Cochrane Library

Cochrane Database of Systematic Reviews

Corticosteroid therapy for nephrotic syndrome in children (Review)

Hahn D, Samuel SM, Willis NS, Craig JC, Hodson EM

Hahn D, Samuel SM, Willis NS, Craig JC, Hodson EM.
Corticosteroid therapy for nephrotic syndrome in children.
Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD001533.
DOI: 10.1002/14651858.CD001533.pub6.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Corticosteroid therapy for nephrotic syndrome in children

Deirdre Hahn[1], Susan M Samuel[2], Narelle S Willis[3,4], Jonathan C Craig[4,5], Elisabeth M Hodson[3,4]

[1]Department of Nephrology, The Children's Hospital at Westmead, Westmead, Australia. [2]Department of Pediatrics, University of Calgary, Calgary, Canada. [3]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [4]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [5]College of Medicine and Public Health, Flinders University, Adelaide, Australia

Contact address: Elisabeth M Hodson, elisabeth.hodson@health.nsw.gov.au.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2020.

Citation: Hahn D, Samuel SM, Willis NS, Craig JC, Hodson EM. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2020, Issue 8. Art. No.: CD001533. DOI: 10.1002/14651858.CD001533.pub6.

ABSTRACT

Background

In nephrotic syndrome protein leaks from blood into 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 death 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 2002, 2005, 2007, and 2015.

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 Kidney and Transplant Register of Studies up to 30 May 2020 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) performed in children (one 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

In this 2020 review update 16 new included studies were identified providing a total of 48 included studies with 3941 randomised participants.

Risk of bias methodology was often poorly performed with only 25 studies and 22 studies respectively assessed to be at low risk for random sequence generation and allocation concealment. Only nine studies (19%) were at low risk of bias for performance (blinding of participants

and personnel) and 11 studies were at low risk of detection bias (blinding of outcome assessment); nine of these studies were placebo-controlled RCTs. Twenty-two studies (fewer than 50%) were at low risk for attrition bias and 23 studies were at low risk for reporting bias (selective outcome reporting).

In seven studies, which evaluated children in their initial episode of SSNS and were at low risk of bias for selection bias, there is little or no difference in the number of children with frequent relapses when comparing two months of prednisone with three months or more (RR 0.99, 95% CI 0.82 to 1.19; 585 participants, 4 studies; I^2 = 0%) or when comparing three months with five to seven months of therapy (RR 0.99, 95% CI 0.74 to 1.33; 376 participants, 3 studies; I^2 = 35%; high certainty evidence). In analyses of eight studies at low risk of selection bias, there is little or no difference in the number of children with any relapse by 12 to 24 months when comparing two months of prednisone with three months or more (RR 0.91, 95% CI 0.78 to 1.06; 637 participants; 5 studies; I^2 = 47%) or when comparing three months with five to seven months of therapy (RR 0.88, 95% CI 0.70 to 1.11; 377 participants, 3 studies; I^2 = 53%). Little or no difference was noted in adverse effects between the different treatment durations.

Among children with relapsing SSNS, two small studies showed that time to remission did not differ between prednisone doses of 1 mg/kg compared with the conventional dose of 2 mg/kg (MD 0.71 days, 95% CI -0.43 to 1.86; 79 participants) and that the total prednisone dose administered was lower (MD -20.60 mg/kg, 95% CI -25.65 to -15.55; 20 participants). Two studies found little or no difference in the number with relapse at six months when comparing dosing by weight with dosing by surface area (RR 1.03, 95% CI 0.71 to 1.49; 146 participants). One study found a reduced risk of relapse with low daily dosing compared with alternate daily dosing (MD -0.90 number of relapses/year, 95% CI -1.33 to -0.47). Four studies found that in children with frequently relapsing disease, daily prednisone during viral infections compared with alternate-day prednisone or no treatment reduced the risk of relapse.

Authors' conclusions

There are now four well designed studies randomising 823 children which have clearly demonstrated that there is no benefit of prolonging prednisone therapy beyond two to three months in the first episode of SSNS. Small studies in children with relapsing disease have identified no differences in the times to remission using half the conventional induction dose of 2 mg/kg or 60 mg/m^2. It is imperative that a much larger study be carried out to confirm these findings.

Lower dose prednisone therapy administered daily during an upper respiratory infection or other infection reduces the risk of relapse compared with continuing alternate-day prednisone or no prednisone based on four small studies. The results of a much larger RCT enrolling more than 300 children are awaited to determine the relative efficacies and adverse effects of using alternate-day compared with daily prednisone to prevent relapse in children with intercurrent infections.

PLAIN LANGUAGE SUMMARY

Corticosteroid therapy for children with nephrotic syndrome

What is the issue?

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. When untreated, children can suffer from serious infections. In most children with nephrotic syndrome, this protein leak resolves with corticosteroid drugs (prednisone, prednisolone) reducing the risk of serious infection. However, children usually have repeat episodes which are often triggered by viral infections. Corticosteroid drugs can have serious side effects in children so we need to know the best way to use them.

What did we do?

We looked at evidence from 48 studies randomising 3941 children. Fourteen 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 quality with only about half of the studies at low risk of producing biased results.

What did we find?

In high quality studies, there was no difference in the risk of relapse or in the number of children who relapse frequently between long duration (three to seven months) and shorter durations (two to three months) of prednisone (high certainty evidence). Giving daily rather than alternate-day prednisone during a viral infection may reduce the number of children who relapse with infection. Two very small studies suggested that lower doses of prednisone can be used to achieve and maintain remission.

Conclusions

Children with their first episode of nephrotic syndrome only need two or three months of prednisone since longer courses do not reduce the risk of relapse or reduce the risk that the child will relapse frequently. We need more information to determine whether giving daily prednisone during an infection reduces the risk of relapse. We need a large study to determine whether we can use lower doses of prednisone to treat a relapse in children with nephrotic syndrome.

SUMMARY OF FINDINGS

Summary of findings 1. Steroid therapy in first episode of nephrotic syndrome: 3 months or more versus 2 months of therapy for nephrotic syndrome in children

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

Patient or population: children with nephrotic syndrome
Setting: paediatric or paediatric nephrology services
Intervention: steroid therapy in first episode of nephrotic syndrome: 3 months or more
Comparison: 2 months of therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Risk with 2 months of therapy	Risk with 3 months or more of therapy			
Number with frequent relapses by 12 to 24 months	450 per 1,000	387 per 1,000 (319 to 477)	RR 0.86 (0.71 to 1.06)	976 (8)	⊕⊕⊕⊖[1] MODERATE
Number of children relapsing by 12 to 24 months	646 per 1,000	497 per 1,000 (407 to 614)	RR 0.77 (0.63 to 0.95)	1309 (12)	⊕⊕⊖⊖[1,2] LOW
Number with frequent relapses by 12 to 24 months stratified by risk of selection bias: Low risk of selection bias	413 per 1,000	409 per 1,000 (339 to 491)	RR 0.99 (0.82 to 1.19)	585 (4)	⊕⊕⊕⊕ HIGH
Number with frequent relapses by 12 to 24 months stratified by risk of selection bias: Unclear or high risk of bias for allocation bias	357 per 1,000	161 per 1,000 (93 to 275)	RR 0.45 (0.26 to 0.77)	220 (3)	⊕⊕⊖⊖ [1,2] LOW
Adverse events: psychological disorders	470 per 1,000	470 per 1,000 (249 to 894)	RR 1.00 (0.53 to 1.90)	456 (4)	⊕⊕⊖⊖[2,3] LOW
Adverse events: hypertension	50 per 1,000	89 per 1,000 (28 to 287)	RR 1.78 (0.55 to 5.73)	548 (7)	⊕⊕⊕⊖ [1] MODERATE
Adverse events: Cushing's syndrome	402 per 1,000	450 per 1,000 (305 to 663)	RR 1.12 (0.76 to 1.65)	547 (5)	⊕⊕⊕⊖[1] MODERATE

*__The risk in the intervention group__ (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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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

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

Steroid therapy in first episode of nephrotic syndrome: 5 to 7 months versus 3 months for nephrotic syndrome in children

Patient or population: children with nephrotic syndrome
Settings: paediatric or paediatric nephrology services
Intervention: steroid therapy in first episode of nephrotic syndrome: 5 to 7 months versus 3 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Risk with 3 months of therapy	Risk with 5 to 7 months of therapy			
Number with frequent relapses by 12 to 24 months	387 per 1000	282 per 1000 (190 to 422)	RR 0.73 (0.49 to 1.09)	706 (6)	⊕⊕⊕⊖ moderate[1]
Number of children relapsing by 12 to 24 months	696 per 1000	432 per 1000 (313 to 592)	RR 0.62 (0.45 to 0.85)	762 (7)	⊕⊕⊖⊖ low[1,2]
Subgroup analysis by risk of bias for number with frequent relapses: low risk of selection bias	440 per 1000	436 per 1000 (326 to 585)	RR 0.99 (0.74 to 1.33)	376 (3)	⊕⊕⊕⊕ high

Subgroup analysis by risk of bias for number with frequent relapses: Unclear or high risk of selection bias	327 per 1000	157 per 1000 (105 to 236)	RR 0.48 (0.32 to 0.72)	330 (3)	⊕⊕⊕⊖ moderate[2]
Adverse events: hypertension	126 per 1000	140 per 1000 (90 to 220)	RR 1.11 (0.71 to 1.74)	752 (6)	⊕⊕⊕⊖ moderate[2]
Adverse events: eye complications	36 per 1000	17 per 1000 (6 to 42)	RR 0.46 (0.18 to 1.17)	614 (5)	⊕⊕⊕⊖ moderate[2]
Adverse events: Cushingoid appearance	375 per 1000	323 per 1000 (225 to 461)	RR 0.86 (0.61 to 1.23)	762 (6)	⊕⊕⊕⊖ moderate[2]
Adverse events: psychological disorders	53 per 1000	16 per 1000 (3 to 96)	RR 0.30 (0.05 to 1.83)	505 (4)	⊕⊕⊖⊖ low[2,3]

*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 the most common acquired childhood kidney disease. 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). There are marked differences in the incidence of nephrotic syndrome depending on ethnicity with proportions ranging from 1.15 to 16.9/100,000 children with the highest incidence in children from south Asia (Noone 2018). Most children have minimal change disease, in which changes on light microscopy are minor or absent and respond to corticosteroid agents. The histological variant seen and the response to immunosuppressive treatment varies with ethnicity (Eddy 2003). Steroid-sensitive nephrotic syndrome (SSNS) is less common in African and African-American children, and in South Africa only 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 leading to injury of the podocyte, a key component of the glomerular filtration barrier.

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 to adverse effects related to corticosteroid therapy and to corticosteroid sparing agents. Children with nephrotic syndrome are at increased risk of bacterial infection (characteristically resulting in peritonitis, cellulitis, or septicaemia), thromboembolic phenomena, protein calorie malnutrition, and acute kidney injury. Before antibiotics became available, two thirds of children with nephrotic syndrome died. Death rates fell to 35% with the introduction of sulphonamides and penicillin (Arneil 1971) and fell further with the use of corticosteroid medications (Arneil 1956).

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 1956, Arneil 1971). Corticosteroid usage has reduced the death 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 treatment 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 well documented adverse effects in children. Major complications related to prolonged corticosteroid use in nephrotic syndrome include growth impairment, particularly with steroid therapy administered daily (Hyams 1988), cataracts (Aydin 2019; Ng 2001), arterial hypertension (Aydin 2019) and excessive weight gain or obesity (Ruth 2005). Two 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 that family background, particularly maternal distress, reduced the quality of life and psychosocial adjustment. Patients and families report challenges in living with the disease because the condition is poorly understood and the clinical course is uncertain (Beanlands 2017). Adverse effects are particularly prevalent in those children who relapse frequently and require multiple courses of corticosteroids.

How the intervention might work

Glucocorticoids are potent anti-inflammatory and immunosuppressant drugs. The effects of glucocorticoids are known to be mediated by both genomic and non-genomic mechanisms (Schijvens 2019). 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 (Kadmiel 2013; Kirshcke 2014; Ponticelli 2018). 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 (Ramamoorthy 2016). These are mediated via interactions of various kinases with cytosolic or membrane-bound glucocorticoid receptors and do not require protein synthesis. At high glucocorticoid doses, suppression of T-cell function occurs. Corticosteroids also act directly to stabilise the podocyte cytoskeleton (Guess 2010; Ohashi 2011).

Why it is important to do this review

The original treatment schedules for childhood nephrotic syndrome were developed in an ad hoc manner more than 50 years ago. 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 RCTs have investigated different durations and total corticosteroid therapy doses in an effort to delineate the optimal doses and durations of corticosteroid therapy balancing efficacy and toxicity. 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. Observational data (Raja 2017) and very small RCTs (Borovitz 2020; Sheikh 2019) suggest that children can be successfully treated with smaller doses and durations of corticosteroid therapy. Therefore, the 2020 update of this review has been undertaken to identify whether new RCTs, which evaluate different corticosteroid regimens in the initial episode of SSNS and in relapsing disease, provide additional information on the most effective corticosteroid therapy for steroid sensitive nephrotic syndrome in children.

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 were included 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.

Types of participants

Inclusion criteria

Children aged one 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/hour 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/day) or congenital or infantile 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 three months or more 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.

Types of outcome measures

Primary outcomes

1. The numbers of children with and without relapse at 12 months or more after completion of treatment.
2. The number of children who developed frequently relapsing nephrotic syndrome (FRNS).

Secondary outcomes

1. Mean relapse rates
2. Serious adverse events including reduced growth rates, hypertension, cataracts/glaucoma, psychological disorders, infections, thromboses and osteoporosis
3. Cumulative corticosteroid dosage

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 30 May 2020 through contact with the Information Specialist using search terms relevant to this review. The 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. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

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

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete 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. Updates in 2003, 2005, 2007 and 2015 were undertaken by three or four authors (DH, EH, NW, JC). The 2020 update was undertaken by three reviewers (DH, SS, EH) with final review by two other reviewers (NW and JC).

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 independently by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- 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

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values is as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

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 of initial treatment with different durations 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.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades

of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

Outcomes included in Summary of Findings Tables

- Number with relapse
- Number with frequent relapse (total and stratified for risk of bias)
- Adverse effects (psychological disturbances, hypertension, Cushing's Syndrome, eye complications)

RESULTS

Description of studies

Results of the search

Search results are shown in Figure 1.

Figure 1. Study flow diagram.

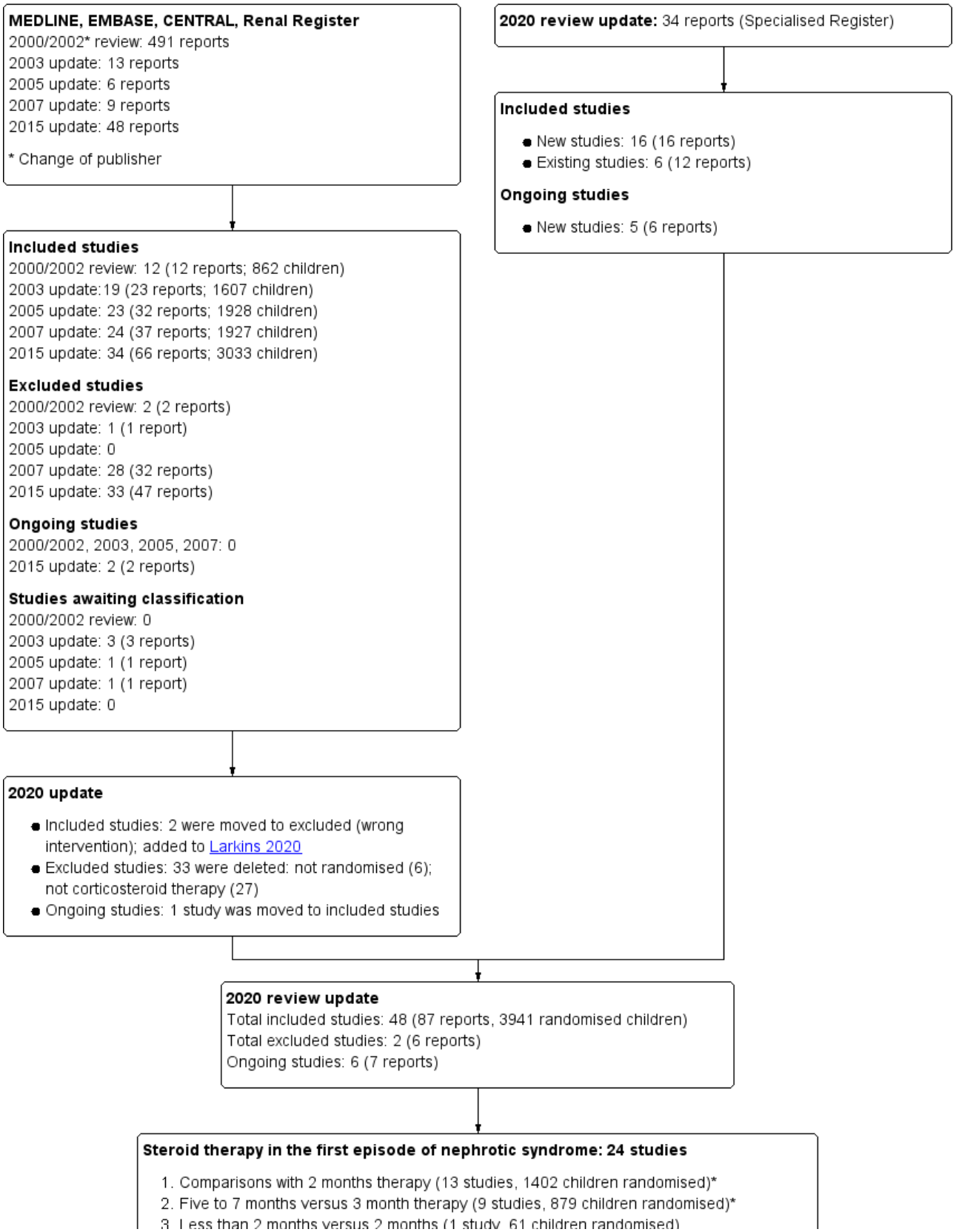


Figure 1. (Continued)

2. Five to 7 months versus 3 month therapy (9 studies, 879 children randomised)*
3. Less than 2 months versus 2 months (1 study, 61 children randomised)
4. 12 months versus 5 months therapy (1 study, 58 children randomised)
5. Different total doses of prednisone (1 study, 68 children randomised)

* One study had children in comparison groups 1 and 2

Children with initial or relapsing SSNS (9 studies)

1. Deflazacort versus prednisone (4 studies, 118 children randomised)
2. Methylprednisolone versus prednisone (3 studies, 113 children randomised)
3. Prednisone dosed/kg versus prednisone dosed/BSA (2 studies, 160 children randomised)

Children with frequently relapsing SSNS: 15 studies

1. Steroid therapy in relapse of nephrotic syndrome (11 studies, 738 children randomised)
2. Daily prednisolone treatment during viral infections (4 studies, 224 children randomised)

For the 2020 update, our search (to 30 May 2020) identified 34 new reports. After full-text review, 14 new included studies were identified (16 reports); one previous ongoing study has now been included. In addition, 12 new reports of six existing studies were identified. Two studies (APN 2006; Zhang 2014), which evaluated non-corticosteroid agents with prednisone in the initial episode of SSNS, have been transferred to the Cochrane review evaluating non-corticosteroid agents in SSNS (Larkins 2020) so that this review now only includes studies assessing corticosteroids. No other new excluded studies were identified. Five new ongoing studies were identified (CTRI/2015/11/006345; CTRI/2018/05/013634; CTRI/2018/05/014075; RESTERN 2017; Sinha 2016) and one study (PREDNOS 2 2014) identified in Hahn 2015 is continuing.

For the search results of our previous reviews please see (Hodson 2002; Hodson 2003; Hodson 2005; Hodson 2007; Hahn 2015).

Included studies

The 48 included studies randomised/analysed 3941/3659 children and were divided into groups according to the 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.

Three months or more versus two months therapy in the initial episode of SSNS (13 studies; 1465 randomised children)

Thirteen studies (APN 1993; Bagga 1999; Jayantha 2002a; Ksiazek 1995 (Groups 1 and 3); Moundekhel 2012; Norero 1996; Paul 2014; PREDNOS 2019; PREDNOS PILOT 2019; Satomura 2001; Ueda 1988; Yoshikawa 1998; Yoshikawa 2015) compared durations of two months with three months or more of prednisone therapy. 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 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 (Group 3) and the group treated for six months (group 1) were included in the meta-analysis. Norero 1996 excluded those children who became steroid dependent. In this update, Yoshikawa 1998, which compared two months of prednisone with 4.5 months with both groups received the Chinese herb, Sairei-to, was included in this analysis on the assumption that the effect of the herb would be the same in both treatment groups. Data from Paul 2014 could not be included in meta-analyses because of differential loss to follow up, with loss to follow up of 15/47 children (33%) in the 12-week treatment group compared with 6/46 children (13%) in the 8-week treatment group.

Five to seven months versus three months therapy in the initial episode of SSNS (nine studies; 992 randomised children)

Nine studies (Al Talhi 2018; Anand 2013; Hiraoka 2003; Ksiazek 1995 (Groups 1 and 2); Mishra 2012, Pecoraro 2003; Sharma 2002; Sinha 2015; Teeninga 2013) compared five to seven months with three months of prednisone therapy. One study including 60 children (Anand 2013) did not report the numbers of children treated in each group so data from only eight studies could be included in the meta-analyses. Increased duration of prednisone treatment led to increased total prednisone dose compared with the three month group in all studies except Teeninga 2013, who 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 (group 2) and six months (group 1) were included in this analysis. Pecoraro 2003 included 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 (total prednisone dose 5235 mg/m^2) were included in the meta-analysis.

Daily prednisone treatment during viral infections in children with relapsing or initial episode of SSNS (four studies; 224 randomised children)

Three studies (Abeyagunawardena 2008; Gulati 2011; 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 viral infections in children not receiving prednisone.

Deflazacort versus prednisone therapy in children with relapsing or initial episode of SSNS (four studies; 118 randomised children)

Four studies explored different regimens of deflazacort versus prednisone.

- Agarwal 2010 compared deflazacort with prednisone in children with the initial episode of SSNS but the details of the intervention were not reported
- Broyer 1997 compared deflazacort with an equivalent dose of prednisone with reducing doses over 12 months in children with steroid dependent SSNS
- Liern 2008 compared deflazacort with methylprednisolone for 12 weeks in children with relapsing SSNS in a cross over study
- Singhal 2015 compared deflazacort with prednisone for 12 weeks in children with the initial episode of SSNS

Oral methylprednisolone regimens in children with the initial episode of SSNS (three studies; 113 randomised children)

Three studies compared different regimens of methylprednisolone with prednisone

- Imbasciati 1985 compared six months of treatment commencing with methylprednisolone with prednisone with six months of prednisone
- Mocan 1999 compared 14 days of high dose methylprednisolone with six months of prednisone
- Zhang 2007d compared six months of treatment involving methylprednisolone with six months of prednisone. The details of interventions were not reported.

One month therapy versus two months of therapy in the initial episode of SSNS (one study; 61 randomised children)

- APN 1988 compared less than two months of prednisone with two months.

Five months versus 12 months therapy in the initial episode of SSNS (one study; 58 randomised children)

- Kleinknecht 1982 compared five months of prednisone with 12 months; the timing of the follow-up period in relation to the duration of initial therapy was not stated.

Different total doses of prednisone given for three months in the initial episode of SSNS (one study; 68 randomised children)

- Hiraoka 2000 compared a higher dose versus a conventional dose of prednisone given for three months.

Alternate-day therapy versus intermittent therapy in relapsing SSNS (one study; 64 randomised children)

- APN 1981 compared an alternate-day prednisone regimen with three out of seven day regimen to maintain remission.

Daily therapy versus intermittent therapy in relapsing SSNS (one study; 64 randomised children)

- ISKDC 1979 compared a daily prednisone regimen with a 3 out of 7 day regimen to maintain remission.

Single daily doses versus multiple daily doses in relapsing nephrotic syndrome (two studies; 150 randomised children)

- Ekka 1997 and Li 1994 compared a single daily dose of prednisone with three times/day dosing to achieve remission

Low versus conventional dose prednisone in relapsing nephrotic syndrome (three studies; 130 randomised children)

- Borovitz 2020 compared two reduced doses (1 mg/kg/day; 1.5 mg/kg/day) with conventional dose prednisone 2 mg/kg/day to achieve remission
- Sheikh 2019 compared reduced dose (1 mg/kg/day) of prednisone with conventional dose (2 mg/kg/day) to achieve remission
- Kansal 2019 compared different alternate-day prednisone doses in the second month of initial treatment to maintain remission

Daily versus alternate-day prednisone in relapsing nephrotic syndrome (one study; 62 randomised children)

- Yadav 2019 compared daily with alternate-day prednisone for one year in children with frequently relapsing SSNS

Weight-based versus body surface area-based dosing of prednisone in the initial episode of SSNS (two studies; 160 randomised children)

- Two studies (Basu 2020; Raman 2016) compared weight-based dosing with body surface area-based dosing in children with their initial episode of SSNS and with relapse of SSNS.

Alternate-day prednisone for four weeks versus eight week weaning regimen in relapsing nephrotic syndrome (one study; 126 randomised children)

- PROPINE 2018 compared four weeks of alternate-day prednisone with an eight week weaning regimen using the same cumulative prednisone dose. The authors reported that the probability of remission at one year was similar between groups.

Three months or more versus two months therapy in relapsing nephrotic syndrome (one study; 129 randomised children)

- Jayantha 2002b compared two months of prednisone with seven months in children with relapsing nephrotic syndrome.

Addition of cortisol to prednisone regimen compared with no cortisol addition in relapsing nephrotic syndrome (one cross-over study: 13 randomised children)

- Leisti 1978 compared the addition of cortisol supplementation with no cortisol In children with relapsing nephrotic syndrome and a subnormal response to 2 hour ACTH test 1 to 12 days after completing prednisone,

Excluded studies

In the 2015 review (Hahn 2015), we excluded 33 studies (47 reports) after full text assessment for this review. Of these 33 excluded studies, six were not RCTs and 27 were RCTs involving non-corticosteroid interventions in children with SSNS. In the 2020 review these studies have been removed. In addition, two studies previously included (APN 2006; Zhang 2014) were excluded from this review and transferred to the Cochrane review of "Non-corticosteroid interventions in children with steroid sensitive nephrotic syndrome" (Larkins 2020).

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.

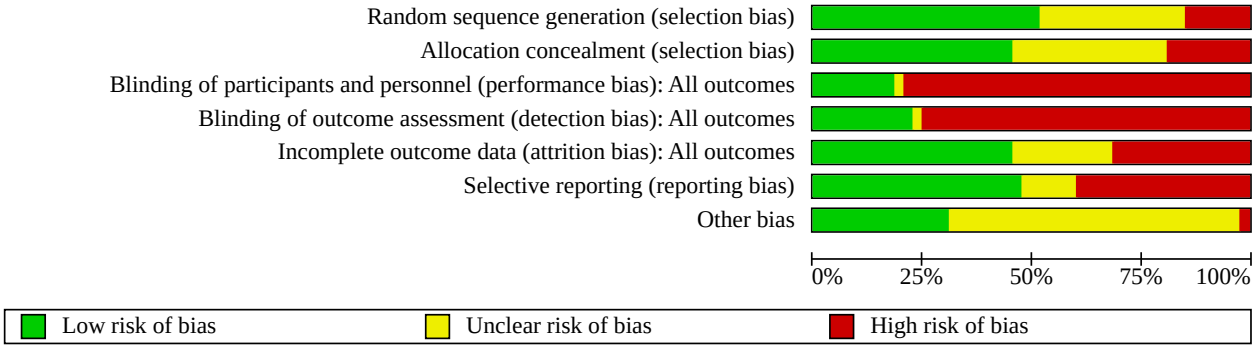


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

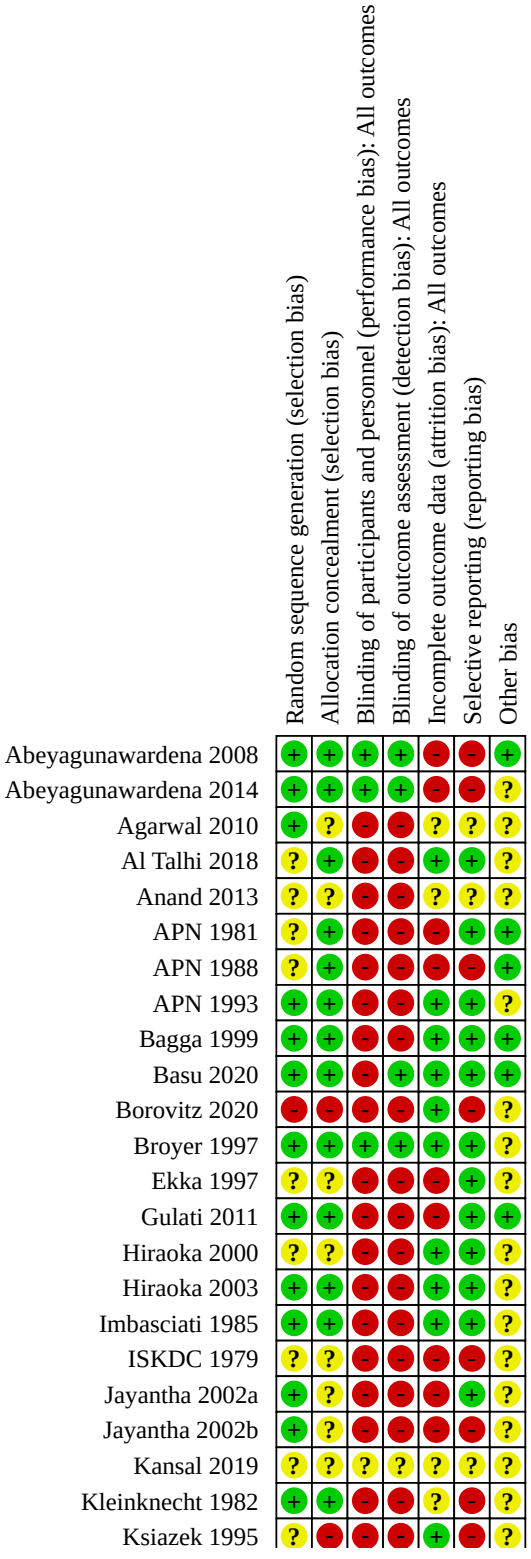
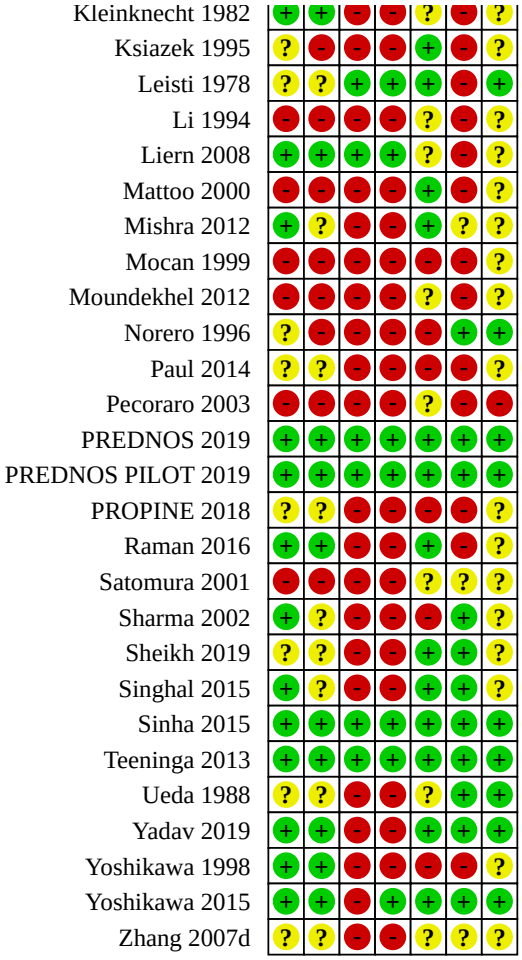


Figure 3. (Continued)



Allocation

Random sequence generation was considered at low risk of bias in 25 studies (Abeyagunawardena 2008; Abeyagunawardena 2014; Agarwal 2010; APN 1993; Bagga 1999; Basu 2020; Broyer 1997; Gulati 2011; Hiraoka 2003; Imbasciati 1985; Jayantha 2002a; Jayantha 2002b; Kleinknecht 1982; Liern 2008; Mishra 2012; PREDNOS 2019; PREDNOS PILOT 2019; Raman 2016; Sharma 2002; Singhal 2015; Sinha 2015; Teeninga 2013; Yadav 2019; Yoshikawa 1998; Yoshikawa 2015) and high risk in seven studies (Borovitz 2020; Li 1994; Mattoo 2000; Mocan 1999; Moundekhel 2012; Pecoraro 2003; Satomura 2001). Sequence generation methods was assessed as unclear in the remaining 16 studies.

Allocation concealment was considered to be at low risk of bias in 22 studies (Abeyagunawardena 2008; Abeyagunawardena 2014; Al Talhi 2018; APN 1981; APN 1988; APN 1993; Bagga 1999; Basu 2020; Broyer 1997; Gulati 2011; Hiraoka 2003; Imbasciati 1985; Kleinknecht 1982; Liern 2008; PREDNOS 2019; PREDNOS PILOT 2019; Raman 2016; Sinha 2015; Teeninga 2013; Yadav 2019; Yoshikawa 1998; Yoshikawa 2015) and at high risk of bias in nine studies (Borovitz 2020; Ksiazek 1995; Li 1994; Mattoo 2000; Mocan 1999; Moundekhel 2012; Norero 1996; Pecoraro 2003; Satomura 2001). Ksiazek 1995 stated that parents could influence which treatment group their child was assigned. Allocation concealment methods was assessed as unclear in the remaining 17 studies.

Blinding

Nine 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; PREDNOS 2019; PREDNOS PILOT 2019; Sinha 2015; Teeninga 2013). Basu 2020 and Yoshikawa 2015 was open-label studies so at high risk of performance bias but were at low risk of detection bias. Kansal 2019 was assessed as unclear risk for both performance and detection bias. The remaining studies 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 22 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 (Al Talhi 2018; APN 1993; Bagga 1999; Basu 2020; Borovitz 2020; Broyer 1997; Hiraoka 2000; Hiraoka 2003; Imbasciati 1985; Ksiazek 1995; Leisti 1978; Mattoo 2000; Mishra 2012; PREDNOS 2019; PREDNOS PILOT 2019; Raman 2016; Sheikh 2019; Singhal 2015; Sinha 2015; Teeninga 2013; Yadav 2019;

Yoshikawa 2015). Fifteen studies were 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; Ekka 1997; Gulati 2011; ISKDC 1979; Jayantha 2002a; Jayantha 2002b; Mocan 1999; Norero 1996; Paul 2014; PROPINE 2018; Sharma 2002; Yoshikawa 1998). The remaining 11 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 FRNS, 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. Twenty-three studies were at low risk of reporting bias (Al Talhi 2018; APN 1981; APN 1993; Bagga 1999; Basu 2020; Broyer 1997; Ekka 1997; Gulati 2011; Hiraoka 2000; Hiraoka 2003; Imbasciati 1985; Jayantha 2002a; Norero 1996; PREDNOS 2019; PREDNOS PILOT 2019; Sharma 2002; Sheikh 2019; Singhal 2015; Sinha 2015; Teeninga 2013; Yadav 2019; Yoshikawa 2015; Ueda 1988). There were 19 studies at high risk of selective reporting bias (Abeyagunawardena 2008; Abeyagunawardena 2014; APN 1988; Borovitz 2020; ISKDC 1979; Jayantha 2002b; Kleinknecht 1982; Ksiazek 1995; Leisti 1978; Li 1994; Liern 2008; Mattoo 2000; Mocan 1999; Moundekhel 2012; Paul 2014; Pecoraro 2003; PROPINE 2018; Raman 2016; Yoshikawa 1998). The remaining six studies were at unclear risk of selective reporting bias.

Other potential sources of bias

Fifteen studies were considered at low risk of potential bias as they were funded by educational or philanthropic organisations or stated that they received no funding (Abeyagunawardena 2008; APN 1981; APN 1988; Bagga 1999; Basu 2020; Gulati 2011; Leisti 1978; Norero 1996; PREDNOS 2019; PREDNOS PILOT 2019; Sinha 2015; Teeninga 2013; Ueda 1988; Yadav 2019; Yoshikawa 2015). 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 32 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.

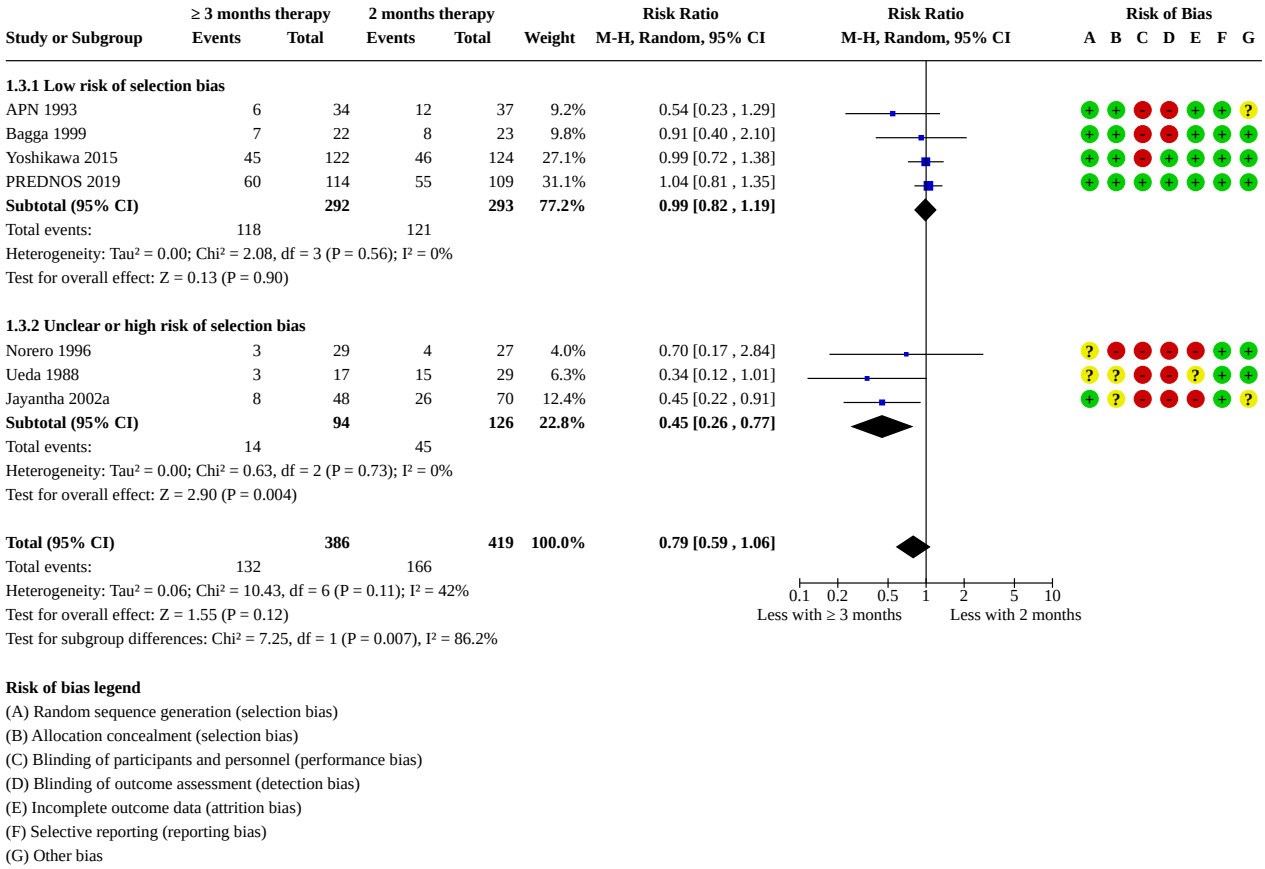
Effects of interventions

See: **Summary of findings 1** Steroid therapy in first episode of nephrotic syndrome: 3 months or more versus 2 months of therapy for nephrotic syndrome in children; **Summary of findings 2** Steroid therapy in first episode of nephrotic syndrome: five to seven months versus three months for nephrotic syndrome in children

Three months or more versus two months therapy in the initial episode of SSNS

- Therapy for three months or more probably makes little or no difference to the number of children with frequent relapses by 12 to 24 months compared to two months of therapy (Analysis 1.1: RR 0.86, 95% CI 0.71 to 1.06; 976 participants, 8 studies; I^2 = 33%; moderate certainty of evidence).
- Therapy for three months or more may reduce the number of children relapsing by 12 to 24 months (Analysis 1.2: RR 0.77, 95% CI 0.63 to 0.95; 1309 participants, 12 studies; I^2 = 77%; low certainty of evidence).
- In subgroups of studies at low risk of selection bias, there is little or no difference in the number with frequent relapses between the two groups (Analysis 1.3.1: RR 0.99, 95% CI 0.82 to 1.19; 585 participants; 4 studies; I^2 = 0%) or the number of children relapsing by 12 to 24 months (Analysis 1.4.1: RR 0.91, 95% CI 0.78 to 1.06; 637 participants; 5 studies; I^2 = 47%) (high certainty of evidence).Figure 4
- In contrast, in subgroups of studies at unclear or high risk of selection bias, longer duration of prednisone therapy probably reduces the number of children with frequent relapses (Analysis 1.3.2: RR 0.45, 95% CI 0.26 to 0.77; 220 participants, 3 studies; I^2 = 0%) (moderate certainty evidence) or the number of children relapsing by 12 to 24 month (Analysis 1.4.2: RR 0.69, 95% CI 0.49 to 0.98; 471 participants, 6 studies; I^2 = 72%).
- Similar differences in results were shown when data were stratified according to risk of bias for detection and performance bias or for attrition bias (data not shown).
- There may be little or no difference in adverse events between the two groups (Analysis 1.5) (low or moderate certainty of evidence). In Yoshikawa 2015, results were reported as events not patients so could not be included in the meta-analyses. The authors reported that frequency and severity of adverse events were similar in both groups.

Figure 4. Forest plot of comparison: 1 Steroid therapy in first episode: ≥ 3 months versus 2 months therapy, outcome: 1.3 Number with frequent relapses by 12 to 24 months stratified by risk of bias for selection bias.

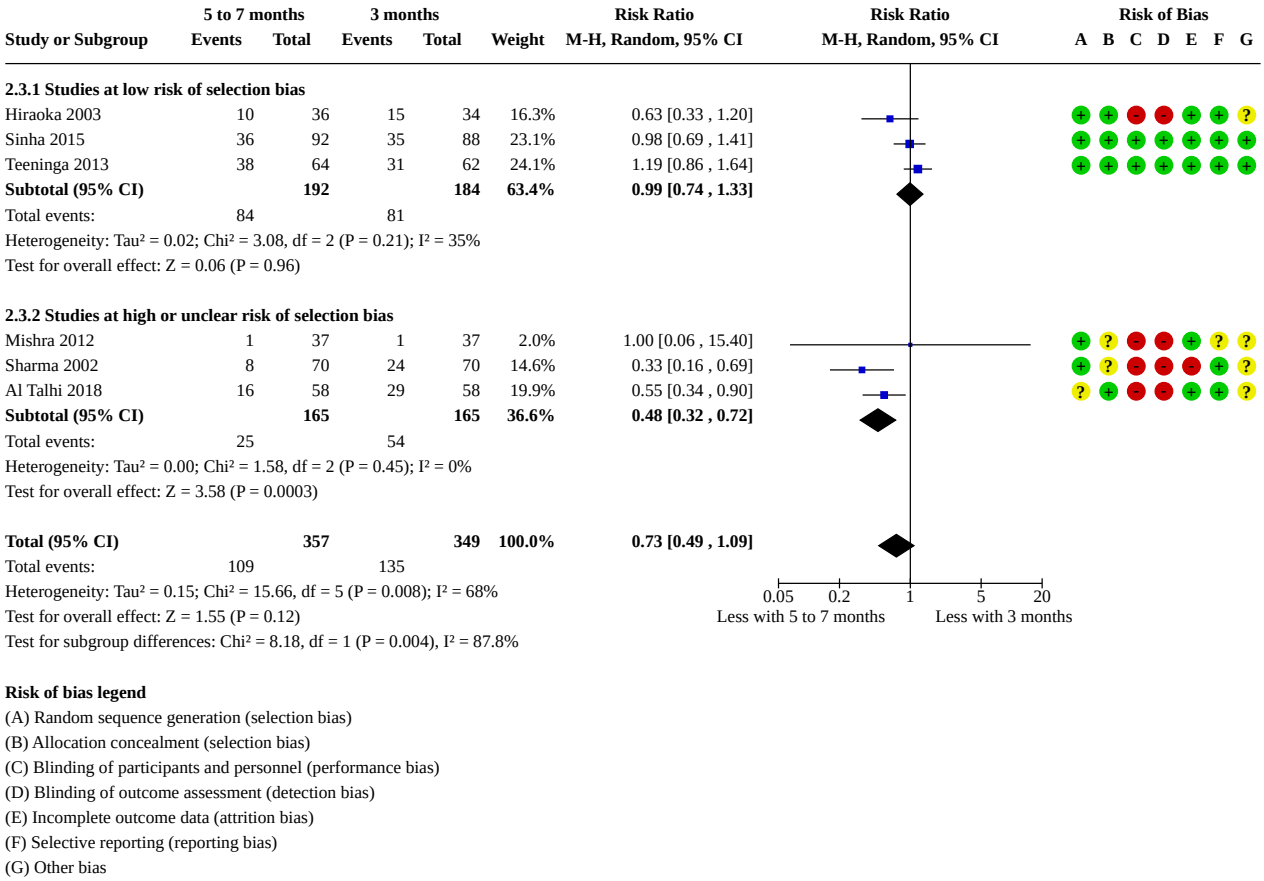


Results were downgraded for medium to high levels of heterogeneity between studies and for risk of bias issues (Summary of findings 1).The heterogeneity between studies was explained by the risk of bias issues (Analysis 1.3.1 and Analysis 1.3.2, and Analysis 1.4.1 and Analysis 1.4.2) but not by inclusion/exclusion of patients with steroid-dependent disease, different durations of prednisone (two months versus three months or more) or different definitions of FRNS (ISKDC definition compared with other definitions) (Data not shown in 2020 update).

Five to seven months versus three months therapy in the initial episode of SSNS

- Five to seven months of therapy probably makes little or no difference to the number of children with frequent relapses by 12 to 24 months compared to three months of therapy (Analysis 2.1: RR 0.73, 95% CI 0.49 to 1.09; 707 participants, 6 studies; I^2 = 68%; moderate certainty of evidence).
- Five to seven months of therapy may reduce the number of children relapsing by 12 to 24 months compared to three months of therapy (Analysis 2.2: RR 0.62, 95% CI 0.45 to 0.85; 763 participants, 7 studies; I^2 = 83%; low certainty of evidence).
- In subgroups of studies at low risk of selection bias there is little or no difference in the number with frequent relapses (Analysis 2.3.1: RR 0.99, 95% CI 0.74 to 1.33; 376 participants, 3 studies; I^2 = 35%; high certainty of evidence) or in the number relapsing by 12 to 24 months (Analysis 2.4.1 (RR 0.88, 95% CI 0.69 to 1.11; 376 participants, 3 studies; I^2 = 53%).Figure 5
- In contrast, in subgroups of studies at high or unclear risk of selection bias, five to seven months therapy probably reduces the risk of FRNS (Analysis 2.3.2: RR 0.48, 95% CI 0.32 to 0.72; 330 participants, 3 studies; I^2 = 0% moderate certainty of evidence) or in the number relapsing by 12 to 24 months (Analysis 2.4.2: RR 0.47, 95% CI 0.34 to 0.67; 386 participants, 4 studies; I^2 = 52%).
- Similar differences in results were shown when data were stratified according to risk of bias for detection and performance bias or for attrition bias (data not shown).
- There was little or no difference in adverse events including psychological disorders, growth retardation, hypertension, cataracts/glaucoma, osteoporosis, infections or Cushingoid features (Analysis 2.5; low or moderate certainty of evidence).
- Anand 2013 reported that the number with relapse at 12 months was lower with six months of prednisone compared with three months. Data could not be included in the meta-analysis as the numbers in each treatment group were not provided.

Figure 5. Forest plot of comparison: 2 Steroid therapy in first episode: 5 to 7 months versus 3 months, outcome: 2.3 Number with frequent relapses stratified by risk of selection bias.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Results were downgraded for medium to high levels of heterogeneity between studies and for risk of bias issues (Summary of findings 2).The heterogeneity between studies was explained by the risk of bias issues (Analysis 2.3.1 and Analysis 2.3.2 and Analysis 2.4.1 and Analysis 2.4.2) but not by inclusion/exclusion of patients with steroid-dependent disease, different durations of prednisone (three months versus five to seven months) or different definitions of FRNS (ISKDC definition compared with other definitions) (Data not shown in 2020 update).

One month versus two months therapy in the initial episode of SSNS (one study)

- APN 1988 reported one month of therapy compared to two months may reduce the risk of relapse at 6 to 12 months (Analysis 3.1: RR 1.60, 95% CI 1.01 to 2.54; 61 participants) and 12 to 24 months (RR 1.46, 95% CI 1.01 to 2.12; 60 participants).

Five months versus 12 months therapy in the initial episode of SSNS (one study)

- It was uncertain whether the number with relapse was reduced with prolonged prednisone therapy at 12 months versus 5 months in Ksiazek 1995 (Analysis 4.1: RR 0.76, 95% CI 0.51 to 1.13; 58 participants).

Different total doses of prednisone given for three months in the initial episode of SSNS (one study)

- Hiraoka 2000 reported a higher dose may reduce the number of children relapsing by 12 months (Analysis 5.1: RR 0.63, 95% CI 0.42 to 0.94; 59 participants); but may make little or no difference to the number with frequent relapses (Analysis 5.2: RR 0.69, 95% CI 0.35 to 1.37; 60 participants).
- Adverse effects may not differ between the groups (Analysis 5.3).

Oral methylprednisolone in children with relapsing or initial episode of SSNS (three studies)

- Methylprednisolone compared with prednisolone may reduce the time to remission (Analysis 6.1: MD -5.54 days, 95% CI -8.46 to -2.61; 38 participants, 2 studies; I^2 = 0%).
- Imbasciati 1985 reported methylprednisolone compared with prednisolone may make little or no difference to the number of children who relapse (Analysis 6.2: RR 1.00, 95% CI 0.71 to 1.41; 62 participants).

Daily prednisone treatment during viral infections in children with relapsing or initial episode of SSNS (four studies)

- Abeyagunawardena 2008 reported daily prednisone therapy during upper respiratory tract infections (URTI) resulted in seven relapses in 40 children compared with 19 relapses in 40 children receiving placebo in a cross-over study continued until all

children had completed two episodes of treatment associated with URTI.

- Gulati 2011 reported daily prednisone therapy may reduce the infection related relapses/patient-year (Analysis 7.2.1: MD -0.70, 95% CI -0.87 to -0.53; 95 participants) and the total number of relapses/patient/year (Analysis 7.2.2: MD -0.90, 95% CI -1.08 to -0.72; 95 participants).
- Mattoo 2000 reported daily prednisone may reduce total relapse episodes/patient at two years compared with alternate-day prednisone (Analysis 7.3: MD -3.30, 95% CI -4.03 to -2.57; 36 participants).
- In a cross-over study in children who had not received alternate-day prednisone for at least three months, Abeyagunawardena 2014 reported daily prednisone administered at the onset of URTI resulted in 11 relapses associated with 115 episodes of URTI in 33 children compared with 25 relapses associated with 101 episodes of URTI in 33 children completing two years.

Deflazacort versus prednisone therapy in children with relapsing or initial episode of SSNS (four studies)

- Deflazacort compared with prednisone may make little or no difference to the number achieving remission (Analysis 8.1: RR 1.08, 95% CI 0.94 to 1.24; 67 participants, 2 studies; I^2 = 0%).
- Deflazacort compared with prednisone may reduce the number of children with relapses by 9 to 12 months (Analysis 8.2: (RR 0.46, 95% CI 0.27 to 0.78; 63 participants, 2 studies; I^2 = 0%).
- No differences in time to remission or time to relapse in 11 children treated with deflazacort or methylprednisolone were found in a cross-over study by Liern 2008.

Alternate-day therapy or daily versus intermittent therapy in relapsing SSNS (one study)

- There may be little or no difference between alternate-day therapy and intermittent therapy in maintaining remission after ceasing therapy (Analysis 9.2.1 (RR 1.20, 95% CI 0.93 to 1.55; 1 study; 48 participants).

Daily therapy versus intermittent therapy in relapsing SSNS (one study)

- There may be little or no difference during therapy between daily and intermittent therapy in maintaining remission after ceasing therapy (Analysis 9.2.5 (RR 1.00, 95% CI 0.89 to 1.12; 1 study; 50 participants).

Single daily doses versus multiple daily doses in relapsing nephrotic syndrome (two studies)

- There may be little or no difference between single daily doses versus divided daily dosing in maintaining remission (Analysis 9.2.2: (RR 1.10, 95% CI 0.78 to 1.54; 56 participants (Ekka 1997), or the time to remission (Analysis 9.6: MD 0.04 days, 95% CI -0.98 to 1.06); 138 participants, 2 studies; I^2 = 0%).
- Serious side effects including hypertension may be less common in the single daily dose patients compared with divided dose patients (Analysis 9.7: RR 0.41, 95% CI 0.18 to 0.91; 138 participants, 2 studies; I^2 = 0%).

Low versus conventional dose prednisone in relapsing nephrotic syndrome (three studies)

- There may be little or no difference in time to remission between reduced (1 mg/kg) and standard prednisone doses (2 mg/kg) (Analysis 10.1: MD 0.71 days, 95% CI -0.43 to 1.86; 79 participants, 2 studies; I^2 = 0%).
- Borovitz 2020 reported that compared to a dose of 2 mg/kg/day, the cumulative dose of prednisone to achieve remission may be less in children treated with a dose of 1 mg/kg/day (Analysis 10.2: MD -20.60 mg/kg, 95% CI -25.65 to -15.55; 20 participants).
- There may be little or no difference in the number with relapse at one month between reduced and standard prednisone doses (Analysis 10.3: RR 0.66, 95% CI 0.16 to 2.68; 59 participants, 2 studies; I^2 = 57%)
- Borovitz 2020 reported that none of the included participants had treatment related complications. Kansal 2019 reported that prednisone adverse effects were more common in the standard dose group compared with the low dose group. Sheikh 2019 did not provide any information on adverse effects.

Daily versus alternate-day prednisone in relapsing nephrotic syndrome (one study)

- Yadav 2019 reported daily compared with alternate-day prednisone may reduce the number of relapses during 12 months of therapy (Analysis 11.1: MD -0.90 relapses/year, 95% CI -1.33 to -0.47; 62 participants).
- There may be little or no difference in the frequency of adverse effects (Analysis 11.2).

Weight-based versus body surface area-based dosing of prednisone in relapsing nephrotic syndrome (two studies)

- Weight-based dosing may make little or no difference to the number with relapse at 6 months compared to BSA-based dosing (Analysis 12.1.1: RR 1.03, 95% CI 0.71 to 1.49; 2 studies; 146 participants; I^2 = 0%).
- Weight-based dosing may make little or no difference to the risk of adverse effects (Analysis 12.2). Raman 2016 reported one patient in the BSA group developed hypertensive encephalopathy.
- Mean cumulative prednisone dose for induction (Analysis 12.3.1) over six months was lower in the weight-based dosing group compared with the BSA-based dosing group (Basu 2020). Median cumulative prednisone dose (Analysis 12.3.2) was lower in the weight-based group (81 g/kg) compared with the BSA-based group (96 g/kg) (Raman 2016).

Seven months of prednisone compared with two months in children with relapsing SSNS (one study)

- Seven months of prednisone may reduce the risk of relapse at 12 months (Analysis 13.1.2) and 24 months (Analysis 13.1.3).
- Adverse effects may not differ between treatment groups (Analysis 13.5)

Cortisol supplementation in children with relapsing nephrotic syndrome and adrenocortical suppression (one study)

In a cross-over study by Leisti 1978, cortisol substitution may result in fewer children with post-prednisone adrenocortical suppression relapsing during a six-month period. After three months of

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.

DISCUSSION

Summary of main results

We have added 16 new included studies to this 2020 update to bring the total number of included studies to 48, which randomised 3941 children.

Prednisone in the first episode of SSNS

In earlier iterations of this review (2000 to 2007), we concluded that prednisone administered for longer durations compared with two or three months reduced the risk of relapse and of FRNS in the initial episode of SSNS. In practice considerable variation exists among paediatric nephrologists in the duration of prednisone used in the initial episode of nephrotic syndrome reflecting in part the poor quality of the evidence from earlier randomised studies (MacHardy 2009; Samuel 2013). The last update of this review (Hahn 2015) included three well designed and adequately powered studies (Sinha 2015; Teeninga 2013; Yoshikawa 2015) which clearly demonstrated that there was no benefit of prolonging prednisone therapy beyond two or three months. In this 2020 update a further well designed study (PREDNOS 2019) also concluded that there was no benefit of prolonging prednisone therapy beyond two months. In our analysis of factors, which might account for the differences in results, we concluded that in studies at low risk of selection or performance bias, no benefit of extending prednisone therapy was identified. In contrast studies at high risk for these biases found a benefit of longer durations of therapy. In this 2020 update we included four new studies (Al Talhi 2018; Anand 2013; Moundekhel 2012; Paul 2014) which evaluated longer durations of prednisone compared with two or three months. All four studies concluded that there was a benefit of longer duration of prednisone therapy. However, all were at high risk of selection and performance bias. Since there are already four well designed studies randomising 823 children with nephrotic syndrome, which clearly demonstrate that there is no benefit of durations of prednisone exceeding two or three months, resources should not be wasted on further studies to evaluate different durations of prednisone in the initial episode of steroid sensitive nephrotic syndrome.

Prednisone in relapsing SSNS

Daily prednisone during viral infections compared with alternate-day prednisone therapy reduced the rate of relapse in four studies involving 204 children suggesting that this regimen may benefit children with FRNS. Confirmation of this benefit depends on the results from the much larger PREDNOS 2 2014 study, in which the planned enrolment is 300 children. Because of limited data (one study, 48 participants), it remains unclear whether children not already on alternate-day prednisone should restart daily prednisone for seven days at the onset of viral infections. In this update, an additional nine studies evaluated prednisone in relapsing disease but these were small studies generally evaluating different interventions. One study (Yadav 2019) enrolling 62 participants found that daily prednisone compared with alternate-day prednisone in children with FRNS was associated with a reduced risk of relapse. Currently the KDIGO 2012 guidelines suggest that alternate-day prednisone should be used. Two important but small studies (Borovitz 2020; Sheikh 2019) evaluated regimens using lower doses of prednisone for relapsing SSNS and suggested that smaller doses were as effective as the conventional regimen for relapse of prednisone 60 mg/m^2 daily till remission followed by four weeks of alternate-day prednisone at 40 mg/m^2. Much larger studies are needed to confirm these findings.

Overall completeness and applicability of evidence

Four well designed studies randomising 823 children in their first episode of SSNS have confirmed that the optimum duration of prednisone therapy is two or three months with no additional benefit found with longer duration of therapy in reducing the number with relapse. Now that we have these data, there is no requirement for further RCTs evaluating duration of prednisone therapy involving children of all ages with their first episode of SSNS. However post hoc analyses in two studies (PREDNOS 2019; Sinha 2015) suggested that a benefit of longer duration therapy in young children has not been completely excluded and this is being assessed in an ongoing study enrolling children below four years of age (Sinha 2016). There are currently no studies assessing whether lower doses of prednisone can be used in the first episode of SSNS.

Data on the management of relapsing syndrome remains inadequate. Four small studies (Abeyagunawardena 2008; Abeyagunawardena 2014; Gulati 2011; Mattoo 2000) report that the risk of relapse associated with infective episodes is reduced with daily prednisone initiated at the onset of the infection. However, clinicians are unlikely to use this regimen without additional data to confirm its efficacy and safety. Similarly although Yadav 2019 demonstrated that daily compared with alternate-day prednisone using the same total dose of prednisone was more effective in maintaining remission without demonstrable additional adverse effects, clinicians are likely to be wary of using this regimen because of the fear of the risk of more serious adverse effects.

Two small studies (Borovitz 2020; Sheikh 2019) are the first studies to examine whether lower doses of prednisone can be used to treat relapsing nephrotic syndrome. It is imperative that a large study is undertaken to confirm that lower doses of prednisone are as effective in achieving and maintaining remission as the conventional dose regimens which have been used for 50 years. Otherwise there is a risk that clinicians will try using smaller doses of prednisone in relapsing nephrotic syndrome without data from RCTs to support such a change in management.

Although adverse effects of medications were reported in more detail in the four recent high quality studies (PREDNOS 2019; Sinha 2015; Teeninga 2013; Yoshikawa 2015), generally there was limited reporting of adverse effects. Among 22 studies evaluating increased duration or dose in the initial episode of SSNS, hypertension, ophthalmological disorders and Cushing's syndrome were reported in 14, 11 and 12 studies, respectively. Prednisone therapy is known to be associated with significant behavioural and psychological adverse effects (Mishra 2010; Neuhaus 2010). However only eight studies reported this outcome. In PREDNOS 2019 detailed analysis of quantitative data collected using the Achenbach child behaviour checklist found no differences in behaviour score between the two durations of prednisone although parents reported more poor behaviour in children treated for two months. No studies reported on the burden of having a chronic kidney condition on the child or their family (Beanlands 2017).

The studies included the major ethnic groups, but there are no separable data on efficacy and safety for African-American or African children. These groups of children, who are known to have a higher incidence of initial and late SRNS (Gipson 2011; Kim 2005), may show different responses in studies of increased dose or duration of prednisone. The four recent high quality studies were carried out in Europe, Japan, and India, so few African children would have been included in the studies.

Quality of the evidence

Of the 48 included studies, only 25 (52%) and 22 (46%) studies reported adequate random sequence generation and allocation concealment, respectively.

Only nine studies (19%) were at low risk of bias for performance (blinding of participants and personnel) and detection bias (blinding of outcome assessment) since these studies were placebo controlled studies. Yoshikawa 2015 was an open-label study and so at high risk of performance bias but this study was at low risk of detection bias. The remaining studies were at high risk of bias for both performance and detection bias. Studies without blinding are considered at high risk of bias because knowledge of treatment groups could influence both patient management and reporting of remission and relapse (Moher 1998; Schulz 1995).

Fewer than 50% of studies were at low risk for both attrition bias (incomplete reporting of outcome data) and reporting bias (selective outcome reporting). Fifteen studies were considered at low risk of other potential bias as they were funded by educational or philanthropic organisations.

In the summary of findings tables (Summary of findings 1; Summary of findings 2), the certainty of the evidence was considered moderate or low for efficacy outcomes related to risk of bias and heterogeneity between studies. When studies were separated into subgroups according to the risk of selection bias, the certainty of the evidence was assessed as high for the primary efficacy outcomes of FRNS in seven well designed studies while the certainty of the evidence was judged low or moderate for these outcomes in studies at high or uncertain risk of selection bias. The quality of studies for the adverse effects was considered moderate or low because of inclusion of some studies at high risk of bias and few included studies.

Only 18 of the 48 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 either single studies of an intervention or data were reported differently for each study so could not be included in the meta-analyses.

Potential biases in the review process

A detailed search using the Cochrane Kidney and Transplant Register of Studies was completed in May 2020. The Cochrane Kidney and Transplant Register of Studies 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 12 (26%) 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 related to study methodology and results, and further information particularly of older studies could not be obtained despite contacting authors. Of the 48 included studies 16 were published in or before 2000 - 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 the 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 benefit in prolonging the corticosteroid treatment of all children for more than two to three months in the initial episode of SSNS. These data are supported from the recent KDIGO Controversies Conference suggesting recent RCTs do not support corticosteroid exposure beyond eight to 12 weeks (KDIGO Executive Conclusions 2019; Vivarelli 2017).

Older guidelines (Gipson 2009; IPNG-IAP 2008; KDIGO 2012) 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 though the results of large study addressing this intervention are awaited (PREDNOS 2 2014).

Current guidelines (Gipson 2009; IPNG-IAP 2008; KDIGO 2012) recommend that alternate-day prednisone therapy be used to reduce the risk of relapse in children with FRNS. However a study (Yadav 2019) identified for this review update showed that the number of relapses was lower in children treated with low dose daily prednisone compared with alternate-day dosing with no differences in adverse effects. Guidelines also recommend that children be dosed with prednisone according to body surface area (BSA) rather than weight in children weighing less than 30 kg because the calculation of dose by weight results in a lower dose compared with calculation based on BSA. However Raman 2016 found no differences in the number with relapse or in adverse effects between the two dosing schedules.

The listed guidelines 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 (Larkins 2020).

AUTHORS' CONCLUSIONS

Implications for practice

Prolongation of prednisone therapy beyond two to three months in the initial episode of SSNS does not reduce the risk of relapse as demonstrated in studies at low risk of bias. This outcome is confirmed in four large well designed studies (PREDNOS 2019; Sinha 2015; Teeninga 2013; Yoshikawa 2015).

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 based on four studies (Abeyagunawardena 2008; Abeyagunawardena 2014; Gulati 2011; Mattoo 2000) undertaken in emerging countries. A further RCT is currently assessing this intervention in European children, where the pattern of intercurrent infections may be different (PREDNOS 2 2014).

Implications for research

Four studies randomising 823 children have clearly demonstrated that there is no benefit from prolonging prednisone therapy beyond two to three months in the first episode of SSNS. Therefore, no further studies are required to evaluate the duration of therapy so scarce resources for RCTs should not be used to look further at the duration of treatment. However all studies evaluating the duration of prednisone have used similar daily and alternate daily doses of prednisone 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 prednisone. Three small studies included in the review update examined lower doses of prednisone and found no differences in efficacy or adverse effects. Therefore, the most important question to be answered currently is whether a lower dose of prednisone is as effective in achieving remission compared with the conventional dose of 2 mg/kg/day. This study should assess time to remission, time to relapse and the number with relapse to determine if children with SSNS can be safely and effectively treated with lower doses of prednisone. Initially such a study should be carried out in children with relapsing disease before lower doses of prednisone are evaluated in new onset disease.

Adverse events including hypertension, ophthalmological disorders and behavioural or psychological effects are not reported in all studies. Recently published studies have provided additional information on adverse effects. In particular the recent PREDNOS 2019 identified no differences in behavioural effects between different treatment durations. To date no studies have evaluated quality of life for the child and his/her family and these data would be valuable in future studies.

Current guidelines recommend that children with FRNS should receive prolonged treatment with alternate-day prednisone although there are no RCT data to support this recommendation. There is now an RCT showing that low dose daily prednisone reduced the number of relapses compared with alternate-day therapy (Yadav 2019) during one year follow up. Further RCTs with longer periods of follow up are required to evaluate further the relative efficacies and safety of using alternate-day compared with daily prednisone to prevent relapse.

There is some evidence from a small cross over study (Leisti 1978) that children with SSNS may 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.

ACKNOWLEDGEMENTS

We are grateful to Dr John F Knight who contributed to the design, quality assessment, data collection, entry, analysis and interpretation, and writing of early versions of this review (Hodson 2000; Hodson 2005).

The authors would like to thank Professor A Bagga, Professor A Abeyagunawardena, Professor PF Hoyer, Professor UK Jayantha, Dr C Kleinknecht, Professor M Liern, Professor TE Mattoo, Professor O Mishra, Professor RK Sharma, Professor Nicholas Webb and Professor N Yoshikawa for the information that they provided about their studies. The authors wish to thank Professors Barratt, Brodehl, Broyer and Ponticelli for responding to our requests for information about unpublished studies.

The authors are grateful to the following peer reviewers for their time and comments for this review update: William Wong (Director of Paediatric Nephrology, Clinical Director, Paediatric Medical Specialties, Starship Children's Hospital, New Zealand); Damien Noone (Division of Nephrology, The Hospital for Sick Children, Toronto, Canada).

REFERENCES

References to studies included in this review

Abeyagunawardena 2008 *{published data only}*

Abeyagunawardena AS, Trompeter RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial. *Archives of Disease in Childhood* 2008;**93**(3):226-8. [MEDLINE: 17573408]

Abeyagunawardena 2014 *{published and unpublished data}*

Abeyagunawardena A, Thalgahagoda S, Illangasekera Y, Trompeter R. A short course of prednisolone during an upper respiratory tract infection reduces the risk of relapse in childhood nephrotic syndrome [abstract no: P12]. *Pediatric Nephrology* 2014;**29**(9):1689. [EMBASE: 71662409]

* Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, Abeyagunawardena S, Illangasekera YA, Karunadasa UI, et al. Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. *Pediatric Nephrology* 2017;**32**(8):1377-82. [MEDLINE: 28341877]

Abeyagunawardena AS, Thalgahagoda S, Illangasekera Y, Trompeter RS. Short course of daily prednisolone during upper respiratory tract infection reduces the risk of relapse in childhood nephrotic syndrome [abstract no: G376(P)]. *Archives of Disease in Childhood* 2014;**99**(Suppl 1):A155-6. [EMBASE: 71566356]

Agarwal 2010 *{published data only}*

Agarwal I, Gemson JA, Moses PD, Mathew L, Prashanth P. Open randomized clinical study to evaluate efficacy and safety of deflazacort versus prednisolone in idiopathic nephrotic syndrome [abstract no: 558]. *Pediatric Nephrology* 2010;**25**(9):1906. [EMBASE: 70438660]

Al Talhi 2018 *{published data only}*

Al Talhi A, Al Saran K, Osman ET, Al Shatri A, Osman M, Mirza K. A randomized study on a 3-month versus a 7-month prednisolone regimen for the initial episode of childhood idiopathic nephrotic syndrome at a large Saudi center. *International Journal of Pediatrics & Adolescent Medicine* 2018;**5**(1):18-23. [EMBASE: 620760413]

Anand 2013 *{published data only}*

Anand P, Pruthi PK, Anand K. Standard versus long term corticosteroid therapy in the treatment of initial episode of nephrotic syndrome in children [abstract no: P-SUN228]. *Pediatric Nephrology* 2013;**28**(8):1609-10. [EMBASE: 620760413]

APN 1981 *{published data only}*

* Alternate-day prednisone is more effective than intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbeitsgemeinschaft fur Padiatrische Nephrologie". *European Journal of Pediatrics* 1981;**135**(3):229-37. [MEDLINE: 7227377]

Alternate-day versus intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbetsgemeinschaft fur Padiatrische Nephrologie". *Lancet* 1979;**1**(8113):401-3. [MEDLINE: 84259]

Brodehl J, Krohn HP. Steroid trial in frequently relapsing nephrotic syndrome in children. In: Glomerulonephritis. International Conference on Pathogenesis, Pathology and Treatment. New York: Wiley, 1977:210-5.

APN 1988 *{published data only}*

Brodehl J, Krohn HP, Ehrich JH. The treatment of minimal change nephrotic syndrome (lipoid nephrosis): cooperative studies of the Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN). *Klinische Padiatrie* 1982;**194**(3):162-5. [MEDLINE: 6752557]

Ehrich JH, Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN). Initial treatment of idiopathic nephrotic syndrome: short vs standard prednisone [abstract]. In: 10th International Congress of Nephrology; 1987 Jul 26-31; London, UK. 1987:59. [CENTRAL: CN-00644361]

Ehrich JH, Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN). Short initial prednisone therapy versus standard prednisone therapy in the steroid responsive nephrotic syndrome [abstract no: F5-1]. *Pediatric Nephrology* 1987;**1**(1):C28. [CENTRAL: CN-00445202]

* Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Lancet* 1988;**1**(8582):380-3. [MEDLINE: 2893190]

APN 1993 *{published data only}*

Ehrich JH, Arbeitsgemeinschaft fur Padiatrische Nephrologie. Minimal change nephrotic syndrome: long prednisone therapy vs standard prednisone therapy [abstract]. *Nephrology Dialysis Transplantation* 1991;**6**(10):771. [CENTRAL: CN-00260613]

* Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *European Journal of Pediatrics* 1993;**152**(4):357-61. [MEDLINE: 8482290]

Bagga 1999 *{published and unpublished data}*

Bagga A, Hari P, Srivastava RN. Long (LP) versus standard (SP) initial prednisolone treatment for idiopathic nephrotic syndrome (NS) [abstract no: P225]. *Pediatric Nephrology* 1998;**12**(1):C155. [CENTRAL: CN-00583944]

Bagga A, Hari P, Srivastava RN. Long (LP) versus standard (SP) initial prednisolone treatment for nephrotic syndrome (NS) [abstract no: FP23]. In: 3rd Congress. Nephrology Urology Transplantation Society (NUTS) of SAARC; 1999 Feb 18 - 21; Colombo, Sri Lanka. 1999:158. [CENTRAL: CN-00460325]

* Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. *Pediatric Nephrology* 1999;**13**(9):824-7. [MEDLINE: 10603129]

Basu 2020 *{published data only}*

Basu B, Bhattacharyya S, Barua S, Naskar A, Roy B. Efficacy of body weight vs body surface area-based prednisolone regimen in nephrotic syndrome. *Clinical & Experimental Nephrology* 2020;**24**(7):622-9. [MEDLINE: 32201918]

Borovitz 2020 *{published data only}*

* Borovitz Y, Alfandary H, Haskin O, Levi S, Kaz S, Davidovits M, et al. Lower prednisone dosing for steroid-sensitive nephrotic syndrome relapse: a prospective randomized pilot study. *European Journal of Pediatrics* 2020;**179**(2):279-83. [MEDLINE: 31728673]

Borovitz Y, Haskin O, Levi S, Kaz S, Alfandary H, Davidovits M, et al. Lower prednisone dosing for nephrotic syndrome relapse: a prospective randomized study [abstract no: O-07]. *Pediatric Nephrology* 2017;**32**(9):1647. [EMBASE: 618119422]

Broyer 1997 *{published data only}*

Broyer M, Terzi F, Gagnadoux MF, Guest G, Niaudet P. A randomized double blind study of deflazacort (D) versus prednisone (P) in the treatment of idiopathic nephrotic syndrome (INS) [abstract no: 1548]. *Journal of the American Society of Nephrology* 1995;**6**(3):414. [CENTRAL: CN-00483349]

* Broyer M, Terzi F, Lehnert A, Gagnadoux MF, Guest G, Niaudet P. A controlled study of deflazacort in the treatment of idiopathic nephrotic syndrome. *Pediatric Nephrology* 1997;**11**(4):418-22. [MEDLINE: 9260237]

Ekka 1997 *{published data only}*

Bagga A, Ekka BK, Srivastava RN. Single versus divided dose prednisolone therapy for relapses of nephrotic syndrome (NS) [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A113. [CENTRAL: CN-00261391]

* Ekka BK, Bagga A, Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. *Pediatric Nephrology* 1997;**11**(5):597-9. [MEDLINE: 9323286]

Gulati 2011 *{published data only}*

Gulati A, Math A, Sreenivas V, Hari P, Bagga A. Administration of daily corticosteroids prevents infection-associated relapses in frequently relapsing NS [abstract]. *Clinical Nephrology* 2010;**74**(7 Suppl 1):S158-9. [EMBASE: 70344148]

Gulati A, Math A, Sreeniwas V, Hari P, Bagga A. Administration of daily corticosteroids prevents infection associated relapses in frequently relapsing nephrotic syndrome [abstract no: SU714]. In: World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009.

Gulati A, Sinha A, Hari P, Bagga A. Efficacy of daily corticosteroids to prevent infection associated relapses in frequently relapsing nephrotic syndrome: A randomized controlled trial [abstract]. *Pediatric Nephrology* 2010;**25**(9):1874. [EMBASE: 70438498]

* Gulati A, Sinha A, Sreenivas V, Math A, Hari P, Bagga A. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2011;**6**(1):63-9. [MEDLINE: 20847092]

Hiraoka 2000 *{published data only}*

Hiraoka M, Sudo M, West Japanese Cooperative Study of Kidney Disease in Children. Low versus standard dosage of prednisolone for initial treatment of idiopathic nephrotic syndrome in children [abstract no: A0445]. *Journal of the American Society of Nephrology* 1996;**7**(9):1335.

* Hiraoka M, Tsukahara H, Haruki S, Hayashi S, Takeda N, Miyagawa K, et al. Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome. The West Japan Cooperative Study of Kidney Disease in Children. *Kidney International* 2000;**58**(3):1247-52. [MEDLINE: 10972687]

Hiraoka M, Tsukahara H, Haruki S, Hayashi S, Takeda N, Miyagawa K, et al. Older boys benefit from intensive initial prednisolone therapy for nephrotic syndrome [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):103A. [CENTRAL: CN-00550605]

Hiraoka 2003 *{published data only}*

* Hiraoka M, Tsukahara H, Matsubara K, Tsurusawa M, Takeda N, Haruki S, et al. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. *American Journal of Kidney Diseases* 2003;**41**(6):1155-62. [MEDLINE: 12776266]

Imbasciati 1985 *{published data only}*

Imbasciati E, Gusmano R, Edefonti A, Zucchelli P, Pozzi C, Grassi C, et al. Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. *British Medical Journal Clinical Research Ed* 1985;**291**(6505):1305-8. [MEDLINE: 3933645]

ISKDC 1979 *{published data only}*

Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. *Journal of Pediatrics* 1979;**95**(2):239-43. [MEDLINE: 109598]

Jayantha 2002a *{published and unpublished data}*

Jayantha UK. Comparison of ISKDC regime with a 7 months steroid regime in the first attack of nephrotic syndrome [abstract no: OPFC26]. *Pediatric Nephrology* 2004;**19**(9):C81. [CENTRAL: CN-00583710]

Jayantha UK. Comparison of ISKDC regime with a six month steroid regime in the treatment of steroid sensitive nephrotic syndrome. Data on file 2002.

* Jayantha UK. Comparison of ISKDC regime with a six month steroid regime in the treatment of steroid sensitive nephrotic syndrome [abstract no: FP2B]. In: 7th Asian Congress of Pediatric Nephrology; 2000 Nov 1-4; Singapore. 2000:28. [CENTRAL: CN-00583708]

Jayantha 2002b *{published and unpublished data}*

Jayantha UK. Comparison of ISKDC regime with 6 month regime in patients with relapsing nephrotic syndrome. Data on file 2002.

* Jayantha UK. Prolong versus standard steroid therapy for children with relapsing course of nephrotic syndrome [abstract no: P026]. *Pediatric Nephrology* 2004;**19**(9):C99. [CENTRAL: CN-00583706]

Kansal 2019 *{published and unpublished data}*

Kansal A, Mantan M, Yadav S. Effectiveness of a low dose prednisolone regimen for treatment of relapses in children with SSNS [abstract no: IPN10471- 84]. *Pediatric Nephrology* 2019;**34**(10):1871.

Kleinknecht 1982 *{published and unpublished data}*

Kleinknecht C, Broyer M, Parchoux B, Loriat C, Nivet H, Palcoux JB, et al. Comparison of short and long treatment at onset of steroid sensitive nephrosis (SSN). Preliminary results of a multicenter controlled trial for the French Society of Pediatric Nephrology [abstract]. *International Journal of Pediatric Nephrology* 1982;**3**(1):45. [CENTRAL: CN-00550480]

Ksiazek 1995 *{published data only}*

Ksiazek J, Wyszynska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. *Acta Paediatrica* 1995;**84**(8):889-93. [MEDLINE: 7488812]

Leisti 1978 *{published data only}*

* Leisti S, Koskimies O, Perheentupa J, Vilska J, Hallman N. Idiopathic nephrotic syndrome: prevention of early relapse. *British Medical Journal* 1978;**1**(6117):892. [MEDLINE: 346147]

Li 1994 *{published data only}*

Li X, Li Z, Cheng Z. Treatment of children with simple nephrotic syndrom using prednison once per day. *Acta Academiae Medicinae Hubei* 1994;**15**(4):386-8. [EMBASE: 1995005617]

Liern 2008 *{published data only}*

Liern M, Dieguez S, Canepa C. Recovery of total immunoglobulin and immunoglobulin subclasses in nephrotic syndrome: deflazacort vs methylprednisone [Recuperacion de la inmnoglobulina total y sus subclases en el sindrome nefrotico: deflazacort vs metilprednisona]. *Nefrologia* 2008;**28**(5):563. [MEDLINE: 18816222]

Mattoo 2000 *{published data only}*

* Mattoo TK, Mahmoud MA. Increased maintenance corticosteroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. *Nephron* 2000;**85**(4):343-5. [MEDLINE: 10940745]

Mishra 2012 *{published data only}*

Mishra OP, Thakur N, Mishra RN, Prasad R. Prolonged versus standard prednisolone therapy for initial episode of idiopathic nephrotic syndrome. *Journal of Nephrology* 2012;**25**(3):394-400. [MEDLINE: 21928226]

Mocan 1999 *{published data only}*

* Mocan H, Erduran E, Karaguzel G. High dose methylprednisolone therapy in nephrotic syndrome. *Indian Journal of Pediatrics* 1999;**66**(2):171-4. [MEDLINE: 10798055]

Mocan H, Mocan MZ, Erduran E, Karaguzel G, Aslan Y. The effect of high dose methylprednisolone therapy in patients with minimal change nephrotic syndrome [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A74. [CENTRAL: CN-00261380]

Moundekhel 2012 *{published data only}*

Moundekhel S, Khan GS, Afridi U. Management of nephrotic syndrome: ISKDC versus APN. *Pakistan Journal of Medical & Health Sciences* 2012;**6**(1):212-5. [EMBASE: 368679233]

Norero 1996 *{published data only}*

* Norero C, Delucchi A, Lagos E, Rosati P. Initial therapy of primary nephrotic syndrome in children: evaluation in a period of 18 months of two prednisone treatment schedules. Chilean Co-operative Group of Study of Nephrotic Syndrome in Children [Cuadro inicial del sindrome nefrosico primario del nino: evaluacion a 18 meses de dos esquemas de tratamiento con prednisona. Groupo Cooperativo Chileno de Estudio del Sindrome Nefrosico del Nino]. *Revista Medica de Chile* 1996;**124**(5):567-72. [MEDLINE: 9035508]

Norero C, Delucchi A, Lagos E, Rosati P. Long term evaluation of two prednisone treatments in initial idiopathic nephrotic syndrome (INS) in children. Preliminary findings [abstract no: P135]. *Pediatric Nephrology* 1995;**9**(6):C88. [CENTRAL: CN-00550669]

Paul 2014 *{published data only}*

Paul SK, Muinuddin G, Jahan S, Begum A, Rahman MH, Hossain MM. Long versus standard initial prednisolone therapy in children with idiopathic nephrotic syndrome. *Mymensingh Medical Journal: MMJ* 2014;**23**(2):261-7. [MEDLINE: 24858152]

Pecoraro 2003 *{published data only}*

Pecoraro C, Caropreso MR, Malgieri G, Ferretti A, Nuzzi F. Therapy of first episode steroid responsive nephrotic syndrome (FESRNS): a randomised controlled trial [abstract no: MP087]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v230. [CENTRAL: CN-00644161]

Pecoraro C, Caropreso MR, Malgieri G, Ferretti AV, Raddi G, Piscitelli A, et al. Therapy of first episode of steroid responsive nephrotic syndrome: a randomised controlled trial [abstract no: OFC41]. *Pediatric Nephrology* 2004;**19**(9):C72. [CENTRAL: CN-00644160]

Pecoraro C, Caropreso MR, Passaro G, Ferretti AV, Malgieri G. Therapy of first episode of steroid responsive nephrotic syndrome: a randomised controlled trial [abstract no: M199]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):63. [CENTRAL: CN-00447140]

PREDNOS 2019 *{published data only}***16645249**

Webb N, Trompeter R, Cummins C, Wheatley K, Frew E. Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic

syndrome: national multicentre randomised double blind trial [protocol]. PREDNOS Clinical Trial Protocol Version 2.1 2013 Sept 1.

Webb N, Wooley R, Brettell E, Cummins C, Trompeter R, Barsoum E, et al. Standard vs extended course prednisolone therapy for the presenting episode of steroid sensitive nephrotic syndrome: the PREDNOS study [abstract no: O-08]. *Pediatric Nephrology* 2017;**32**(9):1647-8. [EMBASE: 618119435]

* Webb NJ, Woolley RL, Lambe T, Frew E, Brettell EA, Barsoum EN, et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. *BMJ* 2019;**365**:l1800. [MEDLINE: 31335316]

Webb NJ, Woolley RL, Lambe T, Frew E, Brettell EA, Barsoum EN, et al. Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT. *Health Technology Assessment (Winchester, England)* 2019;**23**(26):1-108. [MEDLINE: 31156083]

PREDNOS PILOT 2019 *{published data only}*

Webb NJ, Woolley RL, Lambe T, Frew E, Brettell EA, Barsoum EN, et al. Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT. *Health Technology Assessment (Winchester, England)* 2019;**23**(26):1-108. [MEDLINE: 31156083]

PROPINE 2018 *{published data only}*

Gargiulo A, Vivarelli M, Pecoraro C, Pennesi M, Pasini A, Edefonti A, et al. Short versus long courses of prednisone for the treatment of relapses of steroid sensitive nephrotic syndrome. results of the PROPINE study [abstract no: O-4]. *Pediatric Nephrology* 2018;**33**(10):1810. [EMBASE: 618119435]

Raman 2016 *{published data only}*

* Raman V, Krishnamurthy S, Harichandrakumar KT. Body weight-based prednisolone versus body surface area-based prednisolone regimen for induction of remission in children with nephrotic syndrome: a randomized, open-label, equivalence clinical trial. *Pediatric Nephrology* 2016;**31**(4):595-604. [MEDLINE: 26759000]

Satomura 2001 *{published data only}*

Satomura K, Yamaoka K, Shima M, Tanaka Y, Ashino N, Nakagawa K, et al. Standard vs low initial dose of prednisolone therapy for first episodes of nephrotic syndrome in children [abstract no: P238]. *Pediatric Nephrology* 2001;**16**(8):C117. [CENTRAL: CN-00447593]

Sharma 2002 *{unpublished data only}*

Gulati S, Ahmed M, Sharma RK, Gupta A, Pokhariyal S. Comparison of abrupt withdrawal versus slow tapering regimen of prednisolone therapy in the management of first episode of steroid responsive childhood idiopathic nephrotic syndrome [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A87. [CENTRAL: CN-00445595]

* Sharma RK, Ahmed M, Gulati S, Gupta A, Pokhariyal S. Comparison of abrupt withdrawal versus slow tapering regimen of prednisolone therapy in the management of first episode of steroid responsive childhood idiopathic nephrotic syndrome. Data on file 2002.

Sharma RK, Ahmed M, Gupta A, Gulati S, Sharma AP. Comparison of abrupt withdrawal versus slow tapering regimens of prednisolone therapy in management of first episode of steroid responsive childhood idiopathic nephrotic syndrome [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):97A. [CENTRAL: CN-00550434]

Sheikh 2019 *{published data only}*

Sheikh S, Mishra K, Kumar M. Low versus conventional dose prednisolone for nephrotic syndrome relapses: randomised-controlled, non-inferiority-trial [abstract no: IPN10923-86]. *Pediatric Nephrology* 2019;**34**(10):1980.

Singhal 2015 *{published data only}*

Singhal R, Pandit S, Dhawan N. Deflazacort versus prednisolone: randomized controlled trial in treatment of children with idiopathic nephrotic syndrome. *Iranian Journal of Pediatrics* 2015;**25**(2):e510. [MEDLINE: 26196009]

Sinha 2015 *{published and unpublished data}*

Bagga A, Sinha A, Saha A, Kumar M, Afzal K, Mehta A. Randomized double blind, placebo controlled trial to compare the efficacy of 3-months versus 6-months therapy with prednisolone for the first episode of idiopathic nephrotic syndrome (CTRI/2010/091/001095) [abstract no: P139]. *Pediatric Nephrology* 2012;**27**(9):1707. [EMBASE: 71386357]

Sinha A, Bagga A, Sharma S, Saha A, Kumar M, Afzal K, et al. Randomized, double blind, placebo controlled trial to compare the efficacy of 3-months versus 6-months therapy with prednisolone for the first episode of idiopathic nephritic syndrome [abstract no: O-40]. *Pediatric Nephrology* 2013;**28**(8):1361-2. [EMBASE: 71126981]

* Sinha A, Saha A, Kumar M, Sharma S, Afzal K, Mehta A, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid- sensitive nephrotic syndrome. *Kidney International* 2015;**87**(1):217-24. [MEDLINE: 25029428]

Teeninga 2013 *{published data only}***27871415**

Teeninga N, Guan Z, Stevens J, Kist-Van Holthe JE, Ackermans MT, van der Heijden AJ, et al. Population pharmacokinetics of prednisolone in relation to clinical outcome in children with nephrotic syndrome. *Therapeutic Drug Monitoring* 2016;**38**(4):534-45. [EMBASE: 610346284]

Teeninga N, Kist-Van Holthe JE, De Mos NI, Peters N, Hop WC, van der Heijden AJ, et al. Optimal treatment of steroid sensitive nephrotic syndrome in children: a multicenter randomised controlled trial [abstract no: 450]. *Pediatric Nephrology* 2010;**25**(9):1884. [EMBASE: 70438552]

Teeninga N, Kist-Van Holthe JE, De Mos NI, Van Rijswijk-Peeters N, Hop WC, Nauta J. Optimal treatment of steroid sensitive nephrotic syndrome in children: a randomised controlled trial [abstract no: P090]. *Pediatric Nephrology* 2008;**23**(9):1619. [CENTRAL: CN-01657514]

Teeninga N, Kist-van Holthe JE, van den Akker EL, Kersten MC, Boersma E, Krabbe HG, et al. Genetic and in vivo determinants of glucocorticoid sensitivity in relation to clinical outcome of childhood nephrotic syndrome. *Kidney International* 2014;**85**(6):1444-53. [MEDLINE: 24429396]

* Teeninga N, Kist-van Holthe JE, van Rijswijk N, de Mos NI, Hop WC, Wetzels JF, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *Journal of the American Society of Nephrology* 2013;**24**(1):149-59. [MEDLINE: 23274956]

Teeninga N, Kist-Van Holthe JE, Van Ruswuk N, De Mos NI, Hop WC, Wetzels JF, et al. Effect of extended prednisolone treatment from three to six months, with equal cumulative doses, on childhood nephrotic syndrome: a nation-wide randomised controlled trial [abstract no: OP61]. *Pediatric Nephrology* 2012;**27**(9):1637-8. [EMBASE: 71386208]

Ueda 1988 *{published data only}*

Ueda N, Chihara M, Kawaguchi S, Niimomi Y, Nonada T, Matsumoto J, et al. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *Journal of Pediatrics* 1988;**112**(1):122-6. [MEDLINE: 3335948]

Ueda N, Chihara M, Kawaguchi S, Niinomi Y, Yasaki T. Intermittent versus long-term tapering prednisolone regimens as initial therapy in children with steroid-responsive nephrotic syndrome. [abstract]. In: 10th International Congress of Nephrology; 1987 Jul 26-31; London, UK. 1987:98.

Yadav 2019 *{published data only}*

Yadav M, Sinha A, Hari P, Bagga A. Efficacy of low-dose daily versus alternate day prednisone in children with frequently relapsing nephrotic syndrome (FRNS): open-label randomized controlled trial (RCT) [abstract no: FP-S25-09]. *Pediatric Nephrology* 2016;**31**(10):1752. [EMBASE: 612479637]

* Yadav M, Sinha A, Khandelwal P, Hari P, Bagga A. Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. *Pediatric Nephrology* 2019;**34**(5):829-35. [MEDLINE: 30194663]

Yoshikawa 1998 *{published data only}*

Ito H, Yoshikawa N. Multicenter controlled trial in nephrotic syndrome in Japanese children [abstract no: S-13.5]. In: 9th Congress. International Pediatric Nephrology Association; 1992 Aug 30 - Sep 4; Jerusalem, Israel. 1992:C37.

Nakanishi K, Iijima K, Ishikura K, Hataya H, Nakazato H, Sasaki S, et al. Two-year outcome of the ISKDC regimen and frequent-relapsing risk in children with idiopathic nephrotic syndrome. *Clinical Journal of the American Society of Nephrology: CJASN* 2013;**8**(5):756-62. [MEDLINE: 23371961]

Takekoshi Y. Treatment of idiopathic nephrotic syndrome [abstract no: S-1]. *Pediatric Nephrology* 1996;**10**(1):C3. [CENTRAL: CN-00402800]

* Yoshikawa N, Ito H, Takehoshi Y, Honda M, Awazu M, Iijima K, et al. Standard versus long-term prednisolone with sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: a prospective controlled study. *Nippon Jinzon Gakkai Shi [Japanese Journal of Nephrology]* 1998;**40**(8):587-90. [MEDLINE: 9893457]

Yoshikawa 2015 *{published and unpublished data}*

Yoshikawa N, Nakanishi K, Oba MS, Sako M, Ohashi Y, Iijima K. Increased duration and dose of prednisolone (PSL) treatment does not reduce relapses in childhood nephrotic syndrome [abstract no: SA-PO1080]. *Journal of the American Society of Nephrology* 2014;**24**(Abstracts):3B.

* Yoshikawa N, Nakanishi K, Sako M, Oba MS, Mori R, Ota E, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney International* 2015;**87**(1):225-32. [MEDLINE: 25054775]

Zhang 2007d *{published data only}*

Zhang Y, Huang JP, Xiao HJ, Ding J, Yao Y, Yang JY. Prospective clinical randomized controlled trial of pulse methylprednisolone therapy in children with steroid sensitive nephrotic syndrome [abstract no: 797 (P)]. *Pediatric Nephrology* 2007;**22**(9):1609. [CENTRAL: CN-01912552]

References to studies excluded from this review

APN 2006 *{published data only}*

Arbeitsgemeinschaft fur Padiatrische Nephrologie. Results of the nephrotic syndrome study VIII of the APN: new standard treatment versus new standard treatment plus 8 weeks cyclosporin A [abstract]. *Pediatric Nephrology* 1999;**13**:C26. [CENTRAL: CN-00636143] [CRSEF: 329770]

* Hoyer PF, Brodehl J. Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. *Journal of the American Society of Nephrology* 2006;**17**(4):1151–7. [MEDLINE: 16540560] [CRSREF: 3229771]

Hoyer PF, Arbeitsgemeinschaft fur Padiatrische Nephrologie. The initial treatment of idiopathic nephrotic syndrome with prednisone and cyclosporin A: preliminary results of a therapeutic trial [abstract no: P147]. *Pediatric Nephrology* 1995;**9**(6):C91. [CENTRAL: CN-00401335] [CRSREF: 3229770]

Hoyer PF. Results of the Nephrotic Syndrome Study VIII of the APN: new standard treatment versus new standard treatment plus 8 weeks cyclosporin A [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):104A. [CENTRAL: CN-0055522] [CRSREF:3229772]

Zhang 2014 *{published data only}*

* Zhang B, Liu T, Wang W, Zhang X, Fan S, Liu Z, et al. A prospective randomly controlled clinical trial on azithromycin therapy for induction treatment of children with nephrotic syndrome. *European Journal of Pediatrics* 2014;**173**(4):509-15. [MEDLINE: 24240666] [CRSREF: 3229850]

Zhang BL, Liu T. A prospective clinical randomized controlled trial on azithromycin therapy in induction treatment in

children with nephrotic syndrome [abstract no: O-44]. *Pediatric Nephrology* 2013;**28**(8):1364. [EMBASE: 71126985]

References to ongoing studies

CTRI/2015/11/006345 *{published data only}*

Hari P. Efficacy of short prednisolone treatment for relapse in children with steroid sensitive nephrotic syndrome: a randomised controlled study. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=12315 (first received 5 November 2015).

CTRI/2018/05/013634 *{published data only}*

Kalra S. A randomized controlled clinical trial to compare the efficacy of standard dose of steroids vs reduced dose in treating relapses in children with steroid sensitive nephrotic syndrome. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=25815 (first received 3 May 2018).

CTRI/2018/05/014075 *{published data only}*

Mishra K. A comparison of two doses of prednisolone for relapses in children with steroid sensitive nephrotic syndrome: a randomized controlled non inferiority trial. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=26036 (first received 23 May 2018).

PREDNOS 2 2014 *{published data only}***10900733**

Webb NJ, Frew E, Brettell EA, Milford DV, Bockenhauer D, Saleem MA, et al. Short course daily prednisolone therapy during an upper respiratory tract infection in children with relapsing steroid-sensitive nephrotic syndrome (PREDNOS 2): protocol for a randomised controlled trial. *Trials [Electronic Resource]* 2014;**15**:147. [MEDLINE: 24767719]

RESTERN 2017 *{published data only}*

Schijvens A, Schreuder M. Steroid treatment reduction in relapsing childhood nephrotic syndrome: a new nationwide randomized controlled trial in the Netherlands - the RESTERN study [abstract no: P-163]. *Pediatric Nephrology* 2017;**32**(9):1729. [EMBASE: 618120212]

Schijvens AM, Dorresteijn EM, Roeleveld N, Ter Heine R, van Wijk JA, Bouts AH, et al. REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study- protocol of a national, double-blind, randomised, placebo-controlled, non-inferiority intervention study. *BMJ Open* 2017;**7**(9):e018148. [MEDLINE: 28963315]

Sinha 2016 *{published data only}*

Sinha A, Gipson D, Wong C, Massengil S, Ahmad A, Hari P, et al. 6-months versus 3-months prednisolone for initial therapy of steroid sensitive nephrotic syndrome: open label RCT [abstract no: IPN11430-80]. *Pediatric Nephrology* 2019;**34**(10):2076.

Sinha A, Hari P, Bagga A. Randomized controlled trial to compare efficacy of 3-months versus 6-months therapy with prednisolone for the first episode of idiopathic nephrotic syndrome in children <4-yr-old [abstract no: PO-321]. *Pediatric Nephrology* 2016;**31**(10):1867-8. [EMBASE: 612479470]

Additional references

Arneil 1956

Arneil GC. Treatment of nephrosis with prednisolone. *Lancet* 1956;**270**(6920):409-11. [MEDLINE: 13307947]

Arneil 1971

Arneil GC. The nephrotic syndrome. *Pediatric Clinics of North America* 1971;**18**(2):547-59. [MEDLINE: 4945403]

Aydin 2019

Aydin M, Franke I, Kurylowicz L, Ganshow R, Lentze M, Born M, et al. The long-term outcome of childhood nephrotic syndrome in Germany: a cross sectional study. *Clinical & Experimental Nephrology* 2019;**23**(5):676-88. [MEDLINE: 30721392]

Beanlands 2017

Beanlands H, Maione M, Poulton C, Herreshoff E, Hladunewich MA, Hailperin M, et al. Learning to live with nephrotic syndrome: experiences of adult patients and parents of children with nephrotic syndrome. *Nephrology Dialysis Transplantation* 2017;**32**(Suppl 1):i98-105. [MEDLINE: 28391342]

Bhimma 1997

Bhimma R, Coovadia HM, Adhikari M. Nephrotic syndrome in South African children: changing perspectives over 20 years. *Pediatric Nephrology* 1997;**11**(4):429-34. [MEDLINE: 9260239]

Eddy 2003

Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet* 2003;**362**(9384):629-39. [MEDLINE: 12944064]

Egger 2001

Egger M, Dickersin K, Davey Smith G. Problems and limitations in conducting systematic reviews. In: Egger M, Davey Smith G, Altman D, editors(s). Systematic Reviews in Health care: Meta-analysis in context. Second edition. London: BMJ Publishing Group, 2001. [ISBN-13: 978-0727914880]

Gipson 2009

Gipson DS, Massengill SF, Yoa L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. *Pediatrics* 2009;**124**(2):747-57. [MEDLINE: 19651590]

Gipson 2011

Gipson DS, Trachtman H, Kaskel FJ, Radeva MK, Gassman J, Greene TH, et al. Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life. *Kidney International* 2011;**79**(6):678-85. [MEDLINE: 21178977]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

GRADE 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [MEDLINE: 21195583]

Guess 2010

Guess A, Agrawal S, Wei CC, Ransom RF, Benndorf R, Smoyer WE. Dose- and time-dependent glucocorticoid receptor signaling in podocytes. *American Journal of Physiology - Renal Physiology* 2010;**299**(4):F845-53. [MEDLINE: 20630936]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hopewell 2007

Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analysis of randomized trials of health care interventions. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No: MR000010. [DOI: 10.1002/14651858.MR000010.pub3]

Hyams 1988

Hyams JS, Carey DE. Corticosteroids and growth. *Journal of Pediatrics* 1988;**113**(2):249-54. [MEDLINE: 3294360]

IPNG-IAP 2008

Indian Pediatric Nephrology Group, Indian Academy of Pediatrics, Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, et al. Management of steroid sensitive nephrotic syndrome: revised guidelines. *Indian Pediatrics* 2008;**45**(3):203-14. [MEDLINE: 18367765]

ISKDC 1970

Abramowicz M, Barnett HL, Edelmann CM Jr, Greifer I, Kobayashi O, Arneil GC, et al. Controlled trial of azathioprine in children with nephrotic syndrome: A report for the International Study of Kidney Disease in Children. *Lancet* 1970;**1**(7654):959-61. [MEDLINE: 4191931]

ISKDC 1984

Minimal change nephrotic syndrome in children: deaths during the first 5 to 15 years' observation. Report of the International Study of Kidney Disease in Children. *Pediatrics* 1984;**73**(4):497-501. [MEDLINE: 6709428]

Kadmiel 2013

Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends in Pharmacological Sciences* 2013;**34**(9):518-30. [MEDLINE: 23953592]

KDIGO 2012

Lombel RM, Gipson DS, Hodson EM, Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. *Pediatric Nephrology* 2013;**28**(3):415-26. [MEDLINE: 23052651]

KDIGO Executive Conclusions 2019

Rovin BH, Caster DJ, Catran DC, Gibson KL, Hogan JJ, Moeller MJ, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* 2019;**95**(2):281-295. [MEDLINE: 30665569]

Kim 2005

Kim JS, Bellew CA, Silverstein DM, Aviles DH, Boineau FG, Vehaskari VM. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. *Kidney International* 2005;**68**(3):1275-81. [MEDLINE: 16105061]

Kirshcke 2014

Kirschke E, Goswami D, Southworth D, Griffin PR, Agard D. Glucocorticoid receptor function regulated by coordinated action of the Hsp90 and Hsp70 chaparone cycles. *Cell* 2014;**157**(7):1685-97. [MEDLINE: 24949977]

Koskimies 1982

Koskimies O, Vilska J, Rapola J, Hallman N. Long-term outcome of primary nephrotic syndrome. *Archives of Disease in Childhood* 1982;**57**(7):544-8. [MEDLINE: 7103547]

Larkins 2020

Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No: CD002290. [DOI: 10.1002/14651858.CD002290.pub5]

MacHardy 2009

MacHardy N, Miles PV, Massengill SF, Smoyer WE, Mahan JD, Greenbaum L, et al. Management patterns of childhood-onset nephrotic syndrome. *Pediatric Nephrology* 2009;**24**(11):2193-201. [MEDLINE: 19672630]

Mishra 2010

Mishra OM, Basu B, Upadhyay SK, Prasad R, Schaefer F. Behavioural abnormalities in children with nephrotic syndrome. *Nephrology Dialysis Transplantation* 2010;**25**(8):2537-41. [MEDLINE: 20200003]

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**(9128):609-13. [MEDLINE: 9746022]

Moher 2001

Moher D, Jones A, Lepage L, CONSORT Group (Consolidated Standards for Reporting of Trials). Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA* 2001;**285**(15):1992-5. [MEDLINE: 11308436]

Neuhaus 2010

Neuhaus TJ, Langlois V, Licht C. Behavioural abnormalities in children with nephrotic syndrome--an underappreciated complication of a standard treatment? *Nephrology Dialysis Transplantation* 2010;**25**(8):2397-9. [MEDLINE: 20573807]

Ng 2001

Ng JS, Wong W, Law RW, Hui J, Wong EN, Lam DS. Ocular complications of paediatric patients with nephrotic syndrome. *Clinical & Experimental Ophthalmology* 2001;**29**(4):239-43. [MEDLINE: 11545423]

Niaudet 2009

Niaudet P. Long-term outcome of children with steroid-sensitive idiopathic nephrotic syndrome. *Clinical Journal of The American Society of Nephrology: CJASN* 2009;**4**(10):1457-8. [MEDLINE: 19808239]

Noone 2018

Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet* 2018;**392**(10141):61-74. [MEDLINE: 29910038]

Ohashi 2011

Ohashi T, Uchida K, Uchida S, Sasaki S, Nitta K. Dexamethasone increases the phosphorylation of nephrin in cultured podocytes. *Clinical & Experimental Nephrology* 2011;**15**(5):688-93. [MEDLINE: 21695412]

Ponticelli 2018

Ponticelli C, Locatelli F. Glucocorticoids in the treatment of glomerular diseases. *Clinical Journal of The American Society of Nephrology: CJASN* 2018;**13**(5):815-22. [MEDLINE: 29475991]

Raja 2017

Raja K, Parikh A, Webb H, Hothi D. Use of a low-dose prednisolone regimen to treat a relapse of steroid-sensitive nephrotic syndrome in children. *Pediatric Nephrology* 2017;**32**(2):99-105. [MEDLINE: 27677978]

Ramamoorthy 2016

Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. *Rheumatic Diseases Clinics of North America* 2016;**42**(1):15-31. [MEDLINE: 26611548]

Ruth 2005

Rüth EM, Kemper M, Leumann EP, Laube GF, Neuhaus TJ. Children with steroid sensitive nephrotic syndrome come of age: long-term outcome. *Journal of Pediatrics* 2005;**147**(2):202-7. [MEDLINE: 16126050]

Samuel 2013

Samuel S, Morgan CJ, Bitzan N, Mammen C, Dart AB, Manns BJ, et al. Substantial practice variation exists in the management of childhood nephrotic syndrome. *Pediatric Nephrology* 2013;**28**(12):2289-98. [MEDLINE: 23917450]

Schijvens 2019

Schijvens AM, ter Heine R, de Wildt SN, Schreuder MF. Pharmacology and pharmacogenetics of prednisone and prednisolone in patients with nephrotic syndrome. *Pediatric Nephrology* 2019;**34**(3):389-403. [MEDLINE: 29549463]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Schunemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schunemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Tarshish 1997

Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *Journal of the American Society of Nephrology* 1997;**8**(5):769-76. [MEDLINE: 9176846]

Vivarelli 2017

Vivarelli M, Massella l, Ruggiero B, Emma F. Minimal change disease. *Clinical Journal of The American Society of Nephrology: CJASN* 2017;**12**(2):332-45. [MEDLINE: 27940460]

References to other published versions of this review

Hahn 2015

Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No: CD001533. [DOI: 10.1002/14651858.CD001533.pub5]

Hodson 2000

Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials. *Archives of Disease in Childhood* 2000;**83**(1):45-51. [MEDLINE: 10868999]

Hodson 2002

Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No: CD001533. [DOI: 10.1002/14651858.CD001533]

Hodson 2003

Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No: CD001533. [DOI: 10.1002/14651858.CD001533.pub2]

Hodson 2005

Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No: CD001533. [DOI: 10.1002/14651858.CD001533.pub3]

Hodson 2007

Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No: CD001533. [DOI: 10.1002/14651858.CD001533.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abeyagunawardena 2008

Study characteristics	
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 years with FRNS receiving maintenance low dose (0.1 to 0.6 mg/kg) alternate-day oral prednisolone • Number (analysed/recruited): 40/48; treatment group first (18); control group first (22) • 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. Additional medication given on alternate days to achieve daily prednisone Control group • Placebo: alternate days for 7 days at onset of viral infection. Additional medication given on alternate days to achieve placebo administration on alternate days with continuing prednisone on alternate 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 • Funding source: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Abeyagunawardena 2008 *(Continued)*

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) All outcomes	Low risk	Investigators and parents blinded to contents of containers
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

Study characteristics	
Methods	• Study design: double-blind placebo controlled, cross-over RCT • Time frame: recruited January 2011 to March 2011 • 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 or more • Number (analysed/randomised): treatment group first (19/27); control group first (14/21) • Mean age ± SD (years): treatment group first (12.0 ± 2.4); control group first (10.0 ± 2.9) • Sex (M/F): treatment group first (12/7); control group first (9/5) • Exclusion criteria: children with SSNS receiving alternate-day prednisone
Interventions	Treatment group • Prednisolone: 0.5 mg/kg/day 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 publication • Definitions of SDNS, URTI and relapse not reported

Abeyagunawardena 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "At the time of enrolment in the study, the patients were randomised into two groups using the envelope method"
Allocation concealment (selection bias)	Low risk	QUOTE: "At the time of enrolment in the study, the patients were randomised into two groups using the envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Group 1 patients were provided a bottle labeled "Drug A" containing 100 5-mg tablets and group 2 patients received "Drug B" containing 100 5-mg tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Group 1 patients were provided a bottle labeled "Drug A" containing 100 5-mg tablets and group 2 patients received "Drug B" containing 100 5-mg tablets."
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	Insufficient information to permit judgement

Agarwal 2010

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 6 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: children with initial episode of INS • Number: treatment group (22); control group (20) • Mean age ± SD (years): not reported • Gender: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Deflazacort (dose and duration not reported) Control group • Prednisolone (dose and duration not reported)
Outcomes	• Remission at 2 and 6 weeks • BMD

Agarwal 2010 *(Continued)*

Notes	• Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Not all prespecified outcomes mentioned but only abstract available
Other bias	Unclear risk	insufficient information to permit judgement

Al Talhi 2018

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 1 January 2011 to 31 December 2014 • Duration of follow-up: 2 years
Participants	• Country: Saudi Arabia • Setting: single centre, renal clinic • Inclusion criteria: children with the initial episode of nephrotic syndrome; age range 1 to 12 years; no prior therapy with steroids or immunosuppressive therapy; informed consent. • Number (analysed/randomised): treatment group 1 (58/60); treatment group 2 (58/60) • Mean age ± SD (years):treatment group 1 (5 ± 2); treatment group 2 (5.2 ± 1.8) • Sex (M:F) ratio: treatment group 1 (1.9:1); treatment group 2 (2:1) • Exclusion criteria: congenital nephrotic syndrome/ infantile nephrotic syndrome; prior history of poor compliance with medical therapy; known allergy to prednisolone; persistent hypertension or gross haematuria; family history of known genetic causes of nephrotic syndrome
Interventions	Treatment group 1 • Prednisolone: 60 mg/m^2, single dose daily for 6 weeks; then 40 mg/m^2 alternate daily for 6 weeks; then 20 mg/m^2 alternate daily for 1 week and then 10 mg/m^2 alternate daily for 1 week • Total duration: 3.5 months

Al Talhi 2018 *(Continued)*

	• Total dose: 620 (140) mg/m^2/month Treatment group 2 • Prednisolone: 60 mg/m^2 single daily dose for 4 weeks; 40 mg/m^2 on alternate daily for 2 months; 30 mg/m^2 alternate daily for 2 months; 20 mg/m^2 alternate daily for 2 months • Total duration: 7 months • Total dose: 550 (107) mg/m^2/month
Outcomes	• Time to initial relapse • Mean relapse rate, number with frequently relapsing steroid sensitive nephrotic syndrome but no report of number who relapsed overall • Adverse events • Incidence of psychological changes
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes provided to each centre. "One opened when patient qualified to enter the 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	All patients appear accounted for; 4 patients (3%) lost to follow up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Anand 2013

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 12 months
Participants	• Country: India • Setting: single centre, renal clinic

Anand 2013 *(Continued)*

- Inclusion criteria: children with initial episode of SSNS
- Number (analysed/randomised): 60 randomised (numbers per group not reported)
- Age range: 1 to 12 years
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group 1 • Prednisolone: 4 weeks daily; then alternate-day & tapered over 5 months. Daily dose not provided. Total dose 126.5mg/kg over 6 months • Total duration: 6 months Treatment group 2 • Prednisolone: 6 weeks daily then 6 weeks alternate day. Daily doses not provided. Total dose 123.8mg/kg over 3 months • Total duration: 3 months
Outcomes	• Relapse rate by 12 months: 20% (treatment group 1) vs 76.7% (treatment group 2) • Adverse effects
Notes	• Abstract-only publication: numbers of patients in each group not provided so data could not be included in meta-analysis • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relapse defined by urinalysis done by family/staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

APN 1981

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 12 months
Participants	• Country: Germany and Switzerland • Setting: multicentre (11 sites), 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/day 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/day 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)
	• Funding source: supported by grants from the VW Foundation

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"
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	16/64 withdrawn: steroid toxicity (8); incorrect treatment or uncooperative parents (6); late non-response (1); one patient unaccounted for in the text

APN 1981 *(Continued)*

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

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 2 years
Participants	• Country: northern Europe • Setting: multi-centre, 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 (4 weeks) • Prednisone: 60 mg/m^2/day 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/day 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/year • Time to first relapse • Number becoming frequent relapsing patients • Number with serious adverse events

Notes	• Complete one year follow-up
	• Definitions
	  * FRNS using ISKDC definition
	  * Relapse: ISKDC definition
	  * Remission: ISKDC definition with albumin ≥ 35 g/L
	• Supported by grant Ez.1-34844 from the VW-Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement

APN 1988 *(Continued)*

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	QUOTE: "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)" QUOTE: "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

Study characteristics	
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) • 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/day for 6 weeks and then 40 mg/m^2 on alternate days for 6 weeks * Total duration: 3 months Treatment group 2 (2 months)

APN 1993 *(Continued)*

	• Prednisone: 60 mg/m^2/day 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
	• Funding source: not reported

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 permit judgement

Bagga 1999

Study characteristics

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: single centre, renal clinic • Inclusion criteria: children aged 1 to 12 years with first episode SSNS

Bagga 1999 *(Continued)*

- 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, HSP, 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 3 or more occasions); CrCl < 80 mL/min/1.73 m^2

Interventions	Treatment group 1 (4 months) • Prednisolone: 2 mg/kg/day for 4 weeks, 1.5 mg/kg/day 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/day 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 • Funding source: Research grant from the All India Institute of Medical Sciences, New Delhi, India

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)

Bagga 1999 *(Continued)*

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

Basu 2020

Study characteristics

Methods	• Study design: parallel group RCT • Time frame: 12 month period starting April 2015, end date May 2016 • Follow-up: 6 months
Participants	• Country: India • Setting: Single centre renal clinic • Inclusion criteria: children with initial episode or IFR SSNS • Number (analysed/randomised): treatment group 1 (30/30); treatment group 2 (30/30) • Mean age ± SD (years): treatment group 1 (5.77 ± 2.2); treatment group 2 (5.47 ± 2.6) • Sex (M/F): treatment group 1 (19/11); treatment group 2 (21/9) • Initial episode/infrequently relapsing SSNS: treatment group 1 (11/19); treatment group 2 (15/15) • Exclusion criteria: SRNS; secondary nephrotic syndrome; anaemia; leucopenia, thrombocytopenia; abnormal LFT; active chronic infection (HIV, Hepatitis B or C, TB) live vaccination in past month
Interventions	Treatment group 1 (weight-based dosing) • Prednisone 2 mg/kg/day in 3 divided doses for 6 weeks in initial episode or till remission for IFR SSNS • Then prednisone 1.5 mg/kg on alternate days for 6 weeks in initial episode and for 4 weeks in IFR SSNS Treatment group 2 (BSA-based dosing) • Prednisone 60 mg/m^2/day in three divided doses for 6 weeks in initial episode or till remission in IFR SSNS • Then 40 mg/m^2/day on alternate days for 6 weeks in initial episode and for 4 weeks in IFR SSNS

Outcomes	• Primary outcome: relapse-free survival at 6 months
	• Secondary outcomes:
	  * Cumulative steroid dose to achieve remission. All patients and for initial episode/IFR SSNS
	  * Cumulative steroid dose during 6 months. All patients and for initial episode/IFR SSNS
	  * Time to remission. All patients and for initial episode/IFR SSNS
	  * Adverse events

Notes	• Definitions used from Indian Pediatric Nephrology Group, Indian Academy of Pediatrics**.** Management of steroid sensitive nephrotic syndrome: revised guidelines. Indian Pediatr. 2008;45:203-14. • Trial Registration CTRI/2015/03/005655 • Funding source: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with variable blocks; stratified for sex, initial episode versus IFR SSNS

Basu 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes Investigators responsible for enrolment, randomisation, group assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was relapse and this was confirmed by laboratory measurement of urinary protein/creatinine ratio, which is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed 6 months follow up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on
Other bias	Low risk	Authors stated that they received no external funding for the study

Borovitz 2020

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: August 2014 to December 2016 • Follow-up: 3 months
Participants	• Country: Israel • Setting: Single centre, renal clinic • Inclusion criteria: children with relapse of SSNS • Number: treatment group 1 (9); treatment group 2 (11); treatment group 3 (10) • Mean age ± SD (years): treatment group 1 (6.14 ± 3.6); treatment group 2 (6.4 ± 3.3); treatment group 3 (5.9 ± 2.1) • Sex (M/F): treatment group 1 (4/5); treatment group 2 (7/4); treatment group 3 (7/3) • Exclusion criteria: Initial episode of SSNS; SRNS; children on prednisone or other immunosuppressive agents at relapse
Interventions	Treatment group 1 • Prednisone: 1 mg/kg/day; on remission, dose reduced to 1 mg/kg on alternate days for 2 weeks, then reduced in 10 mg increments every 2 weeks till dose of 10 to 15 mg alternate days. Then 5 mg on alternate days for 2 weeks • Total dose: 24.9 ± 7.4 mg/kg • Average duration: 8 to 10 weeks Treatment group 2 • Prednisone: 1.5 mg/kg/day; on remission, dose reduced to 1 mg/kg on alternate days for 2 weeks, then reduced in 10 mg increments every 2 weeks till dose of 10 to 15 mg alternate days. Then 5 mg on alternate days for 2 weeks. • Total dose: 42.7 ± 25.9 mg/kg • Average duration: 8 to 10 weeks

Borovitz 2020 *(Continued)*

	Treatment group 3 • Prednisone: 2 mg/kg/day: on remission, dose reduced to 1.5 mg/kg on alternate days for 2 weeks, then reduced in 10 mg increments every 2 weeks till dose of 10 to 15 mg alternate days. Then 5 mg on alternate days for 2 weeks. • Total dose: 45.5 ± 3.4 mg/kg • Average duration: 10 to 12 weeks
Outcomes	• Primary outcome: cumulative dose of prednisone in each group • Secondary outcomes * Mean time to remission * Number achieving remission * Relapse by 3 months
Notes	• Definition of remission: negative/trace protein on urine dipstick test for 3 consecutive days. • Definition of relapse: proteinuria on dipstick test (> 3+) accompanied by protein/creatinine ratio > 2 mg/mg and/or serum albumin < 3 g/dL and/or oedema. • Only comparison of group 1 (1mg/kg dose) and group 3 (2 mg/kg/dose) were included in meta-analysis • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	QUOTE: "Patients were divided into three prednisone treatment groups in running order of enrolment, as follows: first patient, 2 mg/kg/day; second, 1.5 mg/kg/day; third, 1 mg/kg; and so forth. Patients and clinicians were informed about prednisone dose only after randomization"
Allocation concealment (selection bias)	High risk	QUOTE: "Patients were divided into three prednisone treatment groups in running order of enrolment, as follows: first patient, 2 mg/kg/day; second, 1.5 mg/kg/day; third, 1 mg/kg; and so forth. Patients and clinicians were informed about prednisone dose only after randomization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and lack of blinding could influence assessment of time to remission
Incomplete outcome data (attrition bias) All outcomes	Low risk	All reported participants accounted for
Selective reporting (reporting bias)	High risk	No report of adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

Broyer 1997

Study characteristics

Broyer 1997 *(Continued)*

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/day 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 • Serious adverse events

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Blocks of 10 packages containing equal numbers of each intervention in order determined by random code"
Allocation concealment (selection bias)	Low risk	QUOTE: "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. QUOTE: "Medication in identical bottles and identical tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured. QUOTE: "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))

Broyer 1997 *(Continued)*

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

Study characteristics

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 years 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/day for 2 to 4 weeks given as single morning dose and then 1.5 mg/kg on alternate days for 4 weeks Treatment group 2 (divided dose) • Prednisolone: 2 mg/kg/day 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
	• Funding source: not reported

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	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding

Ekka 1997 *(Continued)*
All outcomes

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 2011

Study characteristics	
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 years 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) • Exclusion criteria: impaired kidney 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

Gulati 2011 *(Continued)*

- Funding source: Funded by the Indian Council of Medical Research

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	QUOTE: "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

Hiraoka 2000

Study characteristics

Methods	• Study design: parallel RCT • 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; 8 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/day (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/day (max 60 mg) for 6 weeks, 40 mg/m^2 on alternate days for 6 weeks • Total duration: 3 months

Hiraoka 2000 *(Continued)*

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
	• Funding source: not reported

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

Study characteristics

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 (7 months)

Hiraoka 2003 *(Continued)*

	• Prednisolone: 60 mg/m^2/day (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: 7 months • Total calculated dose: 4620 mg/m^2 Treatment group 2 (3 months) • Prednisolone: 60 mg/m^2/day for 6 weeks (max 80 mg); 40 mg/m^2 (max 60 mg) on alternate days for 6 weeks • Total duration: 3 months • 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
	• Funding source: not reported

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	QUOTE: "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
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

Study characteristics

Methods	• Study design: parallel RCT • Time frame: June 1980 to June 1983

Imbasciati 1985 *(Continued)*

	• Follow-up: 12 to 24 months
Participants	• Country: Italy • Setting: multicentre, renal clinics • Inclusion criteria: children aged 2 to 14 years with either initial episode SSNS or no relapse in previous year • Number (adults/children): 22/67; treatment group (33/11); treatment group 2 (34/11) * Children (analysed/randomised): treatment group 1 (31/33); treatment group 2 (33/34) • 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/day 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/day 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 to 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
	• Funding source: not reported

Risk of bias

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

Imbasciati 1985 *(Continued)*

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

Study characteristics

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 months to 15 years with SSNS with relapse within 6 months of their initial response to steroid therapy • Number (analysed/randomised): treatment group 1 (25/32); control group (25/32) • 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/day for 4 weeks and tapered daily dose for 4 weeks Control group • Prednisone: 60 mg/m^2/day till remission and 40 mg/m^2 on 3/7 consecutive days for 4 weeks
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
	• 10 patients (4 from group 1; 6 from group 2) were excluded from analysis because of protocol violations
	• 3 patients (2 from group 1 and 1 from group 2) were lost to follow-up and one patient was treated incorrectly so the data on these 4 patients were excluded from analyses.

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

ISKDC 1979 *(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	High risk	14/64 (22%) not included in analyses because of protocol violations or loss to follow up
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

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: September 1994 to 2001 • Follow-up: 2 years
Participants	• Country: Sri Lanka • Setting: renal clinic • Inclusion criteria: 120 children aged 1 to 11.7 years with initial episode of SSNS • Number (analysed/randomised): treatment group 1 (48/48); treatment group 2 (70/74) • 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/day 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/day 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/year • Number with frequent relapses at 1 year • Cumulative dose of steroid • Adverse effects
Notes	• Abstract-only publication; data from author

Jayantha 2002a *(Continued)*

- 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 to permit judgement
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

Study characteristics

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/day 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/day 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/year • Number with frequent relapses, steroid dependence at 1 year • Cumulative dose of steroid • Adverse effects

Notes	• Abstract-only publication; data from author
	• Definitions
	  * ISKDC-relapse: proteinuria ≥ 2+ for 5+ days
	  * Remission: oedema free and urine protein negative/trace
	  * FRNS, SSNS and SDNS: ISKDC and APN definitions
	• Funding source: not reported

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	Insufficient information to permit judgement
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

Kansal 2019

Study characteristics

Methods	• Study design: parallel RCT • Time frame: March 2018 to March 2019 • Follow-up: 3 months after ceasing therapy

Kansal 2019 *(Continued)*

Participants	• Country: India • Setting: single tertiary centre • Inclusion criteria: children with relapsing SSNS • Number (analysed/randomised): treatment group 1 (20/20); treatment group 2 (20/20) • Mean age: 7.5 years • Sex (M/F): not reported • Exclusion criteria: children with serious infections or on stress dose steroids excluded
Interventions	Treatment group 1 • Prednisolone: 2 mg/kg until remission followed by 1mg/kg alternate daily for 4 weeks Treatment group 2 • Prednisolone: 2 mg/kg until remission followed by 1.5 mg/kg alternate daily for 4 weeks
Outcomes	• Number achieving remission • Number with relapse
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear 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	Unclear risk	insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	insufficient information to permit judgement
Other bias	Unclear risk	insufficient information to permit judgement

Kleinknecht 1982

Study characteristics

Methods	• Study design: parallel RCT

Kleinknecht 1982 *(Continued)*

- Time frame: not reported
- Follow-up:15 months

Participants	• Country: France • Setting: multicentre, renal clinics • Inclusion criteria: children with initial episode SSNS • Number (analysed/randomised): treatment group 1 (29/29); treatment group 2 (29/29) • 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/day for 4 weeks and then tapering dose on alternate days for 12 months Treatment group 2 (6 months) • Prednisone: 2 mg/kg/day 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 publication • 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

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: 2 years
Participants	• Country: Poland • Setting: renal clinic • Inclusion criteria: children with initial episode SSNS • Number (analysed/randomised): treatment group 1 (72/72); treatment group 2 (68/68); treatment group 3 (44/44) • 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/day 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/day 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/day 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/year

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	QUOTE: "Parents had an influence on assignment, favouring Protocol C"

Ksiazek 1995 *(Continued)*

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 2 years
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

Study characteristics	
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 (analysed/randomised): 13/13 • Age range: 4.7 to 14.6 years • Sex (M/F): 8/5 • Exclusion criteria: not reported
Interventions	Treatment • 15 mg cortisol/day in ≥ 30 kg and 7.5 mg/day 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

Leisti 1978 *(Continued)*

- Further information requested from authors but not received
- Funding source: Sigrid Juselius Foundation financial support

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
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

Study characteristics

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/day 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)

Li 1994 *(Continued)*

	• Prednisone 2 mg/kg/day 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 • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Study characteristics

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

Liern 2008 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Treatment group 1 • Methylprednisolone: 48 mg/m^2/day 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/day 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
Notes	• Additional data requested from authors and received • Funding source: not reported

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	Insufficient information to permit judgement

Mattoo 2000

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported

Mattoo 2000 *(Continued)*

	• 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 (analysed/randomised): treatment group 1 (18/18); treatment group 2 (18/18) • 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
Outcomes	• Mean relapse rate/patient during 2 year follow-up
Notes	• Definitions * Relapse and remission: ISKDC • Funding source: not reported

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

Study characteristics	
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 to 10 years. no systemic disease • Number (analysed/randomised): treatment group 1 (37/40); treatment group 2 (37/40) • 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 • Calculated total dose: 3990 mg/m^2 Treatment group 2 (standard treatment) • Prednisone: 2 mg/kg/day 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 FRNS • 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
	• Funding source: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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

Mishra 2012 *(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	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

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: March 1990 to April 1996 • Follow-up period: 38 to 42 months
Participants	• Country: Turkey • 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 • Funding source: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mocan 1999 *(Continued)*

Random sequence generation (selection bias)	High risk	QUOTE: "Children arbitrarily randomised into two groups"
Allocation concealment (selection bias)	High risk	QUOTE: "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

Moundekhel 2012

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 12 months
Participants	• Country: Saudi Arabia • Setting: single centre, renal clinic • Inclusion criteria: children with initial episode SSNS or with infrequently relapsing SSNS • Number: treatment group 1 (46); treatment group 2 (46) • Mean age ± SD (years): treatment group 1 (5.76 ± 3.03); treatment group 2 (5.97 ± 2.56) • Sex (M/F): treatment group 1 (26/18); treatment group 2 (31/15) • Exclusion criteria: FRNS, SDNS, SRNS, secondary nephrotic syndrome
Interventions	Treatment group 1 (3 months) • Prednisolone: 6 weeks each of 60 mg/m^2/day and 40 mg/m^2 on alternate days • Total duration: 12 weeks • Total dose: 3020 mg/m^2 Treatment group 2 (2 months) • Prednisolone: 4 weeks each of 60 mg/m^2/day and 40 mg/m^2 on alternate days • Total duration: 8 weeks • Total dose: 2070 mg/m^2
Outcomes	• Relapse by 6 months and 12 months • Adverse effects

Moundekhel 2012 *(Continued)*

Notes	• Number of males and females in treatment group 1 doesn't add up to 46 • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients said to be "randomly divided"; equal numbers in each group suggests that alternation used
Allocation concealment (selection bias)	High risk	Patients said to be "randomly divided"; equal numbers in each group suggests that alternation used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	No report of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all included patients were reported
Selective reporting (reporting bias)	High risk	No report of FRNS/SDNS & limited report of adverse effects
Other bias	Unclear risk	Insufficient information to permit judgement

Norero 1996

Study characteristics

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/day and 40 mg/m^2 on alternate days • Total duration: 12 weeks

Norero 1996 *(Continued)*

	• Total dose: 3600 mg/m^2 Treatment group 2 (2 months) • Prednisolone: 4 weeks each of 60 mg/m^2/day 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/day or 40 mg/m^2/h or urine protein/creatinine ratio > 1 or 3 + on dipstick for > 3 days
	  * Remission: urine protein < 150 mg/day for 3 consecutive days
	• Time to 1st relapse: not reported
	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation 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
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)

Paul 2014

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: January 2006 to May 2008 • Follow-up: 12 months
Participants	• Country: Bangladesh • Setting: single centre, renal clinic • Inclusion criteria: children with initial episode of SSNS aged 1-15 years • Number (analysed/randomised): treatment group 1 (47/50); treatment group 2 (46/50) • Mean age ± SD (months): treatment group 1 (55.2 ± 35.1); treatment group 2 (59.3 ± 37.0) • Sex (M/F): ratio 4:3 • Exclusion criteria: SRNS, secondary nephrotic syndrome, patients requiring methylprednisolone, impaired kidney function
Interventions	Treatment group 1 (12 weeks) • Prednisolone: 60 mg/m^2 daily for 6 weeks, then 40 mg/m^2 alternate days for 6 weeks • Duration 12 weeks • Total cumulative dose: 2146.1 ± 708.1 mg/m^2 Treatment group 2 (8 weeks) • Prednisolone: 60 mg/m^2 daily for 4 weeks, then 40 mg/m^2 for 4 weeks • Duration: 8 weeks • Total cumulative dose: 1573.4 ± 450 mg/m^2
Outcomes	• Time from cessation of prednisolone to first relapse • Number with relapse at 6 months • Cumulative prednisone dose • Adverse effects at 12 months available in 41 and 31 patients

Notes	• Definitions
	  * FRNS: 2 + relapses in 6 months or 3 + in 1 year
	  * SDNS: 2 relapses while on steroids or within 2 weeks of ceasing
	  * Relapse: 3+ proteinuria for 3 days (urinary spot protein/creatinine ratio > 2mg/mg)
	  * Remission: Urine protein nil or trace for 3 consecutive days
	• Differential loss to follow up by 12 months: 15 of 47 (33%) in treatment group 1 vs 6 of 46 (13%) in treatment group 2 so data have not been included in 12-24 month analyses. At 6 months 18/47 in treatment group 1 vs 22/46 in treatment group 2 had relapsed
	• Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Lottery method"
Allocation concealment (selection bias)	Unclear risk	"Lottery method"
Blinding of participants and personnel (performance bias)	High risk	Open label

Paul 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No report of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	7/93 (7.5%) excluded from 6 month analysis (2 died, 3 deviated from protocol, 3 lost to FU). 72 (77%) completed 1 year FU & reported data on number (%) with relapse and FRNS refer to 72 who completed 12 months
Selective reporting (reporting bias)	High risk	Expected outcomes of relapse, FRNS, steroid dose and adverse effects reported but only for patients completing 12 months
Other bias	Unclear risk	No information provided

Pecoraro 2003

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: 12 months
Participants	• Country: Italy • Setting: single centre, 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/day 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/day for 3 days; 1 mg/kg/day 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/day 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

Pecoraro 2003 *(Continued)*

Notes	• No definitions provided • Abstract-only publications • Funding source: educational grant from Fresenius

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

PREDNOS 2019

Study characteristics

Methods	• Study design: parallel RCT • Time frame: July 2011 to October 2014 • Follow-up: 24 months
Participants	• Country: UK • Setting: multicentre (86 sites) • Inclusion criteria: children with initial episode of SSNS • Number (analysed/randomised): treatment group 1 (114/119); treatment group 2 (109/118) • Ethnicity: treatment group 1 (South Asian (23); White (75); other (16)); treatment group 2 (South Asian (21); White (73); other (15)) • Mean age ± SD (years): treatment group 1 (5.1 ± 3.2); treatment group 2 (4.7 ± 2.9) • Sex (M/F): treatment group 1 (68/31); treatment group 2 (78/36) • Exclusion criteria: Children with biopsy showing changes other than minimal change disease; history of poor adherence; allergy to prednisolone; failed to respond to prednisolone
Interventions	Treatment group 1

PREDNOS 2019 *(Continued)*

	• Prednisolone: 60 mg/m^2 (max. 80 mg) daily for 4 weeks; 12 weeks of prednisolone (alternate day) starting at 60 mg/m^2 (max. 80 mg) and tapering by 10 mg/m^2 every two weeks • Total duration: 16 weeks of prednisolone • Total dose: total 3150 mg/m^2 Treatment group 2 • Prednisolone: 60 mg/m^2 (maximum 80 mg) daily for 4 weeks; 4 weeks of prednisolone 40 mg/m^2 (max. 60 mg); matching placebo from weeks 9 to 16 • Total duration: 8 weeks of prednisolone • Total dose: total 2240mg/m^2
Outcomes	• Time to first relapse • Number with relapse • Number with FRNS and SDNS • Adverse effects
Notes	• Trial registration: ISRCTN16645249; EudraCT no. 2010-022489-29 • Funding source: "The PREDNOS study was funded by an investigator led grant from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (HTA grant reference No08/53/31)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "Randomisation online via a secure 24 hour internet based randomisation service or by a telephone call to the Birmingham Clinical Trials Unit." 1:1 ratio using minimisation algorithm to balance ethnicity (South Asian, White, Other) and age (≤ 5, ≥ 6 years). Randomisation took place when child considered to be in remission
Allocation concealment (selection bias)	Low risk	QUOTE: "Randomisation online via a secure 24 hour internet based randomisation service or by a telephone call to the Birmingham Clinical Trials Unit"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment was open-label for first 4 weeks. Then blinded for participants/personnel for 12 weeks with matching placebo in the control group. Blinded trial drugs were dispensed from a central pharmacy in blister packs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants/personnel for 12 weeks after initial 4 weeks of therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes (relapse, FRNS, adverse effects) reported
Other bias	Low risk	National Institute of Health Research's Health Technology Assessment programme

PREDNOS PILOT 2019

Study characteristics

Methods	• Study design: parallel RCT • Time frame: August 2006 to March 2007 • Follow-up: 12 months
Participants	• Country: UK • Setting: multicentre (37 sites) • Inclusion criteria: children with initial episode of SSNS • Number: treatment group 1 (25); treatment group 2 (27) • Mean age ± SD (years): treatment group 1 (6.5 ± 3.1); treatment group 2 (6.1 ± 3.0) • Sex (M/F): treatment group 1 (15/10); treatment group 2 (16/11) • Ethnicity: White (38); South Asian (10); other (4) • Exclusion criteria: biopsy showing changes other than minimal change disease; history of poor adherence; allergy to prednisolone; failed to respond to prednisolone
Interventions	Treatment group 1 • Prednisolone: 60 mg/m^2 (max. 80 mg) daily for 4 weeks; 12 weeks of prednisolone (alternate day) starting at 60 mg/m^2 (max. 80 mg) and tapering by 10 mg/m^2 every two weeks • Total duration: 16 weeks of prednisolone • Total dose: total 3150 mg/m^2 Treatment group 2 • Prednisolone: 60 mg/m^2 (max. 80 mg) daily for 4 weeks; 4 weeks of prednisolone 40 mg/m^2 (max. 60 mg); placebo from weeks 9 to 16 • Total duration: 8 weeks of prednisolone • Total dose: total 2240 mg/m^2
Outcomes	• Time to first relapse • Number with relapse • Adverse effects
Notes	• Pilot study for PREDNOS study 2018 • Funding source: sponsored by Great Ormond Street Hospital for Children NHS Foundation Trust (reference number 03/NU/13)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomisation online via a secure 24 hour Internet based randomisation service or by a telephone call to the Birmingham Clinical Trials Unit". 1:1 ratio using minimisation algorithm to balance ethnicity (South Asian, White, Other) and age (≤5, ≥6 years). Randomisation took place when child considered to be in remission.
Allocation concealment (selection bias)	Low risk	QUOTE: "Randomisation online via a secure 24 hour Internet based randomisation service or by a telephone call to the Birmingham Clinical Trials Unit".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment was open-label for first 4 weeks. Then blinded for participants/personnel for 12 weeks with matching placebo in the control group. Blinded trial drugs were dispensed from a central pharmacy in blister packs

PREDNOS PILOT 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants/personnel for 12 weeks after initial 4 weeks of therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes (relapse, FRNS, adverse effects) reported
Other bias	Low risk	Kidney Research UK and Kid's Kidney Research

PROPINE 2018

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 2013 to 2017 • Follow-up: 12 months
Participants	• Country: Italy • Setting: multicentre • Inclusion criteria: aged 3 to 17 years; had not received a steroid sparing agent in the previous year and experienced at least 1ne relapse • Number: 79 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Prednisone: 40 mg/m^2 alternate daily for 4 weeks Treatment group 2 • Prednisone: progressive tapering schedule over 8 weeks with same cumulative dose of prednisone
Outcomes	• Time to first relapse • Adverse effects
Notes	• Abstract-only publication • EudraCT2012-004326-16 • Information on numbers allocated to each group requested from the authors but not received • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised, insufficient information to permit judgement

PROPINE 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study and outcomes likely to be influenced by non blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study and outcomes likely to be influenced by non blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers in allocated groups not specified
Selective reporting (reporting bias)	High risk	Data reported in medians
Other bias	Unclear risk	Insufficient information to permit judgement

Raman 2016

Study characteristics	
Methods	• Study design: RCT • Time frame: March 2014 to July 2015 • Follow-up: 6 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: children with SSNS, treated with prednisone for first time or following relapse (includes frequently and infrequent relapsers) • Number (analysed/randomised): treatment group 1 (44/50); treatment group 2 (42/50) • Mean age (years): treatment group 1 (5.4 ± 2.9); treatment group 2 (5.2 ± 2.5) • Sex (M/F): treatment group 1 (27/13); treatment group (27/13) • Exclusion criteria: infants; secondary nephrotic syndrome; children with BSA > 1 m^2 and weight > 30 kg; active infection
Interventions	Treatment group 1 (Body weight based) • Prednisolone: 2 mg/kg daily (maximum 60 mg) in two divided doses for 6 weeks, 1.5 mg/kg (maximum 40 mg) on alternate days for 6 weeks Treatment group 2 (BSA-based) • Prednisolone: 60 mg/m^2 daily (maximum 60 mg) in 2 divided doses for 6 weeks, 40mg/m^2 alternate days for 6 weeks,
Outcomes	• Time taken for remission • Number of relapses • Cumulative dose of prednisolone • Adverse effects
Notes	• CTRI/2014/04/004541

Raman 2016 *(Continued)*

- The median cumulative dose of prednisone was 81 mg/kg (IQR 30 to 115) in the BW-based group and 96 mg/kg (IQR 36 to 130) in the BSA group
- Funding source: Supported, in part, by institutional and departmental funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "Block randomization using 20 blocks of two block sizes (4 and 6) was generated using random allocation software version 2.0 (Informer Technologies, Inc.) to allocate the enrolled subjects into one of two groups (BW-based or BSA-based prednisolone regimen) in an allocation ratio of 1:1 by a person not directly involved with data collection, analysis or interpretation. This randomization list was concealed from the investigators carrying out the study"
Allocation concealment (selection bias)	Low risk	QUOTE: "Allocation was concealed placing individual assignments (folded twice) in serially numbered, sealed opaque envelopes by a person not involved in the trial".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinicians not blinded but statistician was blinded to treatment groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	QUOTE: The clinicians were not blinded but "the statistician was blinded to the assigned interventions until initial analysis and preparation of the first draft of manuscript".
Incomplete outcome data (attrition bias) All outcomes	Low risk	44/49 analysed for primary outcome. 7/100 (7%) not analysed
Selective reporting (reporting bias)	High risk	Outcomes presented as medians with ranges and not able to add to meta-analyses
Other bias	Unclear risk	Insufficient information to permit judgement

Satomura 2001

Study characteristics

Methods	• Study design: quasi-RCT • Study duration: not reported • Duration of follow-up: 1 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)

Satomura 2001 *(Continued)*

	• Prednisolone: 60 mg/m^2/day 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/day for 4 weeks; 40 mg/kg on alternate days for 8 weeks • Total duration: 12 weeks
Outcomes	• Number with relapse at 12 months • Time to relapse
Notes	• Abstract-only publication • No definitions provided • Funding source: not reported

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 2002

Study characteristics

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)

Sharma 2002 *(Continued)*

- 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/day 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) • Prednisolone: 60 mg/m^2/day 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 FRNS • Cumulative steroid dose • Adverse events
Notes	• Definitions * Remission and relapse: ISKDC * FRNS: 2+ in 6 months or 6+ in 18 months * SDNS: APN definition • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "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

Sharma 2002 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Sheikh 2019

Study characteristics

Methods	• Study design: RCT • Time frame: not reported (last follow-up September 2019) • Follow-up: 12 months
Participants	• Country: India • Setting: government hospital • Inclusion criteria: children aged 1 to 12 years with relapse of SSNS • Number: treatment group 1 (30); treatment group 2 (30) • Mean age ± SD (years): not reported • Sex (M/F): treatment group 1: not reported • Exclusion criteria: children with infections; co-morbidities; other immunosuppression
Interventions	Treatment group 1 (low dose) • Prednisolone: 1 mg/kg/day until remission • Therapy switched to 2 mg/kg if not in remission by day 15 • Total dose: total 3150mg/m^2 Treatment group 2 (conventional dose) • Prednisolone 2 mg/kg/day until day 15 or disease remission
Outcomes	• Time to remission • Number of relapses in each group
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised, insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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

Sheikh 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear accounted for
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Singhal 2015

Study characteristics

Methods	• Study design: RCT • Time frame: commenced March 2011 • Follow-up: 6 months post initial therapy
Participants	• Country: India • Setting: single centre • Inclusion criteria: children with initial episode of SSNS • Number: treatment group 1 (12); treatment group 2 (13) • Mean age ± SD (years): treatment group 1 (3.54 ± 1.21); treatment group 2 (5.53 ± 3.73) • Sex (M/F): treatment group 1 (7/5); treatment group 2 (7/6) • Exclusion criteria: children with nephrotic syndrome secondary to systemic disorder or drugs
Interventions	Treatment group 1 • Deflazacort: 2.4 mg/kg daily for 6 weeks in 2-3 divided doses; 1.8 mg/kg in a single dose alternate days for 6 weeks • Total duration: 12 weeks Treatment group 2 • Prednisolone: 2 mg/kg daily for 6 weeks; 1.5 mg/kg alternate days for 6 weeks • Total duration: 12 weeks
Outcomes	• Time taken to induce remission • Number of relapses on and off treatment in both groups
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random table
Allocation concealment (selection bias)	Unclear risk	Insufficient data to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Not blinded and lack of blinding may influence outcome

Singhal 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and lack of blinding may influence outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All prespecified outcomes mentioned
Other bias	Unclear risk	Insufficient data to permit judgement

Sinha 2015

Study characteristics	
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 < 2.5 g/dL; oedema • Number (analysed/randomised): treatment group 1 (92/92); treatment group 2 (88/89) • 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 (59/30) • 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/day for 6 weeks, 1.5 mg/kg/day then 1.5 mg/kg on alternate days for 6 weeks. Then matching placebo for 12 weeks • Actual total dose: 2791.7 ± 286.6 mg/m^2 Treatment group 2 (6 months) • Prednisolone: 2 mg/kg/day 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/year from randomisation to 12 and 24 months • Need for steroid sparing therapies at 12 and 24 months

Sinha 2015 *(Continued)*

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

Teeninga 2013

Study characteristics

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 (69 sites); general and university hospitals • Inclusion criteria: children aged 9 months to 7 years with initial episode of SSNS • Number (analysed/randomised): treatment group 1 (62/74); treatment group 2 (64/76) • 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)

Teeninga 2013 *(Continued)*

	• Prednisolone: 60 mg/m^2/day 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

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)
	• Funding source: This study was funded by Dutch Kidney Foundation Grant C03.2072 and the Vrienden van het Sophia Foundation

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

Teeninga 2013 *(Continued)*

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

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 1 year
Participants	• Country: Japan • Setting: single centre, 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 • 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/day for 4 weeks, 60 mg/m^2 on alternate days for 4 weeks and taper by 10 mg/m^2/month • Total duration: 7 months Treatment group 2 (standard) • Prednisolone: 60 mg/m^2/day 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/year • FRNS • Adverse effects

Notes	• Unequal numbers in groups
	• Definitions
	  * FRNS: any relapse occurring within 2 months after ceasing prednisone
	  * Relapse: ISKDC
	  * Remission: ISKDC
	• Funding source: supported by a grant from the Ministry of Health and Welfare in Japan

Risk of bias	

Ueda 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "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

Yadav 2019

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: September 2013 to November 2015 • Follow-up: 1 year
Participants	• Country: India • Setting: single centre, renal clinic • Inclusion criteria: children with relapsing SSNS • Number (analysed/randomised): treatment group 1 (30/31); treatment group 2 (31/31) • Mean age ± SD (months): treatment group 1 (40.2 ± 32.1); treatment group 2 (39.6 ± 21.8) • Sex (M/F): treatment group 1 (22/9); treatment group 2 (20/11) • Exclusion criteria: steroid toxicity (BMI > 2 SD, cataract, glaucoma, stage 2 hypertension); levamisole, cyclophosphamide or calcineurin inhibitors or rituximab in previous 6 months
Interventions	Treatment group 1 • Prednisone: 0.2 to 0.3 mg/kg daily for 12 months Treatment group 2 • Prednisone: 0.5 to 0.7 mg/kg alternate days for 12 months All patients received daily supplements • calcium carbonate: 250 to 500 mg • Vitamin D: 200 to 40 IU

Yadav 2019 *(Continued)*

Outcomes	• Number of relapses • Number with sustained remission • Time to first relapse • Time to treatment failure • Adverse effects
Notes	• One patient did not return for follow-up • Funding source: Indian Council of Medical Research (No 5/5/1090/2013-RHN)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated block randomisation; stratified for steroid dependence. Computer generated allocation Consecutive patients enrolled
Allocation concealment (selection bias)	Low risk	Allocation was concealed in sequentially numbered sealed, opaque envelopes, by personnel not involved in the randomisation process; envelopes were opened following informed written parental consent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessment of relapse based on urinalysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	The pre-specified outcomes of the review have been reported
Other bias	Low risk	Funding by Indian Council of Medical Research (No 5/5/1090/2013-RHN)

Yoshikawa 1998

Study characteristics

Methods	• Study design: parallel RCT • Time frame: January 1990 to December 1992 • Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre (35 sites), 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): treatment group 1 (66%); treatment group 2 (71%) • Exclusion criteria: not reported

Yoshikawa 1998 *(Continued)*

Interventions	Treatment group 1 (prolonged) • Prednisolone: 2 mg/kg/day 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/day 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/day; 20 to 40 kg 5.4 g/day; < 20 kg 2.7 g/day
Outcomes	• Number relapsing by 2 years. • Number of patients with FRNS
Notes	• Definitions * Relapse, FRNS: ISKDC • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: 'randomly assigned, concealed envelopes'
Allocation concealment (selection bias)	Low risk	QUOTE: 'randomly assigned, concealed envelopes'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
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
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 2015

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 6 September 2007 to 9 February 2013

Yoshikawa 2015 *(Continued)*

	• Follow-up: 2 years
Participants	• Country: Japan • Setting: multicentre (90 hospitals) • Inclusion criteria: aged 1 to 15 years with first episode of INS with remission within 3 weeks • Number (analysed/randomised): treatment group 1 (122/127); treatment group 2 (124/128) • 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 to 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
	• Funding source: Grant from the Ministry of Health, Labour and Welfare, Japan

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	QUOTE: "Patients were randomly assigned....at the Japan Clinical Research Support Unit"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label, patients, guardians, treating physicians and individuals were data were not blinded to treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "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)

Yoshikawa 2015 *(Continued)*

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 2007d

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: 3 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: children with SSNS • Number (analysed/randomised): 23/31; treatment group 1 (9); treatment group 2 (14) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 (3 months) • Pulse methylprednisolone. No details on dosing provided Treatment group 2 (2 months) • Prednisone. No details on dosing provided
Outcomes	• Time to remission • Relapse rate by 3 months • Adverse effects
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Said to be randomised; insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence that study was blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical outcomes could be influenced by lack of blinding

Zhang 2007d *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

APN - Arbetsgemeinschaft für Pädiatrische Nephrologie; BMD - bone mineral density; BMI - body mass index; BSA - body surface area; CPA - cyclophosphamide; CrCl - creatinine clearance; CPA - cyclophosphamide; CSA - cyclosporin; eGFR - estimated glomerular filtration rate; FRNS - frequently relapsing steroid-sensitive nephrotic syndrome; HIV - human immunodeficiency virus; HSP - Henoch-Schönlein purpura; IFR - infrequently relapsing; INS - idiopathic nephrotic syndrome; IQR - interquartile range; ISKDC - International Study of Kidney Disease in Children; LFT - liver function test/s; SCr - serum creatinine; SDNS - steroid-dependent nephrotic syndrome; SSNS - steroid-sensitive nephrotic syndrome; SRNS - steroid-resistant nephrotic syndrome; TB - tuberculosis; URTI - upper respiratory tract infection

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

Study	Reason for exclusion
APN 2006	RCT comparing cyclosporin with prednisone. Transferred to Cochrane Review on "Non-corticosteroid immunosuppressive agents for steroid-sensitive nephrotic syndrome in children"
Zhang 2014	RCT comparing azithromycin with prednisone. Transferred to Cochrane Review on "Non-corticosteroid immunosuppressive agents for steroid-sensitive nephrotic syndrome in children"

RCT - randomised controlled trial

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

CTRI/2015/11/006345

Study name	Efficacy of short prednisolone treatment for relapse in children with steroid sensitive nephrotic syndrome: a randomised controlled study
Methods	• Parallel RCT
Participants	• 114 children aged 1 to 16 years with SSNS and relapse
Interventions	Treatment group 1 • Prednisolone: 2 mg/kg daily till remission, then 1.5 mg/kg on alternate days for 2 weeks Treatment group 2 • Prednisolone: 2 mg/kg daily till remission, then 1.5 mg/kg on alternate days for 4 weeks
Outcomes	• Time to first relapse • Relapse rates • Cumulative dose of steroids • Adverse effects of steroids
Starting date	15/12/2015
Contact information	Professor Pankaj Hari; pankajhari@hotmail.com

CTRI/2015/11/006345 *(Continued)*

Notes	

CTRI/2018/05/013634

Study name	A randomised controlled clinical trial to compare the efficacy of standard dose of steroids vs reduced dose in treating relapses in children with steroid sensitive nephrotic syndrome
Methods	• Parallel, open-label RCT • Follow-up for 6 months
Participants	• 60 children aged 1 to 18 years. All children with idiopathic nephrotic syndrome on stable immunosuppression (either long-term alternate-day steroids, levamisole or MMF) or on no immunosuppression for last 6 months with infrequent relapses defined as < 2 relapses in last 6 months
Interventions	Treatment group • Prednisolone: 1 mg/kg every alternate day to treat relapse in children with nephrotic syndrome. Duration unclear. No information on prednisone dose/duration to achieve remission Control group • Prednisolone: 1.5 mg/kg every alternate day to treat relapse. Duration unclear but same as experimental group. No information on prednisone dose/duration to achieve remission
Outcomes	• Proportion of frequent relapsers on the reduced dose regime as compared to standard regime • Number of relapses in children in whom steroid dose is reduced to 1mg/kg on alternate days for 4 weeks instead of the standard 1.5 mg/kg every alternate day in 6 months • Cumulative steroid dose in two groups for 6 months
Starting date	1/6/2018
Contact information	Associate Professor Suprita Kalra. kalrasuprita@gmail.com
Notes	Children with SRNS or SSNS commenced on steroid sparing agent in past 6 months because of FRNS or SDNS

CTRI/2018/05/014075

Study name	A comparison of two doses of prednisolone for relapses in children with steroid sensitive nephrotic syndrome: a randomised controlled non inferiority trial
Methods	• Parallel, open label RCT • Follow-up for 12 months
Participants	• 60 children aged 1 to 12 years with SSNS presenting with relapse
Interventions	Treatment group • Prednisolone: 1mg/kg/day till remission or two weeks whichever is earlier Control group • Prednisolone 2mg/kg/day till remission or 2 weeks whichever is earlier

CTRI/2018/05/014075 *(Continued)*

Outcomes	Primary outcome • The difference in the mean time to achieve remission between experimental and control groups Secondary outcomes • Proportion of children with relapse who achieved remission with 1 mg/kg/day versus 2 mg/kg/day of oral prednisolone within 4 weeks • Time to first relapse after treatment of a relapse over 12 months • Number of relapses over the subsequent 12 months over 12 months • Cumulative dose of steroids • Adverse effects
Starting date	01/06/2018
Contact information	Kirtisudha Mishra. kirtisen@gmail.com
Notes	Children receiving non-corticosteroid immunosuppressive agents are excluded

PREDNOS 2 2014

Study name	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 to 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/day (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/day, weeks 5 to 16 prednisolone 60 mg/m^2 on alternate days tapering by 10 mg/m^2 every 2 weeks
Outcomes	• Primary outcome measure • Incidence of URTI-related relapse following the first URTI during the 12 month follow-up period • Secondary outcome measures • Rate of URTI-related relapse of nephrotic syndrome (relapses per year) • Rate of relapse (URTI-related and non URTI-related) of nephrotic syndrome (relapses per year) • Cumulative dose of prednisolone (mg/kg and mg/m2) received over the 12 month study period • Incidence of serious adverse events • Incidence of adverse effects of prednisolone including assessment of behaviour using the Achenbach Child Behaviour Checklist • Incidence of escalation of background immunosuppressive therapy (e.g. addition of cyclosporin, tacrolimus, cyclophosphamide etc.) • Incidence of reduction of background immunosuppressive therapy (i.e. cessation of long term maintenance prednisolone therapy) • Quality of life using the CHU-9D, EQ-5D and PedsQL • Cost per relapse of nephrotic syndrome

PREDNOS 2 2014 *(Continued)*

	• Cost per QALY gained
Starting date	1 November 2010
Contact information	Martin Christian: Martin.Christian@nuh.nhs.uk
Notes	

RESTERN 2017

Study name	Steroid treatment reduction in relapsing childhood nephrotic syndrome: a new nationwide randomised controlled trial in the Netherlands - the RESTERN study
Methods	• Double-blind, placebo controlled RCT • Follow-up for 2 years
Participants	• 144 children aged 1 to 18 years with relapse of SSNS
Interventions	Treatment group 1 • Prednisolone: daily till remission then alternate days for 2 weeks; placebo for 4 weeks Treatment group 2 Prednisolone: daily till remission then alternate days for 6 weeks
Outcomes	• Time to first relapse • Number of relapses • Progression to FRNS or SDNS • Cumulative dose of prednisolone
Starting date	December 2016
Contact information	Dr Anne Schijivens, Radboudume Amalia Children's Hospital, Nijmegen, The Netherlands. anne.schijvens@radboudumc.nl
Notes	Dutch trial registry NTR5670, EudraCT no 2016-002430-76

Sinha 2016

Study name	Randomised controlled trial to compare efficacy of 3-months versus 6-months therapy with prednisolone for the first episode of idiopathic nephrotic syndrome in children <4-yr-old
Methods	• Study design: multicentric, parallel, open-label RCT • Time frame: July 2015 to August 2019 • Follow-up: 1 year
Participants	• Country: India, USA • Setting: multi-centre (4); academic centres, one India; 3 centres USA • Inclusion criteria: children age 1 year up to 4 years with new onset, idiopathic nephrotic syndrome • Number: treatment group 1 (79); treatment group 2 (81) • Age ± SD (months): treatment group 1 (32 ± 11); treatment group 2 (35 ± 9) • Sex (M/F): not reported

Sinha 2016 *(Continued)*

	• Exclusion criteria: nephrotic syndrome known to be secondary to a systemic disorder, therapy with corticosteroids in the past three months, patients with initial steroid resistance, Patients who show relapse during the first 3 months of pre-randomisation corticosteroid therapy for nephrotic syndrome, prednisolone therapy for prior episodes of nephrotic syndrome
Interventions	Initial treatment • Following 12 weeks standard therapy (prednisolone 60 mg/m^2/day for 6 weeks followed by 40 mg/m^2/day every other day for 6 weeks) patients are randomised 1:1 Treatment group 1 • Prednisolone: tapering dose over 12 weeks Treatment group 2 • Stop therapy: no therapy for 12 weeks
Outcomes	• Proportions of patients with relapse • Frequency of relapses • Proportions of sustained remission • Adverse effects
Starting date	July 2015
Contact information	Dr Aditi Sinha: aditisinhaaiims@gmail.com
Notes	CTRI/2015/06/005939

SSNS - steroid-sensitive nephrotic syndrome; URTI - upper respiratory tract infection; FRNS - frequently relapsing nephrotic syndrome; MMF - mycophenolate mofetil; RCT - randomised controlled trial; SDNS - steroid-dependent nephrotic syndrome

DATA AND ANALYSES

Comparison 1. Steroid therapy in first episode: ≥ 3 months versus 2 months therapy

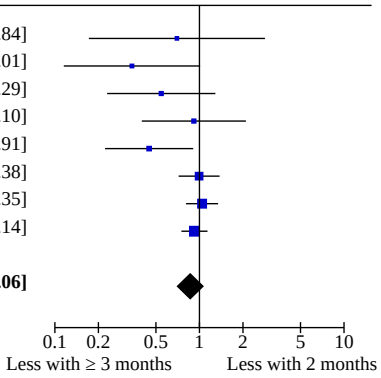
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number with frequent relapses by 12 to 24 months	8	976	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.06]
1.2 Number of children relapsing by 12 to 24 months	12	1309	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.95]
1.3 Number with frequent relapses by 12 to 24 months stratified by risk of bias for selection bias	7	805	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.59, 1.06]
1.3.1 Low risk of selection bias	4	585	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.19]
1.3.2 Unclear or high risk of selection bias	3	220	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.26, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Number of children relapsing by 12 to 24 months stratified by risk of selection bias	11	1108	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.65, 0.95]
1.4.1 Low risk of selection bias	5	637	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
1.4.2 Unclear or high risk of selection bias	6	471	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.49, 0.98]
1.5 Adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Psychological disorders	4	456	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.53, 1.90]
1.5.2 Hypertension	7	548	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.55, 5.73]
1.5.3 Cataracts/eye disorders	6	623	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.11, 1.52]
1.5.4 Retarded growth	4	354	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.18]
1.5.5 Cushingoid facies	5	547	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.76, 1.65]
1.5.6 Infections	2	172	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.17]
1.5.7 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: ≥ 3 months versus 2 months therapy, Outcome 1: Number with frequent relapses by 12 to 24 months

Study or Subgroup	≥ 3 months therapy Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Norero 1996	3	29	4	27	2.0%	0.70 [0.17 , 2.84]
Ueda 1988	3	17	15	29	3.2%	0.34 [0.12 , 1.01]
APN 1993	6	34	12	37	4.9%	0.54 [0.23 , 1.29]
Bagga 1999	7	22	8	23	5.3%	0.91 [0.40 , 2.10]
Jayantha 2002a	8	48	26	70	7.0%	0.45 [0.22 , 0.91]
Yoshikawa 2015	45	122	46	124	20.8%	0.99 [0.72 , 1.38]
PREDNOS 2019	60	114	55	109	26.3%	1.04 [0.81 , 1.35]
Yoshikawa 1998	54	83	62	88	30.6%	0.92 [0.75 , 1.14]
Total (95% CI)		**469**		**507**	**100.0%**	**0.86 [0.71 , 1.06]**
Total events:	186		228			

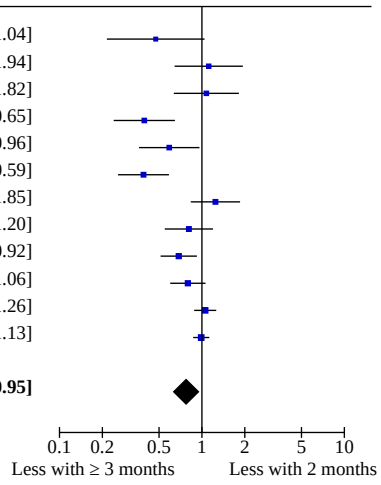
Heterogeneity: Tau² = 0.02; Chi² = 10.45, df = 7 (P = 0.16); I² = 33%
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable



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

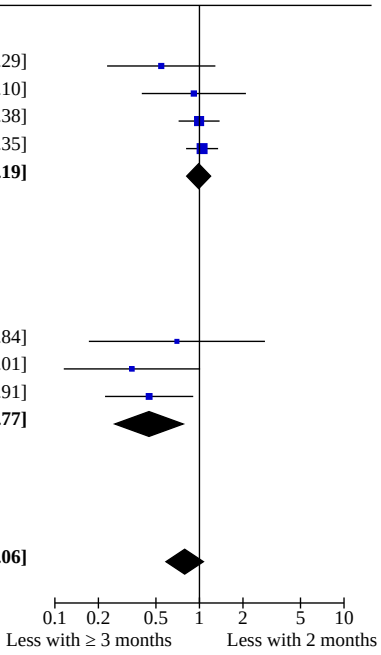
Study or Subgroup	≥ 3 months therapy Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ueda 1988	5	17	18	29	4.2%	0.47 [0.22 , 1.04]
Yoshikawa 1998	20	83	19	88	6.4%	1.12 [0.64 , 1.94]
Norero 1996	15	29	13	27	6.7%	1.07 [0.63 , 1.82]
Moundekhel 2012	13	46	33	46	7.1%	0.39 [0.24 , 0.65]
APN 1993	13	34	24	37	7.2%	0.59 [0.36 , 0.96]
Jayantha 2002a	16	48	60	70	8.2%	0.39 [0.26 , 0.59]
Satomura 2001	23	36	19	37	8.4%	1.24 [0.84 , 1.85]
PREDNOS PILOT 2019	15	25	20	27	8.5%	0.81 [0.55 , 1.20]
Ksiazek 1995	36	72	32	44	9.9%	0.69 [0.51 , 0.92]
Bagga 1999	16	22	21	23	10.0%	0.80 [0.60 , 1.06]
Yoshikawa 2015	83	122	80	124	11.4%	1.05 [0.88 , 1.26]
PREDNOS 2019	91	114	88	109	11.9%	0.99 [0.87 , 1.13]
Total (95% CI)		**648**		**661**	**100.0%**	**0.77 [0.63 , 0.95]**
Total events:	346		427			

Heterogeneity: Tau² = 0.08; Chi² = 48.19, df = 11 (P < 0.00001); I² = 77%
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Not applicable



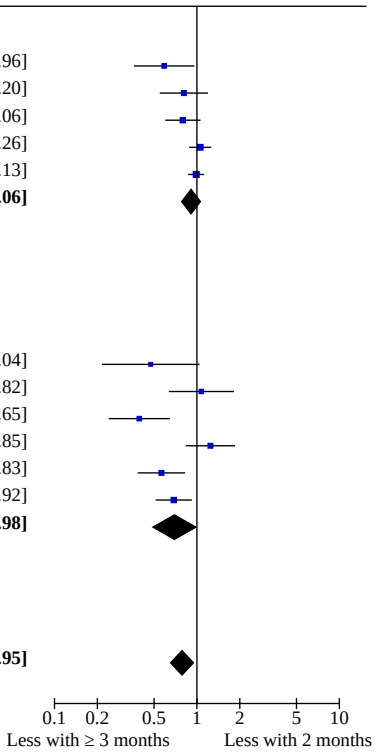
Analysis 1.3. Comparison 1: Steroid therapy in first episode: ≥ 3 months versus 2 months therapy, Outcome 3: Number with frequent relapses by 12 to 24 months stratified by risk of bias for selection bias

Study or Subgroup	≥ 3 months therapy Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Low risk of selection bias						
APN 1993	6	34	12	37	9.2%	0.54 [0.23 , 1.29]
Bagga 1999	7	22	8	23	9.8%	0.91 [0.40 , 2.10]
Yoshikawa 2015	45	122	46	124	27.1%	0.99 [0.72 , 1.38]
PREDNOS 2019	60	114	55	109	31.1%	1.04 [0.81 , 1.35]
Subtotal (95% CI)		**292**		**293**	**77.2%**	**0.99 [0.82 , 1.19]**
Total events:	118		121			
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.3.2 Unclear or high risk of selection bias						
Norero 1996	3	29	4	27	4.0%	0.70 [0.17 , 2.84]
Ueda 1988	3	17	15	29	6.3%	0.34 [0.12 , 1.01]
Jayantha 2002a	8	48	26	70	12.4%	0.45 [0.22 , 0.91]
Subtotal (95% CI)		**94**		**126**	**22.8%**	**0.45 [0.26 , 0.77]**
Total events:	14		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**386**		**419**	**100.0%**	**0.79 [0.59 , 1.06]**
Total events:	132		166			
Heterogeneity: Tau² = 0.06; Chi² = 10.43, df = 6 (P = 0.11); I² = 42%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 7.25, df = 1 (P = 0.007), I² = 86.2%						



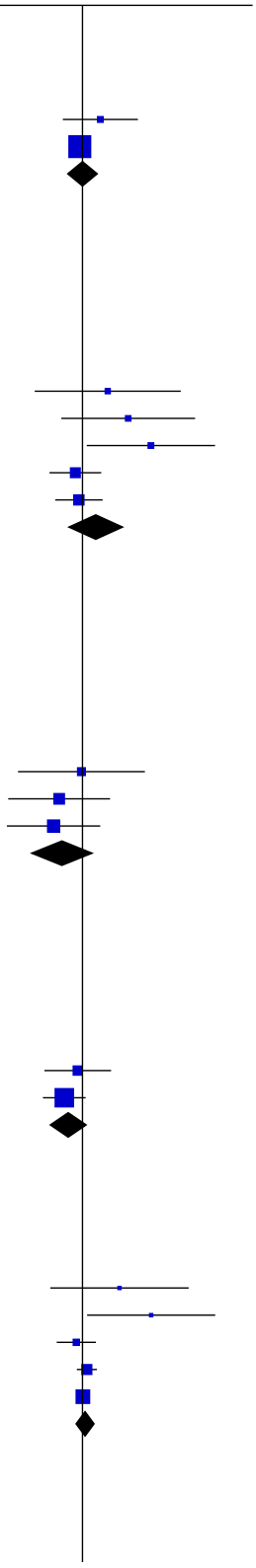
Analysis 1.4. Comparison 1: Steroid therapy in first episode: ≥ 3 months versus 2 months therapy, Outcome 4: Number of children relapsing by 12 to 24 months stratified by risk of selection bias

Study or Subgroup	≥ 3 months therapy Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Low risk of selection bias						
APN 1993	13	34	24	37	7.2%	0.59 [0.36 , 0.96]
PREDNOS PILOT 2019	15	25	20	27	8.9%	0.81 [0.55 , 1.20]
Bagga 1999	16	22	21	23	10.9%	0.80 [0.60 , 1.06]
Yoshikawa 2015	83	122	80	124	13.0%	1.05 [0.88 , 1.26]
PREDNOS 2019	91	114	88	109	13.7%	0.99 [0.87 , 1.13]
Subtotal (95% CI)		**317**		**320**	**53.7%**	**0.91 [0.78 , 1.06]**
Total events:	218		233			
Heterogeneity: Tau² = 0.01; Chi² = 7.53, df = 4 (P = 0.11); I² = 47%						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.4.2 Unclear or high risk of selection bias						
Ueda 1988	5	17	18	29	4.0%	0.47 [0.22 , 1.04]
Norero 1996	15	29	13	27	6.7%	1.07 [0.63 , 1.82]
Moundekhel 2012	13	46	33	46	7.1%	0.39 [0.24 , 0.65]
Satomura 2001	23	36	19	37	8.7%	1.24 [0.84 , 1.85]
Jayantha 2002a	16	35	43	53	9.0%	0.56 [0.38 , 0.83]
Ksiazek 1995	36	72	32	44	10.7%	0.69 [0.51 , 0.92]
Subtotal (95% CI)		**235**		**236**	**46.3%**	**0.69 [0.49 , 0.98]**
Total events:	108		158			
Heterogeneity: Tau² = 0.13; Chi² = 18.14, df = 5 (P = 0.003); I² = 72%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)		**552**		**556**	**100.0%**	**0.79 [0.65 , 0.95]**
Total events:	326		391			
Heterogeneity: Tau² = 0.06; Chi² = 36.26, df = 10 (P < 0.0001); I² = 72%						
Test for overall effect: Z = 2.56 (P = 0.01)						
Test for subgroup differences: Chi² = 1.95, df = 1 (P = 0.16), I² = 48.7%						



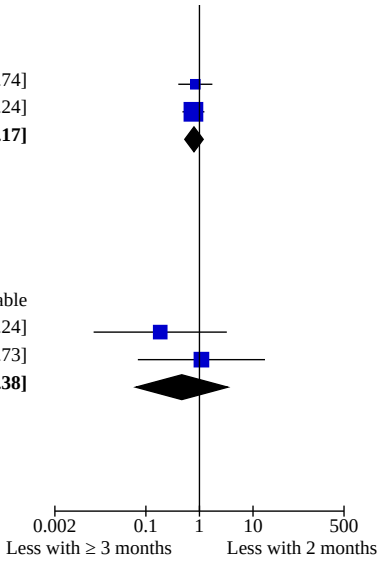
Analysis 1.5. Comparison 1: Steroid therapy in first episode: ≥ 3 months versus 2 months therapy, Outcome 5: Adverse events

Study or Subgroup	≥ 3 months therapy Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Psychological disorders						
Ksiazek 1995	0	72	0	44		Not estimable
Ueda 1988	0	17	0	29		Not estimable
APN 1993	4	34	2	37	13.2%	2.18 [0.43 , 11.13]
PREDNOS 2019	94	114	101	109	86.8%	0.89 [0.81 , 0.98]
Subtotal (95% CI)		**237**		**219**	**100.0%**	**1.00 [0.53 , 1.90]**
Total events:	98		103			
Heterogeneity: Tau² = 0.12; Chi² = 1.35, df = 1 (P = 0.25); I² = 26%						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.5.2 Hypertension						
Ueda 1988	0	17	0	29		Not estimable
APN 1993	0	34	0	37		Not estimable
Moundekhel 2012	1	46	0	46	10.4%	3.00 [0.13 , 71.78]
Bagga 1999	3	22	0	23	11.9%	7.30 [0.40 , 133.75]
Norero 1996	10	29	0	27	12.6%	19.60 [1.20 , 319.08]
Ksiazek 1995	6	72	5	44	31.7%	0.73 [0.24 , 2.26]
Jayantha 2002a	5	48	9	74	33.3%	0.86 [0.31 , 2.40]
Subtotal (95% CI)		**268**		**280**	**100.0%**	**1.78 [0.55 , 5.73]**
Total events:	25		14			
Heterogeneity: Tau² = 0.79; Chi² = 8.04, df = 4 (P = 0.09); I² = 50%						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.5.3 Cataracts/eye disorders						
Ksiazek 1995	0	72	0	44		Not estimable
Jayantha 2002a	0	48	0	74		Not estimable
Bagga 1999	0	22	0	23		Not estimable
PREDNOS 2019	1	114	1	109	22.7%	0.96 [0.06 , 15.10]
APN 1993	1	34	3	37	35.3%	0.36 [0.04 , 3.32]
Ueda 1988	1	17	6	29	42.0%	0.28 [0.04 , 2.17]
Subtotal (95% CI)		**307**		**316**	**100.0%**	**0.41 [0.11 , 1.52]**
Total events:	3		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
1.5.4 Retarded growth						
Bagga 1999	0	22	0	23		Not estimable
APN 1993	0	34	0	37		Not estimable
Ksiazek 1995	4	72	3	44	29.1%	0.81 [0.19 , 3.47]
Jayantha 2002a	5	48	17	74	70.9%	0.45 [0.18 , 1.15]
Subtotal (95% CI)		**176**		**178**	**100.0%**	**0.54 [0.25 , 1.18]**
Total events:	9		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.5.5 Cushingoid facies						
Moundekhel 2012	2	46	0	46	1.6%	5.00 [0.25 , 101.37]
Bagga 1999	9	22	0	23	1.9%	19.83 [1.22 , 321.41]
Ksiazek 1995	10	72	8	44	15.2%	0.76 [0.33 , 1.79]
APN 1993	20	34	18	37	32.3%	1.21 [0.78 , 1.87]
PREDNOS 2019	83	114	78	109	49.0%	1.02 [0.86 , 1.20]
Subtotal (95% CI)		**288**		**259**	**100.0%**	**1.12 [0.76 , 1.65]**
Total events:	124		104			
Heterogeneity: Tau² = 0.07; Chi² = 7.46, df = 4 (P = 0.11); I² = 46%						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.5.6 Infections						



Analysis 1.5. (Continued)

1.5.6 Infections						
Norero 1996	9	29	10	27	29.2%	0.84 [0.40 , 1.74]
Ksiazek 1995	24	72	19	44	70.8%	0.77 [0.48 , 1.24]
Subtotal (95% CI)		**101**		**71**	**100.0%**	**0.79 [0.53 , 1.17]**
Total events:	33		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
1.5.7 Osteoporosis						
Ksiazek 1995	0	72	0	44		Not estimable
Ueda 1988	0	17	4	29	47.7%	0.19 [0.01 , 3.24]
APN 1993	1	34	1	37	52.3%	1.09 [0.07 , 16.73]
Subtotal (95% CI)		**123**		**110**	**100.0%**	**0.47 [0.06 , 3.38]**
Total events:	1		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						



Comparison 2. Steroid therapy in first episode: 5 to 7 months versus 3 months

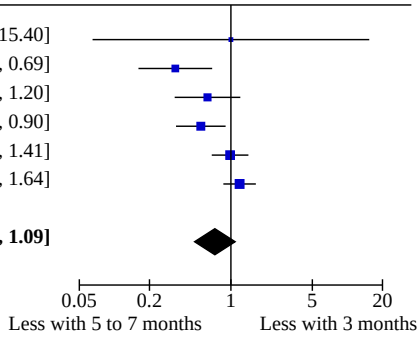
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number with frequent relapses by 12 to 24 months	6	706	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.49, 1.09]
2.2 Number of children relapsing by 12 to 24 months	7	762	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
2.3 Number with frequent relapses stratified by risk of selection bias	6	706	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.49, 1.09]
2.3.1 Studies at low risk of selection bias	3	376	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]
2.3.2 Studies at high or unclear risk of selection bias	3	330	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.32, 0.72]
2.4 Number of children relapsing by 12 to 24 months stratified by risk of selection bias	7	762	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
2.4.1 Studies at low risk of selection bias	3	376	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.11]
2.4.2 Studies at high or unclear risk of selection bias	4	386	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.34, 0.67]
2.5 Adverse events	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 Hypertension	6	752	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.71, 1.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.2 Eye complications	5	614	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.17]
2.5.3 Infections	5	702	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.46]
2.5.4 Cushingoid appearance	6	762	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.60, 1.23]
2.5.5 Gastrointestinal bleeding	1	140	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.26, 8.70]
2.5.6 Addisonian crisis	1	140	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.39]
2.5.7 Psychological disorders	4	505	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.05, 1.83]
2.5.8 Growth	3	436	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.36, 1.48]

Analysis 2.1. Comparison 2: Steroid therapy in first episode: 5 to 7 months versus 3 months, Outcome 1: Number with frequent relapses by 12 to 24 months

Study or Subgroup	5 to 7 months Events	5 to 7 months Total	3 months Events	3 months Total	Weight	Risk Ratio M-H, Random, 95% CI
Mishra 2012	1	37	1	37	2.0%	1.00 [0.06 , 15.40]
Sharma 2002	8	70	24	70	14.6%	0.33 [0.16 , 0.69]
Hiraoka 2003	10	36	15	34	16.3%	0.63 [0.33 , 1.20]
Al Talhi 2018	16	58	29	58	19.9%	0.55 [0.34 , 0.90]
Sinha 2015	36	92	35	88	23.1%	0.98 [0.69 , 1.41]
Teeninga 2013	38	64	31	62	24.1%	1.19 [0.86 , 1.64]
Total (95% CI)		**357**		**349**	**100.0%**	**0.73 [0.49 , 1.09]**
Total events:	109		135			

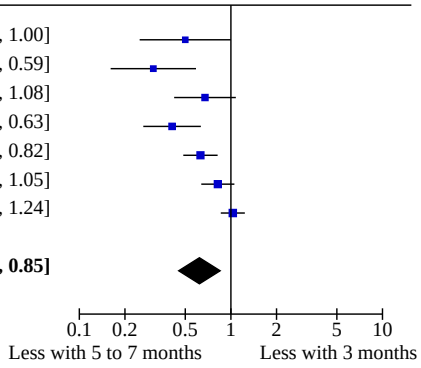
Heterogeneity: Tau² = 0.15; Chi² = 15.66, df = 5 (P = 0.008); I² = 68%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Steroid therapy in first episode: 5 to 7 months versus 3 months, Outcome 2: Number of children relapsing by 12 to 24 months

Study or Subgroup	5 to 7 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Pecoraro 2003	6	16	12	16	9.9%	0.50 [0.25 , 1.00]
Mishra 2012	8	37	26	37	10.6%	0.31 [0.16 , 0.59]
Hiraoka 2003	15	36	21	34	13.5%	0.67 [0.42 , 1.08]
Sharma 2002	18	70	44	70	14.0%	0.41 [0.26 , 0.63]
Ksiazek 1995	36	72	54	68	17.0%	0.63 [0.49 , 0.82]
Sinha 2015	48	92	56	88	17.1%	0.82 [0.64 , 1.05]
Teeninga 2013	51	64	48	62	18.0%	1.03 [0.86 , 1.24]
Total (95% CI)		**387**		**375**	**100.0%**	**0.62 [0.45 , 0.85]**
Total events:	182		261			

Heterogeneity: Tau² = 0.13; Chi² = 34.60, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.99 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Steroid therapy in first episode: 5 to 7 months versus 3 months, Outcome 3: Number with frequent relapses stratified by risk of selection bias

Study or Subgroup	5 to 7 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Studies at low risk of selection bias						
Hiraoka 2003	10	36	15	34	16.3%	0.63 [0.33 , 1.20]
Sinha 2015	36	92	35	88	23.1%	0.98 [0.69 , 1.41]
Teeninga 2013	38	64	31	62	24.1%	1.19 [0.86 , 1.64]
Subtotal (95% CI)		**192**		**184**	**63.4%**	**0.99 [0.74 , 1.33]**
Total events:	84		81			

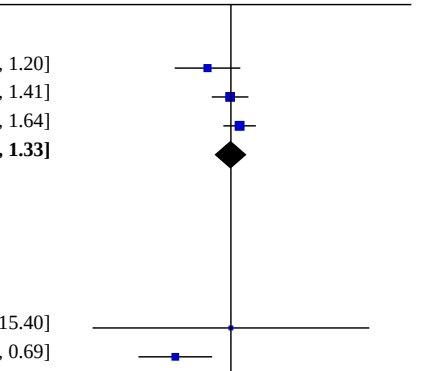
Heterogeneity: Tau² = 0.02; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 0.06 (P = 0.96)

2.3.2 Studies at high or unclear risk of selection bias						
Mishra 2012	1	37	1	37	2.0%	1.00 [0.06 , 15.40]
Sharma 2002	8	70	24	70	14.6%	0.33 [0.16 , 0.69]
Al Talhi 2018	16	58	29	58	19.9%	0.55 [0.34 , 0.90]
Subtotal (95% CI)		**165**		**165**	**36.6%**	**0.48 [0.32 , 0.72]**
Total events:	25		54			

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.58 (P = 0.0003)

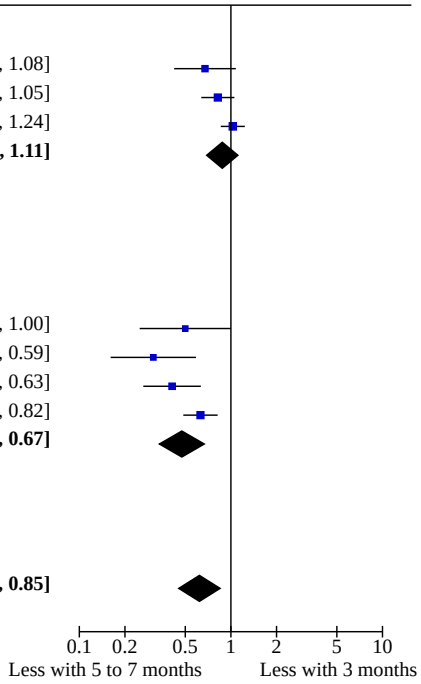
Total (95% CI)		**357**		**349**	**100.0%**	**0.73 [0.49 , 1.09]**
Total events:	109		135			

Heterogeneity: Tau² = 0.15; Chi² = 15.66, df = 5 (P = 0.008); I² = 68%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Chi² = 8.18, df = 1 (P = 0.004), I² = 87.8%



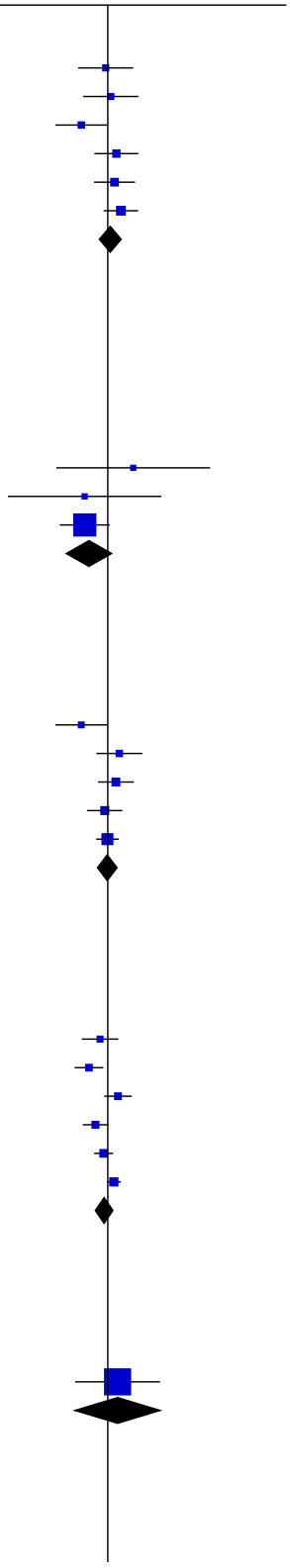
Analysis 2.4. Comparison 2: Steroid therapy in first episode: 5 to 7 months versus 3 months, Outcome 4: Number of children relapsing by 12 to 24 months stratified by risk of selection bias

Study or Subgroup	5 to 7 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Studies at low risk of selection bias						
Hiraoka 2003	15	36	21	34	13.5%	0.67 [0.42 , 1.08]
Sinha 2015	48	92	56	88	17.1%	0.82 [0.64 , 1.05]
Teeninga 2013	51	64	48	62	18.0%	1.03 [0.86 , 1.24]
Subtotal (95% CI)		**192**		**184**	**48.6%**	**0.88 [0.69 , 1.11]**
Total events:	114		125			
Heterogeneity: Tau² = 0.02; Chi² = 4.47, df = 2 (P = 0.11); I² = 55%						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.4.2 Studies at high or unclear risk of selection bias						
Pecoraro 2003	6	16	12	16	9.9%	0.50 [0.25 , 1.00]
Mishra 2012	8	37	26	37	10.6%	0.31 [0.16 , 0.59]
Sharma 2002	18	70	44	70	14.0%	0.41 [0.26 , 0.63]
Ksiazek 1995	36	72	54	68	17.0%	0.63 [0.49 , 0.82]
Subtotal (95% CI)		**195**		**191**	**51.4%**	**0.47 [0.34 , 0.67]**
Total events:	68		136			
Heterogeneity: Tau² = 0.06; Chi² = 6.27, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 4.29 (P < 0.0001)						
Total (95% CI)		**387**		**375**	**100.0%**	**0.62 [0.45 , 0.85]**
Total events:	182		261			
Heterogeneity: Tau² = 0.13; Chi² = 34.60, df = 6 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 2.99 (P = 0.003)						
Test for subgroup differences: Chi² = 8.40, df = 1 (P = 0.004), I² = 88.1%						



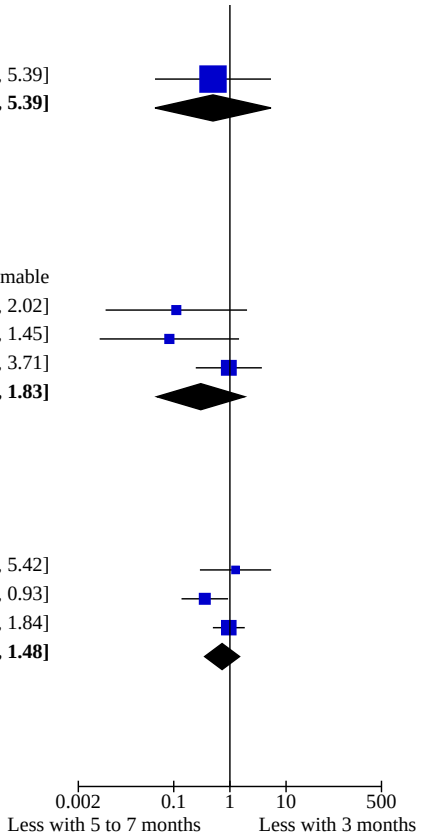
Analysis 2.5. Comparison 2: Steroid therapy in first episode: 5 to 7 months versus 3 months, Outcome 5: Adverse events

Study or Subgroup	5 to 7 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Hypertension						
Hiraoka 2003	5	36	5	33	12.4%	0.92 [0.29 , 2.88]
Ksiazek 1995	6	72	5	68	12.5%	1.13 [0.36 , 3.54]
Al Talhi 2018	4	58	12	58	13.8%	0.33 [0.11 , 0.97]
Sharma 2002	10	70	7	70	17.7%	1.43 [0.58 , 3.54]
Teeninga 2013	10	52	8	55	19.4%	1.32 [0.57 , 3.09]
Sinha 2015	18	92	10	88	24.2%	1.72 [0.84 , 3.52]
Subtotal (95% CI)		**380**		**372**	**100.0%**	**1.11 [0.71 , 1.74]**
Total events:	53		47			
Heterogeneity: Tau² = 0.09; Chi² = 6.86, df = 5 (P = 0.23); I² = 27%						
Test for overall effect: Z = 0.44 (P = 0.66)						
2.5.2 Eye complications						
Ksiazek 1995	0	72	0	68		Not estimable
Sharma 2002	0	70	0	70		Not estimable
Sinha 2015	1	92	0	88	8.7%	2.87 [0.12 , 69.55]
Teeninga 2013	0	46	1	53	8.7%	0.38 [0.02 , 9.18]
Hiraoka 2003	4	28	10	27	82.6%	0.39 [0.14 , 1.08]
Subtotal (95% CI)		**308**		**306**	**100.0%**	**0.46 [0.18 , 1.17]**
Total events:	5		11			
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
2.5.3 Infections						
Al Talhi 2018	4	58	12	58	11.5%	0.33 [0.11 , 0.97]
Teeninga 2013	10	64	6	62	14.0%	1.61 [0.62 , 4.17]
Sharma 2002	14	70	10	70	20.1%	1.40 [0.67 , 2.94]
Sinha 2015	12	92	13	88	20.5%	0.88 [0.43 , 1.83]
Ksiazek 1995	24	72	23	68	33.9%	0.99 [0.62 , 1.57]
Subtotal (95% CI)		**356**		**346**	**100.0%**	**0.98 [0.65 , 1.46]**
Total events:	64		64			
Heterogeneity: Tau² = 0.07; Chi² = 5.94, df = 4 (P = 0.20); I² = 33%						
Test for overall effect: Z = 0.11 (P = 0.91)						
2.5.4 Cushingoid appearance						
Ksiazek 1995	10	72	13	68	12.0%	0.73 [0.34 , 1.55]
Hiraoka 2003	10	36	20	33	15.0%	0.46 [0.25 , 0.83]
Teeninga 2013	21	58	14	59	15.5%	1.53 [0.86 , 2.70]
Al Talhi 2018	15	58	25	58	16.4%	0.60 [0.35 , 1.02]
Sinha 2015	30	92	34	88	19.4%	0.84 [0.57 , 1.25]
Sharma 2002	45	70	35	70	21.6%	1.29 [0.96 , 1.72]
Subtotal (95% CI)		**386**		**376**	**100.0%**	**0.86 [0.60 , 1.23]**
Total events:	131		141			
Heterogeneity: Tau² = 0.14; Chi² = 16.54, df = 5 (P = 0.005); I² = 70%						
Test for overall effect: Z = 0.83 (P = 0.41)						
2.5.5 Gastrointestinal bleeding						
Sharma 2002	3	70	2	70	100.0%	1.50 [0.26 , 8.70]
Subtotal (95% CI)		**70**		**70**	**100.0%**	**1.50 [0.26 , 8.70]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
2.5.6 Addisonian crisis						



Analysis 2.5. (Continued)

2.5.6 Addisonian crisis						
Sharma 2002	1	70	2	70	100.0%	0.50 [0.05 , 5.39]
Subtotal (95% CI)		**70**		**70**	**100.0%**	**0.50 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.5.7 Psychological disorders						
Ksiazek 1995	0	72	0	68		Not estimable
Al Talhi 2018	0	58	4	58	24.8%	0.11 [0.01 , 2.02]
Hiraoka 2003	0	36	5	33	25.3%	0.08 [0.00 , 1.45]
Sinha 2015	4	92	4	88	49.9%	0.96 [0.25 , 3.71]
Subtotal (95% CI)		**258**		**247**	**100.0%**	**0.30 [0.05 , 1.83]**
Total events:	4		13			
Heterogeneity: Tau² = 1.21; Chi² = 3.73, df = 2 (P = 0.15); I² = 46%						
Test for overall effect: Z = 1.30 (P = 0.19)						
2.5.8 Growth						
Ksiazek 1995	4	72	3	68	18.5%	1.26 [0.29 , 5.42]
Al Talhi 2018	5	58	14	58	33.2%	0.36 [0.14 , 0.93]
Sinha 2015	15	92	15	88	48.3%	0.96 [0.50 , 1.84]
Subtotal (95% CI)		**222**		**214**	**100.0%**	**0.73 [0.36 , 1.48]**
Total events:	24		32			
Heterogeneity: Tau² = 0.16; Chi² = 3.35, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.88 (P = 0.38)						

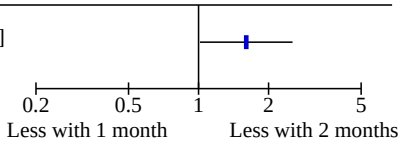


Comparison 3. Steroid therapy in the first episode: 1 month versus 2 months therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Number of children relapsing by 6 to 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.2 Number of children relapsing by 12 to 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.3 Number with frequent relapses	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

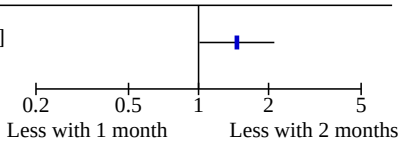
Analysis 3.1. Comparison 3: Steroid therapy in the first episode: 1 month versus 2 months therapy, Outcome 1: Number of children relapsing by 6 to 12 months

Study or Subgroup	1 month Events	1 month Total	2 months Events	2 months Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1988	23	32	13	29	1.60 [1.01 , 2.54]	



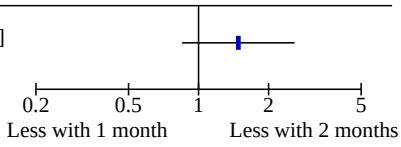
Analysis 3.2. Comparison 3: Steroid therapy in the first episode: 1 month versus 2 months therapy, Outcome 2: Number of children relapsing by 12 to 24 months

Study or Subgroup	1 month Events	1 month Total	2 months Events	2 months Total	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: 1 month versus 2 months therapy, Outcome 3: Number with frequent relapses

Study or Subgroup	1 month Events	1 month Total	2 months Events	2 months Total	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]	

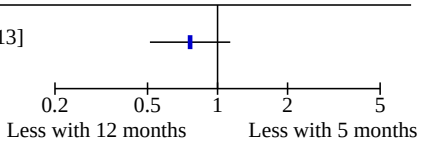


Comparison 4. Steroid therapy in the first episode: 12 months versus 5 months therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 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: 12 months versus 5 months therapy, Outcome 1: Number with relapse

Study or Subgroup	12 months Events	12 months Total	5 months Events	5 months Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kleinknecht 1982	16	29	21	29	0.76 [0.51 , 1.13]	

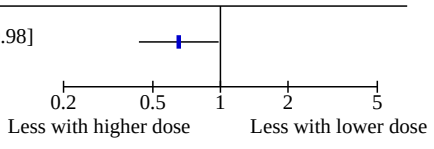


Comparison 5. Steroid therapy in the first episode of nephrotic syndrome: different total doses given over the same duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2 Number with FRNS	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3.1 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3.2 Psychological disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3.3 Cushing's Syndrome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

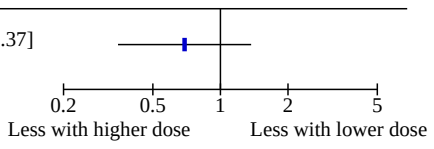
Analysis 5.1. Comparison 5: Steroid therapy in the first episode of nephrotic syndrome: different total doses given over the same duration, Outcome 1: Relapse at 12 months

Study or Subgroup	Higher total dose Events	Higher total dose Total	Lower total dose Events	Lower total dose Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hiraoka 2000	15	30	23	30	0.65 [0.43 , 0.98]	



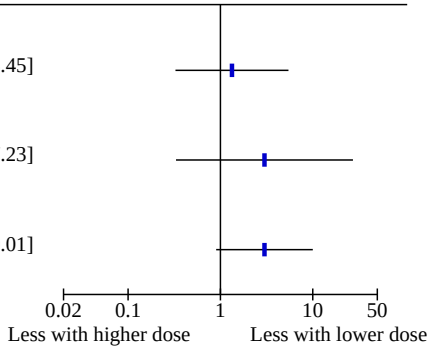
Analysis 5.2. Comparison 5: Steroid therapy in the first episode of nephrotic syndrome: different total doses given over the same duration, Outcome 2: Number with FRNS

Study or Subgroup	Higher total dose Events	Higher total dose Total	Lower total dose Events	Lower total dose Total	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 the same duration, Outcome 3: Adverse effects

Study or Subgroup	Higher total dose Events	Total	Lower total dose Events	Total	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	3.00 [0.33 , 27.23]
5.3.3 Cushing's Syndrome					
Hiraoka 2000	9	30	3	30	3.00 [0.90 , 10.01]



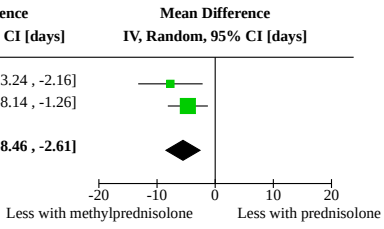
Comparison 6. Methylprednisolone in steroid therapy in first episode of nephrotic syndrome: methylprednisone versus prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Time to remission	2	38	Mean Difference (IV, Random, 95% CI)	-5.54 [-8.46, -2.61]
6.2 Number with relapse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Methylprednisolone in steroid therapy in first episode of nephrotic syndrome: methylprednisone versus prednisolone, Outcome 1: Time to remission

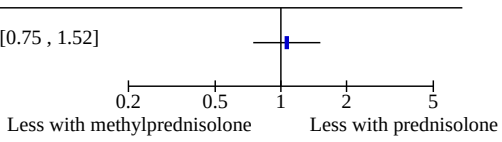
Study or Subgroup	Methylprednisolone Mean [days]	SD [days]	Total	Prednisolone Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]
Mocan 1999	5.6	1.13	8	13.3	7.4	7	27.9%	-7.70 [-13.24 , -2.16]
Zhang 2007d	4.9	1.5	9	9.6	6.3	14	72.1%	-4.70 [-8.14 , -1.26]
Total (95% CI)			**17**			**21**	**100.0%**	**-5.54 [-8.46 , -2.61]**

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Methylprednisolone in steroid therapy in first episode of nephrotic syndrome: methylprednisone versus prednisolone, Outcome 2: Number with relapse

Study or Subgroup	Methylprednisolone Events	Total	Prednisolone Events	Total	Risk Ratio M-H, Random, 95% CI
Imbasciati 1985	21	31	21	33	1.06 [0.75 , 1.52]

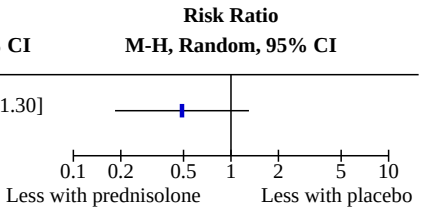


Comparison 7. Daily prednisolone treatment during viral infections

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

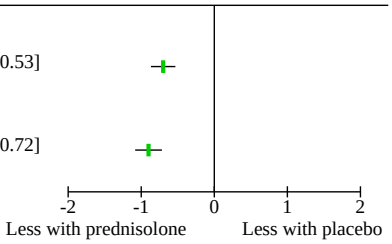
Analysis 7.1. Comparison 7: Daily prednisolone treatment during viral infections, Outcome 1: Number with relapse with infection

Study or Subgroup	Prednisolone Events	Prednisolone Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Abeyagunawardena 2008	4	18	10	22	0.49 [0.18 , 1.30]



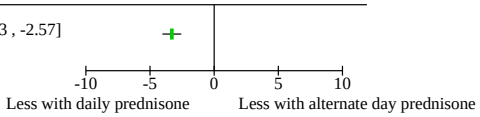
Analysis 7.2. Comparison 7: Daily prednisolone treatment during viral infections, Outcome 2: Number of relapses/patient

Study or Subgroup	Prednisolone Mean	Prednisolone SD	Prednisolone Total	Placebo/no treatment Mean	Placebo/no treatment SD	Placebo/no treatment Total	Mean Difference IV, Random, 95% CI
7.2.1 Number of infection-related relapses/patient/year							
Gulati 2011	0.7	0.3	49	1.4	0.5	46	-0.70 [-0.87 , -0.53]
7.2.2 Total relapses (episodes/patient/1 year)							
Gulati 2011	0.9	0.4	49	1.8	0.5	46	-0.90 [-1.08 , -0.72]



Analysis 7.3. Comparison 7: Daily prednisolone treatment during viral infections, Outcome 3: Number of relapses/patient at 2 years

Study or Subgroup	Daily prednisone Mean	SD	Total	Alternate day prednisone Mean	SD	Total	Mean Difference IV, Random, 95% CI
Mattoo 2000	2.2	0.87	18	5.5	1.33	18	-3.30 [-4.03 , -2.57]



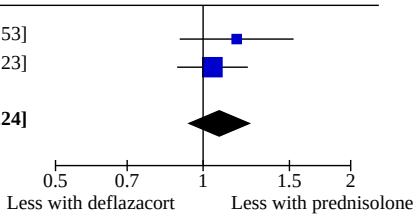
Comparison 8. Deflazacort versus prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Number with remission	2	67	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
8.2 Number of children with relapse by 9 to 12 months	2	63	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.27, 0.78]

Analysis 8.1. Comparison 8: Deflazacort versus prednisolone, Outcome 1: Number with remission

Study or Subgroup	Deflazacort Events	Total	Prednisolone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Singhal 2015	12	12	11	13	27.8%	1.17 [0.90 , 1.53]
Agarwal 2010	19	20	20	22	72.2%	1.04 [0.89 , 1.23]
Total (95% CI)		**32**		**35**	**100.0%**	**1.08 [0.94 , 1.24]**
Total events:	31		31			

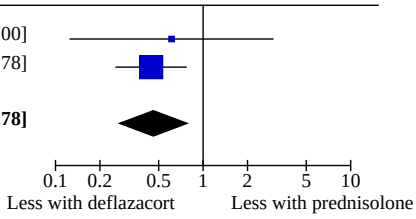
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Deflazacort versus prednisolone, Outcome 2: Number of children with relapse by 9 to 12 months

Study or Subgroup	Deflazacort Events	Total	Prednisolone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Singhal 2015	2	12	3	11	10.9%	0.61 [0.12 , 3.00]
Broyer 1997	8	20	18	20	89.1%	0.44 [0.25 , 0.78]
Total (95% CI)		**32**		**31**	**100.0%**	**0.46 [0.27 , 0.78]**
Total events:	10		21			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)
Test for subgroup differences: Not applicable

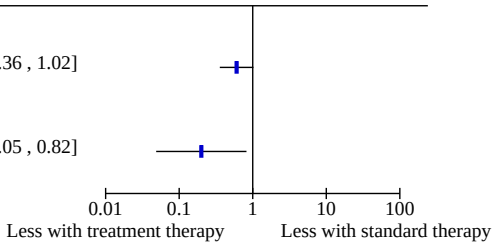


Comparison 9. Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Number of children relapsing during therapy	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.1 Intermittent dose versus alternate-day therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.2 Daily versus intermittent therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2 Number of children with relapses by 9 to 12 months	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.1 Intermittent dose versus alternate-day therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.2 Single versus divided dose therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.3 Intravenous versus oral therapy (6 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.4 Prolonged oral versus intermittent therapy (2 months therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.3 Mean time to relapse	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.3.1 Single versus divided dose therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.3.2 Daily versus intermittent therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.4 Mean relapse rate/patient/year	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.4.1 Single versus divided dose therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.4.2 Daily versus intermittent therapy (2 months therapy)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.5 Cumulative steroid dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.6 Mean time to remission	2	138	Mean Difference (IV, Random, 95% CI)	0.04 [-0.98, 1.06]
9.7 Serious adverse events	2	138	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.18, 0.91]

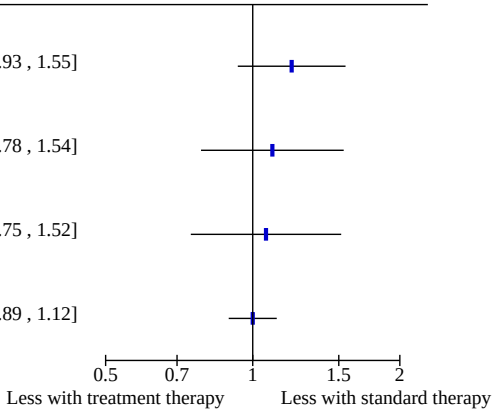
Analysis 9.1. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 1: Number of children relapsing during therapy

Study or Subgroup	Treatment therapy Events	Total	Standard therapy Events	Total	Risk Ratio M-H, Random, 95% CI
9.1.1 Intermittent dose versus alternate-day therapy (6 months therapy)					
APN 1981	10	23	18	25	0.60 [0.36 , 1.02]
9.1.2 Daily versus intermittent therapy (2 months therapy)					
ISKDC 1979	2	25	10	25	0.20 [0.05 , 0.82]



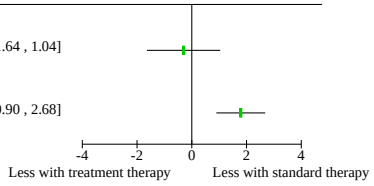
Analysis 9.2. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 2: Number of children with relapses by 9 to 12 months

Study or Subgroup	Treatment therapy Events	Total	Standard therapy Events	Total	Risk Ratio M-H, Random, 95% CI
9.2.1 Intermittent dose versus alternate-day therapy (6 months therapy)					
APN 1981	21	23	19	25	1.20 [0.93 , 1.55]
9.2.2 Single versus divided dose therapy (2 months therapy)					
Ekka 1997	29	47	27	48	1.10 [0.78 , 1.54]
9.2.3 Intravenous versus oral therapy (6 months therapy)					
Imbasciati 1985	21	31	21	33	1.06 [0.75 , 1.52]
9.2.4 Prolonged oral versus intermittent therapy (2 months therapy)					
ISKDC 1979	24	25	24	25	1.00 [0.89 , 1.12]



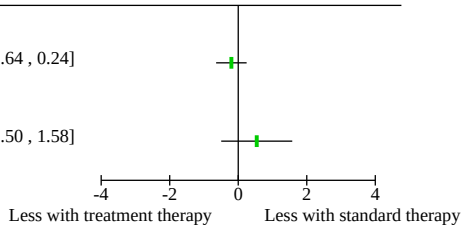
Analysis 9.3. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 3: Mean time to relapse

Study or Subgroup	Treatment therapy Mean [months]	SD [months]	Total	Standard therapy Mean [months]	SD [months]	Total	Mean Difference IV, Random, 95% CI [months]
9.3.1 Single versus divided dose therapy (2 months therapy)							
Ekka 1997	5.6	3.3	47	5.9	3.32	47	-0.30 [-1.64 , 1.04]
9.3.2 Daily versus intermittent therapy (2 months therapy)							
ISKDC 1979	3.27	2	25	1.48	1.09	25	1.79 [0.90 , 2.68]



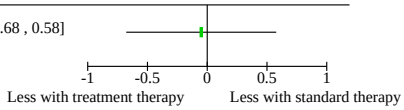
Analysis 9.4. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 4: Mean relapse rate/patient/year

Study or Subgroup	Treatment therapy Mean	SD	Total	Standard therapy Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
9.4.1 Single versus divided dose therapy (2 months therapy)								
Ekka 1997	1.7	1.1	47	1.9	1.1	47	-0.20 [-0.64 , 0.24]	
9.4.2 Daily versus intermittent therapy (2 months therapy)								
ISKDC 1979	3.79	2.15	25	3.25	1.54	25	0.54 [-0.50 , 1.58]	



Analysis 9.5. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 5: Cumulative steroid dose

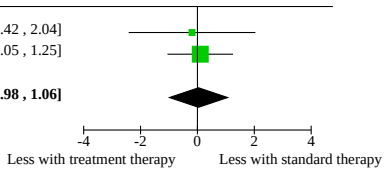
Study or Subgroup	Treatment therapy Mean [g/m²]	SD [g/m²]	Total	Standard therapy Mean [g/m²]	SD [g/m²]	Total	Mean Difference IV, Random, 95% CI [g/m²]	Mean Difference IV, Random, 95% CI [g/m²]
Ekka 1997	2.71	1.47	47	2.76	1.63	47	-0.05 [-0.68 , 0.58]	



Analysis 9.6. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 6: Mean time to remission

Study or Subgroup	Treatment therapy Mean [days]	SD [days]	Total	Standard therapy Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]	Mean Difference IV, Random, 95% CI [days]
Li 1994	10.81	3.61	19	11	3.89	25	21.1%	-0.19 [-2.42 , 2.04]	
Ekka 1997	8.6	2.8	47	8.5	2.9	47	78.9%	0.10 [-1.05 , 1.25]	
Total (95% CI)			**66**			**72**	**100.0%**	**0.04 [-0.98 , 1.06]**	

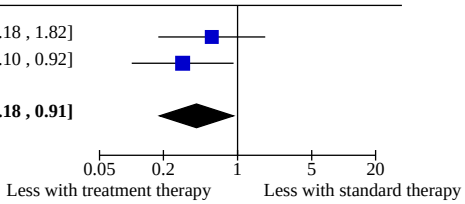
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 9.7. Comparison 9: Treatment therapy (various) versus standard therapy in relapsing nephrotic syndrome, Outcome 7: Serious adverse events

Study or Subgroup	Treatment therapy Events	Total	Standard therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ekka 1997	4	47	7	47	47.6%	0.57 [0.18 , 1.82]	
Li 1994	3	19	13	25	52.4%	0.30 [0.10 , 0.92]	
Total (95% CI)		**66**		**72**	**100.0%**	**0.41 [0.18 , 0.91]**	
Total events:	7		20				

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable



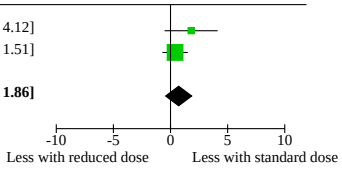
Comparison 10. Steroid therapy for relapse: different prednisone doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Time to remission with different prednisone doses	2	79	Mean Difference (IV, Random, 95% CI)	0.71 [-0.43, 1.86]
10.2 Cumulative prednisone dose to achieve remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.3 Number with relapse	2	59	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.16, 2.68]

Analysis 10.1. Comparison 10: Steroid therapy for relapse: different prednisone doses, Outcome 1: Time to remission with different prednisone doses

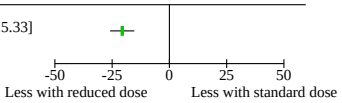
Study or Subgroup	Reduced dose prednisone Mean [days]	SD [days]	Total	Standard dose prednisone Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]
Borovitz 2020	9	3.3	9	7.2	1.4	10	22.4%	1.80 [-0.52 , 4.12]
Sheikh 2019	9	2.2	30	8.6	2.2	30	77.6%	0.40 [-0.71 , 1.51]
Total (95% CI)			**39**			**40**	**100.0%**	**0.71 [-0.43 , 1.86]**

Heterogeneity: Tau² = 0.12; Chi² = 1.13, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Steroid therapy for relapse: different prednisone doses, Outcome 2: Cumulative prednisone dose to achieve remission

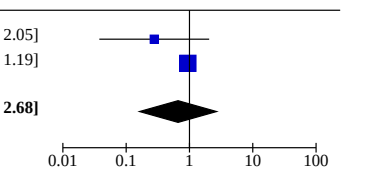
Study or Subgroup	Reduced dose prednisone Mean [mg/kg]	SD [mg/kg]	Total	Standard dose prednisone Mean [mg/kg]	SD [mg/kg]	Total	Mean Difference IV, Random, 95% CI [mg/kg]
Borovitz 2020	24.9	7.4	9	45.5	3.4	10	-20.60 [-25.87 , -15.33]



Analysis 10.3. Comparison 10: Steroid therapy for relapse: different prednisone doses, Outcome 3: Number with relapse

Study or Subgroup	Reduced dose prednisone Events	Total	Standard dose prednisone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borovitz 2020	1	9	4	10	29.2%	0.28 [0.04 , 2.05]
Kansal 2019	17	20	18	20	70.8%	0.94 [0.75 , 1.19]
Total (95% CI)		**29**		**30**	**100.0%**	**0.66 [0.16 , 2.68]**
Total events:	18		22			

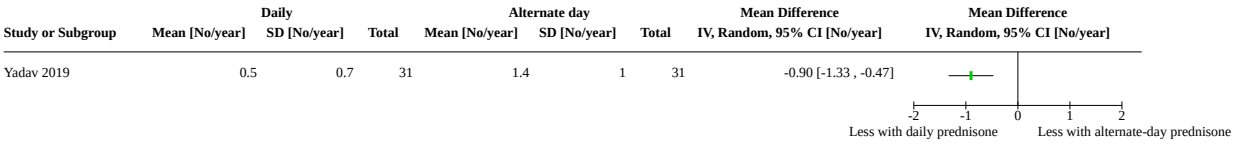
Heterogeneity: Tau² = 0.71; Chi² = 2.34, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



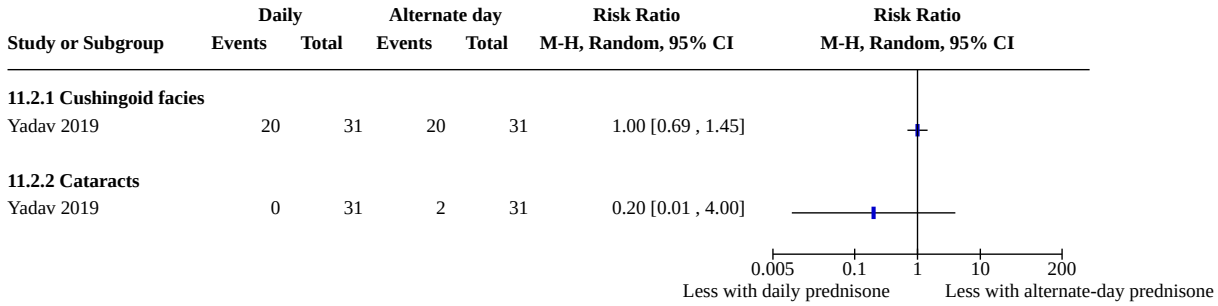
Comparison 11. Daily versus alternate-day prednisone for relapsing nephrotic syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Number of relapses in 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.2.1 Cushingoid facies	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.2.2 Cataracts	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11: Daily versus alternate-day prednisone for relapsing nephrotic syndrome, Outcome 1: Number of relapses in 12 months



Analysis 11.2. Comparison 11: Daily versus alternate-day prednisone for relapsing nephrotic syndrome, Outcome 2: Adverse effects



Comparison 12. Weight-based versus body surface area (BSA)-based dosing of prednisolone

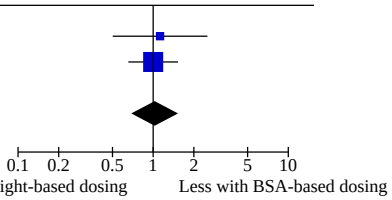
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Relapse at 6 months	2	146	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.71, 1.49]
12.2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.2.1 Cushingoid features	2	144	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.58, 2.32]
12.2.2 Serious infections	2	144	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.66]
12.2.3 Eye changes	1	84	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2.4 Hypertension	2	144	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.05, 1.73]
12.3 Prednisone dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.3.1 Induction dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.3.2 Cumulative dose over 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

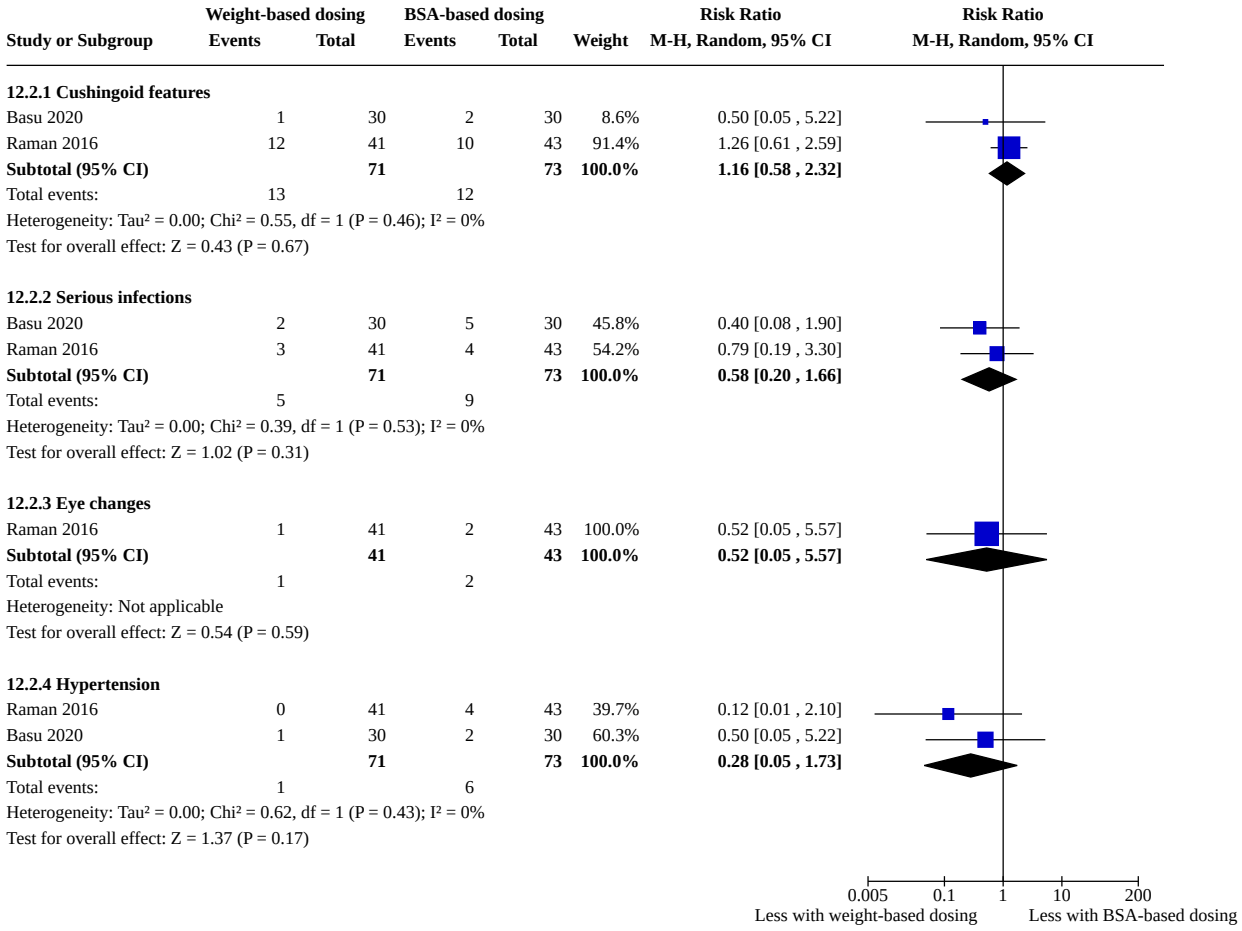
Analysis 12.1. Comparison 12: Weight-based versus body surface area (BSA)-based dosing of prednisolone, Outcome 1: Relapse at 6 months

Study or Subgroup	Weight-based dosing Events	Total	BSA-based dosing Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Basu 2020	9	30	8	30	21.5%	1.13 [0.50 , 2.52]
Raman 2016	22	44	21	42	78.5%	1.00 [0.66 , 1.53]
Total (95% CI)		**74**		**72**	**100.0%**	**1.03 [0.71 , 1.49]**
Total events:	31		29			

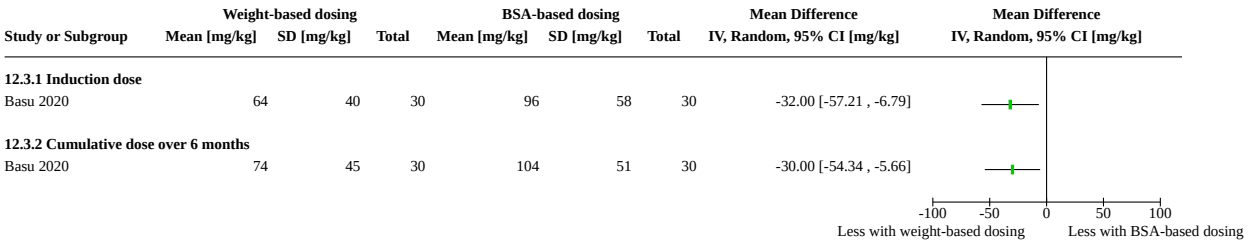
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Weight-based versus body surface area (BSA)-based dosing of prednisolone, Outcome 2: Adverse effects



Analysis 12.3. Comparison 12: Weight-based versus body surface area (BSA)-based dosing of prednisolone, Outcome 3: Prednisone dose



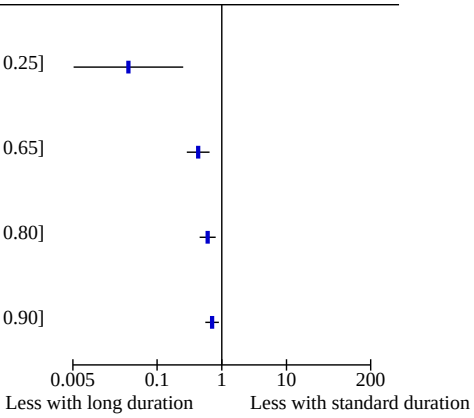
Comparison 13. Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1.2 Relapse by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.3 Relapse by 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.4 Relapse by 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2 Relapse rate/patient/year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.2.1 Relapse rate at 1 year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.2.2 Relapse rate at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.2.3 Relapse rate at 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.3 Number with FRNS or SDNS	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.4 Cumulative steroid dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.4.1 After 1 year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.4.2 After 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.4.3 After 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.5 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.5.1 Number with hypertension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.5.2 Number with growth failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

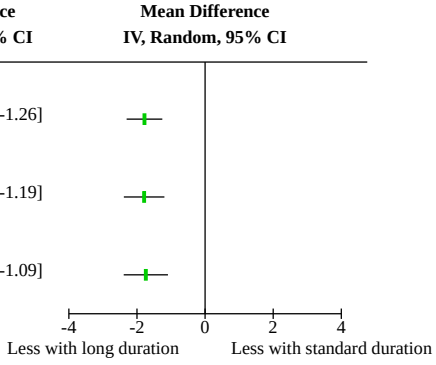
Analysis 13.1. Comparison 13: Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 1: Number with relapses

Study or Subgroup	Long duration Events	Total	Standard duration Events	Total	Risk Ratio M-H, Random, 95% CI
13.1.1 Relapse by 6 months					
Jayantha 2002b	1	44	29	46	0.04 [0.01 , 0.25]
13.1.2 Relapse by 12 months					
Jayantha 2002b	16	42	30	34	0.43 [0.29 , 0.65]
13.1.3 Relapse by 2 years					
Jayantha 2002b	21	36	27	28	0.60 [0.45 , 0.80]
13.1.4 Relapse by 3 years					
Jayantha 2002b	21	30	23	23	0.71 [0.56 , 0.90]



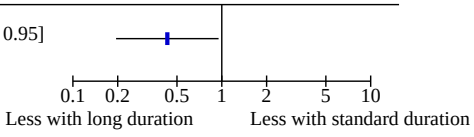
Analysis 13.2. Comparison 13: Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 2: Relapse rate/patient/year

Study or Subgroup	Long duration Mean	SD	Total	Standard duration Mean	SD	Total	Mean Difference IV, Random, 95% CI
13.2.1 Relapse rate at 1 year							
Jayantha 2002b	0.35	0.48	40	2.13	1.45	32	-1.78 [-2.30 , -1.26]
13.2.2 Relapse rate at 2 years							
Jayantha 2002b	0.41	0.44	33	2.2	1.41	23	-1.79 [-2.39 , -1.19]
13.2.3 Relapse rate at 3 years							
Jayantha 2002b	0.41	0.43	25	2.15	1.28	16	-1.74 [-2.39 , -1.09]

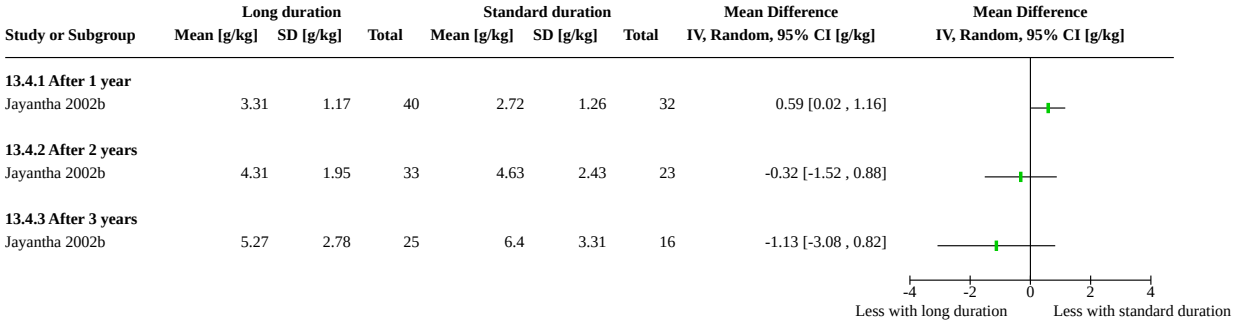


Analysis 13.3. Comparison 13: Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 3: Number with FRNS or SDNS

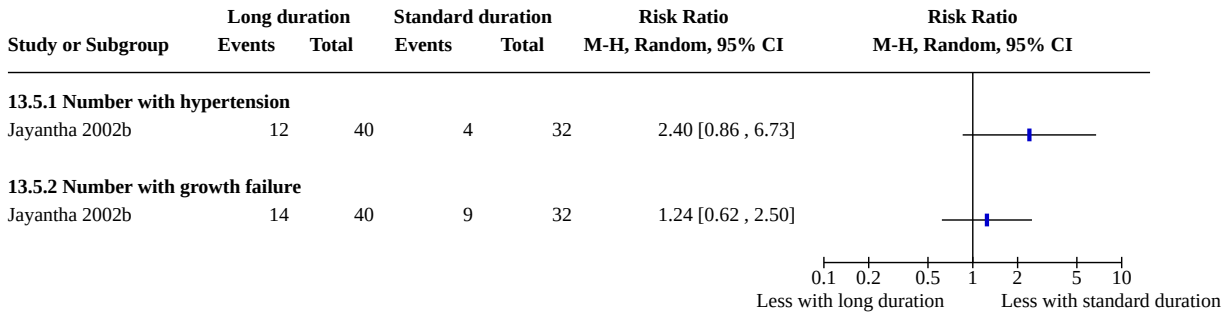
Study or Subgroup	Long duration Events	Total	Standard duration Events	Total	Risk Ratio M-H, Random, 95% CI
Jayantha 2002b	7	40	13	32	0.43 [0.19 , 0.95]



Analysis 13.4. Comparison 13: Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 4: Cumulative steroid dose



Analysis 13.5. Comparison 13: Prolonged steroid therapy (7 months) for relapsing nephrotic syndrome, Outcome 5: Adverse effects



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

(Continued)

	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$.tw. 9. (boy$ 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.

(Continued)

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
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.

(Continued)

	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
30 May 2020	New citation required but conclusions have not changed	Conclusions unchanged from previous update
30 May 2020	New search has been performed	16 new studies added to review

HISTORY

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

Date	Event	Description
16 September 2015	Amended	Minor amendment to forest plot description 2.8.2 - changed from 'Low risk...' to "High risk..."
11 March 2015	New search has been performed	New studies identified
11 March 2015	New citation required and conclusions have changed	10 new studies included
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

- Deirdre Hahn: Study selection, quality appraisal, data extraction, data analysis, writing review, updating review.
- Susan Samuel: Study selection, data extraction, 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.
- Elisabeth Hodson: Study selection, quality appraisal, data extraction, data analysis, writing review, updating review.

DECLARATIONS OF INTEREST

- Deirdre Hahn: none known
- Susan Samuel: none known

- Narelle Willis: none known
- Jonathan Craig: none known
- Elisabeth Hodson: none known

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