number relapsing during treatment and within 12 months • Mean time to next relapse • Mean relapse rate/patient

Notes	• Definitions
	  * Relapse: ISKDC definition
	  * Remission: ISKDC definition

Risk of bias

Bias	Authors' judgement	Support for judgement

ISKDC 1979 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomly allocated " - insufficient information about sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	10/64 (15.6%) not included in analysis because of protocol violation
Selective reporting (reporting bias)	High risk	Not all of the review's pre-specified primary outcomes have been reported. Adverse events not reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Jayantha 2002a

Methods	• Study design: parallel RCT • Time frame: September 1994 to 2001 • Follow-up: 2 years
Participants	• Country: Sri Lanka • Setting: renal clinic • Inclusion criteria: children aged 1 to 11.7 y with initial episode of SSNS • Number: treatment group 1 (48); treatment group 2 (74) • Mean age ± SD (years): not reported • Sex (M/F): treatment group 1 (28/20); treatment group 2 (52/22) • Exclusion criteria: not reported
Interventions	Treatment group (7 months) • Prednisolone: 60 mg/m^2/d for 4 weeks, 60 mg/m^2 on alternate days; reducing alternate day-dose by 10 mg/m^2 every 4 weeks • Total duration: 7 months Control group (ISKDC) • ISKDC regimen-prednisolone 60 mg/m^2/d for 4 weeks; 40 mg/m^2 on alternate days for 4 weeks • Total duration: 2 months
Outcomes	• Number relapsing by 12 and 24 months • Relapse rate/patient/y • Number with frequent relapses at 1 year • Cumulative dose of steroid • Adverse effects

Jayantha 2002a *(Continued)*

Notes	• Abstract and data from author
	• Definitions
	  * ISKDC (relapse): proteinuria ≥ 2+ for 5+ days
	  * Remission: oedema free and urine protein negative/trace
	  * FRNS and SDNS: ISKDC and APN definitions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random allocation table" - notes received from author
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal/loss to follow-up: 46/135 (34%) lost to follow-up at 2 years
Selective reporting (reporting bias)	Low risk	Reported on all of review's pre-specified outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Jayantha 2002b

Methods	• Study design: parallel RCT • Time frame: September 1994 to September 2002 • Follow-up: 6 months
Participants	• Country: Sri Lanka. • Setting: renal clinic • Inclusion criteria: children with relapsing SSNS; patients with SDNS • Number (analysed/randomised): treatment group 1 (46/69); treatment group 2 (44/60) • Age range: 1 to 11.1 years • Sex (M/F): 50/45 • Exclusion criteria: not reported
Interventions	Treatment group 1 (7 months) • Prednisolone: 60 mg/m^2/d for 4 weeks, then 60 mg/m^2 on alternate days. Reducing alternate-day dose by 10 mg/m^2 every 4 weeks • Total duration: 7 months

Jayantha 2002b *(Continued)*

	Treatment group 2 (2 months) • ISKDC regimen: prednisolone 60 mg/m^2/d till urine protein-free for 3 days, then 40 mg/m^2 on alternate days for 4 weeks • Total duration: 2 months
Outcomes	• Number relapsing by 6, 12 and 24 months • Relapse rate/patient/y • Number with frequent relapses, steroid dependence at 1 year • Cumulative dose of steroid • Adverse effects

Notes	• Abstract and data from author
	• Definitions
	  * SKDC-relapse: proteinuria ≥ 2+ for 5+ days
	  * Remission: oedema free and urine protein negative/trace
	  * FRNS, SSNS and SDNS: ISKDC and APN definitions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random allocation table". Information from author
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not mentioned and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	24% lost to follow-up at 1 year (23/95)
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes have been reported. No report on adverse effects
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Kleinknecht 1982

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up:15 months
Participants	• Country: France • Setting: multicentre, renal clinics • Inclusion criteria: children with initial episode SSNS

Kleinknecht 1982 *(Continued)*

	• Number: treatment group 1 (29); treatment group 2 (29) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 (13 months) • Prednisone: 2 mg/kg/d for 4 weeks and then tapering dose on alternate days for 12 months Treatment group 2 (6 months) • Prednisone: 2 mg/kg/d for 4 weeks and then tapering dose on alternate days for 5 months
Outcomes	• Number relapsing by 6, 12 and 15 months or more
Notes	• Abstract only • Authors confirmed adequate allocation but unable to supply further study information • Definitions of FRNS /SSNS /relapse /remission: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Sealed closed number envelopes in series of ten". Information obtained from author
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on adverse effects
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Ksiazek 1995

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: two years
Participants	• Country: Poland • Setting: renal clinic

Ksiazek 1995 *(Continued)*

- Inclusion criteria: children with initial episode SSNS
- Number: treatment group 1 (72); treatment group 2 (68); treatment group 3 (44)
- Mean age (range): 3.6 years (13 months to 11 years)
- Sex (M/F): 113/71
- Exclusion criteria: not reported

Interventions	Treatment group 1 (6 months) • Prednisone: 1 to 2 mg/kg/d for 4 weeks, 1 mg/kg on alternate days for 4 weeks and taper by 25% each month for 4 months • Total duration: 6 months • Total calculated steroid dose 2922 mg/m^2 Treatment group 2 (3 months) • Prednisone 1 to 2 mg/kg/d for 4 weeks, 1 mg/kg on alternate days for 4 weeks and taper by 25%/week for 4 weeks. • Total duration: 3 months • Total calculated steroid dose 2410 mg/m^2 Treatment group 3 (2 months) • Prednisone 4 weeks each of 1 to 2 mg/kg/d and 1 mg/kg on alternate days • Total duration: 2 months
Outcomes	• Number relapsing by 6 months and 2 years after completing daily and alternate-day prednisone • Relapse rate/patient/y
Notes	• Unequal numbers in groups • Only treatment group 2 used in analyses * Definitions * FRNS: ISKDC definition * Relapse: ISKDC definition * Remission: ISKDC definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	High risk	"Parents had an influence on assignment, favouring Protocol C"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed for two years

Ksiazek 1995 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on numbers with FRNS
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Leisti 1978

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up: 2.4 years
Participants	• Country: Finland • Setting: renal clinic • Inclusion criteria: children with relapsing SSNS and subnormal response to 2 hour ACTH test 1 to 12 days after completing prednisone • Number: 13 • Age range: 4.7 to 14.6 years • Sex (M/F): 8/5 • Exclusion criteria: not reported
Interventions	Treatment • 15 mg cortisol/d in ≥ 30 kg and 7.5 mg/d in < 30 kg for 6 months or till relapse • Treated for 6 months or till relapse. After next relapse treated and post steroid adrenal suppression confirmed, patient given alternate therapy • Dose of either medication doubled for 3 days when proteinuria or infection developed Group 1 • Cortisol then placebo Group 2 • Placebo then cortisol
Outcomes	• Number with relapse during cortisol or placebo at 3 months and 6 months
Notes	• Data for 2 periods combined • Definitions * Remission and relapse: ISKDC definitions • Further information requested from authors but not received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"allotted". No other information
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on allocation concealment provided

Leisti 1978 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and personnel blinded. Tablets were of identical taste and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants and personnel blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on adverse events
Other bias	Low risk	Sigrid Juselius Foundation financial support, Medica OY, Helsenki drug preparations

Li 1994

Methods	• Study design: parallel RCT • Time frame: 1990 to December 1992 • Follow-up period: unclear; at least 6 months
Participants	• Country: China • Setting: university hospital • Inclusion criteria: SSNS • Number: treatment group 1 (19); treatment group 2 (25) • Mean age ± SD (years): treatment group 1 (7.21 ± 3.52); treatment group 2 (7.54 ± 4.24) • Sex (M/F): treatment group 1 (14/5); treatment group 2 (18/7) • Exclusion criteria: not reported
Interventions	Treatment group 1 (single dose) • Prednisone 2 mg/kg/d as single morning dose for 4 weeks; prednisone 2 mg/kg on alternate days for 5 weeks then gradually reduced till 6 months Treatment group 2 (divided dose) • Prednisone 2 mg/kg/d given as three divided doses for 4 weeks; prednisone 2 mg/kg on alternate days for 5 weeks then gradually reduced till 6 months
Outcomes	• Time to remission • Toxicities
Notes	• Exclusions post randomisation but pre-intervention: unclear • Stop or end point/s: not reported • Additional data requested from authors: yes

Risk of bias

Bias	Authors' judgement	Support for judgement

Li 1994 *(Continued)*

Random sequence generation (selection bias)	High risk	Patients allocated by alternation
Allocation concealment (selection bias)	High risk	Patients allocated by alternation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to permit judgement
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on frequent relapses
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Liern 2008

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: not reported
Participants	• Country: Argentina • Setting: teaching hospital • Inclusion criteria: children with SSNS enrolled after first relapse • Number: 11 • Mean age (range): 48 months (16 to 52) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Methylprednisolone: 48 mg/m^2/d for 6 weeks (maximum dose not reported), followed by 2/3 of dose on alternate days for 6 weeks Treatment group 2 • Deflazacort: 72 mg/m^2/d for 6 weeks (maximum dose 90 mg), followed by 2/3 of dose on alternate days for 6 weeks
Outcomes	• Mean time to remission • Mean time to relapse • Total IgG and its subclasses • Adverse effects

Liern 2008 *(Continued)*

Notes	• Additional data requested from authors and received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer generated table (information received from author)
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind to patients and medical caregivers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind to patients and medical caregivers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients completed both arms of the study
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on relapse, frequent relapses and minimal data on adverse effects
Other bias	Unclear risk	No information provided

Mattoo 2000

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 2 years
Participants	• Country: Saudi Arabia • Setting: university renal clinic • Inclusion criteria: children with relapsing SSNS receiving prednisone 0.5 mg/kg on alternate days for frequent relapses or following CPA • Number: treatment group 1 (18); treatment group 2 (18) • Mean age ± SD (years): treatment group 1 (7.2 ± 3.3); treatment group 2 (6.8 ± 3.6) • Sex (M/F): treatment group 1 (10/8); treatment group 2 (12/6) • Exclusion criteria: children who were not compliant or lost to follow-up were excluded from the analysis
Interventions	Treatment group 1 • Prednisone: daily (0.5 mg/kg) for 5 days during URTI Treatment group 2 • Prednisone: 0.5 mg/kg on alternate days continued during URTI

Mattoo 2000 *(Continued)*

Outcomes	• Mean relapse rate/patient during 2 year follow-up
Notes	• Definitions * Relapse and remission: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Data received from authors, alternate patients allocated to groups
Allocation concealment (selection bias)	High risk	"alternate patients allocated to groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Each patient was followed for a period of two years
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on adverse events. Only steroid dependent patients included.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Mishra 2012

Methods	• Study design: parallel RCT • Time frame: July 2007 to June 2009 • Follow-up period: 12 months
Participants	• Country: India • Setting: university teaching hospital • Inclusion criteria: children with first episode of SSNS, aged 1-10 years. no systemic disease • Number (analysed/randomised): treatment group 1 (40/37); treatment group 2 (40/37) • Mean age ± SD (years): treatment group 1 (4.4 ± 3.0); treatment group 2 (5.3 ± 3.1) • Sex (M/F): treatment group 1 (25/12); treatment group 2 (27/10) • Exclusion criteria: < 1year and > 10 years; persistent hypertension (> 95th percentile for age, gender on 3 occasions); gross haematuria; CrCl < 80 mL/min/1.73 $m^{2;}$ azotaemia; failure to achieve remission by end of 4 weeks prednisone
Interventions	Treatment group 1 (prolonged treatment) • Prednisolone: 2 mg/kg day for 6 weeks followed by 1.5 mg/kg on alternate days for 6 weeks,1 mg/kg for 4 weeks, 0.5 mg/kg on alternate days for 4 weeks • Total duration: 20 weeks

Mishra 2012 *(Continued)*

	• Calculated total dose: 3990 mg/m^2 Treatment group 2 (standard treatment) • Prednisone: 2 mg/kg/d for 6 weeks, followed by 1.5 mg/kg on alternate days for 6 weeks • Total duration: 12 weeks • Calculated total dose: 3360 mg/m^2
Outcomes	• Mean relapse rate/patient during 2 year follow-up • Number with frequently relapsing nephrotic syndrome • Adverse effects

Notes	• Definitions
	  * Relapse and remission: ISKDC
	  * No definition of FRNS provided
	• Children who did not complete treatment or were not followed for 12 months after treatment completion were excluded from the study
	• Additional data requested from authors and received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	"randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/80, 6.3% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Did not reported on all of review's pre-specified outcomes The number of patients with at least one relapse is unclear
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Mocan 1999

Methods	• Study design: parallel RCT • Time frame: March 1990 to April 1996 • Follow-up period: 38 to 42 months
Participants	• Country: Turkey

Mocan 1999 *(Continued)*

- Setting: single centre; university teaching hospital
- Inclusion criteria: Initial episode of SSNS
- Number: treatment group 1 (8); treatment group 2 (7)
- Mean age ± SE (years): treatment group 1 (3.6 ± 2.2); treatment group 2 (4.0 ± 1.7)
- Sex (M/F): treatment group 1 (7/1); treatment group 2 (5/2)
- Exclusion criteria: Not reported

Interventions	Treatment group 1 (high dose group) • Methylprednisolone: 30 mg/kg for 3 days; 20 mg/kg for four days; 10 mg/kg for one week • Total duration: 14 days Treatment group 2 (standard therapy) • Prednisolone: 60 mg/m^2 for 4 weeks, followed by 45, 30, 20,10 and 5 mg/m^2 on alternate days for a further 5 months • Total duration: 6 months
Outcomes	• Time to remission • Time to first relapse • Mean relapse rate during study • Adverse effects
Notes	• Definitions of relapse and remission not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Children arbitrarily randomised into two groups"
Allocation concealment (selection bias)	High risk	"Children arbitrarily randomised into two groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	6/21 excluded; 4/21 (21%) lost to follow-up and this could influence results; 2/21 SRNS
Selective reporting (reporting bias)	High risk	Reported on adverse events, relapse rate but not number with FRNS
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Norero 1996

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 18 months
Participants	• Country: Chile • Setting: multicentre (11), renal clinics • Inclusion criteria: children with initial episode SSNS • Age: 6 months to 15 years • Number: treatment group 1 (29); treatment group 2 (27) • Mean age, range (months): treatment group 1 (25.5, 11 to 156); treatment group 2 (26, 16 to 144) • Sex (M/F): not reported • Exclusion criteria: secondary INS; initially or became SRNS or SDNS; deviations from therapeutic scheme; release 3 months before end of therapy; biopsy showing a different histology to minimal changes
Interventions	Treatment group 1 (3 months) • Prednisolone: 6 weeks each of 60 mg/m^2/d and 40 mg/m^2 on alternate days • Total duration: 12 weeks • Total dose: 3600 mg/m^2 Treatment group 2 (2 months) • Prednisolone: 4 weeks each of 60 mg/m^2/d and 40 mg/m^2 on alternate days • Total duration: 8 weeks • Total dose: 2400 mg/m^2
Outcomes	• Number with relapse by 12 months and 18 months • Mean relapse rate/patient in 18 months • Number with frequent relapses • Adverse effects

Notes	• Children with SDNS (relapse on reducing dose of steroids) were excluded
	• Renal biopsy showing minimal change disease required for study entry
	• Definitions:
	  * FRNS: 2 + relapses in 6 months or 3 + in 1 year
	  * Relapse: urinary protein 100 mg/kg/d or 40 mg/m^2/h or urine protein/creatinine ratio > 1 or 3 + on dipstick for > 3 days
	  * Remission: urine protein < 150 mg/d for 3 consecutive days
	• Time to 1st relapse: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	High risk	Patients allocated by odd or even numbers
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding

Norero 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Number excluded or lost to follow-up: 56/96 completed follow-up. Of 40 excluded patients, 19 had SRNS. Remaining 21 excluded inappropriately: SDNS (5); deviation from protocol (3); duration of follow-up insufficient (11); loss to follow-up (2)
Selective reporting (reporting bias)	Low risk	Reported on all of review's pre-specified outcomes
Other bias	Low risk	Grant No 1940506 from FONDECYT (National Scientific and Technology Foundation)

Pecoraro 2003

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: 12 months
Participants	• Country: Italy • Setting: renal clinic • Inclusion criteria: children with initial episode of SSNS • Number: treatment group 1 (16); treatment group 2 (16); treatment group 3 (16) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Prednisone: 2 mg/kg/d for 6 weeks; 2 mg/kg on alternate days for 6 weeks, reduced by 0.25 mg/2 weeks • Total duration: 26 weeks • Total calculated dose: 5235 mg/m^2 Treatment group 2 • IV methylprednisolone: 20 mg/kg/d for 3 days; 1 mg/kg/d for 6 weeks; 1 mg/kg on alternate days for 6 weeks; reduced by 0.25 mg/2 to 4 weeks • Total duration: 26 weeks Treatment group 3 • Prednisone: 2 mg/kg/d for 4 weeks; 2 mg/kg on alternate days for 4 weeks; decreased by 0.25 mg/week • Total duration: 12 weeks • Total calculated dose: 2362 mg/m^2
Outcomes	• Number with relapse at 1 year and 2 years • Adverse effects • Cumulative steroid dose
Notes	• No definitions provided • Abstracts only

Pecoraro 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Information from authors suggests "alternation" was used
Allocation concealment (selection bias)	High risk	'Alternation" was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Said that all patients completed follow-up but unclear whether any patients had been excluded
Selective reporting (reporting bias)	High risk	Not all review's pre-specified outcomes have been reported. No data on frequent relapses
Other bias	High risk	Educational grant from Fresenius

Satomura 2001

Methods	• Study design: quasi RCT • Study duration: not reported • Duration of follow-up: I year
Participants	• Country: Japan • Setting: multicentre renal clinics • Inclusion criteria: initial episode of SSNS • Number: treatment group 1 (37); treatment group 2 (36) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 (high dose) • Prednisolone: 60 mg/m^2/d for 4 weeks; 40 mg/m^2 on alternate days for 4 weeks • Total duration: 8 weeks Treatment group 2 (low dose) • Prednisolone: 40 mg/m^2/d for 4 weeks; 40 mg/kg on alternate days for 8 weeks • Total duration: 12 weeks
Outcomes	• Number with relapse at 12 months

Satomura 2001 *(Continued)*

	• Time to relapse
Notes	• Abstract only • No definitions provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients assigned "alternately"
Allocation concealment (selection bias)	High risk	"Alternation" used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported and outcome measurement likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient data to permit judgement
Other bias	Unclear risk	Insufficient data to permit judgement

Sharma 2000

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: at least 1 year
Participants	• Country: India • Setting: university renal clinic • Inclusion criteria: initial episode of SSNS. 156 enrolled in study and 140 evaluated • Number: treatment group 1 (70); treatment group 2 (70) • Mean age ± SD: 8.9 ± 6.8 years • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 (6 months) • Prednisolone: 60 mg/m^2/d for 6 weeks; 40 mg/m^2 on alternate days for 6 weeks; taper by 10 mg/m^2 each month for 3 months • Total duration: 6 months • Total dose: 4200 mg/m^2 Treatment group 2 (3 months)

Sharma 2000 *(Continued)*

	• Prednisolone: 60 mg/m^2/d for 6 weeks; 40 mg/m^2 on alternate days for 6 weeks; abrupt cessation at 12 weeks without tapering • Total duration: 3 months • Total calculated dose: 3360 mg/m^2
Outcomes	• Number with relapse by 6 and 12 months • Mean relapse rate • Number with frequently relapsing nephrotic syndrome • Cumulative steroid dose • Adverse events
Notes	• Definitions * Remission and relapse: ISKDC * FRNS: 2+ in 6 months or 6+ in 18 months * SDNS: APN definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'table of random numbers". Randomisation at 12 weeks after the beginning of initial therapy. Information provided by authors
Allocation concealment (selection bias)	Unclear risk	'table of random numbers'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	16/156 excluded (10.3%); 160 consecutive patients, 4 refused consent. Of 156 entered, 10 were non-compliant and 6 lost to follow-up and their results were excluded from analysis
Selective reporting (reporting bias)	Low risk	All the reviews pre-specified outcomes have been reported
Other bias	Unclear risk	Non information provided

Sinha 2014

Methods	• Study design: parallel RCT • Time frame: July 2010 to May 2012 • Follow-up: 1 year
Participants	• Country: India • Setting: multicentre (5); academic centres • Inclusion criteria: children aged 1 to 12 years with first episode of SSNS; 3 to 4+ proteinuria or urinary protein/creatinine ≥ 2 mg/mg; albumin < 2.5g/dL; oedema

Sinha 2014 *(Continued)*

	• Number: treatment group 1 (92); treatment group 2 (89) • Median age, IQR (months): treatment group 1 (44.2, 34.2 to 74.4); treatment group 2 (42.4, 30.0 to 70.5) • Sex (M/F): treatment group 1 (56/36); treatment group 2 (59/0) • Exclusion criteria: eGFR < 60 mL/min/1.73 m^2; known secondary cause (HSP, SLE, hepatitis B or haematuria); residence > 200 km away; previous steroid therapy
Interventions	Treatment group 1 (3 months) • Prednisolone 2 mg/kg/d for 6 weeks, 1.5 mg/kg/d then 1.5 mg/kg on alternate days for 6 weeks • Actual total dose 2791.7 ± 286.6 mg/m^2 Treatment group 2 (6 months) • 2 mg/kg/d for 6 weeks, 1.5 mg/kg on alternate days for 6 weeks, 1 mg/kg, 0.75 mg/kg, and 0.5 mg/kg on alternate days for 4 weeks each • Actual total dose 3529.7 ± 398.7 mg/m^2 Co-interventions • Patients on long term steroids received daily supplements of calcium (250 to 500 mg) and vitamin D (200 to 400 U) • Hypertension was treated with amlodipine or enalapril
Outcomes	• Number of steroid sensitive relapses during 12 months of follow-up • Proportion with FRNS at 12 and 24 months • Cumulative steroid dose mg/m^2/y from randomisation to 12 and 24 months • Need for steroid sparing therapies at 12 and 24 months • Mean relapse rate at 12 and 24 months • Frequency and type of serious adverse events
Notes	• Funded by Indian Council of Medical Research • Definitions * Relapse, remission, FRNS: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated. Randomly assigned 1:1 in permuted blocks of four
Allocation concealment (selection bias)	Low risk	"Procedures for randomisation and packing and distribution were conducted at this centre by individuals, who were not involved in trial implementation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"External pharmacy manufactured identical-appearing sugar coated tablets of prednisolone and placebo, packaged in matching blister packs of 10 tablets each"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators, patients and outcome assessors were blinded to randomisation schedule. Masking was maintained during data analysis, following which the randomisation code was broken"
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/181 (3%) excluded (SRNS 1, loss to follow-up 5)

Sinha 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Funded by Indian Council of Medical Research

Teeninga 2013

Methods	• Study design: parallel RCT • Time frame: February 2005 to December 2009 • Duration of study: up to 5 years. Minimum follow-up 18 months
Participants	• Country: The Netherlands, Belgium • Setting: multicentre; general and university hospitals • Inclusion criteria: children aged 9 months to 7 years with initial episode of SSNS • Number: treatment group 1 (62); treatment group 2 (64) • Median age, IQR (years): treatment group 1 (47, 3.2 to 6.2); treatment group 2 (3.8, 3.2 to 6.4) • Sex (M/F): treatment group 1 (39/23); treatment group 2 (47/27) • Exclusion criteria: secondary nephrotic syndrome. SRNS
Interventions	Treatment group 1 (3 months) • Prednisolone: 60 mg/m^2/d for 6 weeks; 40 mg/m^2 on alternate days for 6 weeks; placebo on alternate days for 12 weeks • Cumulative dose: 3360 mg/m^2 • Total duration: 12 weeks • Median duration of follow-up: 47 months (IQR 32 to 60) Treatment group 2 (6 months) • Prednisolone: 60 mg/m^2 daily for 10 days; 50 mg/m^2 daily till 6 weeks; 40 mg/m^2 on alternate days till end week 10; 30 mg/m^2 till end week 14, 10 mg/m^2 on alternate days till end week 24 • Total duration: 24 weeks • Cumulative dose 3320 to 3710 mg/m^2 • Median duration of follow-up: 47 months (IQR 37 to 60)
Outcomes	• Primary outcome event was FRNS • Cumulative incidences of first relapse, steroid dependence • Number of relapses per patient year • Cumulative steroid dose • Adverse events

Teeninga 2013 *(Continued)*

Notes	• Definitions * Nephrotic syndrome: > 200 mg protein/mmol creatinine in urine and albumin < 25 g/L in serum * Remission: urinary protein excretion < 20mg/L or negative/trace on dipstick analysis on 3 consecutive days * Relapse: proteinuria ≥2+ on dipstick analysis or > 200 mg protein/mmol creatinine for 3 consecutive days after previously achieved remission * FRNS: "Strict" definition: a) 2 or more relapses in 6 months after completing initial therapy; b) 4 relapses within any 12 month period, including relapses during initial treatment * FRNS: "Clinical" definition: Frequently relapsing NS based on clinically relevant decision that included additional treatment of prednisolone maintenance therapy(> 3 months) or other immunosuppressive agents * SDNS: 2 or more consecutive relapses either during or within 2 weeks after cessation of prednisolone (APN definition)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central pharmacy with a computer generated random number table
Allocation concealment (selection bias)	Low risk	Central pharmacy, controlled allocation concealment with a computer generated random number table. Provided prepackaged medications, with fixed and blinded dose.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, health care providers, data collectors and researchers were blinded to group allocation. Identical tasteless capsules containing prednisolone or placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, health care providers, data collectors and researchers were blinded to group allocation. Randomisation code broken September 2011.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients with consent and not SRNS were included and followed up (13 withdrew consent, 11 steroid resistant).
Selective reporting (reporting bias)	Low risk	All the review's pre-specified outcomes have been reported
Other bias	Low risk	No disclosures. Trial registered Netherlands Trial Registry number 255. Funded by Dutch kidney Foundation Grant C03 and by Vrienden van het Sophia Foundation

Ueda 1988

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 1 year
Participants	• Country: Japan. • Setting: university renal clinic • Inclusion criteria: children aged 12 weeks to 16 years with first episode SSNS; severe proteinuria, ≥ 40 mg/h/m^2; hypoalbuminaemia, ≤ 2.5 g/dL

Ueda 1988 *(Continued)*

- Number: treatment group 1 (17); treatment group 2 (29)
- Mean age ± SD (years): treatment group 1 (5.6 ± 3.2); treatment group 2 (7.2 ± 3.2)
- Sex (M/F): treatment group 1 (10/7); treatment group 2 (23/6)
- Exclusion criteria: prior treatment with steroids or cytotoxic agents; evidence of underlying systemic illness; exposure to agents know to be associated with nephrotic syndrome

Interventions	Treatment group 1 (prolonged) • Prednisolone: 60 mg/m^2/d for 4 weeks, 60 mg/m^2 on alternate days for 4 weeks and taper by 10 mg/m^2/mo • Total duration: 7 months Treatment group 2 (standard) • Prednisolone: 60 mg/m^2/d for 4 weeks and 40 mg/m^2 on 3/7 days for 4 weeks • Total duration: 2 months
Outcomes	• Number relapsing by 6 month and 12 months after completing daily and alternate-day prednisolone • Relapse rate/patient/y • FRNS • Adverse effects
Notes	• Unequal numbers in groups • Definitions * FRNS: any relapse occurring within 2 months after ceasing prednisone * Relapse: ISKDC * Remission: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'allocated randomly', insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Not mentioned, randomisation stated but no information on method used available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether any patients, who were randomised, were not included in analysis; complete 1 year follow-up
Selective reporting (reporting bias)	Low risk	The pre-specified outcomes of the review have been reported
Other bias	Low risk	Supported by a grant from the Ministry of Health and Welfare in Japan

Yoshikawa 1998

Methods	• Study design: parallel RCT • Time frame: January 1990 to December 1992 • Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre renal clinics • Inclusion criteria: children with first episode of SSNS • Number (analysed/randomised): treatment group 1 (83/96); treatment group 2 (88/98) • Mean age ± SD (years): treatment group 1 (7.1 ± 3.7); treatment group 2 (8.0 ± 4.1) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 (prolonged) • Prednisolone: 2 mg/kg/d for 4 weeks, 2 mg/kg on alternate days for 8 weeks, 1.5 mg/kg on alternate days for 2 weeks, 1 mg/kg on alternate days for 2 weeks, 0.5 mg/kg on alternate days for 2 weeks • Total duration: 18 weeks Treatment group 2 (standard) • Prednisone: 2 mg/kg/d for 4 weeks, 1.3 mg/kg on alternate day for 4 weeks • Total duration: 8 weeks Co-interventions • Both groups given Chinese herb Sairei-to: > 40 kg 8.1 g/d; 20 to 40 kg 5.4 g/d; < 20 kg 2.7 g/d
Outcomes	• Number relapsing by 2 years. • Number of patients with FRNS
Notes	• Definitions * Relapse, FRNS: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'randomly assigned, concealed envelopes'
Allocation concealment (selection bias)	Low risk	'randomly assigned, concealed envelopes'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and outcome is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25/196 (13%) did not complete study

Yoshikawa 1998 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all the reviews, pre-specified outcomes were reported. No reports of adverse effects of steroids
Other bias	Unclear risk	Insufficient data to permit judgment

Yoshikawa 2014

Methods	• Study design: parallel RCT • Time frame: 6 September 2007 to 9 February 2013 • Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre (90 hospitals) • Inclusion criteria: children aged 1 to 15 years with first episode of INS with remission within 3 weeks • Number (analysed/randomised): treatment group 1 (124/127); treatment group 2 (122/128) • Mean age ± SD (years): treatment group 1 (6.3 ± 4.1); treatment group 2 (6.7 ± 4.1) • Sex (M/F): treatment group 1 (87/35); treatment group 2 (89/35) • Exclusion criteria: secondary nephrotic syndrome; renal insufficiency defined as CrCl ≤ 60 mL/min/1.73 m^2; active infections; poorly controlled hypertension; severe liver dysfunction; pregnancy or a history of immunosuppressant medication
Interventions	Treatment group 1 (6 months) • Prednisolone: 60 mg/m^2 weeks 1-4 in 3 divided doses daily, 60 mg/m^2 on alternate days weeks 5 to 8, 45 mg/m^2 on alternate days for weeks 9 to 12, 15 mg/m^2 on alternate days for weeks 17 to 20 Treatment group 2 (2 months) • Prednisolone 60 mg/m^2 weeks 1 to 4, in 3 divided doses daily, 40 mg/m^2 on alternate days weeks 5 to 8
Outcomes	• Number relapsing by 2 years • Number of patients with frequent relapses at 2 years • Number needing steroid sparing agents at 2 years • Number of relapses/patient-year • Adverse events

Notes	• Grant from the Ministry of Health, Labour and Welfare, Japan
	• Definitions
	  * Relapse, FRNS: ISKDC
	  * Diagnosis of nephrotic syndrome and remission: ISKDC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence in 1:1 ratio, stratified for age (1 to 10 years or 11 to 15 years), sex and institution
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned....at the Japan Clinical Research Support Unit"
Blinding of participants and personnel (performance bias)	High risk	Open label, patients, guardians, treating physicians and individuals were data were not blinded to treatment groups

Yoshikawa 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Apart from trial statistician and data monitoring committee, all treating physicians and other investigators remained blinded to the trial results until follow up was completed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Excluded 9/255 (3%): early relapses after remission (5), 3 no follow-up data available (3), withdrew consent before allocated study medication (1)
Selective reporting (reporting bias)	Low risk	All studies pre-specified outcomes mentioned
Other bias	Low risk	Grant from the Ministry of Health, Labour and Welfare, Japan

Zhang 2014

Methods	• Study design: parallel RCT • Time frame: November 2009 to May 2012 • Follow-up: 6 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: children, treated with prednisone for first time, no previous medications, have normal liver and renal functions, no concurrent infection, no systemic signs such as fever, normal white cell count, negative elisa-linked immunospot or negative PPD • Number (analysed/randomised): treatment group 1 (95/106); treatment group 2 (98/105) • Mean age, range (years): treatment group 1 (4.0, 1.0 to 15.0); treatment group 2 (3.0, 0.7 to 17.0) • Sex (M/F): treatment group 1 (71/24); treatment group 2 (73/25) • Exclusion criteria: secondary nephrotic syndrome; glomerular haematuria; repeated or sustained hypertension; impaired kidney function except for hypovolaemia; hypocomplementaemia; severe infections after prednisone; received incomplete course of azithromycin
Interventions	Treatment group 1 • Prednisone: 2 mg/kg daily (maximum 60 mg/kg/d) in divided doses for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks, decrease by 5 mg every 2 weeks till 30 mg/kg, then decrease by 2.5 mg very every 2 weeks until withdrawal • Azithromycin: 10 mg/kg daily for 3 days Treatment group 2 • Prednisone: 2 mg/kg daily (maximum 60 mg/kg/d) in divided doses for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks, decrease by 5 mg every 2 weeks till 30 mg/kg, then decrease by 2.5 mg every 2 weeks every 2 weeks until withdrawal
Outcomes	• Number relapsing by 3 months • Number relapsing by 6 months • Number with frequent relapses at 6 months • Time to remission

Zhang 2014 *(Continued)*

Notes	• Definitions * Primary nephrotic syndrome: treated with prednisone for first time * SRNS: no complete remission after treatment with 2 mg/kg/day for 8 weeks * Relapse: morning urinalysis showed ≥ 3 + proteinuria after being negative for 3 days during follow-up of 6 months * Complete remission: negative or trace proteinuria for 3 consecutive days, serum albumin ≥ 2.5 g/L

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"randomly categorized into intervention and control groups using a random number table of odd or even numbers"
Allocation concealment (selection bias)	High risk	Allocation sequence could be predicted
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and lack of blinding could influence outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/208 (excludes 4 patients with SRNS); 10.1% lost to follow-up or excluded (15 lost to follow-up, 6 excluded for hypocomplementaemia)
Selective reporting (reporting bias)	High risk	Not all reviews prespecified outcomes are mentioned - no adverse events mentioned
Other bias	Low risk	Tiajin Bureau of Health Sciences and Technology Fund. Project number 09KZ34

APN - Arbetsgemeinschaft für Pädiatrische Nephrologie; BMI - body mass index; CPA - cyclophosphamide; CrCl - creatinine clearance; CPA - cyclophosphamide; CSA - cyclosporin; eGFR - estimated glomerular filtration rate; FRNS - frequently relapsing steroid-sensitive nephrotic syndrome; INS - idiopathic nephrotic syndrome; IQR - interquartile range; ISKDC - International Study of Kidney Disease in Children; SCr - serum creatinine; SDNS - steroid-dependent nephrotic syndrome; SSNS - steroid-sensitive nephrotic syndrome; SRNS - steroid-resistant nephrotic syndrome; URTI - upper respiratory tract infection

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

Study	Reason for exclusion
Alatas 1978	RCT; non-corticosteroid interventions (chlorambucil)
Anonymous 1968	Not RCT
APN 1982	RCT, non-corticosteroid interventions (cyclophosphamide/chlorambucil)
Arun 2009	RCT; non-corticosteroid interventions (zinc)
Baluarte 1978	RCT; non-corticosteroid interventions (chlorambucil)

Study	Reason for exclusion
BAPN 1991	RCT; non-corticosteroid interventions (levamisole)
Barratt 1970	RCT; non-corticosteroid interventions (cyclophosphamide)
Barratt 1973	RCT; non-corticosteroid interventions (cyclophosphamide)
Barratt 1977	RCT; non-corticosteroid interventions (azathioprine)
Cerkauskiene 2005	RCT; non-corticosteroid interventions (fusidic acid)
Chiu 1973	RCT; non-corticosteroid interventions (cyclophosphamide)
Dayal 1994	RCT; non-corticosteroid interventions (levamisole)
Donia 2005	RCT; non-corticosteroid interventions (cyclophosphamide/levamisole)
Edefonti 1988	RCT; non-corticosteroid interventions (cyclosporin/cyclophosphamide)
Grupe 1976	RCT; non-corticosteroid interventions (chlorambucil)
Hu 2006	Probably RCT; non-corticosteroid interventions (herbal medicines)
Idczak-Nowicka 1996	Not RCT
ISKDC 1970	RCT; non-corticosteroid interventions (azathioprine)
ISKDC 1974	RCT; non-corticosteroid interventions (cyclophosphamide)
Liu 1995	Non-corticosteroid interventions (Chinese medicines). Not sure whether it is RCT
Martinelli 2004	Non-corticosteroid interventions (cyclophosphamide) in children with FSGS. Not sure whether it is RCT
McCrory 1973	RCT; non-corticosteroid interventions (cyclophosphamide)
Niaudet 1992	RCT; non-corticosteroid interventions (cyclosporin/chlorambucil)
Prasad 2004	RCT; non-corticosteroid interventions (cyclophosphamide)
Rashid 1996	RCT; non-corticosteroid interventions (levamisole)
Sharipov 2007	Not RCT
Ueda 1990	RCT; non-corticosteroid interventions (cyclophosphamide)
Wang 2005	Possibly RCT; non-corticosteroid interventions
Weiss 1993	RCT; non-corticosteroid interventions (levamisole)
Wingen 1990	Not RCT
Yamashita 1971	Not RCT
Yang 2001	Non-corticosteroid interventions (herbal). Unclear whether RCT

Study	Reason for exclusion
Yoshioka 2000	RCT; non-corticosteroid interventions (mizoribine)

FSGS - focal segmental glomerulonephritis; RCT - randomised controlled trial

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

PREDNOS 2 Study 2014

Trial name or title	Short course daily prednisolone therapy at the time of upper respiratory infection in children with relapsing steroid sensitive nephrotic syndrome: The PREDNOS 2 study
Methods	Parallel RCT
Participants	Subjects aged over 1 year and less than 19 years with relapsing SSNS who have had two or more relapses in the preceding 12 months
Interventions	Standard course therapy: weeks 1 to 4 prednisolone 60 mg/m^2/d (max 80 mg), weeks 5 to 8, prednisolone 40 mg/m^2 on alternate days for 28 days Extended course therapy: weeks 1 to 4 60mg/m^2/d, weeks 5 to 16 prednisolone 60 mg/m^2 on alternate days tapering by 10 mg/m^2 every 2 weeks
Outcomes	The primary end point will be the incidence of URTI-related relapse following the first URTI during the 12 month follow-up period
Starting date	
Contact information	Nicholas Webb. nicholas.webb@cmft.nhs.uk
Notes	

PREDNOS Study 2013

Trial name or title	Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of nephrotic syndrome: national multicentre randomised double blind trial
Methods	Parallel RCT
Participants	Children presenting with first episode of SSNS, over 1 year and less than 1 year
Interventions	Treatment group: children will receive daily prednisolone for 6 days at the onset of URTI at the onset of each URTI during 12 months Control group: children will continue their current treatment (with placebo to maintain double blind) at the onset of each URTI during 12 months
Outcomes	Time to first relapse. To determine whether an extended course of prednisolone reduces the relapse rate, reduces the proportion of children who develop frequently relapsing or steroid dependent disease, reduces the requirement for a second or third line agent, is associated with an increased incidence of steroid related adverse events including behavioural problems, is more effective than standard course therapy
Starting date	

PREDNOS Study 2013 *(Continued)*

Contact information	nicholas.webb@cmft.nhs.uk
Notes	

SSNS - steroid-sensitive nephrotic syndrome; URTI - upper respiratory tract infection

DATA AND ANALYSES

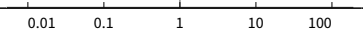
Comparison 1. Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with frequent relapses by 12 to 24 months	6	582	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 1.00]
2 Number of children relapsing by 12 to 24 months	8	741	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.00]
3 Mean relapse rate/patient/y	4	295	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.29, -0.00]
4 Cumulative steroid dose	3	245	Mean Difference (IV, Random, 95% CI)	0.71 [-0.67, 2.09]
5 Number with frequent relapses by 12 to 24 months stratified by definition of FRNS	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 FRNS by ISKDC definition	3	435	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.20]
5.2 Variation from ISKDC definition of FRNS	3	147	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.19]
6 Number with frequent relapses by 12 to 24 months stratified by risk of bias for allocation concealment	6	582	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 1.00]
6.1 Low risk of bias for allocation concealment	3	362	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
6.2 Unclear or high risk of bias for allocation bias	3	220	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.26, 0.77]
7 Adverse events	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Psychological disorders	3	233	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.43, 11.13]
7.2 Hypertension	6	456	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.47, 6.86]
7.3 Ophthalmological disorders	5	400	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.07, 1.42]
7.4 Retarded growth	4	354	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.18]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.5 Cushing's syndrome	3	232	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.51, 3.39]
7.6 Infections	2	172	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.17]
7.7 Osteoporosis	3	233	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.06, 3.38]

Analysis 1.1. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 1 Number with frequent relapses by 12 to 24 months.

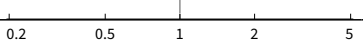
Study or subgroup	3 months or more n/N	2 months therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Norero 1996	3/29	4/27		6.48%	0.7[0.17,2.84]
Ueda 1988	3/17	15/29		9.94%	0.34[0.12,1.01]
APN 1993	6/34	12/37		14.07%	0.54[0.23,1.29]
Bagga 1999	7/22	8/23		14.87%	0.91[0.4,2.1]
Jayantha 2002a	8/48	26/70		18.52%	0.45[0.22,0.91]
Yoshikawa 2014	45/122	46/124		36.12%	0.99[0.72,1.38]
Total (95% CI)	**272**	**310**		**100%**	**0.68[0.47,1]**
Total events: 72 (3 months or more), 111 (2 months therapy)					
Heterogeneity: Tau^2=0.08; Chi^2=7.8, df=5(P=0.17); I^2=35.93%					
Test for overall effect: Z=1.94(P=0.05)					



Three months or more — Two months

Analysis 1.2. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 2 Number of children relapsing by 12 to 24 months.

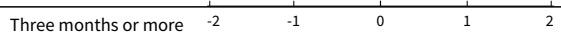
Study or subgroup	3 months or more n/N	2 months therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ueda 1988	5/17	18/29		5.68%	0.47[0.22,1.04]
Norero 1996	15/29	13/27		9.55%	1.07[0.63,1.82]
APN 1993	13/34	24/37		10.32%	0.59[0.36,0.96]
Satomura 2001	23/36	19/37		12.44%	1.24[0.84,1.85]
Jayantha 2002a	16/35	43/53		12.81%	0.56[0.38,0.83]
Ksiazek 1995	36/72	32/44		15.28%	0.69[0.51,0.92]
Bagga 1999	16/22	21/23		15.51%	0.8[0.6,1.06]
Yoshikawa 2014	83/122	80/124		18.42%	1.05[0.88,1.26]
Total (95% CI)	**367**	**374**		**100%**	**0.8[0.64,1]**
Total events: 207 (3 months or more), 250 (2 months therapy)					
Heterogeneity: Tau^2=0.06; Chi^2=20.88, df=7(P=0); I^2=66.48%					
Test for overall effect: Z=1.95(P=0.05)					



Three months or more — Two months

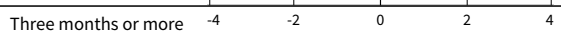
Analysis 1.3. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 3 Mean relapse rate/patient/y.

Study or subgroup	3 months or more N	3 months or more Mean(SD)	2 months therapy N	2 months therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
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]
Total ***	**146**		**149**			**100%**	**-0.65[-1.29,-0]**
Heterogeneity: Tau^2=0.36; Chi^2=24.93, df=3(P<0.0001); I^2=87.97%							
Test for overall effect: Z=1.97(P=0.05)							



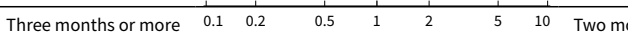
Analysis 1.4. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 4 Cumulative steroid dose.

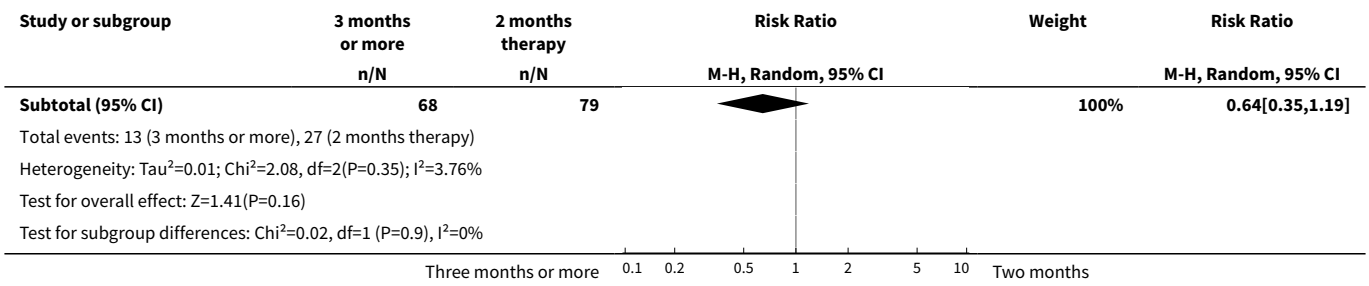
Study or subgroup	3 months or more N	3 months or more Mean(SD)	2 months therapy N	2 months therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bagga 1999	22	6.5 (2.6)	23	5.2 (2.7)		33.34%	1.26[-0.27,2.79]
Jayantha 2002a	32	7.1 (2.9)	52	5.7 (2.5)		39.32%	1.45[0.24,2.66]
Ksiazek 1995	72	5.6 (4.4)	44	6.6 (5.4)		27.34%	-1.02[-2.91,0.87]
Total ***	**126**		**119**			**100%**	**0.71[-0.67,2.09]**
Heterogeneity: Tau^2=0.89; Chi^2=4.96, df=2(P=0.08); I^2=59.72%							
Test for overall effect: Z=1.01(P=0.31)							



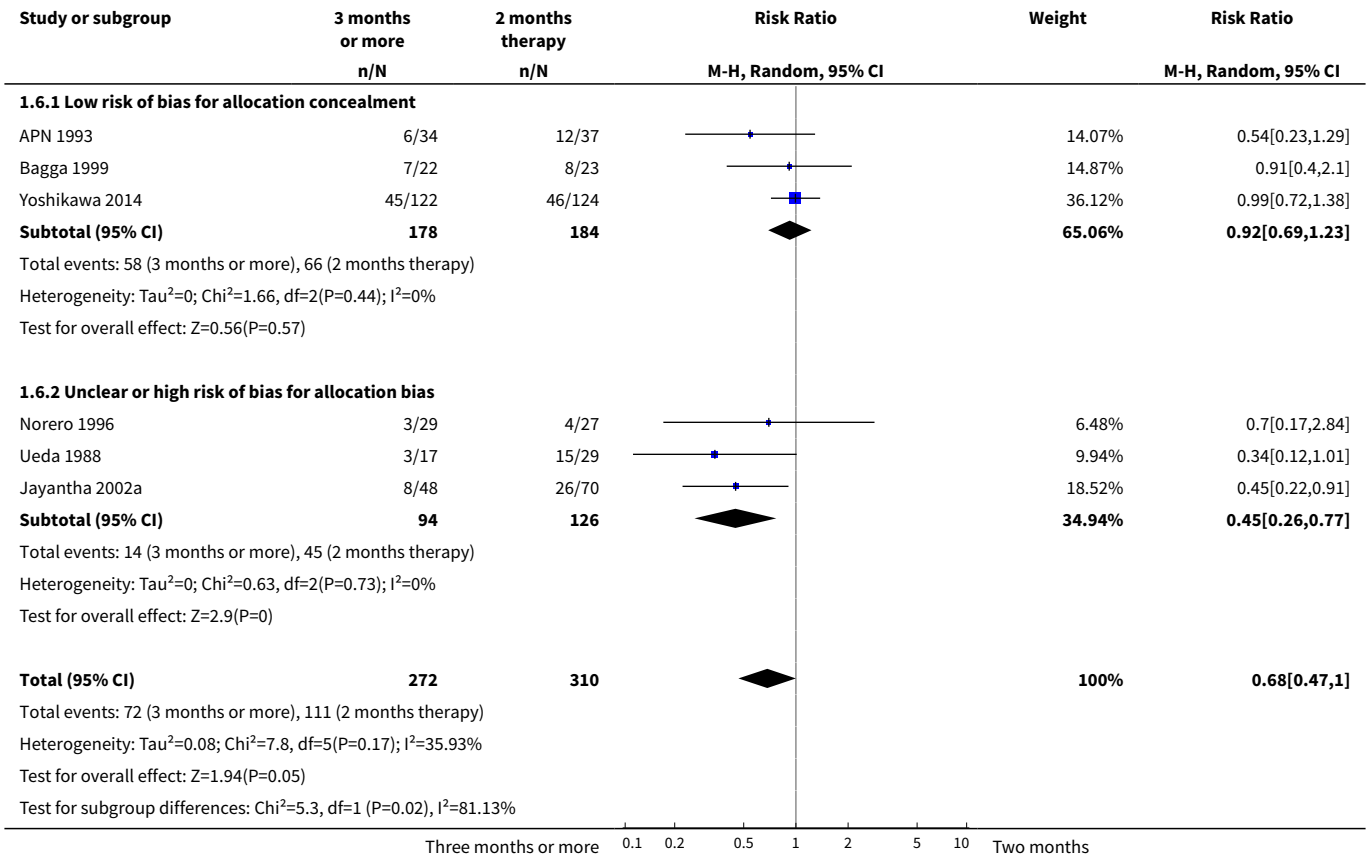
Analysis 1.5. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 5 Number with frequent relapses by 12 to 24 months stratified by definition of FRNS.

Study or subgroup	3 months or more n/N	2 months therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 FRNS by ISKDC definition					
APN 1993	6/34	12/37		24.11%	0.54[0.23,1.29]
Jayantha 2002a	8/48	26/70		29.69%	0.45[0.22,0.91]
Yoshikawa 2014	45/122	46/124		46.2%	0.99[0.72,1.38]
Subtotal (95% CI)	**204**	**231**		**100%**	**0.68[0.39,1.2]**
Total events: 59 (3 months or more), 84 (2 months therapy)					
Heterogeneity: Tau^2=0.15; Chi^2=5.17, df=2(P=0.08); I^2=61.35%					
Test for overall effect: Z=1.34(P=0.18)					
1.5.2 Variation from ISKDC definition of FRNS					
Bagga 1999	7/22	8/23		50.93%	0.91[0.4,2.1]
Norero 1996	3/29	4/27		18.56%	0.7[0.17,2.84]
Ueda 1988	3/17	15/29		30.51%	0.34[0.12,1.01]

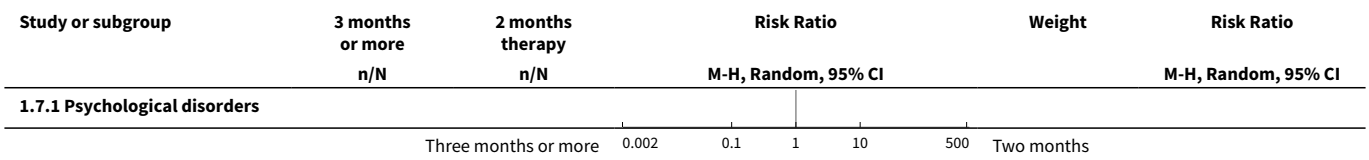


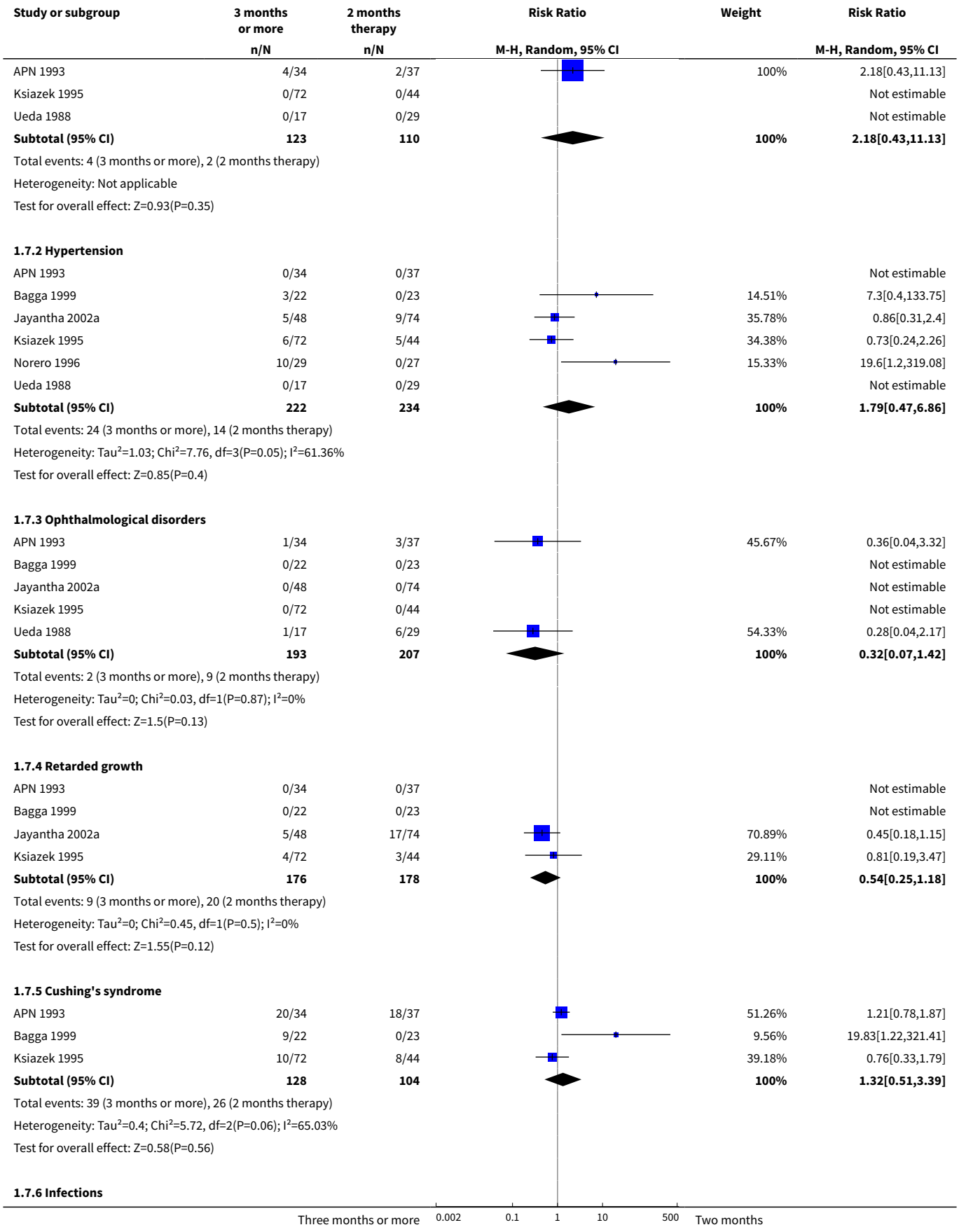


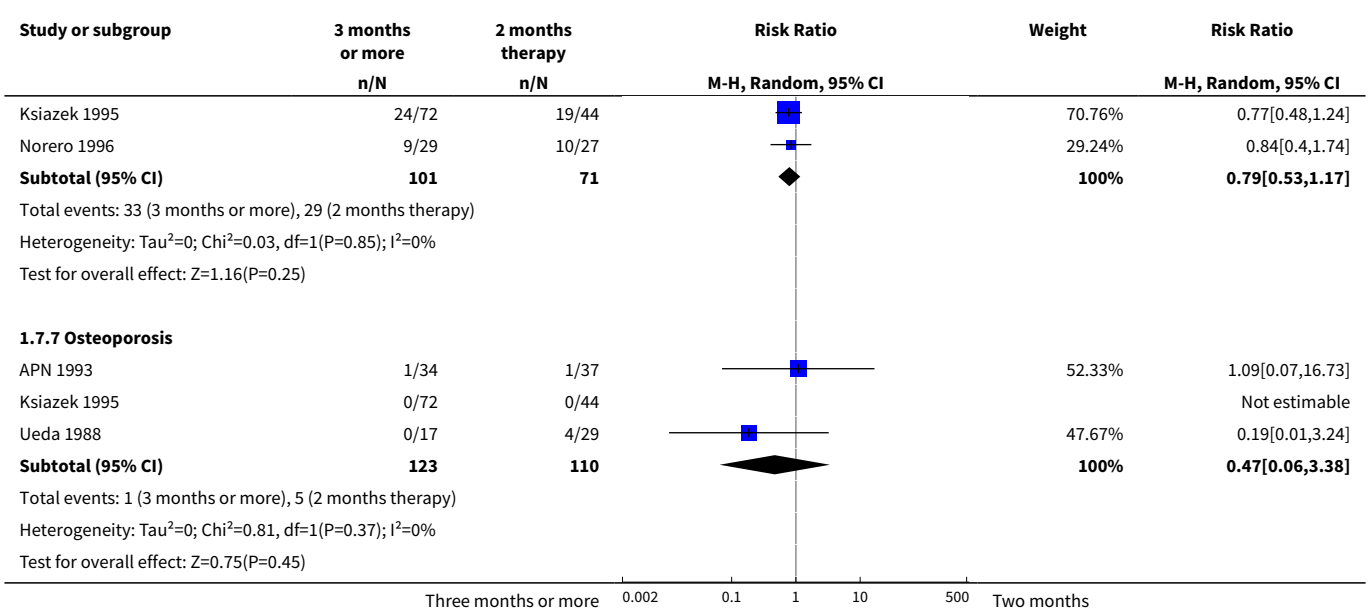
Analysis 1.6. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 6 Number with frequent relapses by 12 to 24 months stratified by risk of bias for allocation concealment.



Analysis 1.7. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: 3 months versus 2 months of therapy, Outcome 7 Adverse events.







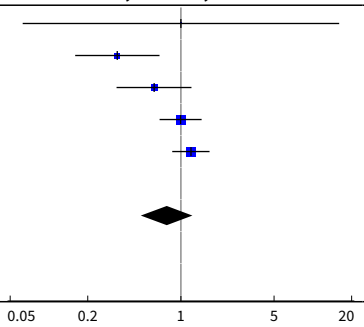
Comparison 2. Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with frequent relapses by 12 to 24 months	5	591	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.22]
2 Number of children relapsing by 12 to 24 months	7	763	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
3 Mean relapse rate/patient/y	3	460	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.64, -0.14]
4 Cumulative steroid dose	3	460	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.67, 0.73]
5 Number with frequent relapses stratified by definition of FRNS	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 FRNS by ISKDC definition	3	377	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.74, 1.34]
5.2 Variation from ISKDC definition of FRNS	2	214	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.72]
6 Number with frequent relapses stratified by risk of bias for allocation concealment	5	591	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.22]
6.1 Studies at low risk of bias for allocation concealment	3	377	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.74, 1.34]
6.2 Studies at high or unclear risk of bias for allocation concealment	2	214	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.72]

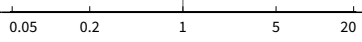
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Number with frequent relapses stratified by risk of bias for blinding	5	591	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.16]
7.1 Low risk of bias for blinding	2	307	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.20]
7.2 High or unclear risk of bias for blinding	3	284	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.30, 0.78]
8 Number with frequent relapses stratified by risk of bias for attrition	5	591	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.16]
8.1 Low risk of bias for attrition	4	451	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.16]
8.2 High risk of bias for attrition	1	140	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.16, 0.69]
9 Adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Hypertension	5	636	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.91, 2.05]
9.2 Eye complications	5	614	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.17]
9.3 Infections	4	586	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.79, 1.51]
9.4 Cushingoid appearance	5	646	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.62, 1.36]
9.5 Gastrointestinal bleeding	1	140	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.26, 8.70]
9.6 Addisonian crisis	1	140	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.39]
9.7 Psychological disorders	3	389	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.03, 4.39]
9.8 Growth	2	320	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.55, 1.82]

Analysis 2.1. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 1 Number with frequent relapses by 12 to 24 months.

Study or subgroup	5 or 6 months n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mishra 2012	1/37	1/37		2.49%	1[0.06,15.4]
Sharma 2000	8/70	24/70		18.31%	0.33[0.16,0.69]
Hiraoka 2003	10/36	15/34		20.35%	0.63[0.33,1.2]
Sinha 2014	36/92	35/89		28.81%	1[0.69,1.43]
Teeninga 2013	38/64	31/62		30.04%	1.19[0.86,1.64]
Total (95% CI)	**299**	**292**		**100%**	**0.78[0.5,1.22]**
Total events: 93 (5 or 6 months), 106 (Three months)					
Heterogeneity: Tau^2=0.15; Chi^2=12.05, df=4(P=0.02); I^2=66.81%					



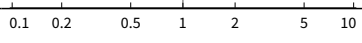
Study or subgroup	5 or 6 months n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.07(P=0.28)					



Five or six months | Three months

Analysis 2.2. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 2 Number of children relapsing by 12 to 24 months.

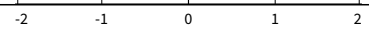
Study or subgroup	5 or 6 months n/N	Three months n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pecoraro 2003	6/16	12/16		9.93%	0.5[0.25,1]
Mishra 2012	8/37	26/37		10.57%	0.31[0.16,0.59]
Hiraoka 2003	15/36	21/34		13.46%	0.67[0.42,1.08]
Sharma 2000	18/70	44/70		14%	0.41[0.26,0.63]
Ksiazek 1995	36/72	54/68		16.95%	0.63[0.49,0.82]
Sinha 2014	48/92	56/89		17.08%	0.83[0.64,1.07]
Teeninga 2013	51/64	48/62		18.02%	1.03[0.86,1.24]
Total (95% CI)	**387**	**376**		**100%**	**0.62[0.45,0.85]**
Total events: 182 (5 or 6 months), 261 (Three months)					
Heterogeneity: Tau^2=0.13; Chi^2=34.65, df=6(P<0.0001); I^2=82.68%					
Test for overall effect: Z=2.97(P=0)					



Five or six months | Three months

Analysis 2.3. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 3 Mean relapse rate/patient/y.

Study or subgroup	5 or 6 months N	Mean(SD)	Three months N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ksiazek 1995	72	0.5 (0.6)	68	0.8 (0.6)		50.95%	-0.28[-0.49,-0.07]
Sharma 2000	70	0.5 (1)	70	1.2 (1.3)		28.15%	-0.67[-1.04,-0.3]
Sinha 2014	92	1.3 (1.6)	88	1.5 (1.6)		20.89%	-0.28[-0.74,0.18]
Total ***	**234**		**226**			**100%**	**-0.39[-0.64,-0.14]**
Heterogeneity: Tau^2=0.02; Chi^2=3.32, df=2(P=0.19); I^2=39.74%							
Test for overall effect: Z=3.1(P=0)							

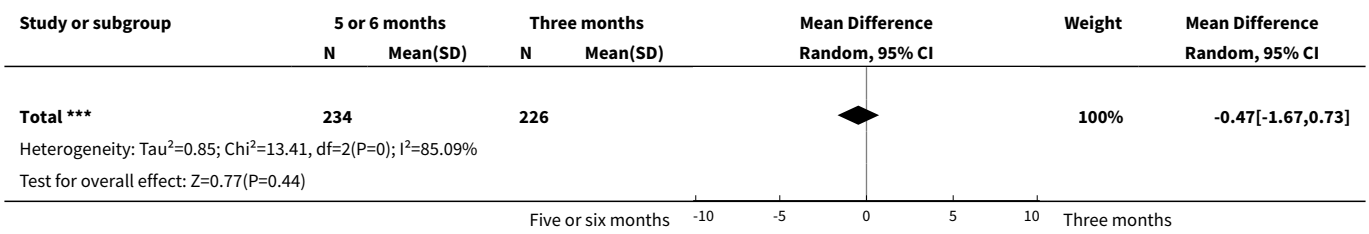


Five or six months | Three months

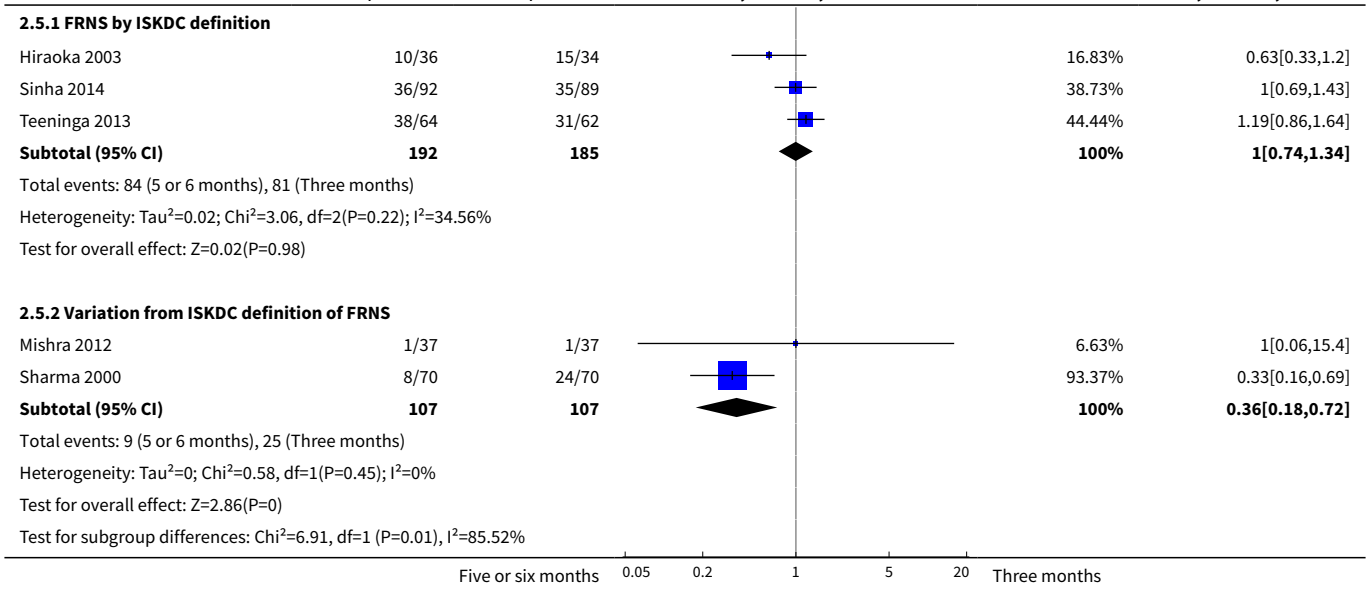
Analysis 2.4. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 4 Cumulative steroid dose.

Study or subgroup	5 or 6 months N	Mean(SD)	Three months N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ksiazek 1995	72	5.6 (4.4)	68	9 (7.3)		19.72%	-3.45[-5.46,-1.44]
Sharma 2000	70	6.3 (1.8)	70	6.2 (1.7)		40.06%	0.08[-0.49,0.65]
Sinha 2014	92	2.3 (1.9)	88	1.9 (1.9)		40.23%	0.44[-0.12,1]

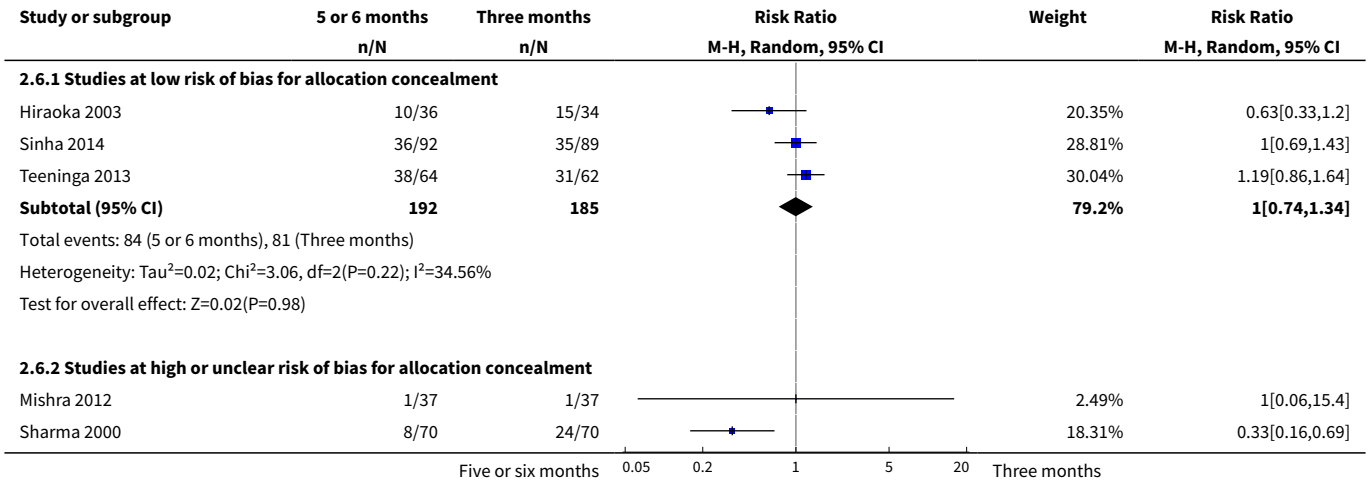
Five or six months | Three months

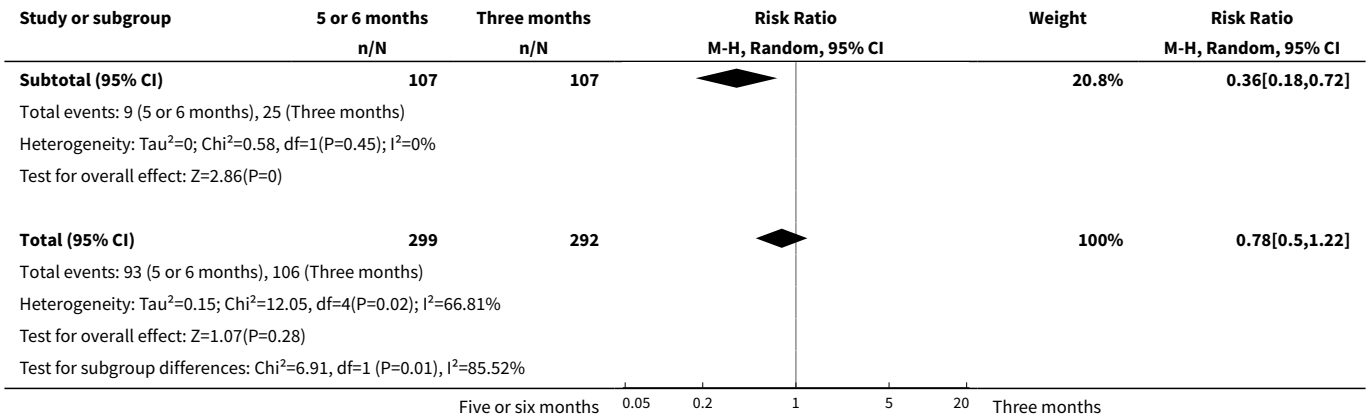


Analysis 2.5. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 5 Number with frequent relapses stratified by definition of FRNS.

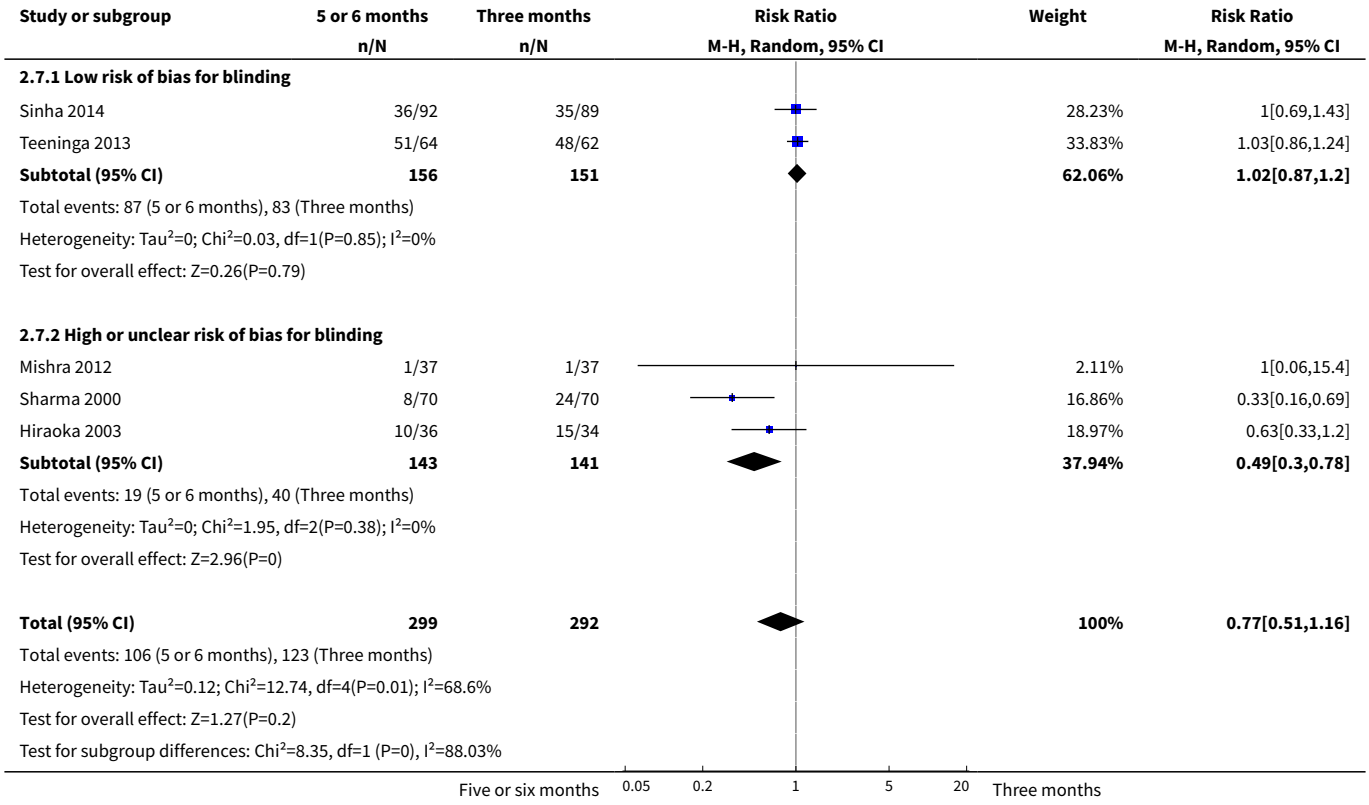


Analysis 2.6. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 6 Number with frequent relapses stratified by risk of bias for allocation concealment.

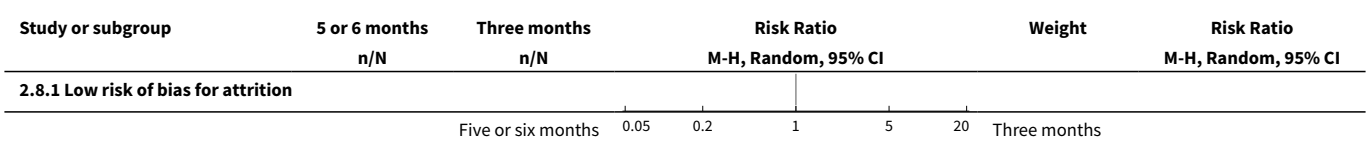


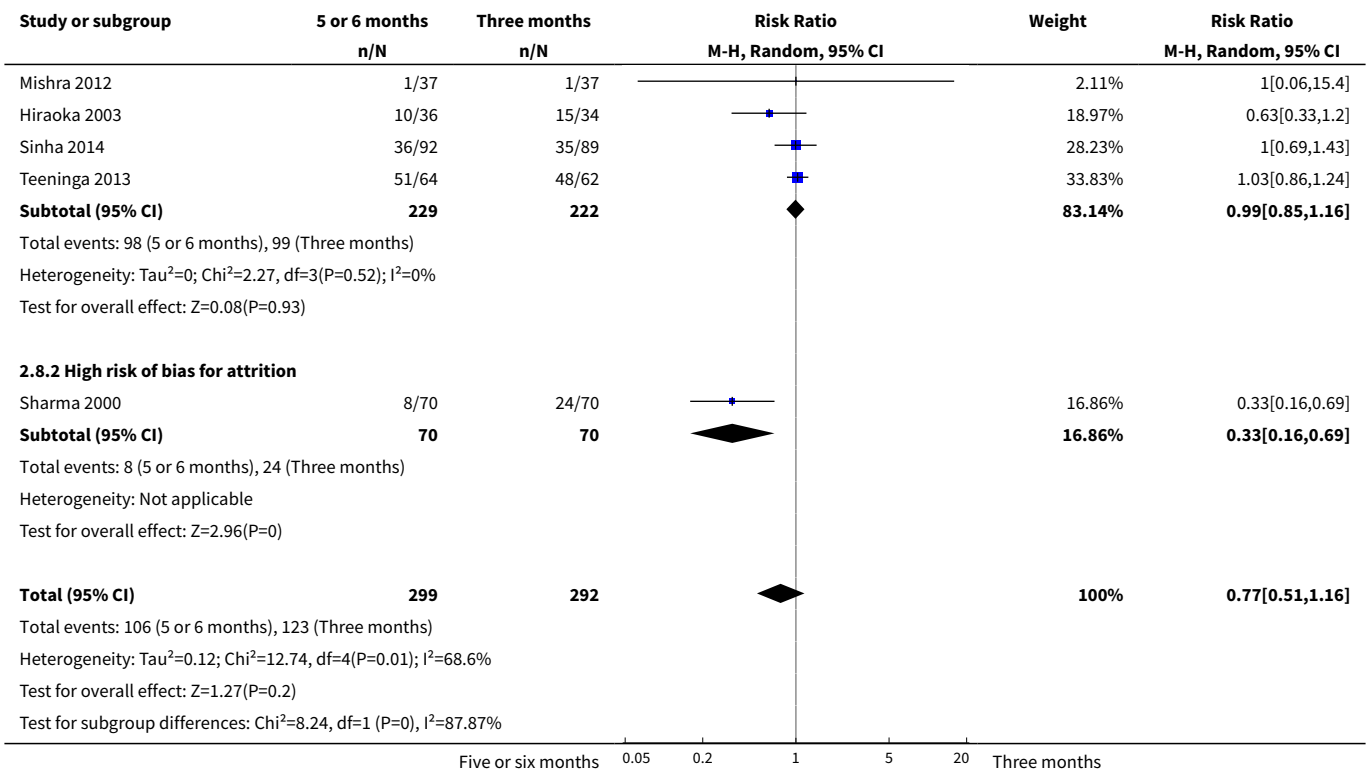


Analysis 2.7. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 7 Number with frequent relapses stratified by risk of bias for blinding.

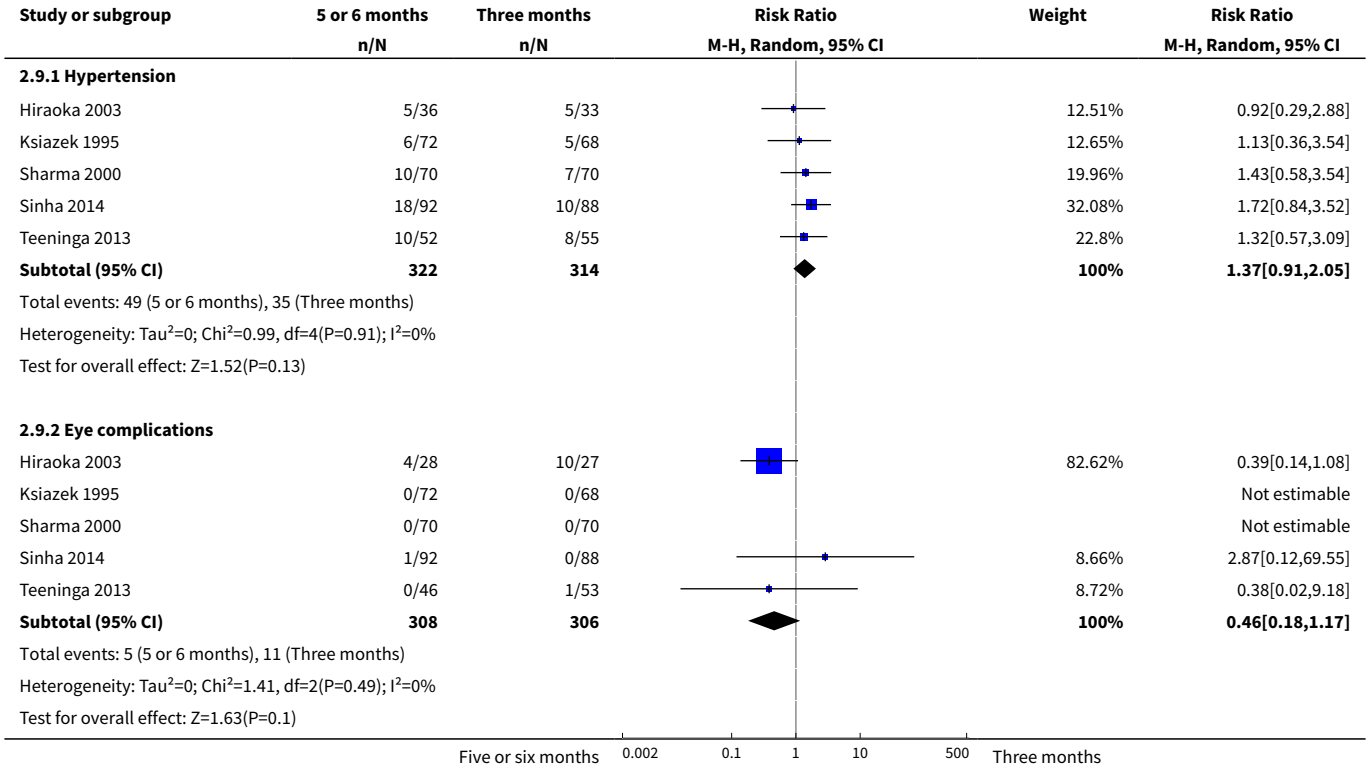


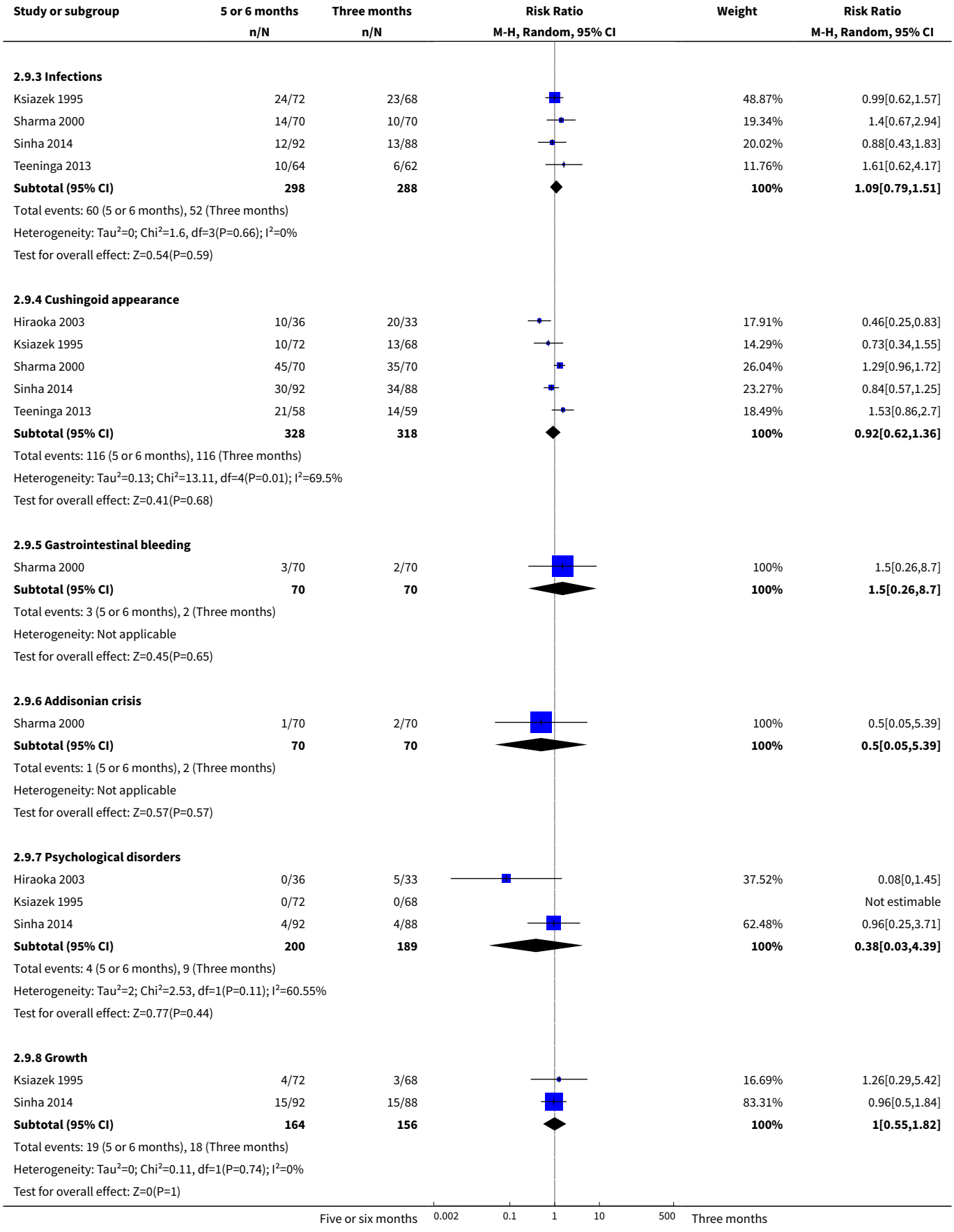
Analysis 2.8. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 8 Number with frequent relapses stratified by risk of bias for attrition.





Analysis 2.9. Comparison 2 Steroid therapy in first episode of nephrotic syndrome: 5 or 6 months versus 3 months of therapy, Outcome 9 Adverse events.





Comparison 3. Steroid therapy in the first episode of nephrotic syndrome: 1 month versus 2 months of therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of children relapsing by 12 to 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Number with frequent relapses	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Cumulative steroid dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Steroid therapy in the first episode of nephrotic syndrome: 1 month versus 2 months of therapy, Outcome 1 Number of children relapsing by 6 months.

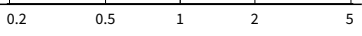
Study or subgroup	1 month n/N	2 months n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1988	23/32	13/29		1.6[1.01,2.54]

Analysis 3.2. Comparison 3 Steroid therapy in the first episode of nephrotic syndrome: 1 month versus 2 months of therapy, Outcome 2 Number of children relapsing by 12 to 24 months.

Study or subgroup	1 month n/N	2 months n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1988	25/31	16/29		1.46[1.01,2.12]

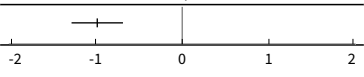
Analysis 3.3. Comparison 3 Steroid therapy in the first episode of nephrotic syndrome: 1 month versus 2 months of therapy, Outcome 3 Number with frequent relapses.

Study or subgroup	1 month n/N	2 months n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1988	18/32	11/29		1.48[0.85,2.59]



Analysis 3.4. Comparison 3 Steroid therapy in the first episode of nephrotic syndrome: 1 month versus 2 months of therapy, Outcome 4 Cumulative steroid dose.

Study or subgroup	1 month		2 months		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
APN 1988	32	1.2 (0.7)	29	2.2 (0.5)		-0.98[-1.28,-0.68]

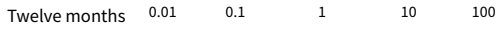


Comparison 4. Steroid therapy in the first episode of nephrotic syndrome: 12 months versus 5 months therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Steroid therapy in the first episode of nephrotic syndrome: 12 months versus 5 months therapy, Outcome 1 Number with relapse.

Study or subgroup	12 months	5 months	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kleinknecht 1982	16/29	21/29		0.76[0.51,1.13]

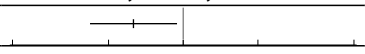


Comparison 5. Steroid therapy in the first episode of nephrotic syndrome: different total doses given over same duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at twelve months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number with frequently relapsing nephrotic syndrome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Psychological disorders	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Cushing's Syndrome	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

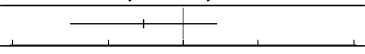
Analysis 5.1. Comparison 5 Steroid therapy in the first episode of nephrotic syndrome: different total doses given over same duration, Outcome 1 Relapse at twelve months.

Study or subgroup	Higher total dose n/N	Lower total dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hiraoka 2000	15/30	23/29		0.63[0.42,0.94]



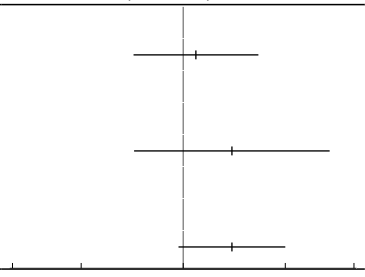
Analysis 5.2. Comparison 5 Steroid therapy in the first episode of nephrotic syndrome: different total doses given over same duration, Outcome 2 Number with frequently relapsing nephrotic syndrome.

Study or subgroup	Higher total dose n/N	Lower total dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hiraoka 2000	9/30	13/30		0.69[0.35,1.37]



Analysis 5.3. Comparison 5 Steroid therapy in the first episode of nephrotic syndrome: different total doses given over same duration, Outcome 3 Adverse effects.

Study or subgroup	Higher total dose n/N	Lower total dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 Hypertension				
Hiraoka 2000	4/30	3/30		1.33[0.33,5.45]
5.3.2 Psychological disorders				
Hiraoka 2000	3/30	1/30		3[0.33,27.23]
5.3.3 Cushing's Syndrome				
Hiraoka 2000	9/30	3/30		3[0.9,10.01]

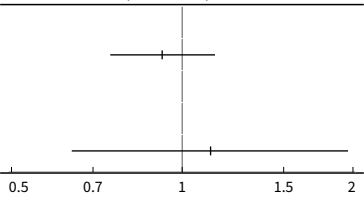


Comparison 6. Steroid therapy and Sairei-to in first episode of nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long prednisone & Sairei-to versus standard prednisone & Sairei-to	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Relapse at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Number with frequent relapses at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Steroid therapy and Sairei-to in first episode of nephrotic syndrome, Outcome 1 Long prednisone & Sairei-to versus standard prednisone & Sairei-to.

Study or subgroup	Long duration n/N	Standard duration n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 Relapse at 2 years				
Yoshikawa 1998	54/83	62/88		0.92[0.75,1.14]
6.1.2 Number with frequent relapses at 2 years				
Yoshikawa 1998	20/83	19/88		1.12[0.64,1.94]

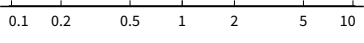


Comparison 7. Cyclosporin (CSA) and steroid therapy in first episode of childhood nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Relapse by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Number needing cytotoxic agents	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Serum creatinine at end of study	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

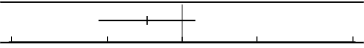
Analysis 7.1. Comparison 7 Cyclosporin (CSA) and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 1 Relapse by 6 months.

Study or subgroup	CSA+prednisone n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1999	5/49	17/55		0.33[0.13,0.83]



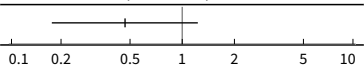
Analysis 7.2. Comparison 7 Cyclosporin (CSA) and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 2 Relapse by 12 months.

Study or subgroup	CSA+prednisone n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1999	18/49	28/55		0.72[0.46,1.13]



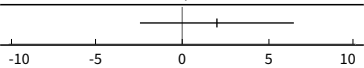
Analysis 7.3. Comparison 7 Cyclosporin (CSA) and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 3 Number needing cytotoxic agents.

Study or subgroup	CSA+prednisone n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1999	5/49	12/55		0.47[0.18,1.23]



Analysis 7.4. Comparison 7 Cyclosporin (CSA) and steroid therapy in first episode of childhood nephrotic syndrome, Outcome 4 Serum creatinine at end of study.

Study or subgroup	CSA+prednisone N	CSA+prednisone Mean(SD)	Prednisone N	Prednisone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
APN 1999	44	48.2 (11.1)	43	46.2 (10)		2[-2.44,6.44]

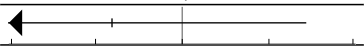


Comparison 8. Steroid therapy in first episode of nephrotic syndrome: high dose methylprednisone versus 2 month therapy

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Time to first relapse	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Relapse rate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Time to remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

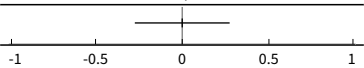
Analysis 8.1. Comparison 8 Steroid therapy in first episode of nephrotic syndrome: high dose methylprednisone versus 2 month therapy, Outcome 1 Time to first relapse.

Study or subgroup	Methylprednisolone N	Methylprednisolone Mean(SD)	Prednisolone N	Prednisolone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Mocan 1999	8	8.5 (24)	7	16.6 (20.3)		-8.1[-30.51,14.31]



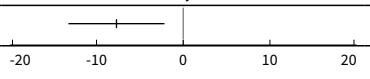
Analysis 8.2. Comparison 8 Steroid therapy in first episode of nephrotic syndrome: high dose methylprednisone versus 2 month therapy, Outcome 2 Relapse rate.

Study or subgroup	Methylprednisolone N	Methylprednisolone Mean(SD)	Prednisolone N	Prednisolone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Mocan 1999	8	0.8 (0.3)	7	0.8 (0.3)		0[-0.27,0.27]



Analysis 8.3. Comparison 8 Steroid therapy in first episode of nephrotic syndrome: high dose methylprednisone versus 2 month therapy, Outcome 3 Time to remission.

Study or subgroup	Methylprednisolone N	Methylprednisolone Mean(SD)	Prednisolone N	Prednisolone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Mocan 1999	8	5.6 (1.1)	7	13.3 (7.4)		-7.7[-13.24,-2.16]

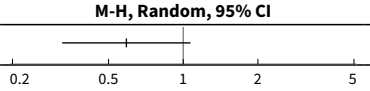


Comparison 9. Steroid therapy and azithromycin (AZM) in the first episode of nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Steroid therapy and azithromycin (AZM) in the first episode of nephrotic syndrome, Outcome 1 Number of children relapsing by 6 months.

Study or subgroup	Prednisone+AZM n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Zhang 2014	14/94	24/95		0.59[0.33,1.07]

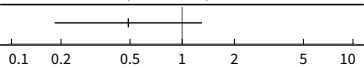


Comparison 10. Daily prednisolone treatment during viral infections

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse with infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of relapses/patient	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Number of infection-related relapses/patient/year	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Total relapses (episodes/patient/1 year)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Number of relapses/patient at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Daily prednisolone treatment during viral infections, Outcome 1 Number with relapse with infection.

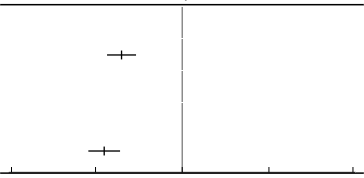
Study or subgroup	Prednisolone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Abeyagunawardena 2008	4/18	10/22		0.49[0.18,1.3]



Favours prednisolone — Favours placebo

Analysis 10.2. Comparison 10 Daily prednisolone treatment during viral infections, Outcome 2 Number of relapses/patient.

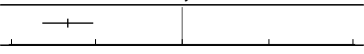
Study or subgroup	Prednisolone N	Prednisolone Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
10.2.1 Number of infection-related relapses/patient/year						
Gulati 2009	49	0.7 (0.3)	46	1.4 (0.5)		-0.7[-0.87,-0.53]
10.2.2 Total relapses (episodes/patient/1 year)						
Gulati 2009	49	0.9 (0.4)	46	1.8 (0.5)		-0.9[-1.08,-0.72]



Favours prednisolone — Favours placebo

Analysis 10.3. Comparison 10 Daily prednisolone treatment during viral infections, Outcome 3 Number of relapses/patient at 2 years.

Study or subgroup	Daily prednisone N	Daily prednisone Mean(SD)	Alternate day prednisone N	Alternate day prednisone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Mattoo 2000	18	2.2 (0.9)	18	5.5 (1.3)		-3.3[-4.03,-2.57]



Daily prednisone — Alternate day prednisone

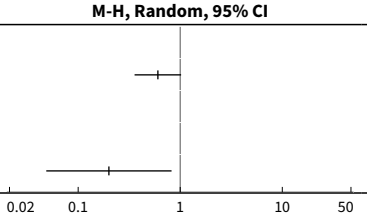
Comparison 11. Steroid therapy in relapse of nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of children relapsing during therapy	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Intermittent dose versus alternate-day therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Daily versus intermittent therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Number of children with further relapses by 9 to 12 months	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Intermittent dose versus alternate-day therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Single versus divided dose therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Intravenous versus oral therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Deflazacort versus prednisone (12 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Prolonged oral versus intermittent therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Mean relapse rate/patient/y	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Single versus divided dose therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Daily versus intermittent therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Deflazacort versus prednisone (12 months therapy)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Mean time to relapse	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Single versus divided dose therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Daily versus intermittent therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Cumulative steroid dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Mean time to remission	2	138	Mean Difference (IV, Random, 95% CI)	0.04 [-0.98, 1.06]
7 Serious adverse events	2	138	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.18, 0.91]

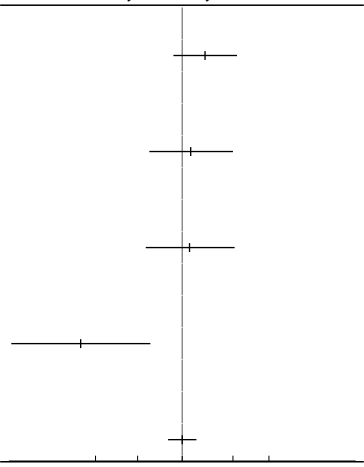
Analysis 11.1. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 1 Number of children relapsing during therapy.

Study or subgroup	Treatment therapy n/N	Standard therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.1.1 Intermittent dose versus alternate-day therapy (6 months therapy)				
APN 1981	10/23	18/25		0.6[0.36,1.02]
11.1.2 Daily versus intermittent therapy (2 months therapy)				
ISKDC 1979	2/25	10/25		0.2[0.05,0.82]



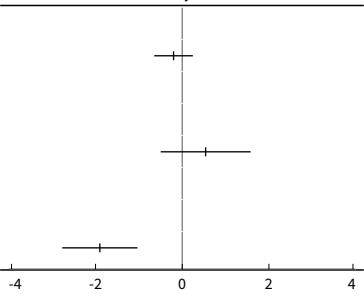
Analysis 11.2. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 2 Number of children with further relapses by 9 to 12 months.

Study or subgroup	Treatment therapy n/N	Standard therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.2.1 Intermittent dose versus alternate-day therapy (6 months therapy)				
APN 1981	21/23	19/25		1.2[0.93,1.55]
11.2.2 Single versus divided dose therapy (2 months therapy)				
Ekka 1997	29/47	27/47		1.07[0.77,1.5]
11.2.3 Intravenous versus oral therapy (6 months therapy)				
Imbasciati 1985	21/31	21/33		1.06[0.75,1.52]
11.2.4 Deflazacort versus prednisone (12 months therapy)				
Broyer 1997	8/20	18/20		0.44[0.25,0.78]
11.2.5 Prolonged oral versus intermittent therapy (2 months therapy)				
ISKDC 1979	24/25	24/25		1[0.89,1.12]



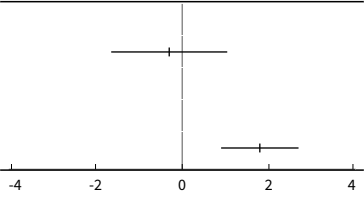
Analysis 11.3. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 3 Mean relapse rate/patient/y.

Study or subgroup	Treatment therapy N	Mean(SD)	Standard therapy N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
11.3.1 Single versus divided dose therapy (2 months therapy)						
Ekka 1997	47	1.7 (1.1)	47	1.9 (1.1)		-0.2[-0.64,0.24]
11.3.2 Daily versus intermittent therapy (2 months therapy)						
ISKDC 1979	25	3.8 (2.2)	25	3.3 (1.5)		0.54[-0.5,1.58]
11.3.3 Deflazacort versus prednisone (12 months therapy)						
Broyer 1997	20	0.9 (1.4)	20	2.8 (1.4)		-1.9[-2.77,-1.03]

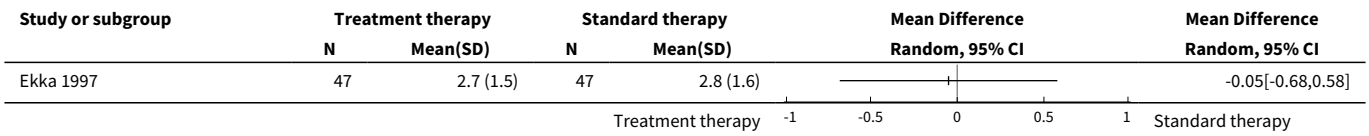


Analysis 11.4. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 4 Mean time to relapse.

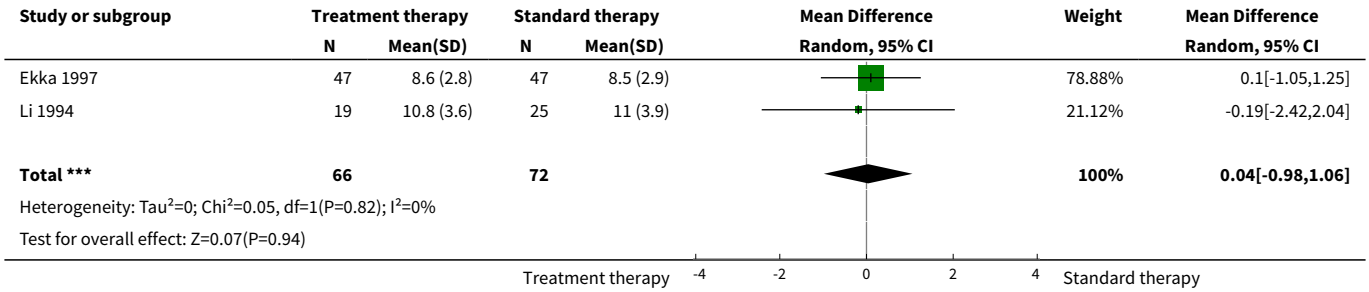
Study or subgroup	Treatment therapy N	Mean(SD)	Standard therapy N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
11.4.1 Single versus divided dose therapy (2 months therapy)						
Ekka 1997	47	5.6 (3.3)	47	5.9 (3.3)		-0.3[-1.64,1.04]
11.4.2 Daily versus intermittent therapy (2 months therapy)						
ISKDC 1979	25	3.3 (2)	25	1.5 (1.1)		1.79[0.9,2.68]



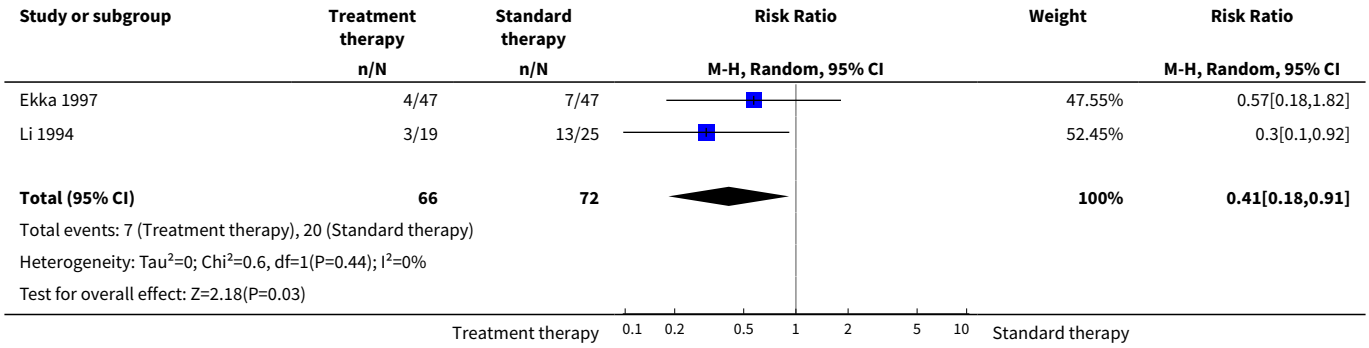
Analysis 11.5. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 5 Cumulative steroid dose.



Analysis 11.6. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 6 Mean time to remission.



Analysis 11.7. Comparison 11 Steroid therapy in relapse of nephrotic syndrome, Outcome 7 Serious adverse events.



Comparison 12. 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)	Totals not selected
1.1 Relapse by 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Relapse by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3 Relapse by 2 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Relapse by 3 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Relapse rate/patient/y	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Relapse rate at 1 year	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Relapse rate at 2 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Relapse rate at 3 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Number with frequently relapsing or steroid dependent nephrotic syndrome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Cumulative steroid dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 After 1 year	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 After 2 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 After 3 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Number with hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Number with growth failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 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	Risk Ratio M-H, Random, 95% CI
12.1.1 Relapse by 6 months				
Jayantha 2002b	1/44	29/46		0.04[0.01,0.25]

Study or subgroup	Long duration n/N	Standard duration n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.1.2 Relapse by 12 months				
Jayantha 2002b	16/42	30/34		0.43[0.29,0.65]
12.1.3 Relapse by 2 years				
Jayantha 2002b	21/36	27/28		0.6[0.45,0.8]
12.1.4 Relapse by 3 years				
Jayantha 2002b	21/30	23/23		0.71[0.56,0.9]

Long duration Standard duration

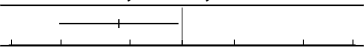
Analysis 12.2. Comparison 12 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 2 Relapse rate/patient/y.

Study or subgroup	Long duration N	Long duration Mean(SD)	Standard duration N	Standard duration Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
12.2.1 Relapse rate at 1 year						
Jayantha 2002b	40	0.4 (0.5)	32	2.1 (1.5)		-1.78[-2.3,-1.26]
12.2.2 Relapse rate at 2 years						
Jayantha 2002b	33	0.4 (0.4)	23	2.2 (1.4)		-1.79[-2.39,-1.19]
12.2.3 Relapse rate at 3 years						
Jayantha 2002b	25	0.4 (0.4)	16	2.2 (1.3)		-1.74[-2.39,-1.09]

Long duration Standard duration

Analysis 12.3. Comparison 12 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 3 Number with frequently relapsing or steroid dependent nephrotic syndrome.

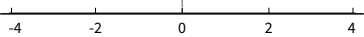
Study or subgroup	Long duration n/N	Standard duration n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jayantha 2002b	7/40	13/32		0.43[0.19,0.95]



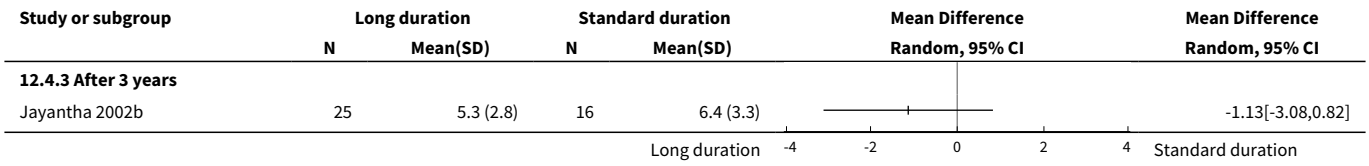
Long duration Standard duration

Analysis 12.4. Comparison 12 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 4 Cumulative steroid dose.

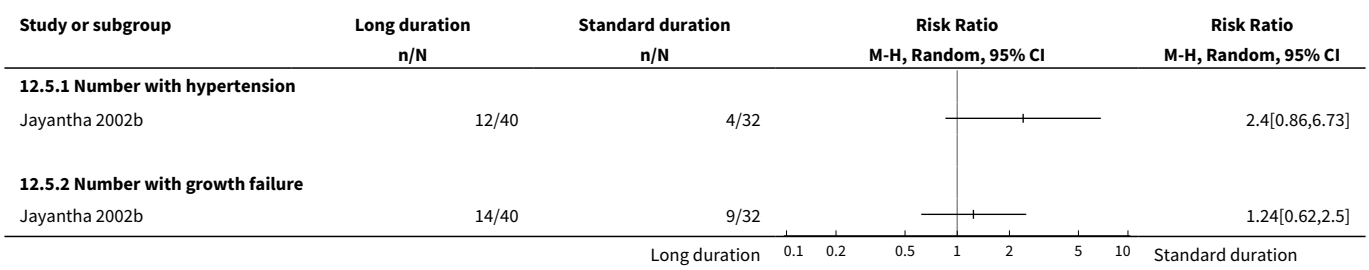
Study or subgroup	Long duration N	Long duration Mean(SD)	Standard duration N	Standard duration Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
12.4.1 After 1 year						
Jayantha 2002b	40	3.3 (1.2)	32	2.7 (1.3)		0.59[0.02,1.16]
12.4.2 After 2 years						
Jayantha 2002b	33	4.3 (2)	23	4.6 (2.4)		-0.32[-1.52,0.88]



Long duration Standard duration



Analysis 12.5. Comparison 12 Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 5 Adverse effects.



ADDITIONAL TABLES

Table 1. Outcomes of studies in children with relapsing nephrotic syndrome

Study ID	Relapse on therapy (RR (95% CI))	Relapse by 9 months (RR (95% CI))	Relapse by 12 months (RR (95% CI))	Mean relapse rate MD (95% CI))	Mean time to remission (MD (95% CI)	Steroid therapy
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 versus intermittent
Broyer 1997			0.44 (0.25 to 0.78)	-1.90 (-2.77 to -1.03)		Deflazacort versus prednisone
Ekka 1997		1.07 (0.77 to 1.50)				Daily versus divided dose prednisone
Imbasciati 1985			1.06 (0.75 to 1.52)			IV and oral versus oral prednisone
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 prednisone
Jayantha 2002b			0.43 (0.29 to 0.65)	-1.78 (-2.30 to -1.26)		7 months prednisone versus standard ISKDC regimen for relapse
Leisti 1978						Cortisol versus placebo in FRNS (cross-over): 5/13 (38%) on cortisol relapsed versus 12/13 (92%) on placebo

Table 1. Outcomes of studies in children with relapsing nephrotic syndrome *(Continued)*

Li 1994	0.04 days (-0.98 to 1.06)	Daily versus divided dose prednisone
Liern 2008		Time to relapse (cross-over): deflazacort 105 ± 4.19 days versus methylprednisolone 85 ± 3.8 days

FRNS - frequently relapsing nephrotic syndrome; ISKDC - International Study of Kidney Disease in Children

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Nephrotic Syndrome] this term only 2. MeSH descriptor: [Nephrosis, Lipoid] this term only 3. "nephrotic syndrome" 4. "lipoid nephrosis" 5. #1 or #2 or #3 or #4 6. child* or infant* 7. boy* or girl* 8. pediatric* or paediatric* 9. #6 or #7 or #8 10.#5 and #9
MEDLINE	1. nephrotic syndrome/ 2. nephrosis, lipoid/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-4 6. exp child/ 7. exp Infant/ 8. child$.tw. 9. infant$.tw. 10.(boy$ or girl$).tw. 11.(pediatric or paediatric).tw. 12.or/7-12 13.and/5,12
EMBASE	1. nephrotic syndrome/ 2. lipoid nephrosis/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-4 6. exp Child/ 7. child$.tw. 8. infant$.tw.

(Continued)

9. (boy$ or girl$).tw.
10.(pediatric or paediatric).tw
11.or/6-10
12.and/5,11

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement

(Continued)

Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
16 September 2015	Amended	Minor amendment to forest plot description 2.8.2 - changed from 'Low risk...' to "High risk..."

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 4, 2000

Date	Event	Description
11 March 2015	New citation required and conclusions have changed	10 new studies included
11 March 2015	New search has been performed	New studies identified
13 May 2009	Amended	Contact details updated.
23 September 2008	Amended	Converted to new review format.
21 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

- Deirdre Hahn: none known
- Elisabeth Hodson: none known
- Narelle Willis: none known
- Jonathan Craig: 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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced the Quality assessment checklist list used in the previous versions of this review.

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