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[Intervention Review]

Non-corticosteroid treatment for nephrotic syndrome in children

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ABSTRACT

Background

Eighty to ninety per cent of children with steroid-sensitive nephrotic syndrome (SSNS) have relapses. About half relapse frequently and are at risk of the adverse effects of corticosteroids. Non-corticosteroid immunosuppressive agents are used to prolong periods of remission in children who relapse frequently. However these non-corticosteroid agents also have significant potential adverse effects. Currently there is no consensus as to the most appropriate second line agent in children who are steroid sensitive, but who continue to relapse.

Objectives

To evaluate the benefits and harms of non-corticosteroid immunosuppressive agents in relapsing SSNS in children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, reference lists of articles, abstracts from proceedings and contact with known investigators.
Search date: August 2004

Selection criteria

RCTs or quasi-RCTs were included if they were undertaken in children with relapsing SSNS, if they compared non-corticosteroid agents with placebo, prednisone or no treatment, different doses and/or durations of the same non-corticosteroid agent, different non-corticosteroid agents and outcome data at six months.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using a random effects model and results expressed as relative risk (RR) with 95% confidence intervals (CI).

Main results

Twenty trials involving 923 children were identified. Cyclophosphamide (three trials: RR 0.44, 95% CI 0.26 to 0.73) and chlorambucil (two trials: RR 0.13, 95% CI 0.03 to 0.57) significantly reduced the relapse risk at six to twelve months compared with prednisone alone. In the single chlorambucil versus cyclophosphamide trial, there was no observed difference in relapse risk at two years (RR 1.31, 95% CI 0.80 to 2.13). Cyclosporin was as effective as cyclophosphamide (one trial: RR 1.07, 95% CI 0.48 to 2.35) and chlorambucil (one trial: RR 0.82, 95% CI 0.44 to 1.53) but the effect was not sustained when cyclosporin was ceased. During treatment, levamisole (three trials: RR 0.60, 95% CI 0.45 to 0.79) was more effective than steroids alone but the effect was not sustained. Mizoribine (one trial) and azathioprine (two trials) were no more effective than placebo or prednisone alone in maintaining remission.

Authors' conclusions

Eight week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone. Clinically important differences in efficacy among these agents are possible and further comparative trials are still needed.

PLAIN LANGUAGE SUMMARY

Loss of protein in children with nephrotic syndrome can be reduced with non-corticosteroid drugs

Children with nephrotic syndrome lose excessive amounts of protein from their blood stream into their urine. This loss of protein causes tissue swelling, especially in the face, stomach and legs. The risk of infection also increases because important proteins used by their immune system have been lost. Corticosteroids such as prednisone can stop the protein leak but the leak frequently recurs and further corticosteroids can have adverse effects of poor growth, cataracts, osteoporosis and high blood pressure. The review of trials compared several drugs and found cyclophosphamide, chlorambucil, cyclosporin and levamisole are more effective than prednisone alone in preventing leaks reoccurring. More research is needed.

BACKGROUND

Nephrotic syndrome (NS) is a condition in which the glomeruli of the kidney leak protein from the blood into the urine. It results in hypoproteinaemia and generalised oedema. In children the incidence of NS in Europe and North America is 2/100,000 children (Arneil 1961; Schlesinger 1968). The majority of children have minimal change disease, in which changes on light microscopy are minor or absent. The cause of minimal change NS is unknown.

Oral corticosteroids are the first-line treatment of a child presenting with idiopathic NS. Of children who present with their first episode of NS, about 90% will achieve remission with corticosteroid therapy and have steroid sensitive nephrotic syndrome (SSNS) (Koskimies 1982). However 80% of children experience a relapsing course with recurrent episodes of oedema and proteinuria (Koskimies 1982; Tarshish 1997) and half of these children relapse frequently either a few weeks after ceasing corticosteroids (frequently relapsing SSNS) or while on reducing doses of corticosteroids (steroid dependent SSNS) (ISKDC 1982). These children are likely to develop the adverse effects of corticosteroids, such as obesity, poor growth, hypertension, diabetes mellitus and osteoporosis.

Other non-corticosteroid agents have been sought that would provide longer periods of remission and allow corticosteroids to be withdrawn. The alkylating agents cyclophosphamide and chlorambucil were shown in controlled trials to produce prolonged remissions in children with SSNS, who relapsed frequently (Barratt 1970; Grupe 1976). The potential of these agents for carcinogenesis and infertility (Fairley 1972; Queshi 1972; Rapola 1973), which has limited their use to one or two courses, led to investigation of other agents such as cyclosporin A and levamisole for the treatment of children who relapse frequently. Cyclosporin, levamisole, azathioprine, mizoribine, disodium cromoglycate, IgG immunoglobulin and Chinese medicines have also been used to treat relapsing SSNS (Abramowicz 1970; BAPN 1991; Jin 1994; Niaudet 1992; Rowe 1990;Trompeter 1978; Yoshioka 2000). However these newer agents, while potentially less toxic, have been less effective in maintaining prolonged remissions once the agent has been ceased (BAPN 1991; Niaudet 1992). Currently there is no consensus as to the most appropriate second-line agent in children who are steroid sensitive, but who continue to relapse. Recent guidelines (BAPN 1994; Bargman 1999; Brodehl 1991) recommend cyclophosphamide, chlorambucil, long-term steroids or levamisole in these children.

OBJECTIVES

To evaluate the benefits and harms of different agents, other than corticosteroids, that are used in children who pursue a relapsing course of SSNS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs were included if they were carried out in children (aged three months to 18 years) with relapsing SSNS, if they compared non-corticosteroid agents with placebo, prednisone or no treatment, different doses and/or durations of the same non-corticosteroid agent, different non-corticosteroid agents and if they had outcome data at six months or more.

Types of participants

Inclusion criteria

Children aged three months to 18 years with relapsing SSNS (i.e. the child became oedema-free and his/her urine protein was = 1+ on dipstick or < 4 mg/m^2/h for three consecutive days while receiving corticosteroid therapy). Relapse of NS is defined as the recurrence of proteinuria measured semi-quantitatively on urine analysis or quantitatively using albumin or protein to creatinine ratios or timed urine specimens. A renal biopsy diagnosis of minimal change disease was not required for inclusion of the trial.

Exclusion criteria

Children with their first episode of SSNS, children with steroid resistant NS (SRNS), children with congenital NS and children with other renal or systemic forms of NS defined on renal biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schonlein nephritis, systemic lupus erythematosus).

Types of interventions

Interventions considered were:-
1. Non-corticosteroid agent versus inactive placebo or no immunosuppressive treatment.
2. Non-corticosteroid agent (with or without concomitant use of prednisone or prednisolone) versus prednisone or prednisolone used alone.
3. Two different non-corticosteroid agents (with or without concomitant use of prednisone or prednisolone).
4. Different doses and durations of the same non-corticosteroid agent (with or without concomitant use of prednisone or prednisolone).

Types of outcome measures

Primary outcome measure

- The numbers of children with and without relapse at six months, 12 months and two years.

Secondary outcome measures

- Mean relapse rates/patient/year
- Mean length of time to next relapse
- Serious adverse effects of therapy

Search methods for identification of studies

The following electronic biomedical databases were searched (Additional Table 1 -*Electronic search strategies*)
1) Cochrane Renal Group's specialised register (August 2004)
2) Cochrane Central Register of Controlled Trials (CENTRAL) (in *The Cochrane Library,* Issue 3, 2004)
3) MEDLINE (1966 to September 2004) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1998) with a specific search strategy for NS in children.
4) EMBASE (1980 - September 2004) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of randomised controlled clinical trials (Lefebvre 1996) together with a specific search strategy for NS in children.
5) To reduce publication bias, searches were made of reference lists of nephrology textbooks, review articles and relevant trials and of nephrology scientific meetings. In addition letters seeking

information about unpublished or incomplete trials were sent to investigators known to be involved in previous trials. It was planned to attempt to exclude publication bias using a funnel plot and to include the publication with the most complete data set, where duplicate publications were identified.
6) The reviewers contacted authors of recent review articles and RCTs for information about any possible unpublished data. No additional studies were identified in this manner.

Data collection and analysis

Included and excluded studies

The review was undertaken by four reviewers (AD, EH, NW and JC). The search strategy described was used to obtain titles and abstracts of studies that could be relevant to the review. The titles and abstracts were screened independently by AD and EH, who discarded studies that were irrelevant (e.g. studies of lipid lowering agents) although studies and reviews that might include relevant data or information on trials were retained initially. Reviewers AD and EH or EH and NW independently assessed abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. Data extraction was carried out by the same reviewers independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Disagreements were resolved in consultation with JC.

Study quality

The quality of studies to be included was assessed independently by AD and EH or EH and NW without blinding to authorship or journal of publication using the check list shown (Crowther 1998). Discrepancies were resolved in discussion with JC. The quality items assessed were allocation concealment, blinding, intention-to-treat analysis and completeness of follow-up.

1. Allocation concealment

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

2. Blinding

Investigators: Yes/No/not stated
Participants: Yes/No/not stated
Outcome assessor/s: Yes/No/not stated
Data analysis: Yes/No/not stated
The above are considered not blinded if the treatment group can be identified in >20% of participants because of the side effects of treatment.

3. Intention-to-treat analysis

YES: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
YES: Not specifically reported but confirmed on study assessment.
NO: Not reported and lack of intention-to-treat analysis confirmed on study assessment (i.e. patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
NO: Stated but not confirmed on study assessment.
UNCLEAR: Unable to determine or confirm with authors.

4. Completeness of follow-up

Per cent of patients lost to follow-up

Statistical assessment

For dichotomous outcomes (relapse or no relapse) results were expressed as relative risk (RR) with 95% confidence intervals (95% CI). Data was pooled using the random effects model but the fixed effects model was also employed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (time to relapse), the weighted mean difference (WMD) was used, or the standardised mean difference (SMD) if different scales have been used. Heterogeneity was analysed using a Chi squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and by I^2, which is calculated from Cochran Q and describes the percentage of total variation across studies that is due to heterogeneity (Higgins 2003). A value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity.

The data were displayed in meta-analytic trees. Subgroup analysis according to three possible sources of heterogeneity, participants, treatments and study quality was attempted. The summary measure data was translated into absolute risk reductions (ARR) for a range of baseline risks. Adverse effects were tabulated and assessed with descriptive techniques, as they were different for the various agents used.

RESULTS

Description of studies

Of the 832 titles and abstracts screened, 20 studies were identified by full text review to be RCTs or quasi-RCTs and to have follow-up data to six months or more; an additional trial is awaiting translation before assessment (Tohjoh 1994). An additional search of databases in August 2003 found no new trials. In 2004 six further RCTs involving children with relapsing SSNS treated with non-corticosteroid agents were identified; five were identified from hand searching of conference proceedings and were in abstract form only. There was no disagreement between the two reviewers regarding the inclusion of trials. In total 6/26 potential trials identified were excluded. Three assessing Chinese herbs (Gong 1997; Jin 1994; Zou 1997) one assessing lefluonomide (Zhao 2003) and one comparing cyclophosphamide and cyclosporin (Naigui 1997) were excluded because both children and adults were included and the paediatric data could not be separated. The sixth trial, evaluating levamisole, was in abstract form only and the primary outcome measure could not be determined from the data included (Kirubakaran 1984) and information to allow inclusion of the trial could not be obtained from the author. Twenty studies were therefore included in this updated review. No duplicate publications were identified.

The characteristics of the 20 trials are shown in the table of included studies. A total of 923 children were assessed and the highest number of trials available for any one comparison was four; levamisole compared with placebo, steroid alone or no treatment (n = 187) (BAPN 1991; Dayal 1994; Rashid 1996; Weiss 1993). Cyclophosphamide was compared with steroid alone in three trials (n = 106 children) (Barratt 1970; Chiu 1973; ISKDC 1974). Two trials compared azathioprine (n = 60) (Abramowicz 1970; Barratt 1977) and two trials compared chlorambucil with placebo or steroid alone (n = 41) (Grupe 1976; Alatas 1978). Four trials compared different cyclophosphamide regimens (n = 166) (Barratt 1973; McCrory 1973; Prasad 2004; Ueda 1990) and a further trial compared different chlorambucil regimes (n = 21) (Baluarte 1978). There were single trials comparing cyclosporin with cyclophosphamide (n = 55) (Ponticelli 1993), cyclosporin with chlorambucil (n = 40) (Niaudet 1992), cyclophosphamide with chlorambucil (n = 50) (APN 1982) and mizoribine with placebo (n = 197) (Yoshioka 2000). Prednisolone was used in all the trials either in combination with the trial agent or to treat relapses (see *Table of included studies*). No eligible RCTs comparing levamisole, mizoribine, azathioprine or mycophenolate with other non-corticosteroid agents or comparing Chinese medicines, IgG immunoglobulin, disodium cromoglycate or mycophenolate with corticosteroids or placebo were found.

Risk of bias in included studies

Study quality was variable (Additional Table 2 - *Methodological quality assessment*). All trials were small except the trial of mizoribine, which included 197 patients and reported a power analysis (Yoshioka 2000).

Allocation concealment

Only eight trials had adequate allocation concealment (Abramowicz 1970; APN 1982; BAPN 1991; Chiu 1973; ISKDC 1974; Ponticelli 1993; Weiss 1993; Yoshioka 2000). In one trial allocation concealment was inadequate (McCrory 1973) and in the remaining trials it was unclear whether allocation was concealment.

Blinding

In five trials there was blinding of the participants and investigators (Abramowicz 1970; Alatas 1978; BAPN 1991; Weiss 1993; Yoshioka 2000). Outcome assessors were reported to be blinded in one trial (BAPN 1991) and not blinded in one trial (Prasad 2004); in the remaining trials it was not stated whether the outcome assessors were blinded.

Intention-to-treat analysis

Intention-to-treat analysis was carried out in three trials (Dayal 1994; Prasad 2004) and was not carried out in six trials (Abramowicz 1970; BAPN 1991; Barratt 1973; Ponticelli 1993; Weiss 1993; Yoshioka 2000). In the remaining studies it was unclear whether intention-to-treat analysis had been undertaken.

Completeness of follow-up

Seventeen trials reported no loss to follow-up and two trials had losses of 3% and 2% respectively (Dayal 1994; Weiss 1993). The number completing follow-up was unclear in one study (Yoshioka 2000).

Four trials did not define relapse (Alatas 1978; Baluarte 1978; Niaudet 1992; Rashid 1996) and the remaining studies used a variety of definitions.

Effects of interventions

Cyclophosphamide (comparisons 01, 02, 03, 04, 15)

Cyclophosphamide resulted in a decreased incidence of relapse at six to twelve months compared with prednisolone alone (outcome 01.01 102 children: RR 0.44, 95% CI 0.26 to 0.73) (Barratt 1970; Chiu 1973; ISKDC 1974). In 27 children followed beyond 12 months the RR for relapse at 13-24 months was 0.21 (outcome 01.02: 95% CI 0.07 to 0.65).

Cyclophosphamide given for eight weeks resulted in fewer children relapsing within 12 months or 24 months than a two week course (outcome 02.02: RR 0.25, 95% CI 0.07 to 0.92) (Barratt 1973).

There was no evidence that prolonging the course of cyclophosphamide from eight weeks to 12 weeks further reduced the number of children experiencing a relapse at 12 or 24 months (outcome 03.01 12 months: RR 1.04, 95% CI 0.75 to 1.44; outcome 03.02 24 months: RR 0.98, 95% CI 0.74 to 1.28) (Ueda 1990).

The same total dose of cyclophosphamide given over six weeks rather than 12 weeks did not reduce the number of children who relapsed by 12 months (outcome 04.01: RR 2.33, 95% CI 0.11 to 48.99) but did increase the numbers experiencing side effects (McCrory 1973).

Intravenous cyclophosphamide given monthly for six months reduced the risk for relapse and the number of children with frequently relapsing or steroid dependent SSNS at six months after the end of therapy when compared with oral cyclophosphamide given for 12 weeks (outcome 15.01 47 children: RR 0.56, 95% CI 0.33 to 0.92; outcome 15.03: RR 0.40, 95% CI 0.18 to 0.89) (Prasad 2004). However there was no difference between therapies at the end of the study (outcome 15.02: RR 1.00, 95% CI 0.75 to 1.32).

Chlorambucil (comparisons 08, 09)

Chlorambucil reduced the risk for relapse at six and 12 months (outcome 08.01 41 children: RR 0.19, 95% CI 0.03 to 1.09; outcome 08.02; 32 children: RR 0.13, 95% CI 0.03 to 0.57) compared with placebo or prednisone alone (Alatas 1978; Grupe 1976).

There was no significant decrease in relapse rates when using an increasing dose regimen of chlorambucil compared with a stable dose regimen (outcome 09.01 21 children: RR 0.18, 95% CI 0.01 to 3.41) but there was a 34% increase in incidence of leucopenia and an 18% increase in thrombocytopenia with the higher dose (Baluarte 1978).

Cyclophosphamide and chlorambucil (comparisons 06, 07, 11)

On direct comparison there was no significant difference between chlorambucil and cyclophosphamide treatment in the risk of relapse at 12 and 24 months (outcome 06.01 12 months: RR 1.15, 95% CI 0.69 to 1.94: outcome 06.02 24 months: RR 1.31, 95% CI 0.80 to 2.13) (APN 1982).

Because both agents belong to the same class of drug, and because the single direct comparison did not show a statistically significant difference in efficacy, the results of the five trials of alkylating agents versus prednisone alone were combined (outcome 11.01 134 children: RR 0.32, 95% CI 0.16 to 0.63) (Alatas 1978; Barratt 1970; Chiu 1973; Grupe 1976; ISKDC 1974).

On post hoc analysis, chlorambucil and cyclophosphamide were more effective in preventing relapse in children with frequently

relapsing SSNS (outcome 07.01 24 months: RR 0.35, 95% CI 0.15 to 0.85) compared with children with steroid dependent SSNS (APN 1982).

Cyclosporin (comparisons 05,10)
Cyclosporin given for 24 weeks was as effective as chlorambucil given for six weeks when assessed at six months from the start of therapy in maintaining remission (outcome 10.01 40 children: RR 0.82, 95% CI 0.44 to 1.53) (Niaudet 1992).

Cyclosporin was significantly less effective in maintaining remission than chlorambucil (outcome 10.02: RR 0.47, 95% CI 0.29 to 0.78: outcome 10.03: RR 0.74, 95% CI 0.54 to 1.00) by 12 and 24 months after the start of therapy (Niaudet 1992).

Cyclosporin, given for 12 months, was as effective as cyclophosphamide given for eight weeks during cyclosporin therapy (outcome 05.01 55 children: RR 1.07, 95% CI 0.48 to 2.35) (Ponticelli 1993).

Cyclosporin was significantly less effective in maintaining remission 12 months after ceasing cyclosporin compared with cyclophosphamide (outcome 05.02: RR 0.40, 95% CI 0.22 to 0.73) (Ponticelli 1993).

Levamisole (comparison 12)
Levamisole was administered for four months (BAPN 1991), six months (Rashid 1996; Weiss 1993) or 12 months (Dayal 1994).

Levamisole was more effective than placebo or no treatment during administration in three trials (BAPN 1991; Dayal 1994; Rashid 1996) but there was no significant difference between levamisole and placebo in the fourth trial, which was a multicentre trial which was only published in abstract form (outcome 12.04 (mean relapse rate/patient/month): MD 0.10, 95% CI -0.08 to 0.28) (Weiss 1993).

In a meta-analysis of the four trials, there was no significant difference in the number of children, who relapsed (outcome 12.01 185 children: RR 0.71, 95% CI 0.41 to 1.23) but there was significant heterogeneity (Q = 20.99, I^2 = 85.7%). When the trial (Weiss 1993) showing no effect was excluded, levamisole was significantly more effective than prednisone alone (outcome 12.02 137 children: RR 0.60, 95% CI 0.45 to 0.79) with no significant heterogeneity (Q = 0.36).

There was no statistically significant benefit of levamisole (outcome 12.03: RR 0.83, 95% CI 0.63 to 1.10) over steroid alone at six to twelve months when levamisole treatment had been ceased for three to six months in three trials. However there was significant heterogeneity of effect (Q = 11.29; P = 0.01; I^2 = 73.4%) which could be explained by the duration of treatment, suggesting that levamisole is effective during treatment but the effect is not sustained when treatment is ceased.

Azathioprine (comparison 13)
Azathioprine did not cause a statistically significant reduction in the number of children who relapsed at six months compared with placebo or steroid alone (outcome 13.01 60 children: RR 0.90, 95% CI 0.59 to 1.38) (Abramowicz 1970; Barratt 1977).

Mizoribine
The reported relapse rate/patient-months was 0.0055 with mizoribine and 0.0067 with placebo (relapse rate ratio 0.81, 95% CI 0.61 to 1.05). Also the cumulative remission rate did not differ between the two groups (hazard ratio of cumulative remission rate 0.79, 95% CI 0.57 to 1.08) (Yoshioka 2000).

Data on the number of children with relapse at six and 12 months who had received mizoribine or placebo could not be extracted.

Side effects of therapy
Side effects were reported in 16 trials; in three trials only the lack of serious infections and leucopenia sufficient to cause cessation of the medication were reported (Barratt 1970; Barratt 1973; Barratt 1977). Side effects were not reported in the final trial (Weiss 1993).

Alkylating agents: The number of trials reporting each adverse event, the number of events and the total number of patients at risk and the percentage for each adverse event are shown for cyclophosphamide (CPA), chlorambucil (CHL) in Additional Table 3 - *Adverse effects during treatment of steroid sensitive nephrotic syndrome*. Both alkylating agents were associated with leucopenia, thrombocytopenia and infections. Hair loss was reported uncommonly and cystitis was not seen with chlorambucil. There were two severe infections reported with cyclophosphamide (APN 1982) and three serious viral infections with chlorambucil, the latter reported with the higher dose regime (Baluarte 1978).

Cyclosporin: Side effects of cyclosporin (CSA) are shown in Additional Table 3 - *Adverse effects during treatment of steroid sensitive nephrotic syndrome*. Gum hypertrophy and hirsutism were seen commonly with cyclosporin; elevated creatinine levels and hypertension occurred in 9% and 4% of children respectively.

Levamisole: With levamisole there was one case of gastrointestinal upset (BAPN 1991) and two trials reported that no side effects occurred (Dayal 1994; Rashid 1996). There was a single case of pulmonary embolus associated with azathioprine treatment (Abramowicz 1970).

Mizoribine: Adverse effects overall were slightly but not significantly higher with mizoribine compared with placebo (outcome 14.01: RR 1.56, 95% CI 0.97 to 2.49) but hyperuricaemia was significantly more common with mizoribine (outcome 14.02: RR 3.96, 95% CI 1.37 to 11.42) (Yoshioka 2000).

There were insufficient data to assess the mean relapse rate/patient/year and the mean time to next relapse in meta-analyses. There were insufficient trials of any treatment combination to allow detailed subgroup analyses.

DISCUSSION

RCTs in children with relapsing SSNS show that oral cyclophosphamide (2-3 mg/kg/d for eight weeks), intravenous cyclophosphamide (500 mg/m^2/mo for six months), chlorambucil (0.2 mg/kg/d for eight weeks) and cyclosporin (6 mg/kg/d) substantially reduce the risk of relapse compared with corticosteroids alone. These interventions typically reduce the risk for relapse in comparison with prednisone by about 50% for one to two years during and after a treatment course. This benefit is sustained beyond the on-treatment period for the alkylating agents but only occurs during treatment with cyclosporin. Treatment with azathioprine or mizoribine was ineffective. Since corticosteroids were used in combination with the trial agents in most studies, there are insufficient data available to determine the efficacy

of non-corticosteroid agents in comparison with placebo or no immunosuppressive treatment.

Levamisole (2.5 mg/kg on alternate days) also reduced the risk for relapse compared with placebo or no treatment in a meta-analysis of three trials (BAPN 1991; Dayal 1994; Rashid 1996). However a fourth trial (Weiss 1993) showed no benefit. Three trials limited enrolment to children with frequently relapsing (Rashid 1996; Weiss 1993) and steroid dependent SSNS (BAPN 1991; Rashid 1996; Weiss 1993) while the fourth trial (Dayal 1994) enrolled children following a relapse regardless of the frequency of relapse. Thus it is unlikely that the difference in efficacy between Weiss 1993 and the other trials related to different patient populations. Levamisole was administered twice weekly but on consecutive days in the Weiss 1993 trial to provide a monthly dose of 20 mg/kg while it was administered on alternate days in the BAPN 1991and Rashid 1996 trials to provide a monthly dose of 35 mg/kg. Thus the interval between doses was shorter and the total dose higher in the two trials demonstrating efficacy in frequently relapsing and steroid dependent patients. This difference in dose frequency and total dose may be responsible for the difference in efficacy.

Although these trial data show that non-corticosteroid agents are more effective than corticosteroids alone, between-agent trials have not demonstrated a clear benefit of one over any other in preventing relapse of NS. The relative efficacy of levamisole is not known. Comparative trials of cyclophosphamide, chlorambucil and cyclosporin have been done but, because of insufficient power, clinically important differences in treatment effects have not been excluded. For example, using the upper and lower bounds of the 95% CI of the RR estimate obtained from the single comparative trial of chlorambucil versus cyclophosphamide, chlorambucil could reduce the risk of recurrence by 20% or could double the risk of recurrence compared with cyclophosphamide. Similarly, compared with cyclophosphamide, cyclosporin could reduce the risk of relapse by 50% or could more than double the risk for relapse at 24 months. Adequately powered RCTs are required to determine which of the four agents is most effective. Because cyclosporin and cyclophosphamide are the two interventions in most widespread use (Bargman 1999) a comparative trial of these two medications would have most applicability. Assuming a 50% recurrence rate in the cyclosporin treated group, 130 patients would need to be recruited to a RCT to detect a 50% statistically significant relative risk reduction for relapse between the two agents. Until then choice between these agents must be based upon other non-effectiveness considerations, such as local availability or licensing, costs and physician and patient preferences concerning duration of treatment and frequency and nature of complications. By stratifying recruited patients into frequent relapsers and steroid dependent, this trial could also test the hypothesis that alkylating agents are more effective in the frequent relapsing group and cyclosporin is more effective in the steroid dependent group as suggested by post-hoc analysis of published trials of alkylating agents (APN 1982) and from uncontrolled studies of cyclosporin (Hulton 1994; Niaudet 1987). A recent review of 26 studies (controlled trials and cohort studies) found that on average the two and five year relapse rates following treatment with either cyclophosphamide or chlorambucil were 72% and 36% in frequently relapsing SSNS compared with 40% and 24% in steroid dependent SSNS (Latta 2001) providing further evidence for a differential efficacy of the alkylating agents in these patient groups.

Our conclusions differ somewhat from recently published guidelines (Bargman 1999), which recommend eight weeks of chlorambucil for frequently relapsing SSNS and twelve weeks of cyclophosphamide for steroid dependent SSNS. In part this may reflect the differences in information sources used. For example a study, which has been influential in shaping guidelines about cyclophosphamide use, found that twelve weeks of cyclophosphamide was more effective than eight weeks in preventing relapse in children with steroid dependent SSNS (APN 1987). However this study used historical controls, which may be associated with an overestimate of the treatment effect (Sacks 1982). In contrast in a RCT increasing the duration of cyclophosphamide from eight to twelve weeks did not improve efficacy (Ueda 1990).

What would the benefits and harms be of using an immunosuppressive agent in a child with relapsing NS? Cohort studies (Koskimies 1982; Tarshish 1997) show that between 35% and 53% relapse frequently at some time during their disease. Intervention with immunosuppressive agents would only be undertaken in this group of children whose risk for further recurrences approaches 100% with corticosteroid treatment alone. The meta-analysis shows that the relative risk for relapse is 0.44 following cyclophosphamide so the risk for relapse is reduced from 100% to about 40%. Hence, on the benefit side of the equation, assuming that all children will relapse, 60 fewer children would relapse for every 100 children treated with cyclophosphamide (Glasziou 1995). On the harm side of the equation, for every 100 children treated with cyclophosphamide about one child will suffer a significant infection, four develop cystitis and 14 lose their hair (Additional Table 3 - *Adverse effects during treatment of steroid sensitive nephrotic syndrome*). Children, who relapse only once during the first six months after the initial course of prednisone treatment, have only a 10% risk of becoming a frequent relapser (Tarshish 1997). Thus only 10/100 such children are considered at risk of relapsing frequently. Since cyclophosphamide, if administered to such children would reduce the risk of relapse by 60%, only 6/100 children would benefit while the number suffering adverse effects would be unchanged. Thus the benefits of treatment would outweigh the harms only in children who relapse frequently.

This study has several potential problems because of the limitations of the primary data. Overall the study quality was poor with only eight of 20 trials demonstrating adequate allocation concealment. Trials with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30 to 40% (Schulz 1995) and meta-analyses of low quality trials may overestimate the benefit of therapy (Moher 1998). This observation makes the need for adequately powered, well designed and reported trials even more necessary. Because trials are not generally designed to evaluate harms of interventions unless the primary outcome is a harm-benefit composite such as death, the small number of serious adverse effects reported here may be an underestimate and may not be directly applicable to larger groups of children treated under non-trial conditions. However a review (Latta 2001) of 38 articles on the treatment of relapsing SSNS involving 866 children who received 902 courses of cyclophosphamide and 638 children who received 671 courses of chlorambucil found similar frequencies of adverse effects except that leucopenia and infections were more common with chlorambucil (occurring in 33% and 6% respectively). The effects

of publication bias could not be formally assessed because of the small number of studies for each agent. Key investigators in this field, who were contacted, did not reveal any unpublished data.

This systematic review of RCTS shows that eight week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin or levamisole substantially reduce the incidence of relapse in children with NS. Published recommendations (BAPN 1994; Bargman 1999; Brodehl 1991) generally favour using courses of cyclophosphamide or chlorambucil initially in children with relapsing SSNS. However, using efficacy criteria, there are no data to show that alkylating agents should be preferred over cyclosporin or levamisole. Side effect profiles indicate serious infections, hair loss and cystitis with the alkylating agents and hypertension and reduced renal function with cyclosporin. Few side effects were reported in the levamisole trials. However important side effects reported in other studies include neutropenia and disseminated vasculitis (Barbano 1999; Palcoux 1994). Thus this review cannot determine which agent should be preferred for relapsing SSNS.

The use of mycophenolate mofetil (MMF) in children with relapsing SSNS is increasing. In two case series of children with frequently relapsing or steroid dependent SSNS, mycophenolate has been demonstrated to reduce the risk for relapse during therapy (Bagga 2003; Hogg 2003; Hogg 2004). These uncontrolled data indicate that MMF should be subjected to RCTs in comparison with prednisone alone and other non-corticosteroid agents.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, this systematic review and meta-analysis of RCTs show that eight week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin or levamisole substantially reduce the incidence of relapse in children with NS in comparison with corticosteroids alone. However there are no data to show which agent should be preferred. Thus the decision as to which medication should be used in a child with frequently relapsing or steroid dependent SSNS will largely depend on patient and physician preference following discussion of the possible side effects and the costs of eight week courses of alkylating agents and those of prolonged courses of cyclosporin or levamisole.

Implications for research

Further adequately powered RCTs are needed to identify clinically important differences in efficacy among the immunosuppressive agents in widespread use.
- RCT comparing the commonly used agents, cyclophosphamide and cyclosporin should be carried out.
- RCT comparing levamisole with prednisone
- RCT comparing levamisole with cyclophosphamide
- RCT comparing MMF with prednisone
- RCT comparing MMF with cyclophosphamide

In these trials patients should be stratified according to whether they are frequent relapsers or steroid dependent to determine the relative efficacies of agents in the patients groups.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abramowicz 1970

Methods	Country: International Setting/Design: Tertiary centres. Parallel groups Time frame: January 1967 - December 1969 Randomisation method: Random numbers Blinding - Participants: Yes - Investigators:Yes - Outcome assessors:NS - Data analysis:NS Intention-to-treat: No Follow-up period: 6 mths Loss to follow-up: 0%
Participants	INCLUSION CRITERIA: FR SSNS (2 relapses in any 6 mths); Age 12 wks - 15.9 yrs TREATMENT GROUP Number: 18 Age: Not stated Sex (M/F): Not stated CONTROL GROUP Number: 18

Abramowicz 1970 *(Continued)*

	Age: Not stated Sex (M/F): Not stated EXCLUSIONS: Previous treatment with prednisone, immunosuppressive or cytotoxic drugs
Interventions	TREATMENT GROUP Oral azathioprine 60 mg/m2/d for 26 wk with "Maintenance'" prednisone CONTROL GROUP Placebo for 26 wk with "maintenance" prednisone CO-INTERVENTIONS: None reported
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 mths (defined as proteinuria >4mg/m2/day for 3 consecutive days out of 7 days)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 4 withdrawn after randomisation (3 withdrawn during treatment) and data not included in results STOP OR END POINT/S: Not stated ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Alatas 1978

Methods	Country: Indonesia Setting/Design: Tertiary centre. Parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 20 followed to 6 mths & 11 to 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2 relapses in 6 mths or 4 relapses in 1yr) Age 12 wks - 15.9 yrs TREATMENT GROUP Number: 11 Age: 6.95 +/- 2.82 yrs Sex (M/F): 8M/3F CONTROL GROUP Number: 9 Age: 8.56 +/- 2.17 yrs Sex (M/F): 7M/2F EXCLUSIONS: Secondary nephrotic syndrome
Interventions	TREATMENT GROUP Oral Chlorambucil 0.3 mg/kg/d & prednisone 40mg/m2/d for 8 wk CONTROL GROUP

Alatas 1978 *(Continued)*

	Placebo & prednisone 40mg/m2/d for 8 wk. CO-INTERVENTIONS All treated with prednisone 60mg/m2/d till remission and then randomised
Outcomes	STUDY OUTCOMES: 1.Number in relapse at 6 mths (definition not stated) 2. Number in relapse at 12 mths 3. Mean relapse rate/patient
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reportedSTOP OR END POINT/S: Not statedADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

APN 1982

Methods	Country: Germany Setting/Design:Multicentre tertiary centres. Parallel groups Time frame: 1977-1981 Randomisation method: NS Blinding - Participants: No - Investigators:No - Outcome assessors:NS - Data analysis:NS Intention-to-treat: Unclear Follow-up period: 2 yrs Loss to follow-up: 0%
Participants	INCLUSION CRITERIAFR SSNS (2+ relapses in 6 mths or 4+ in 1 yr)SD SSNS (relapsed on alternate day prednisone or within 14 days of ceasing)CYCLOPHOSPHAMIDE GROUPNumber: 26Age: 2-16 yrsSex (M/F): 14M/12FCHLORAMBUCIL GROUPNumber: 24Age: 2-16 yrsSex (M/F): 17M/7FEXCLUSIONS: Previous treatment with cytotoxic agents
Interventions	CYCLOPHOSPHAMIDE GROUP Oral CPA 2 mg/kg/d for 8 wk & prednisone for 4 wk. CHLORAMBUCIL GROUP Oral chlorambucil 0.15 mg/kg/d for 8 wk & prednisone for 4 wk. CO-INTERVENTIONS All treated with prednisone 60mg/m2/d till remission and then randomised
Outcomes	STUDY OUTCOMES 1. Number with relapse at 12 mths (ISKDC definition) 2. Number with relapse at 24 mths 3. Number with relapse in FR compared with SD patients regardless of treatment (Post hoc analysis)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: Not stated ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on relapse rates in groups according to medication given and for adverse effects requested and provided.

Risk of bias

APN 1982 *(Continued)*

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

Baluarte 1978

Methods	Country: USA Setting/Design: Tertiary centre/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: Average 28.6 mths (stable dose) 1); 27.2 mths (increasing dose) Loss to follow-up: 0% at 1 yr
Participants	INCLUSION CRITERIAFR SSNS (ISKDC criteria)CHLORAMBUCIL STABLE DOSE GROUPNumber: 10Age: Av 7yrs 8mths (3.5-14 yrs)Sex (M/F): NSCHLORAMBUCIL INCREASING DOSE GROUPNumber: 11Age: Av. 8yrs 9mth (5-15yrs)Sex (M/F): NSEXCLUSIONS:
Interventions	CHLORAMBUCIL STABLE DOSE GROUP Oral chlorambucil 0.2 mg/kg/d for 8 wk CHLORAMBUCIL INCREASING DOSE GROUP Oral chlorambucil 0.2 mg/kg/d increasing by about 0.1mg/kg every 2 wk for 6 - 11 wk till leucopenia. CO-INTERVENTIONS Prednisone 60mg/m2/d till urine protein-free for 5-7 days. Prednisone 60mg/m2 on alternate days until wcc above 4000 in both groups.
Outcomes	STUDY OUTCOMES 1. Number with relapse at 6 mths (no definition provided) 2. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reportedSTOP OR END POINT/S: Not statedADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

BAPN 1991

Methods	Country: UK/Ireland Setting/Design: Multicentre tertiary/Parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: Yes

BAPN 1991 *(Continued)*

	- Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 28 wks Loss to follow-up: 0%
Participants	INCLUSION CRITERIASD SSNS (relapse on prednisolone > 0.5mg/kg on alt daysTREATMENT GROUP-Number: 31Age: 8.3 +/- 3.6yrsSex (M/F): 21M/10FCONTROL GROUPNumber: 30Age: 8.8 +/- 3.7yrsSex (M/F): 20M/10EXCLUSIONS: Not reported
Interventions	TREATMENT GROUP Oral levamisole 2.5 mg/kg on alternate days for 16wk CONTROL GROUP Placebo on alternate days for 16wk CO-INTERVENTIONS Prednisone 2mg/kg/d till remission; prednisone 1mg/kg on alt days for 28d, reduced by 0.25mg/kg every 14d & ceased at 8wks
Outcomes	STUDY OUTCOMES 1. Relapse at end of treatment (defined as 3+ proteinuria for 3 consecutive days, confirmed on albumin/creatinine ratio > 2mg/mg or protein/creatinine ratio > 200mg/mmol) 2. Relapse at 6 mths 3. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reportedSTOP OR END POINT/S: not reportedADDITIONAL DATA REQUESTED FROM AUTHORS: information on allocation concealment requested and obtained.

Risk of bias

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

Barratt 1970

Methods	Country: UK Setting/Design: Tertiary centre/parallel groups Time frame: NS Randomisation method: Sealed cards Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 18-123 wk Loss to follow-up: 0%
Participants	INCLUSION CRITERIAFR SSNS (3+ relapses in at least 6 mths)Age <14 yrTREATMENT GROUPNumber: 15Age: 3.7-12.5yrSex (M/F): NSCONTROL GROUPNumber: 15Age: 2.9-12.9yrSex (M/F): NSEXCLUSIONS: Children unable to tolerate 8 wks prednisone

Barratt 1970 *(Continued)*

Interventions	TREATMENT GROUPOral CPA 3 mg/kg/d for 8 wk. Prednisone for 8 wk & reduced over 8 wkCONTROL GROUPReducing dose of prednisone for 8 wkCO-INTERVENTIONSPenicillin 125mg twice day to wk 16
Outcomes	STUDY OUTCOMES 1. Relapse at 6mth (defined as oedema & albumin/creatinine ratio >1.0 or Albustix 3+ or 4+ on 2 days) 2. Relapse at 12mth 3. Relapse at 2yr
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reportedSTOP OR END POINT/S: not reportedADDITIONAL DATA REQUESTED FROM AUTHORS: : None

Risk of bias

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

Barratt 1973

Methods	Country: UKSetting/Design: Tertiary centre/parallel groupsTime frame: NSRandomisation method: Sealed cardsBlinding - Participants: No- Investigators: No- Outcome assessors:NS- Data analysis:NSIntention-to-treat: NoFollow-up period: 20-104 wksLoss to follow-up: 0%
Participants	INCLUSION CRITERIAFR SSNS (3+ relapses in at least 6 mths)Age <14 yrSHORT CPA GROUPNumber: 16Age: 3.7-13.8 yrSex (M/F): NSSTANDARD CPA GROUPNumber: 16Age: 4.1-12.9 yrSex (M/F): NSEXCLUSIONS: Children unable to tolerate 8 wks prednisone
Interventions	SHORT CPA GROUP Oral CPA 3 mg/kg/d for 2 wk STANDARD CPA GROUP Oral CPA 3 mg/kg/d for 8 wk CO-INTERVENTIONS: Maintenance prednisone for 8 wk; taper for 8 wk after CPA completed
Outcomes	STUDY OUTCOMES 1. Relapse at 6mth (defined as albumin/creatinine ratio >1.0)2. Relapse at 12mth3. Need to cease CPA because of leucopenia
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 3 excluded from Short CPA groupSTOP OR END POINT/S: Not reportedADDITIONAL DATA REQUESTED FROM AUTHORS: none

Risk of bias

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

Barratt 1977

Methods	Country: UK Setting/Design: Tertiary centre/parallel groups Time frame: Not stated Randomisation method: Sealed cards Blinding

Barratt 1977 *(Continued)*

	- Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 32 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (previous relapse on at least 0.2mg/kg of prednisone on alternate days) Age <14 yr TREATMENT GROUP Number: 12 Age: < 14 yrs Sex (M/F): NS CONTROL GROUP Number: 12 Age: < 14 yrs Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral azathioprine 2mg/kg/d for 8 wk Prednisone for 8 wk, tapered over next 8 wk (total 16 wks) CONTROL GROUP Prednisone for 8 wks, tapered over next 8 wks (total 16 wks) CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 32 wks (defined as urine albumin/creatinine > 1.0 in 2 specimens)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: Trial stopped after 24 children reached 32 weeks as no difference between groups demonstrated ADDITIONAL DATA REQUESTED FROM AUTHORS: Reference to trial provided by the authors

Risk of bias

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

Chiu 1973

Methods	Country: Canada Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: September 1967-November 1971 Randomisation method: Treatment lots of 2-8 children set up by independent person Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 26.6 (20-38) mths in control group. 25.7 (14-39) mths in treatment group

Chiu 1973 *(Continued)*

	Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SSNS with at least 3 episodes. Children in relapse at entry TREATMENT GROUP Number: 12 Age: 10 (2yr 11mth - 15yr 10mth) Sex (M/F): 4M/8F CONTROL GROUP Number: 11 Age: 9yr 7mth (6yr 2mth - 9yr 11mth) Sex (M/F): 7M/4F EXCLUSIONS Absence of definite history of varicella regarded as relative contraindication
Interventions	TREATMENT GROUP Oral CPA 75 mg/m2/d for 16 wks. Prednisone 60mg/m2/d till urine protein free for 2 wks, then same dose on alternate days. Total 16 wk. CONTROL GROUP Prednisone 60mg/m2/d till urine protein free for 2 wks, then same dose on alternate days. Total 16 wk. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 10 mths (proteinuria >2gm/m2/d) 2. Number in relapse at 20 mths
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Dayal 1994

Methods	Country: India Setting/Design: Single tertiary centre/parallel groups Time frame: 1988-1990 Randomisation method: Block randomisation Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 mths in treatment group, 10.5 mths in control group Loss to follow-up: 3%
Participants	INCLUSION CRITERIA Children with initial episode of SSNS (24 children, 1 lost to follow up) Children with relapsing SSNS (no definition provided; 37 children, 1 lost to follow up) TREATMENT GROUP (Relapsing SSNS only) Number: 23 (1 lost to follow up and not included in analysis)

Dayal 1994 *(Continued)*

	Age: 65.5 +/- 30.9 mths Sex (M/F): 19M/4F CONTROL GROUP (Relapsing SSNS only) Number: 14 Age: 60.1 +/- 37.2 mths Sex (M/F): 10M/4F EXCLUSIONS: Clinical features not consistent with minimal change nephrotic syndrome. Steroid resistant nephrotic syndrome
Interventions	TREATMENT GROUP Oral levamisole 2-3 mg/kg twice a week for 52 wk CONTROL GROUP No treatment for 52 wk CO-INTERVENTIONS Prednisolone 60mg/m2/d for 4 wks, prednisolone 40mg/m2 on alt days for wks to achieve initial remission and for relapse
Outcomes	STUDY OUTCOMES 1. Number in relapse at end of treatment (12 mths) (defined as oedema, urine protein >1g/m2/d & serum albumin < 2.5g/100mL) 2. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported. Consecutive enrollment of children STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Grupe 1976

Methods	Country: USA Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 19.6 (12-34) mths in treatment group; 20.0 (12-33) mths in control group Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses per year) SD SSNS (Prednisone required for 6mths + to maintain remission) TREATMENT GROUP Number: 10 Age: 11.0 (3-15.5) yrs Sex (M/F): 6M/4F CONTROL GROUP

Grupe 1976 *(Continued)*

	Number: 11 Age: 7.0 (3.3-12) yrs Sex (M/F): 7M/4F EXCLUSIONS: None recorded
Interventions	TREATMENT GROUP Oral chlorambucil started at 0.1-0.2 mg/kg/d & increased every 2 wks (average maximum dose 0.33 mg/kg/d, range 0.26-0.41) until wcc fell (av 9.7 wks, range 6-12 wk). Total average dose 16.9 mg/kg (range 9.5-23.7 mg/kg) Prednisone 80-120 mg on alt days for 2 mths, taper over 4-6 wks. Prednisone given till wcc above 5000 CONTROL GROUP Prednisone 80-120 mg on alt days for 2 mths, taper over 4-6 wks CO-INTERVENTIONS To induce remission, both groups given prednisone 40-60 mg/day till urine protein free for 2 wks
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 mths (defined as urine protein 100mg/24 h for > 10 d) 2. Number in relapse at 12 mths 3. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

ISKDC 1974

Methods	Country: International Setting/Design: Multicentre tertiary institutions/Parallel groups Time frame: April 1970 - June 1972 Randomisation method: Not stated Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 1.8 yrs in treatment group, 1.7 yrs in control group Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2 relapses within 6 mths of initial response, 4 relapses in any 1 yr) TREATMENT GROUP Number: 27 Age: NS Sex (M/F): NS CONTROL GROUP Number: 26 Age: NS Sex (M/F): NS EXCLUSIONS: None reported

ISKDC 1974 *(Continued)*

Interventions	TREATMENT GROUP Oral CPA 5 mg/kg/d till WCC 3-5000 & then 1-3 mg/kg/d to maintain WCC 3-5000. Total 6 wk Prednisone 10mg/m2/d for 10 d CONTROL GROUP Prednisone 40mg/m2 on 3 out of 7 days for 26 wk. CO-INTERVENTIONS None
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 mths (defined as urine protein >4mg/m2/h on 3 out of 7d) 2. Mean relapse rate/patient 3. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 10 patients excluded STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

McCrory 1973

Methods	Country: USA Setting/Design: Single tertiary centre/ parallel groups Time frame: September 1969 - October 1970 Randomisation method: Odds and even numbers from medical record numbers Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 18 mths Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2+ relapses in 6 mths) HIGH DOSE CPA GROUP Number: 6 Age: 41 mths - 14 yrs Sex (M/F): NS LOW DOSE CPA GROUP Number: 8 Age: 41 mths - 14 yrs Sex (M/F): NS EXCLUSIONS: None reported
Interventions	HIGH DOSE CPA GROUP Oral CPA 5 mg/kg/d for 45 days Prednisone 1.5mg/kg on alt days for 45 days LOW DOSE CPA GROUP Oral CPA 2.5 mg/kg/d for 90 days Prednisone 1.5mg/kg on alt days for 90 days

McCrory 1973 *(Continued)*

	CO-INTERVENTIONS: None reported
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6, 12 and 18 mths (defined as urine protein >4mg/m2/h on 3 out of 7d) 2. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Niaudet 1992

Methods	Country: France Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: October 1985 - May 1989 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 2-3 yrs Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (relapse on alt day prednisone) with evidence of steroid toxicity (growth retardation, obesity, osteoporosis etc) CYCLOSPORIN GROUP Number: 20 Age: NS Sex (M/F): NS CHLORAMBUCIL GROUP Number: 20 Age: NS Sex (M/F): NS EXCLUSIONS: Creatinine clearance <50ml/min/1.73m2, abnormal liver function tests, uncontrolled hypertension Previous cytotoxic therapy
Interventions	CYCLOSPORIN GROUP Oral CSA 6 mg/kg/d for 3 mths and then tapered over 3 mths. Dose adjusted to trough CSA level of 50-150 ng/ml CHLORAMBUCIL GROUP Oral Chlorambucil 0.2 mg/kg/d for 40 d (cumulative dose 8 mg/kg) CO-INTERVENTIONS For relapse prednisone 30-60 mg/m2 till remission, then same dose on alt days & tapered over 3 mths.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 mths (Relapse criteria not defined)

Niaudet 1992 *(Continued)*

	2. Number in relapse at 12 mths 3. Number in relapse at 24 mths .
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Ponticelli 1993

Methods	Country: Italy Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 3 mths-2 yrs Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2+ relapses in 6mths or 3+ in 1yr) SD SSNS (Relapse within 2 wks of discontinuation or reduction in prednisone) Children 2-15 yrs. Adults >16 yrs CYCLOSPORIN GROUP Number: 30 children; 6 adults Age: Median 10.5 yr Sex (M/F): 24M/12F CYCLOPHOSPHAMIDE GROUP Number: 25 children. 5 adults Age: Median 10.0 yrs Sex (M/F): 24M/6F EXCLUSIONS: Patients not achieving complete remission with steroids. Patients given steroid regimens different from protocol
Interventions	CYCLOSPORIN GROUP Oral CSA 6 mg/kg/d for 9 mths (dose adjusted for trough level 200-600 ng/ml), reducing over next 3 mth. (total duration 12 mths) CYCLOPHOSPHAMIDE GROUP Oral CPA 2.5 mg/kg/d for 8 wk. CO-INTERVENTIONS For relapse prednisone 60mg/m2/day till remission, prednisone 40mg/m2 on alt days for 4 wks
Outcomes	STUDY OUTCOMES 1. Number in relapse at 9 mths (defined as urine protein >4 mg/m2/h for 2 wk) 2. Number in relapse at 24 mths

Ponticelli 1993 *(Continued)*

	3. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 7 excluded post randomisation when did not return for follow up STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: Detailed paediatric data requested but not obtained

Risk of bias

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

Prasad 2004

Methods	Country: India Setting/Design: Single tertiary care centre. Parallel groups Time frame: NS Randomisation method: Random numbers Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: Not stated Intention-to-treat: Yes Follow-up period: Median 24 mths (treatment group); 21 mths (control group) Loss to follow-up: 0%
Participants	INCLUSION CRITERIA: SD SSNS (2 + relapses on prednisone or within 2 weeks of ceasing prednisone in 6 mths before study entry). Age 1-16 yrs. Steroid toxicity (2 + of severe cushingoid appearance, hypertension, growth suppression, cataract. diabetes mellitus, glaucoma, psychosis. IV CYCLOPHOSPHAMIDE GROUP Number: 26 Age: 4.7 +/- 4.4yrs Sex (M/F): 22M; 4F ORAL CYCLOPHOSPHAMIDE GROUP Number: 21 Age: 7.6 +/- 5.3yrs Sex (M/F): 18M; 3F EXCLUSIONS: Previous use of cytotoxic therapy
Interventions	IV CYCLOPHOSPHAMIDE GROUP IV CPA 500mg/m2 mthly for 6 doses (total dose 100mg/kg) ORAL CYCLOPHOSPHAMIDE GROUP Oral CPA 2mg/kg/day for 12 weeks (total dose 180mg/kg) CO-INTERVENTIONS: Prednisone 60mg/m2 till remission for 3 days, 40mg/m2 on alternate days for 4 wks, tapering dose of prednisone for 4 weeks.
Outcomes	STUDY OUTCOMES 1. Number with relapse at 6 months after the end of therapy (relapse defined as 1+ proteinuria for 3 consecutive days or development of nephrotic syndrome) 2. Number with FR (2+ relapses in 6 mths) or SD SSNS 3. Median protein free days (+/- SE) 4. Adverse effects (leucopenia, cystitis, hair loss, all infections, nausea and vomiting)

Prasad 2004 *(Continued)*

Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: Consecutive recruitment of patients reported and no exclusions post randomisation STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

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

Rashid 1996

Methods	Country: Bangladesh Setting/Design: Single tertiary centre/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 44 wk Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (ISKDC definition) SD SSNS (ISKDC definition) TREATMENT GROUP Number: 20 Age: Average 8 yrs Sex (M/F): 13M/7F CONTROL GROUP Number: 20 Age: average 6 yrs Sex (M/F): 14M/6F EXCLUSIONS: None stated
Interventions	TREATMENT GROUP Oral levamisole 2.5 mg/kg on alternate days for 26 wk. Prednisone 2mg/kg/d for 2 wk, 1mg/kg/d for 4-6 wk, tapering dose to 6 mths (Total duration 6 mths) CONTROL GROUP Prednisone 2mg/kg/d for 2 wk, 1mg/kg/d for 4-6 wk, tapering dose to 6 mths (Total duration 6 mths) CO-INTERVENTIONS: None
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (Criteria for relapse not defined) 2. Number in relapse at end of treatment (44 wks)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Rashid 1996 *(Continued)*

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

Ueda 1990

Methods	Country: Japan Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: February 1975-August 1988 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 8 wk CPA group 66.2 (50.6) mths; 12 wk CPA group 63.1 (33.7) mths Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (relapse during reducing prednisone dose or within 2 wks of ceasing) 2+ of growth retardation, hypertension, gross cushingoid appearance, osteoporosis, psychosis, diabetes, cataracts, glaucoma 8 WEEK CYCLOPHOSPHAMIDE GROUP Number: 32 Age: 7.7 (3.7) yrs Sex (M/F): 26M/6F 12 WEEK CYCLOPHOSPHAMIDE GROUP Number: 41 Age: 7.8 (3.7) yrs Sex (M/F): 28M/13F EXCLUSIONS: Patients in relapse
Interventions	8 WEEK CYCLOPHOSPHAMIDE GROUP Oral CPA 2 mg/kg/d for 8 wk (total dose 112mg/kg) 12 WEEK CYCLOPHOSPHAMIDE GROUP CPA 2 mg/kg/d for 12 wk (total dose 168mg/kg) CO-INTERVENTIONS Relapses treated with prednisone 60mg/m2/d for 4 wks, then taper by 5-10mg/m2 over 3-4 mths
Outcomes	STUDY OUTCOMES 1. Number in relapse at 12 mths (defined as urine protein >40 mg/m2/h for 3 consecutive days) 2. Number in relapse at 24 mths 3. Mean relapse rate/pt 4. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement

Ueda 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Weiss 1993

Methods	Country: USA Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 12 mths Loss to follow-up: 2%
Participants	INCLUSION CRITERIA: FR SSNS: 2+ relapses on alt day prednisone within 6 mths of initial espisode or 4+ relapses in an year SD SSNS: 2 consecutive relapses on alt day prednisone of within 2 wks of ceasing or 4 relapses in a year while on alt day prednisone or within 2 wks of ceasing TREATMENT GROUP Number: 23 Age: 7.3 +/- 4.4 yrs Sex (M/F): 19M/4F CONTROL GROUP Number: 26 Age: 7.5 +/- 3.8 yrs Sex (M/F): 19M/7F EXCLUSIONS: Other immunosuppressive agents in previous 6 mths, post menarchal girls, WCC < 4000, abnormal liver function tests, Creatinine clearance <90ml/min/1.73m2, Complement C3 <50mg/dl, co-existent medical condition likely to interfere with procedures or results
Interventions	TREATMENT GROUP Levamisole oral suspension 2.5mg/kg orally twice weekly (Saturday, Sunday) for 6 mths CONTROL GROUP Placebo oral suspension twice weekly (Saturday, Sunday) for 6 mths CO-INTERVENTIONS: Relapses treated with prednisone 60mg/m2/day till remission and then 40mg/m2 on alt days for 28 days (ISKDC protocol)
Outcomes	STUDY OUTCOMES 1. Mean relapse rate/patient by 6mths (defined as > 1+ proteinuria on 3 consecutive first morning urines) 2. Mean time to next relapse 3. Mean number of days/mth of prednisone treatment 4. Number with relapse at end of treatment 5. Number with relapse at 6 mths after end of treatment
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 4 withdrawn from levamisole group (steroid toxicity 2, withdrew consent 1, administrative reasons 2) before treatment completed. 8 withdrawn from placebo group (newly developed steroid resistance 2, acute renal failure 1, administrative reasons 5). STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: Draft manuscript of trial obtained from author

Weiss 1993 *(Continued)*

Risk of bias

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

Yoshioka 2000

Methods	Country: Japan Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: NS Randomisation method: Computer-generated Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 18 mths Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses in 12 mths or 2+ in 6 mths). Age >2-17.9 yrs. TREATMENT GROUP Number: 99 Age: Age 2-17.9yr Sex (M/F): 72M/27F CONTROL GROUP Number: 98 Age: 2-17.9yr Sex (M/F): 70M/28F EXCLUSIONS: Immunosuppressive treatment in previous 6 mths, Creatinine clearance <50 ml/min/1.73m2, secondary nephrotic syndrome
Interventions	TREATMENT GROUP Oral mizoribine 4 mg/kg/d for 48 wk Prednisone 1-2mg/kg/d for 4 wk, then reducing dose & ceased at 12 wk CONTROL GROUP Placebo for 48 wk Prednisone 1-2mg/kg/d for 4 wk, then reducing dose & ceased at 12 wk CO-INTERVENTIONS: None reported
Outcomes	STUDY OUTCOMES 1.No. of relapses/patient.mo of study (defined as urinary protein >100mg/L or 2+ on 3 or more consecutive days) 2.Cumulative remission rate 3. Adverse events
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 3 excluded from Treatment Group and 1 from Control Group STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on numbers relapsing sought but not obtained

Risk of bias

Yoshioka 2000 *(Continued)*

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

CPA = cyclophosphamide
CSA = cyclosporin
SSNS = steroid sensitive nephrotic syndrome
FR = frequent relapsing
SD = steroid dependent
NS = Not stated

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

Study	Reason for exclusion
Beige 2003	Adult patients
Bizo 2004	Not an RCT
El-Husseini 2004	Not an RCT
Gong 1997	Cannot separate children from adults & treatments not fully specified
Jin 1994	Data from children and adults could not be separated
Kirubakaran 1984	Available only in abstract form and data on primary outcome could not be extracted
Naigui 1997	Data from children and adults could not be separated
Pecoraro 2003	RCT of corticosteroids not non-corticosteroid therapy
Sancewicz-Pach 1995	Children with steroid resistant nephrotic syndrome Unclear whether this is RCT
Stavrovskaya 2001	Probably adults only. Includes steroid resistant and steroid sensitive patients. Outcomes do not include remission of nephrotic syndrome.
Zhao 2003	Data from children and adults could not be separated. Includes diseases other than idiopathic nephrotic syndrome and data cannot be separated.
Zou 1997	Interventions in treatment groups unclear. No data on outcomes at 6 and 12 months

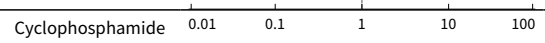
DATA AND ANALYSES

Comparison 1. Cyclophosphamide versus prednisone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6-12 months	3	102	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.73]
2 Number with relapse at 12-24 months	2	27	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.07, 0.65]

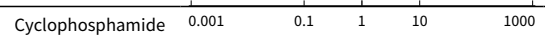
Analysis 1.1. Comparison 1 Cyclophosphamide versus prednisone, Outcome 1 Number with relapse at 6-12 months.

Study or subgroup	Cyclophosphamide n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barratt 1970	3/11	13/15		26.17%	0.31[0.12,0.84]
Chiu 1973	1/12	5/11		6.45%	0.18[0.03,1.33]
ISKDC 1974	9/27	16/26		67.39%	0.54[0.29,1]
Total (95% CI)	**50**	**52**		**100%**	**0.44[0.26,0.73]**
Total events: 13 (Cyclophosphamide), 34 (Prednisone)					
Heterogeneity: Tau^2=0; Chi^2=1.71, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=3.21(P=0)					



Analysis 1.2. Comparison 1 Cyclophosphamide versus prednisone, Outcome 2 Number with relapse at 12-24 months.

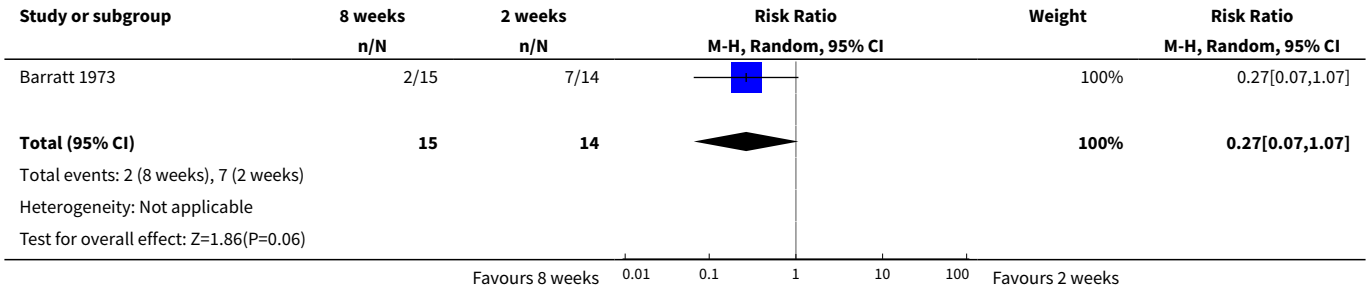
Study or subgroup	Cyclophosphamide n/N	Prednisone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barratt 1970	0/4	3/3		17.82%	0.11[0.01,1.63]
Chiu 1973	2/9	10/11		82.18%	0.24[0.07,0.84]
Total (95% CI)	**13**	**14**		**100%**	**0.21[0.07,0.65]**
Total events: 2 (Cyclophosphamide), 13 (Prednisone)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=1(P=0.61); I^2=0%					
Test for overall effect: Z=2.7(P=0.01)					



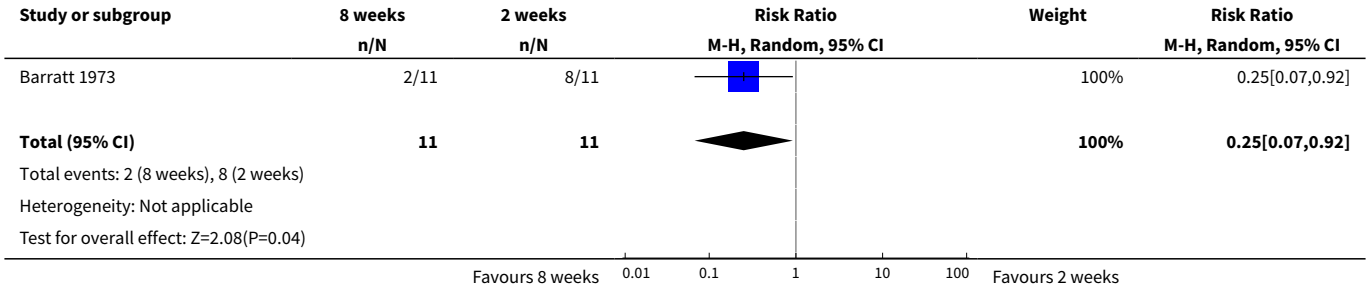
Comparison 2. Cyclophosphamide: 8 weeks versus 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6 months	1	29	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.07, 1.07]
2 Number with relapse at 12 months	1	22	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.92]

Analysis 2.1. Comparison 2 Cyclophosphamide: 8 weeks versus 2 weeks, Outcome 1 Number with relapse at 6 months.



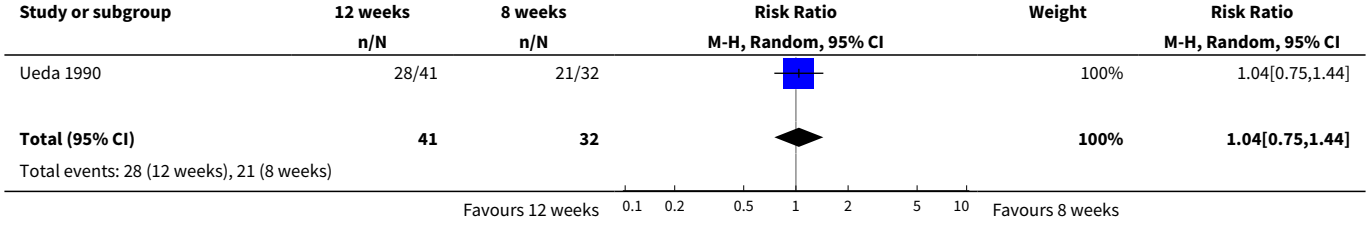
Analysis 2.2. Comparison 2 Cyclophosphamide: 8 weeks versus 2 weeks, Outcome 2 Number with relapse at 12 months.

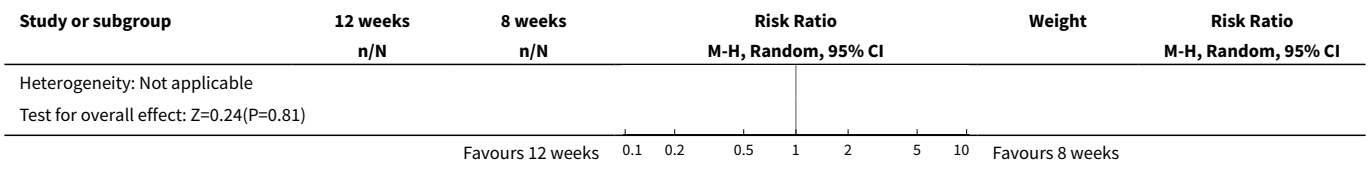


Comparison 3. Cyclophosphamide: 12 weeks versus 8 weeks

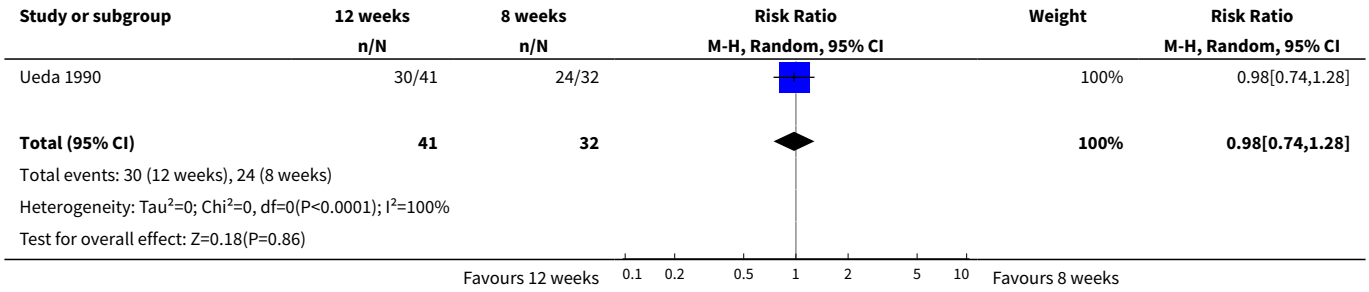
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 12 months	1	73	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.75, 1.44]
2 Number with relapse at 24 months	1	73	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.28]

Analysis 3.1. Comparison 3 Cyclophosphamide: 12 weeks versus 8 weeks, Outcome 1 Number with relapse at 12 months.





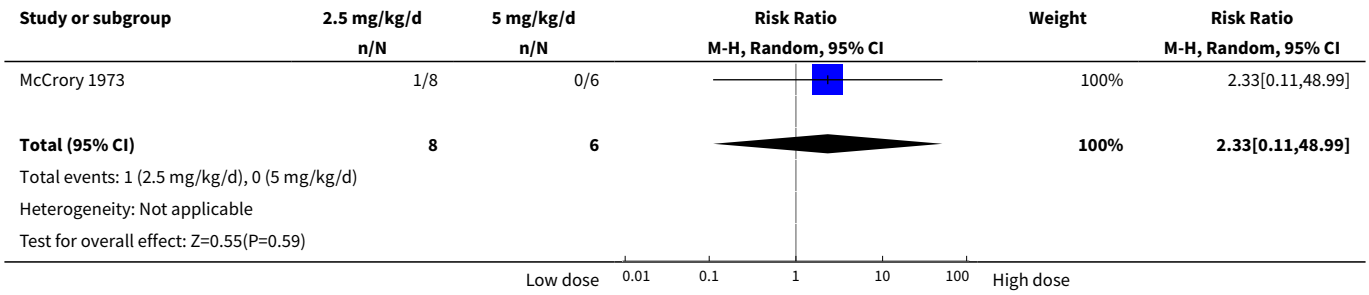
Analysis 3.2. Comparison 3 Cyclophosphamide: 12 weeks versus 8 weeks, Outcome 2 Number with relapse at 24 months.



Comparison 4. Cyclophosphamide: different doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 12 months	1	14	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.11, 48.99]

Analysis 4.1. Comparison 4 Cyclophosphamide: different doses, Outcome 1 Number with relapse at 12 months.

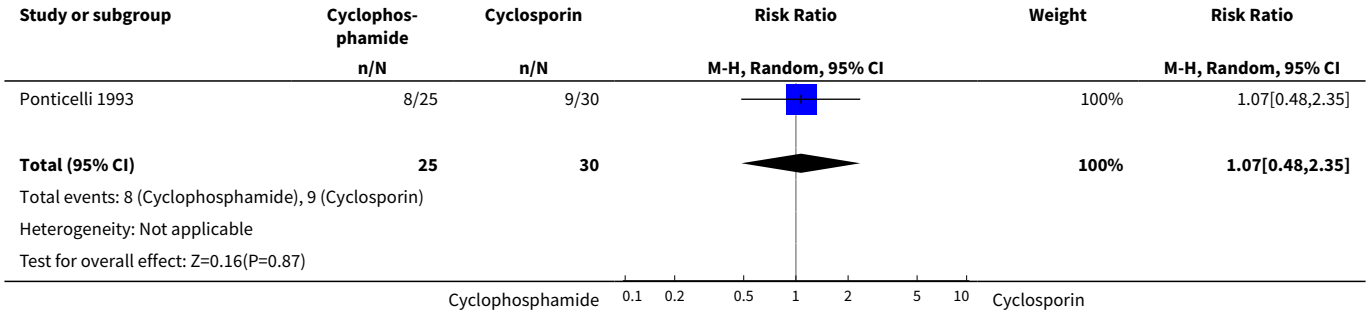


Comparison 5. Cyclophosphamide versus cyclosporin

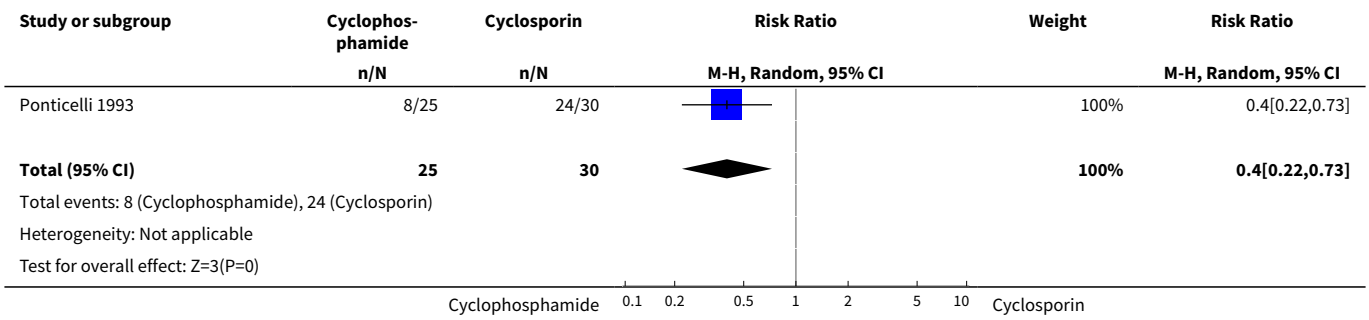
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 9 months	1	55	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.48, 2.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number with relapse at 24 months	1	55	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.22, 0.73]

Analysis 5.1. Comparison 5 Cyclophosphamide versus cyclosporin, Outcome 1 Number with relapse at 9 months.



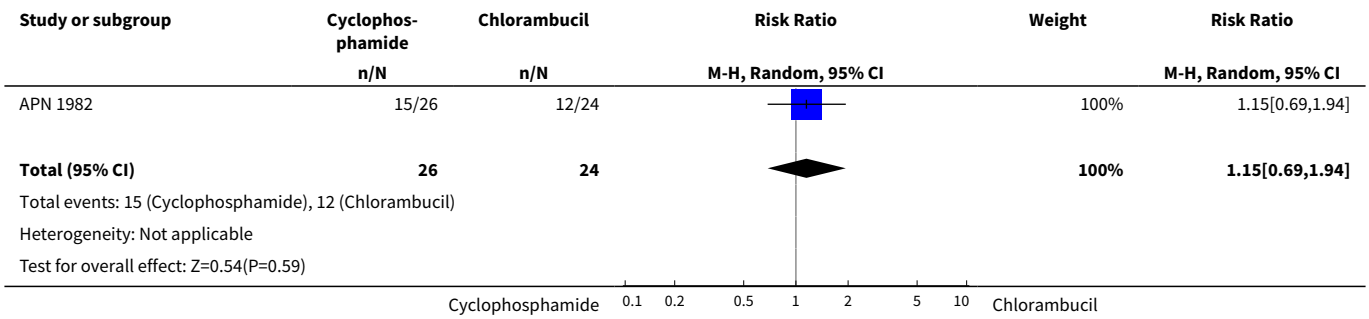
Analysis 5.2. Comparison 5 Cyclophosphamide versus cyclosporin, Outcome 2 Number with relapse at 24 months.



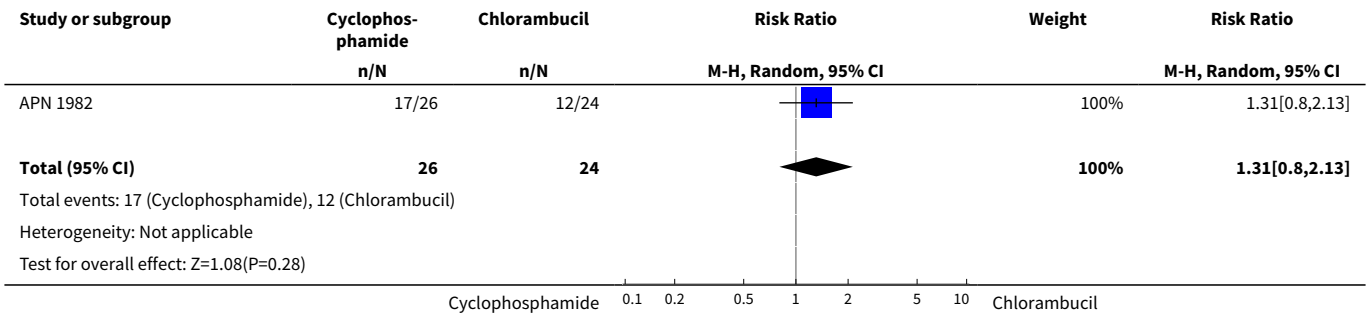
Comparison 6. Cyclophosphamide versus chlorambucil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 12 months	1	50	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.69, 1.94]
2 Number with relapse at 24 months	1	50	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.80, 2.13]

Analysis 6.1. Comparison 6 Cyclophosphamide versus chlorambucil, Outcome 1 Number with relapse at 12 months.



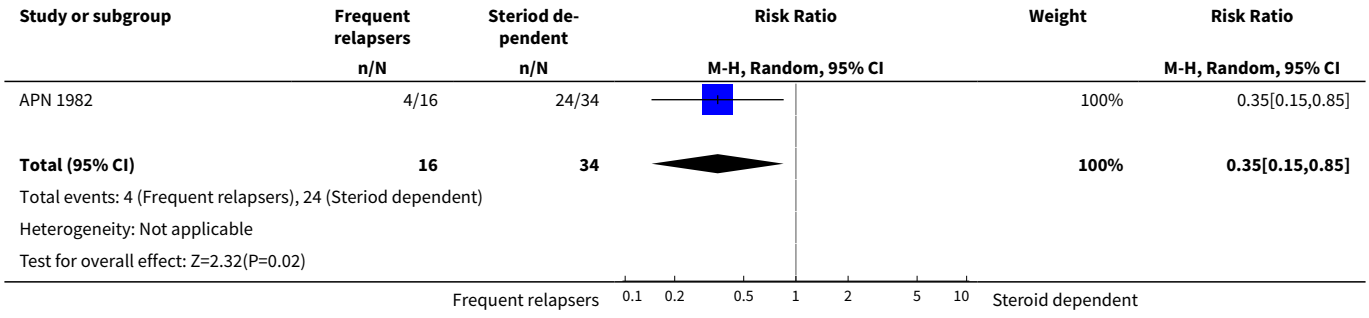
Analysis 6.2. Comparison 6 Cyclophosphamide versus chlorambucil, Outcome 2 Number with relapse at 24 months.



Comparison 7. Cyclophosphamide & chlorambucil in frequently relapsing & steroid dependent patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 24 months	1	50	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.85]

Analysis 7.1. Comparison 7 Cyclophosphamide & chlorambucil in frequently relapsing & steroid dependent patients, Outcome 1 Number with relapse at 24 months.

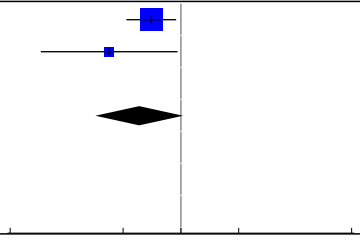


Comparison 8. Chlorambucil versus prednisone/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6 months	2	41	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.09]
2 Number with relapse at 12 months	2	32	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 0.95]

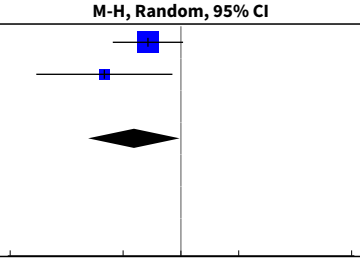
Analysis 8.1. Comparison 8 Chlorambucil versus prednisone/placebo, Outcome 1 Number with relapse at 6 months.

Study or subgroup	Chlorambucil n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alatas 1978	3/11	8/9		71.46%	0.31[0.11,0.83]
Grupe 1976	0/10	9/11		28.54%	0.06[0,0.87]
Total (95% CI)	**21**	**20**		**100%**	**0.19[0.03,1.09]**
Total events: 3 (Chlorambucil), 17 (Prednisone/placebo)					
Heterogeneity: Tau^2=0.86; Chi^2=1.78, df=1(P=0.18); I^2=43.94%					
Test for overall effect: Z=1.86(P=0.06)					



Analysis 8.2. Comparison 8 Chlorambucil versus prednisone/placebo, Outcome 2 Number with relapse at 12 months.

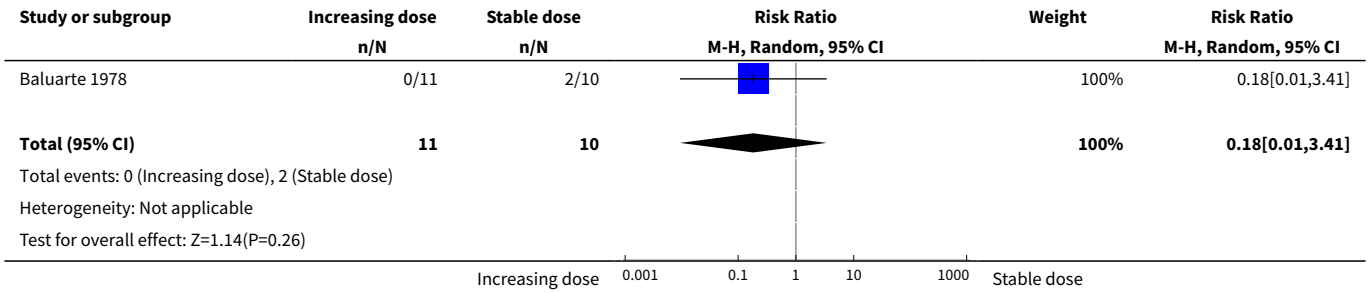
Study or subgroup	Chlorambucil n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alatas 1978	1/5	6/6		67.72%	0.27[0.07,1.09]
Grupe 1976	0/10	11/11		32.28%	0.05[0,0.71]
Total (95% CI)	**15**	**17**		**100%**	**0.15[0.02,0.95]**
Total events: 1 (Chlorambucil), 17 (Prednisone/placebo)					
Heterogeneity: Tau^2=0.77; Chi^2=1.63, df=1(P=0.2); I^2=38.72%					
Test for overall effect: Z=2.01(P=0.04)					



Comparison 9. Chlorambucil: stable dose versus increasing dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 12 months	1	21	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.41]

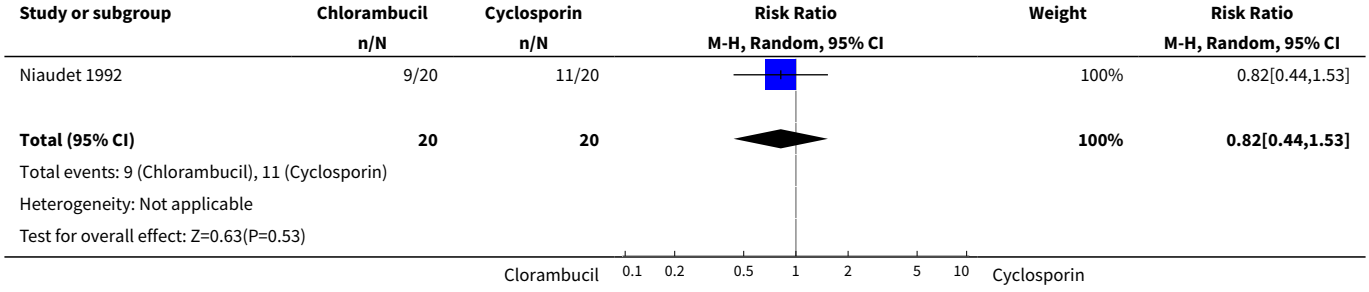
Analysis 9.1. Comparison 9 Chlorambucil: stable dose versus increasing dose, Outcome 1 Number with relapse at 12 months.



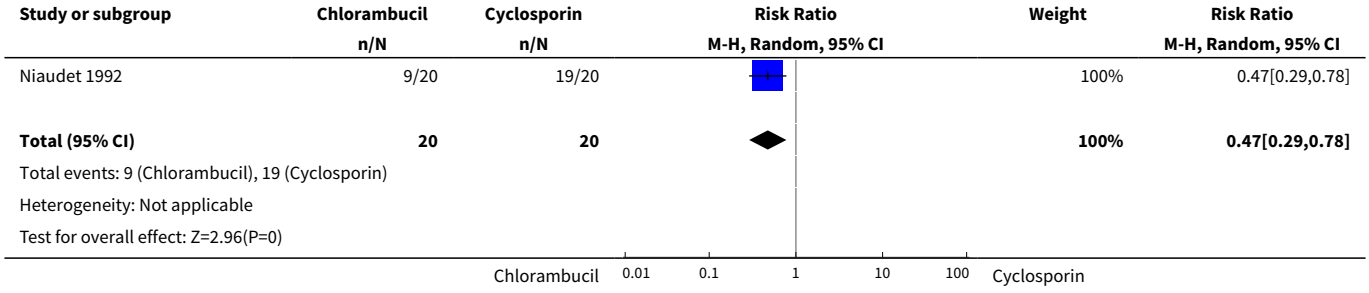
Comparison 10. Chlorambucil versus cyclosporin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Number with relapse at 6 months	1	40	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.44, 1.53]
2 Number with relapse at 12 months	1	40	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.78]
3 Number with relapse at 24 months	1	40	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.54, 1.00]

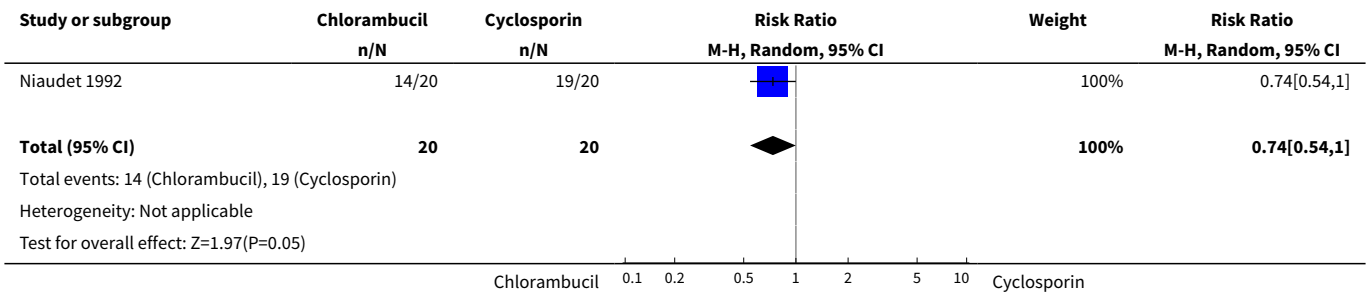
Analysis 10.1. Comparison 10 Chlorambucil versus cyclosporin, Outcome 1 Number with relapse at 6 months.



Analysis 10.2. Comparison 10 Chlorambucil versus cyclosporin, Outcome 2 Number with relapse at 12 months.



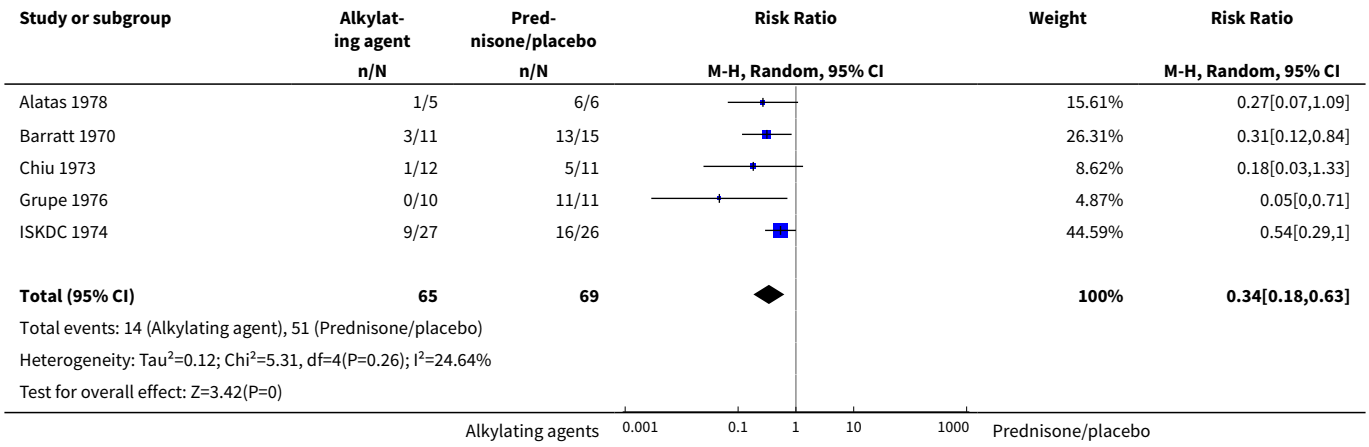
Analysis 10.3. Comparison 10 Chlorambucil versus cyclosporin, Outcome 3 Number with relapse at 24 months.



Comparison 11. Alkylating agents versus prednisone/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6-12 months	5	134	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.18, 0.63]

Analysis 11.1. Comparison 11 Alkylating agents versus prednisone/placebo, Outcome 1 Number with relapse at 6-12 months.



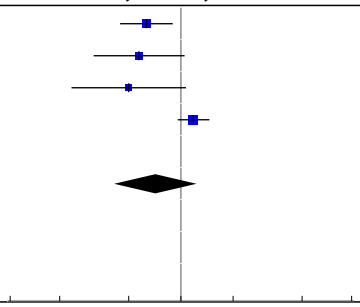
Comparison 12. Levamisole versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse during treatment (4-12 months)	4	185	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.41, 1.23]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Number with relapse during treatment (4-12 months) excluding Weiss 1993	3	137	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.45, 0.79]
3 Number with relapse at 6-12 months	4	171	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.63, 1.10]
4 Mean relapse rate/patient/month	1	34	Mean Difference (IV, Random, 95% CI)	0.10 [-0.08, 0.28]

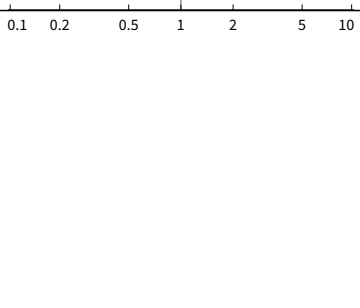
Analysis 12.1. Comparison 12 Levamisole versus placebo/no treatment, Outcome 1 Number with relapse during treatment (4-12 months).

Study or subgroup	Levamisole n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
BAPN 1991	17/31	26/30		27.77%	0.63[0.45,0.9]
Dayal 1994	9/22	10/14		22.73%	0.57[0.31,1.05]
Rashid 1996	6/20	12/20		19.56%	0.5[0.23,1.07]
Weiss 1993	21/22	21/26		29.93%	1.18[0.96,1.46]
Total (95% CI)	**95**	**90**		**100%**	**0.71[0.41,1.23]**
Total events: 53 (Levamisole), 69 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.25; Chi^2=20.99, df=3(P=0); I^2=85.71%					
Test for overall effect: Z=1.21(P=0.23)					

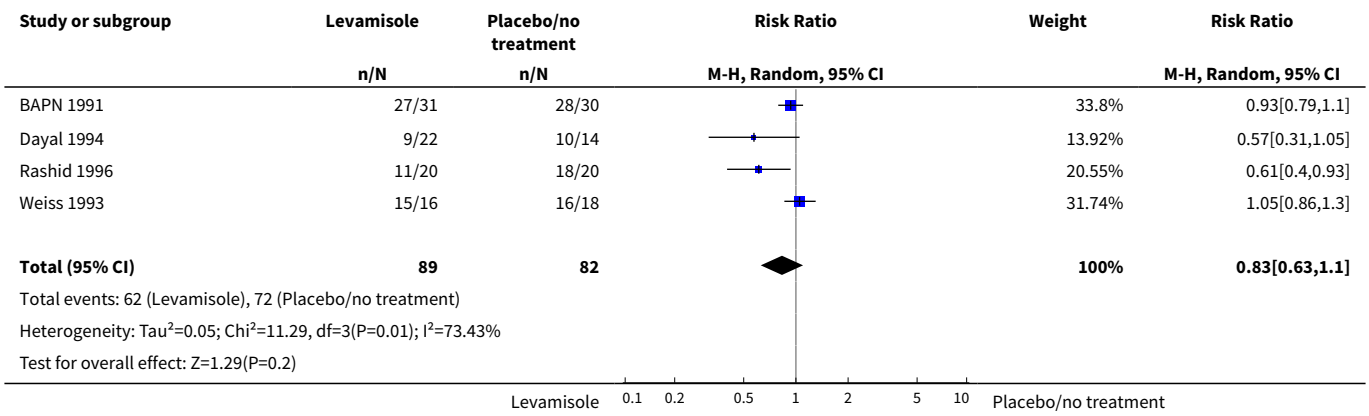


Analysis 12.2. Comparison 12 Levamisole versus placebo/no treatment, Outcome 2 Number with relapse during treatment (4-12 months) excluding Weiss 1993.

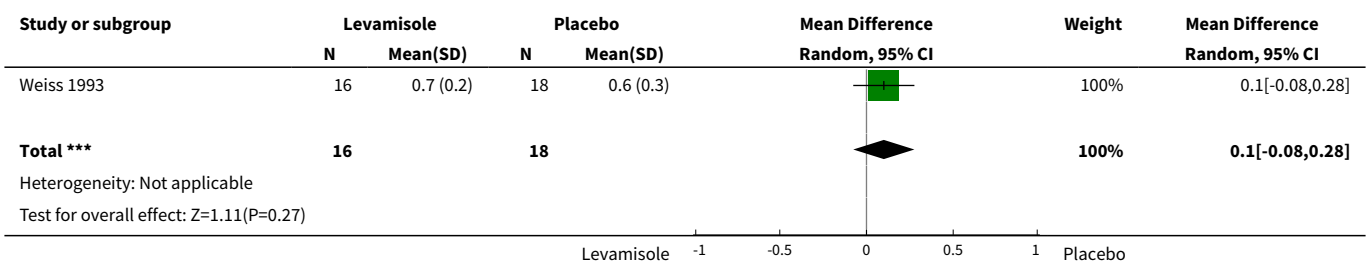
Study or subgroup	Levamisole n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
BAPN 1991	17/31	26/30		64.61%	0.63[0.45,0.9]
Dayal 1994	9/22	10/14		21.73%	0.57[0.31,1.05]
Rashid 1996	6/20	12/20		13.65%	0.5[0.23,1.07]
Total (95% CI)	**73**	**64**		**100%**	**0.6[0.45,0.79]**
Total events: 32 (Levamisole), 48 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=3.57(P=0)					



Analysis 12.3. Comparison 12 Levamisole versus placebo/ no treatment, Outcome 3 Number with relapse at 6-12 months.



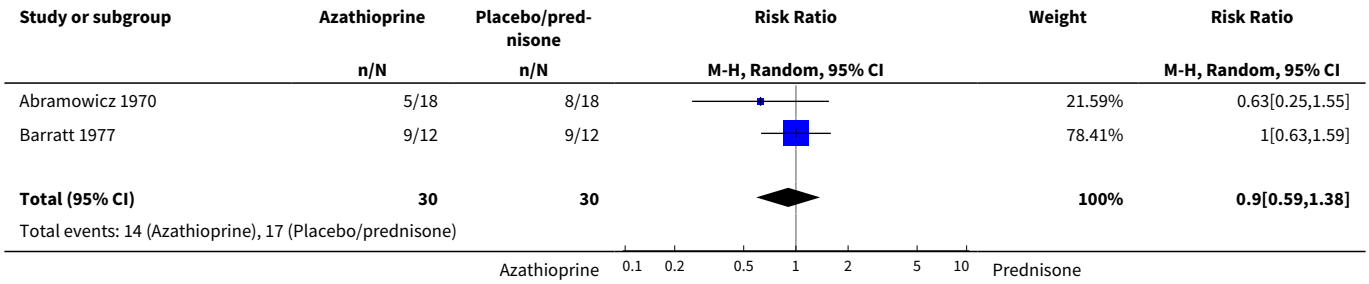
Analysis 12.4. Comparison 12 Levamisole versus placebo/ no treatment, Outcome 4 Mean relapse rate/patient/month.

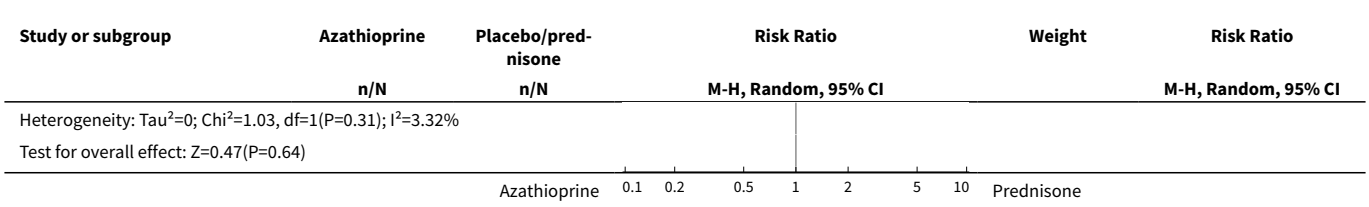


Comparison 13. Azathioprine versus placebo/prednisone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6 months	2	60	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.38]

Analysis 13.1. Comparison 13 Azathioprine versus placebo/ prednisone, Outcome 1 Number with relapse at 6 months.

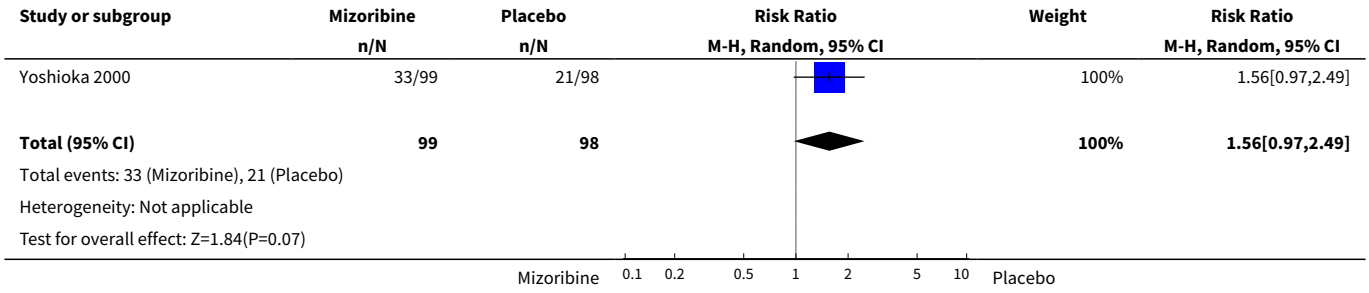




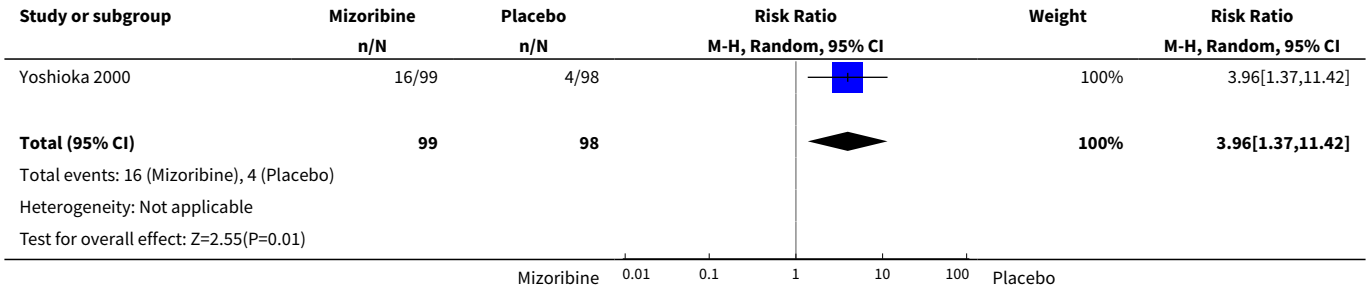
Comparison 14. Mizoribine versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Adverse effects during treatment	1	197	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.97, 2.49]
2 Adverse effect: Hyperuricaemia	1	197	Risk Ratio (M-H, Random, 95% CI)	3.96 [1.37, 11.42]

Analysis 14.1. Comparison 14 Mizoribine versus placebo, Outcome 1 Adverse effects during treatment.



Analysis 14.2. Comparison 14 Mizoribine versus placebo, Outcome 2 Adverse effect: Hyperuricaemia.



Comparison 15. Intravenous versus oral cyclophosphamide

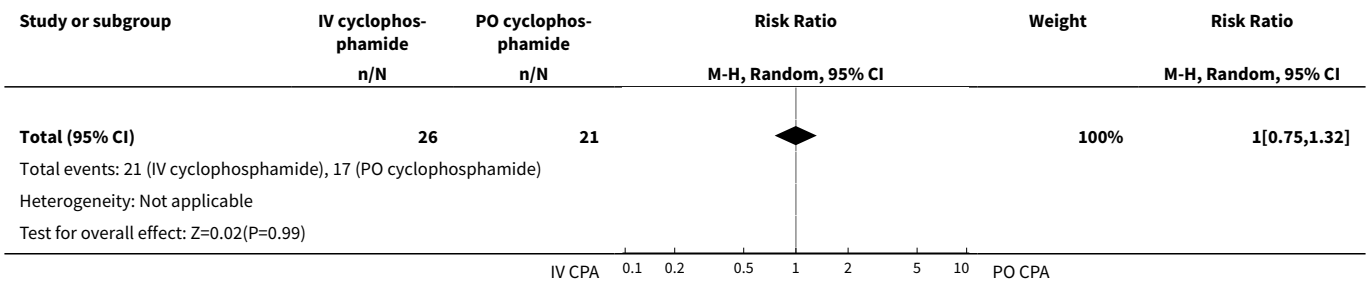
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with relapse at 6 months	1	47	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.33, 0.92]
2 Number with relapse at end of study	1	47	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.32]
3 Number with continuing frequently relapsing or steroid dependent SSNS at 6 months	1	47	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.89]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Leucopenia	1	47	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.99]
4.2 Hair loss	1	47	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.07, 1.50]
4.3 All infections	1	47	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.87]
4.4 Nausea and vomiting	1	47	Risk Ratio (M-H, Random, 95% CI)	4.07 [0.21, 80.51]

Analysis 15.1. Comparison 15 Intravenous versus oral cyclophosphamide, Outcome 1 Number with relapse at 6 months.

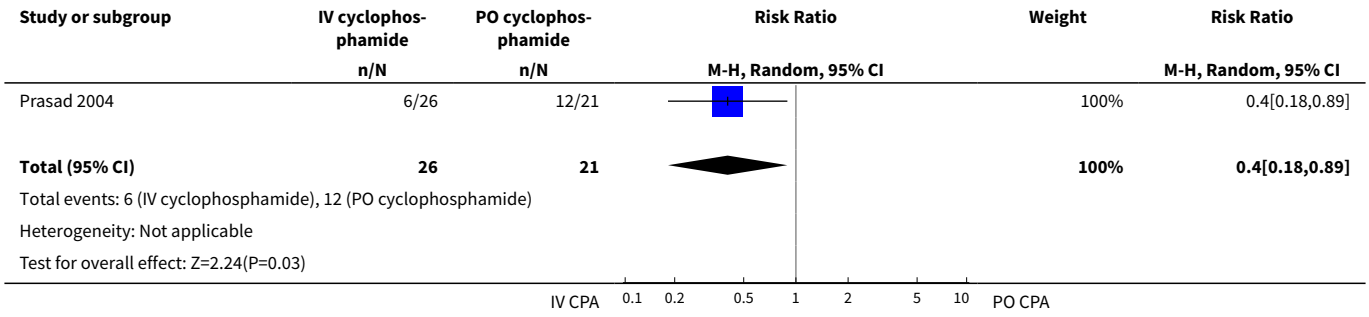
Study or subgroup	IV cyclophosphamide n/N	PO cyclophosphamide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Prasad 2004	11/26	16/21		100%	0.56[0.33,0.92]
Total (95% CI)	**26**	**21**		**100%**	**0.56[0.33,0.92]**
Total events: 11 (IV cyclophosphamide), 16 (PO cyclophosphamide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.27(P=0.02)					

Analysis 15.2. Comparison 15 Intravenous versus oral cyclophosphamide, Outcome 2 Number with relapse at end of study.

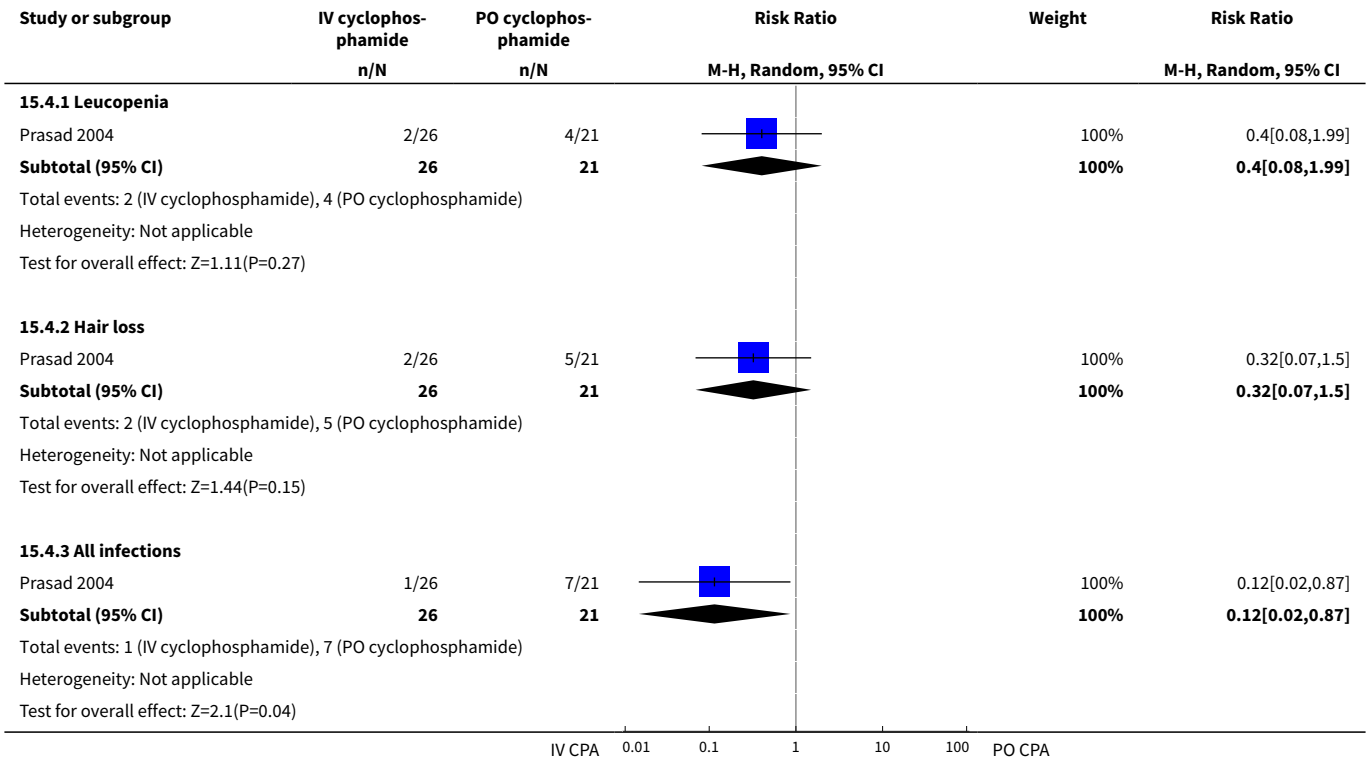
Study or subgroup	IV cyclophosphamide n/N	PO cyclophosphamide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Prasad 2004	21/26	17/21		100%	1[0.75,1.32]

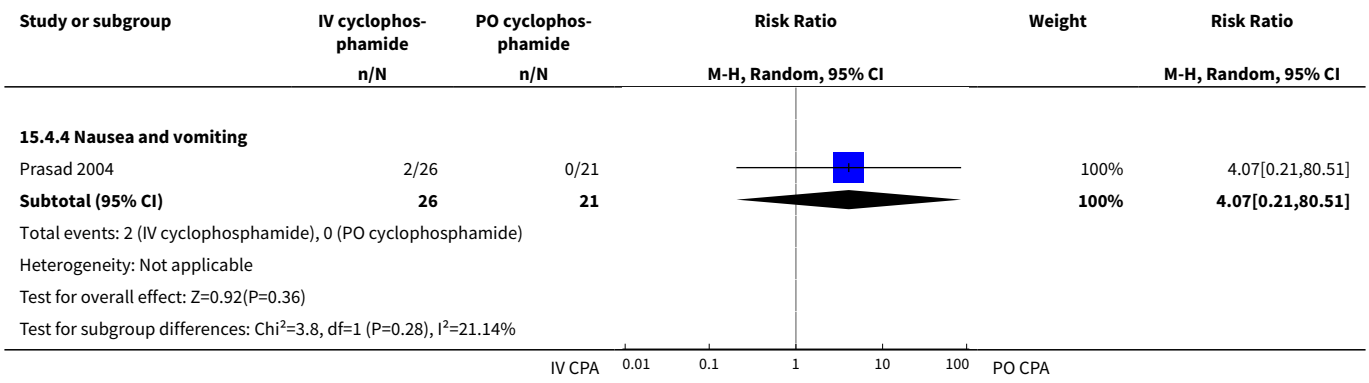


Analysis 15.3. Comparison 15 Intravenous versus oral cyclophosphamide, Outcome 3 Number with continuing frequently relapsing or steroid dependent SSNS at 6 months.



Analysis 15.4. Comparison 15 Intravenous versus oral cyclophosphamide, Outcome 4 Adverse events.





ADDITIONAL TABLES

Table 1. Electonic search strategies

Database & date/s	Search terms
CENTRAL Date last search: issue 1, 2005	#1 (Nephrotic and syndrome) #2 Child #3 Nephrosis*.ME #4 Nephrosis-Lipoid*.ME #5 Nephrotic - Syndrome*.ME #6 #1 or #3 or #4 or #5 #7 #2 and #6
MEDLINE initial (1966-March 2001) Update 1 (2001 - August 2003) Update 2 (November 2004)	1 RANDOMIZED CONTROLLED TRIAL.pt. 2 CONTROLLED CLINICAL TRIAL.pt. 3 RANDOMIZED CONTROLLED TRIALS.sh. 4 RANDOM ALLOCATION.sh. 5 DOUBLE BLIND METHOD.sh. 6 SINGLE BLIND METHOD.sh. 7 1 or 2 or 3 or 4 or 5 or 6 8 (ANIMAL not HUMAN).sh. 9 7 not 8 10 CLINICAL TRIAL.pt. 11 exp CLINICAL TRIALS/ 12 (clin$ adj25 trial$).ti,ab. 13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 14 PLACEBOS.sh. 15 placebo$.ti,ab. 16 random$.ti,ab. 17 RESEARCH DESIGN.sh. 18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 19 18 not 8 20 19 not 9 21 9 or 20 22 exp nephrotic syndrome/ or nephrotic syndrome.ti,ab,sh. 23 exp nephrosis, lipoid/ or lipoid nephrosis.ti,ab,sh. 24 22 or 23 25 exp child/ or child$.ti,ab,sh. 26 21 and 24 and 25 27 21 and 24
EMBASE (1988 - January 2001)	1 exp controlled study/ or controlled study.ti,ab,hw,tn,mf.

Table 1. Electonic search strategies *(Continued)*

2 exp statistical analysis/ or clinical study.ti,ab,hw,tn,mf.
3 exp major clinical study/ or major clinical study.ti,ab,hw,tn,mf.
4 exp randomized controlled trial/ or randomised controlled study.ti,ab,hw,tn,mf.
5 random$.ti,ab,hw,tn,mf.
6 exp double blind procedure/ or double blind procedure.ti,ab,hw,tn,mf.
7 exp single blind procedure/ or single blind procedure.ti,ab,hw,tn,mf.
8 exp multicenter study/ or multicenter study.ti,ab,hw,tn,mf.
9 exp placebo/ or placebo.ti,ab,hw,tn,mf.
10 or/1-9
11 (human not animal).sh,de,hw.
12 10 and 11
13 exp nephrotic syndrome/ or nephrotic syndrome.ti,ab,hw,tn,mf.
14 12 and 13

Table 2. Methodological quality assessment

Study ID	Allocation concealed	Blind:participants	Blind:investigators	Blind:assessors	Intent to treat	loss to follow up
Abramowicz 1970	Adequate	Yes	Yes	NS	No	0%
Alatas 1978	Unclear	Yes	Yes	NS	Unclear	0%
APN 1982	Adequate	No	No	NS	Unclear	0%
Baluarte 1978	Unclear	No	No	NS	Unclear	0%
BAPN 1991	Adequate	Yes	Yes	Yes	No	0%
Barratt 1970	Unclear	No	No	NS	Unclear	0%
Barratt 1973	Unclear	No	No	NS	No	0%
Barratt 1977	Unclear	No	No	NS	Unclear	0%
Chiu 1973	Adequate	No	No	NS	Unclear	0%
Dayal 1994	Unclear	No	No	NS	Yes	3%
Grupe 1976	Unclear	No	No	NS	Unclear	0%
ISKDC 1974	Adequate	No	No	NS	Unclear	0%
McCrory 1973	Inadequate	No	No	NS	Unclear	0%
Niaudet 1992	Unclear	No	No	NS	Unclear	0%
Ponticelli 1993	Adequate	No	No	NS	No	0%
Prasad 2004	Unclear	No	No	NS	Yes	0%
Rashid 1996	Unclear	No	No	NS	Unclear	0%
Ueda 1990	Unclear	No	No	NS	Unclear	0%

Table 2. Methodological quality assessment *(Continued)*

Weiss 1993	Adequate	Yes	Yes	NS	No	2%
Yoshioda 2000	Adequate	Yes	Yes	NS	No	Unclear

Table 3. Adverse effects during treatment of steroid sensitive nephrotic syndrome

Adverse event	CPA trials	CPA events/ patients	CPA (95% CI)	CHL trials	CHL events/ patients	CHL (95% CI)	CSA trials	CSA events/ patients	CSA (95% CI)
Infections	7	2/203	1% (0.1-3.5%)	5	3/97	3% (0.6-8.8%)			
Leucopenia < 5000 mm3	6	57/176	32% (26-39%)	4	14/76	18% (10-29%)			
Medication ceased due to leucopenia	6	17/132	9% (6-15%)	3	3/52	6% (1.2-15%)			
Thrombocytopenia	4	3/143	2% (0.4-5.7%)	4	8/86	9% (4.1-18%)			
Hair loss	4	26/188	14% (9-19%)	4	3/86	3% (0.7-10%)			
Cystitis	4	7/188	4% (1.5-7.5%)	4	0/86	0% (0-4.2%)			
Gum hypertrophy							2	13/56	28% (33-60%)
Hirsutism							2	19/56	34% (22-48%)
Hypertension							2	2/56	4% (0.4-12%)
Elevated creatinine level							2	5/56	9% (3-20%)

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 4, 2001

Date	Event	Description
10 January 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AM Durkan: Wrote the protocol, literature searching, assessment for eligibility and quality, data extraction, data synthesis, wrote the review
EM Hodson: Wrote the protocol, assessment of eligibility and quality, data extraction, data synthesis, wrote the review
NS Willis: Literature searching, data synthesis
JC Craig: wrote the review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Kidney Foundation, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Azathioprine [therapeutic use]; Chlorambucil [therapeutic use]; Cyclophosphamide [therapeutic use]; Cyclosporine [therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Levamisole [therapeutic use]; Nephrotic Syndrome [*drug therapy] [prevention & control]; Randomized Controlled Trials as Topic; Ribonucleosides [therapeutic use]; Secondary Prevention

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant