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Non-corticosteroid treatment for nephrotic syndrome in children (Review)

Hodson EM, Willis NS, Craig JC

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[Intervention Review]

Non-corticosteroid treatment for nephrotic syndrome in children

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ABSTRACT

Background

Eighty to 90% 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 these children, however these agents 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, conference abstracts and contact with known investigators.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs were included 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.

Data collection and analysis

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

Main results

We identified 26 studies (1173 children). Cyclophosphamide (RR 0.44, 95% CI 0.26 to 0.73) and chlorambucil (RR 0.15, 95% CI 0.02 to 0.95) significantly reduced the relapse risk at six to twelve months compared with prednisone alone. There was no difference in relapse risk at two years between chlorambucil and cyclophosphamide (RR 1.31, 95% CI 0.80 to 2.13). There was no difference at one year between intravenous and oral cyclophosphamide (RR 0.99, 95% CI 0.76 to 1.29). Cyclosporin was as effective as cyclophosphamide (RR 1.07, 95% CI 0.48 to 2.35) and chlorambucil (RR 0.82, 95% CI 0.44 to 1.53) and levamisole (RR 0.43, 95% CI 0.27 to 0.68) was more effective than steroids alone but the effects were not sustained once treatment was stopped. There was no difference in the risk for relapse between mycophenolate mofetil and cyclosporin (RR 5.00, 95% CI 0.68 to 36.66) but CI were large. Mizoribine and azathioprine 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 are possible and further comparative studies are still needed.

PLAIN LANGUAGE SUMMARY

Non-corticosteroid treatment for nephrotic syndrome in children

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 (relapse) and further corticosteroids can have adverse effects of poor growth, cataracts, osteoporosis and high blood pressure. This review identified 26 studies (1173 children). These studies compared several drugs and found cyclophosphamide, chlorambucil, cyclosporin and levamisole are more effective than prednisone alone in reducing the risk of relapse.

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, North America and New Zealand is 2/100,000 children (Arneil 1961; McKinney 2001; Schlesinger 1968; Wong 2007). 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 studies 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 study.

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

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

Types of outcome measures

Primary outcomes

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

Secondary outcomes

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

Search methods for identification of studies

Initial search

The following electronic biomedical databases were searched (Table 1 - *Electronic search strategies*)

- Cochrane Renal Group's specialised register.
- Cochrane Central Register of Controlled Trials (CENTRAL) (in *The Cochrane Library*).
- MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy for NS in children.
- EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification

of RCTs (Lefebvre 1996) together with a specific search strategy for NS in children.

- To reduce publication bias, searches were made of reference lists of nephrology textbooks, review articles and relevant studies and of nephrology scientific meetings. In addition letters seeking information about unpublished or incomplete studies were sent to investigators known to be involved in previous studies. 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.
- The authors contacted authors of recent review articles and RCTs for information about any possible unpublished data. No additional studies were identified in this manner.

Review update

The Cochrane Renal Group's specialised register and CENTRAL was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2007). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched.

Data collection and analysis

Included and excluded studies

The review was initially undertaken by four authors (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, EH or NW, 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 studies were retained initially. Authors 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 authors 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. If necessary, disagreements could be 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.

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): 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

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.

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.

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 risk ratio (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 mean difference (MD) 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

In the initial search, 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. One study evaluating Chinese herbs was excluded because both adults and children were included and the paediatric data could not be separated (Jin 1994) and Kirubakaran 1984 (assessing levamisole), was excluded because the primary outcome could not be determined. A third study in Japanese has not been translated for assessment (Tohjoh 1994). Therefore seventeen studies were included in the initial review (Durkan 2001a). An additional search of databases in August 2003 found no new studies. In 2004 seven RCTs involving children with relapsing SSNS treated with non-corticosteroid agents were identified; five were identified from handsearching of conference proceedings and were in abstract form only. Four studies were excluded; two assessing Chinese herbs (Gong 1997; 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. Therefore 20 studies were included in the 2004 updated review. The three newly included studies were Prasad 2004, Weiss 1993 and Yoshioka 2000. A further search in January 2007 identified 17 studies; of these five studies were RCTs not previously included, one study was an abstract of a previously included study (Abramowicz 1970), and 11 were excluded (not randomised 8; reviews 2; mixed population of primary and secondary nephrotic syndrome 1). In September 2007 an additional study was identified in abstract form. The 2007 update of this review therefore contains 26 RCTs, including six new studies (Abeyagunawardena 2006a; Abeyagunawardena 2006b; Al-Saran 2006; Cerkauskiene 2005; Donia 2005; Dorresteijn 2007).There was no disagreement between the two authors regarding the inclusion of studies.

The characteristics of the 26 studies are shown in the table *Characteristics of included studies*. A total of 1173 children were assessed and the highest number of studies available for any one comparison was six; levamisole compared with placebo, steroid alone or no treatment (n = 319 children) (Abeyagunawardena 2006a; Al-Saran 2006; BAPN 1991; Dayal 1994; Rashid 1996; Weiss 1993). Cyclophosphamide was compared with steroid alone in three studies (n = 106 children) (Barratt 1970; Chiu 1973; ISKDC 1974). Two studies compared azathioprine (n = 60) (Abramowicz 1970; Barratt 1977) and two studies compared chlorambucil with placebo or steroid alone (n = 41) (Grupe 1976; Alatas 1978). Five studies compared different cyclophosphamide regimens (n = 202) (Abeyagunawardena 2006b; Barratt 1973; McCrory 1973; Prasad 2004; Ueda 1990) and a further study compared different chlorambucil regimes (n = 21) (Baluarte 1978). There were single studies comparing cyclosporin with cyclophosphamide (n = 55) (Ponticelli 1993), cyclosporin with chlorambucil (n = 40) (Niaudet 1992), cyclosporin with mycophenolate mofetil (Dorresteijn 2007), cyclophosphamide with chlorambucil (n = 50) (APN 1982), mizoribine with placebo (n = 197) (Yoshioka 2000) and levamisole with intravenous cyclophosphamide (n=40) (Donia 2005). One study compared fusidic acid (which is reported to have immunosuppressive properties similar to cyclosporin) and prednisone with prednisone alone in a crossover study (n=18) (Cerkauskiene 2005). Prednisolone was used in all the studies either in combination with the study agent or to treat relapses. No eligible RCTs comparing mizoribine or azathioprine with other non-corticosteroid agents or comparing Chinese medicines, IgG immunoglobulin, disodium cromoglycate or mycophenolate mofetil with corticosteroids or placebo were found.

Risk of bias in included studies

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

Allocation concealment

Twelve studies had adequate allocation concealment (Abeyagunawardena 2006a; Abeyagunawardena 2006b;Abramowicz 1970; APN 1982; BAPN 1991; Chiu 1973; Donia 2005; Dorresteijn 2007; ISKDC 1974; Ponticelli 1993; Weiss 1993; Yoshioka 2000). In one study allocation concealment was inadequate (McCrory 1973) and in the remaining studies it was unclear whether allocation was concealment.

Blinding

In five studies 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 study (BAPN 1991) and not blinded in one study (Prasad 2004). In the remaining studies it was not stated whether the outcome assessors were blinded.

Intention-to-treat analysis

Intention-to-treat analysis was carried out in six studies (Abeyagunawardena 2006a; Abeyagunawardena 2006b; Dayal 1994; Dorresteijn 2007; Prasad 2004) and was not carried out in eight studies (Al-Saran 2006;Abramowicz 1970; BAPN 1991; Barratt 1973;Donia 2005 ;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

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

Nine studies did not define relapse (Abeyagunawardena 2006a; Abeyagunawardena 2006b; Alatas 1978; Al-Saran 2006; Baluarte 1978; Cerkauskiene 2005; Dorresteijn 2007; Niaudet 1992; Rashid 1996) and the remaining studies used a variety of definitions.

Effects of interventions

Cyclophosphamide

Cyclophosphamide resulted in a decreased incidence of relapse at six to 12 months compared with prednisolone alone (Analysis 1.1 (102 children): RR 0.44, 95% CI 0.26 to 0.73, I^2 = 0%) (Barratt 1970; Chiu 1973; ISKDC 1974). In 27 children followed beyond 12 months the RR for relapse at 13-24 months was 0.21 (Analysis 1.2: 95% CI 0.07 to 0.65, I^2 = 0%).

Cyclophosphamide given for eight weeks resulted in fewer children relapsing within 12 months than a two-week course (Analysis 2.2: 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 (Analysis 3.1 (12 months): RR 1.04, 95% CI 0.75 to 1.44; Analysis 3.2 (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 (Analysis 4.1: RR 2.33, 95% CI 0.11 to 48.99) but did increase the numbers experiencing side effects (Analysis *04.02*) (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 (Analysis 12.1 (83 children): RR 0.54, 95% CI 0.34 to 0.88; Analysis 12.3 (47 children): RR 0.40, 95% CI 0.18 to 0.89) (Abeyagunawardena 2006b; Prasad 2004). However there was no difference between therapies at the end of the study (21-24 months) (Analysis 12.2 (83 children): RR 0.99, 95% CI 0.76 to 1.29). The cumulative dose of cyclophosphamide was lower with intravenous cyclophosphamide (100 mg/kg - Prasad 2004; 132 mg/kg - Abeyagunawardena 2006b) compared with oral cyclophosphamide (180 mg/kg - Prasad 2004); 168 mg/kg - Abeyagunawardena 2006b).

Chlorambucil

Chlorambucil reduced the risk for relapse at six and 12 months (Analysis 8.1 (6 months, 41 children): RR 0.19, 95% CI 0.03 to 1.09; I^2 = 43.9%) (Analysis 8.2 (12 months, 32 children): RR 0.15, 95% CI 0.02 to 0.95; I^2 = 38.7%) 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 (Analysis 9.1 (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

On direct comparison there was no significant difference between chlorambucil and cyclophosphamide treatment in the risk of relapse at 12 and 24 months (Analysis 6.1 (12 months, 50 children): RR 1.15, 95% CI 0.69 to 1.94) (Analysis 6.2 (24 months, 50 children): RR 1.31, 95% CI 0.80 to 2.13) (APN 1982).

On post hoc analysis, chlorambucil and cyclophosphamide were more effective in preventing relapse in children with frequently relapsing SSNS (Analysis 7.1 (24 months, 50 children): RR 0.35, 95% CI 0.15 to 0.85) compared with children with steroid dependent SSNS (APN 1982).

Alkylating agents compared with placebo/prednisone/no treatment

Because cyclophosphamide and chlorambucil 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 studies of alkylating agents versus prednisone alone were combined (Analysis 11.1 (134 children): RR 0.34, 95% CI 0.18 to 0.63) (Alatas 1978; Barratt 1970; Chiu 1973; Grupe 1976; ISKDC 1974).

Cyclosporin

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 (Analysis 10.1 (40 children): RR 0.82, 95% CI 0.44 to 1.53) (Niaudet 1992).

Cyclosporin was significantly less effective in maintaining remission than chlorambucil by 12 and 24 months after the start of therapy (Analysis 10.2 (12 months, 40 children): RR 0.47, 95% CI 0.29 to 0.78) (Analysis 10.3 (24 months, 40 children): RR 0.74, 95% CI 0.54 to 1.00) (Niaudet 1992).

Cyclosporin, given for 12 months, was as effective as cyclophosphamide given for eight weeks during cyclosporin therapy (Analysis 5.1 (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 (Analysis 5.2 (55 children): RR 0.40, 95% CI 0.22 to 0.73) (Ponticelli 1993).

There was no significant difference in the risk of relapse between cyclosporin and mycophenolate mofetil at 12 months (Analysis 17.1 (24 children): RR 5.00, 95% CI 0.68 to 36.66) (Dorresteijn 2007). Relapse rates were 0.75/year in the mycophenolate mofetil group compared with 0.08/year in the cyclosporin group.

Levamisole

Levamisole was administered for four months (BAPN 1991), six months (Rashid 1996; Weiss 1993) or 12 months (Abeyagunawardena 2006a; Al-Saran 2006; Dayal 1994).

Significantly fewer children relapsed during levamisole treatment compared to placebo, prednisone or no treatment (Analysis 13.1.1 (317 children): RR 0.50, 95% CI 0.25 to 0.99) but there was significant heterogeneity (I^2 = 91.8%). When the study (Weiss 1993) showing no effect was excluded, levamisole was significantly more effective than prednisone alone (Analysis 13.1.2 (269 children): RR 0.43, 95% CI 0.27 to 0.68); some heterogeneity persisted (I^2 = 62.7%) but all summary estimate in all five studies favoured levamisole.

There remained a statistically significant benefit of levamisole (Analysis 13.2 (305 children): RR 0.60, 95% CI 0.38 to 0.96) over steroid alone at six to 12 months when levamisole treatment had been ceased for three to six months in three studies (BAPN 1991; Rashid 1996; Weiss 1993). However there was significant heterogeneity (I^2 = 92.2%) 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.

There was no statistical difference between levamisole treatment compared to placebo, prednisone or no treatment for mean relapse rate/patient/month (Analysis 13.3: MD -0.03, 95% CI -0.27 to 0.20). Again there was significant heterogeneity between the two studies (I^2 = 83.1%). However there was significant heterogeneity between the two studies (I^2 = 83.1%) with one study (Weiss 1993) showing no

benefit and the other (Al-Saran 2006) showing significant benefit of levamisole compared with prednisone.

Levamisole compared with intravenous cyclophosphamide

There was no significant difference in the risk of relapse at the end of therapy (Analysis 14.1.1 (40 children): RR 0.91, 95% CI 0.50 to 1.64) and at six months (Analysis 14.1.2 (40 children): RR 1.00, 95% CI 0.70 to 1.43), 12 months (Analysis 14.1.3 (40 children): RR 0.89, 95% CI 0.68 to 1.16) and 24 months (Analysis 14.1.4 (40 children): RR 0.89, 95% CI 0.73 to 1.10) after the end of therapy (Donia 2005).

Azathioprine

Azathioprine did not cause a statistically significant reduction in the number of children who relapsed at six months compared with placebo or steroid alone (Analysis 15.1 (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.

Fusidic acid

Fusidic acid and prednisone was compared with prednisone alone in a crossover study involving 18 children (Cerkauskiene 2005). The results for all courses of fusidic acid and prednisone (14 courses) and prednisone alone (17 courses) were combined. There was no significant difference in the mean time to remission (12.6 ± 6.6 days for fusidic acid/prednisone versus 13.9 ± 7.4 days for prednisone alone) or in time to relapse (18.3 ± 23.9 weeks versus 17.8 ± 20.4 weeks). One child developed an allergic rash with fusidic acid.

Side effects of therapy

Side effects were reported in 22 studies; in three studies 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 Weiss 1993.

Alkylating agents

The number of studies 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 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).

In two studies (Abeyagunawardena 2006b; Prasad 2004) infections were significantly more common in children treated with oral cyclophosphamide compared with intravenous medication (Analysis 12.4.3 (83 children): RR 0.14, 95% CI 0.03 to 0.72). Hair loss was slightly but not significantly more common with oral cyclophosphamide (Analysis 12.4.2 (83 children): RR 0.19, 95% CI 0.04 to 1.03). There were no significant differences in the likelihood of nausea and vomiting (Analysis 12.4.4 (47 children): RR 4.07, 95% CI 0.21 to 80.51) and bone marrow suppression (Analysis 12.4.1 (83 children): RR 0.37, 95% CI 0.09 to 1.51) though small numbers resulted in imprecision of results. Nausea and vomiting was only reported with intravenous cyclophosphamide.

Cyclosporin

Side effects of cyclosporin (CSA) are shown in 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.

Cyclosporin compared with mycophenolate mofetil

There was no significant difference in the risk of hypertension with mycophenolate mofetil compared with cyclosporin (Analysis 17.2 (24 children); RR 0.25, 95% CI 0.03 to 1.92). Compared with baseline, glomerular filtration rate (GFR) was significantly lower at three months, six months and 1 year in the cyclosporin treated group but there was no change in GFR in the mycophenolate mofetil treated group.

Levamisole

With levamisole single cases of gastrointestinal upset were reported in two studies (Al-Saran 2006; BAPN 1991), one study reported no children with leucopenia (Al-Saran 2006) and three studies reported that no side effects occurred (Abeyagunawardena 2006b; Dayal 1994; Rashid 1996).

Levamisole compared with cyclophosphamide

Single patients developed leucopenia and abnormal liver function tests while on intravenous cyclophosphamide. No patient developed haemorrhagic cystitis. No patient developed leucopenia on levamisole. Infections were equally common on both treatments (Analysis 14.2.1 (40 children): RR 1.08, 95% CI 0.67 to 1.75) (Donia 2005).

Azathioprine

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 (Analysis 16.1 (197 children): RR 1.56, 95% CI 0.97 to 2.49) but hyperuricaemia was significantly more common with mizoribine (Analysis *16.2* (197 children): 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 studies 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), chlorambucil (0.2 mg/kg/d for eight weeks) and levamisole (2.5 mg/kg on

alternate days) substantially reduce the risk of relapse compared with prednisone 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. In comparative studies the efficacy of intravenous cyclophosphamide (500 mg/m^2/mo for six months) did not differ significantly from that of oral cyclophosphamide or levamisole and the efficacy of cyclosporin (6 mg/kg/d) did not differ significantly from that of alkylating agents or mycophenolate mofetil (1,200 mg/m^2/d). The benefit of non-corticosteroid agents is sustained beyond the on-treatment period for the alkylating agents but rarely with cyclosporin and levamisole. Treatment with azathioprine or mizoribine was ineffective. Since corticosteroids were used in combination with the study 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 reduced the risk for relapse compared with placebo or no treatment in a meta-analysis of five studies (Abeyagunawardena 2006a; Al-Saran 2006; BAPN 1991; Dayal 1994; Rashid 1996). However a sixth study (Weiss 1993) showed no benefit. Five studies limited enrolment to children with frequently relapsing (Rashid 1996; Weiss 1993) and steroid dependent SSNS (Abeyagunawardena 2006a; Al-Saran 2006; BAPN 1991; Rashid 1996; Weiss 1993) while the sixth study (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 studies related to different patient populations. Levamisole was administered twice weekly but on consecutive days in the Weiss 1993 study to provide a monthly dose of 20 mg/kg. It was administered on alternate days in the Abeyagunawardena 2006a, Al-Saran 2006, BAPN 1991 and Rashid 1996 studies to provide a monthly dose of 35 mg/kg. Thus the interval between doses was shorter and the total dose higher in the five studies 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. A multicentre double blind, placebo-controlled RCT of levamisole is commencing in Europe with the principal investigators based in The Netherlands (Gruppen 2006).

Although these study data show that non-corticosteroid agents are more effective than corticosteroids alone, between-agent studies have not demonstrated a clear benefit of one over any other in preventing relapse of NS. Comparative studies of cyclophosphamide, chlorambucil, cyclosporin, levamisole and mycophenolate mofetil have been done but, because of insufficient power, clinically important differences in treatment effects have not been completely excluded. For example, using the upper and lower bounds of the 95% CI of the RR estimate obtained from the single comparative study 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 five agents is most effective. While cyclosporin and cyclophosphamide are the two interventions most widely used in many countries, additional comparative studies of these agents with each other or with levamisole or mycophenolate mofetil and new studies comparing these agents with tacrolimus are required. 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 cyclophosphamide and cyclosporin. Until such studies are available, the 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, studies 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 studies of alkylating agents (APN 1982) and from uncontrolled studies of cyclosporin (Hulton 1994; Niaudet 1987). A recent review of 26 studies (controlled studies 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 published guidelines (Bagga 2001; Bargman 1999), which recommend 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 RR 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 (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 12/26 studies demonstrating adequate allocation concealment. Studies with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30% to 40% (Schulz 1995) and meta-analyses of low quality studies may overestimate the benefit of therapy (Moher 1998). This observation makes the need for adequately powered, well designed and reported studies even more necessary. Because studies 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, monthly intravenous cyclophosphamide given for 6 months and prolonged courses of cyclosporin or levamisole substantially reduce the incidence of relapse in children with SSNS. Published recommendations (Bagga 2001; 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 studies. 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.

Though mycophenolate mofetil is now widely used in children with relapsing SSNS, only one small study comparing this agent with cyclosporin has been identified (Dorresteijn 2007). This study only recruited 24 children so that no significant difference in the risk of relapse was detected although there was a tendency for more children treated with mycophenolate mofetil to relapse. Another study (Hoyer 2006 - a crossover study) comparing cyclosporin and mycophenolate is in progress. In case series of children with frequently relapsing or steroid dependent SSNS, mycophenolate mofetil has been demonstrated to reduce the risk for relapse during therapy (Bagga 2003; Fujinaga 2007; Hogg 2003; Hogg 2004; Mendizabal 2004; Novak 2005). Tacrolimus is also widely used in North America in preference to cyclosporin because of the side effect profile. Two small case series have reported that tacrolimus is probably as effective as cyclosporin (Dotsch 2006; Sinha 2006). Recently case reports have been published on the successful use of the anti-CD 20 monoclonal antibody, rituximab, in children with steroid dependent SSNS (Kemper 2007). These data indicate that mycophenolate mofetil, tacrolimus and possibly rituximab should be subjected to RCTs in comparison with other non-corticosteroid agents.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of RCTs shows that oral or intravenous cyclophosphamide, oral chlorambucil, cyclosporin and levamisole substantially reduce the incidence of relapse in children with relapsing SSNS. However there are inadequate data available to determine which agent should be preferred initially. 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 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. Suggested RCTs include:

- RCT comparing mycophenolate mofetil with cyclosporin or cyclophosphamide.
- RCT comparing mycophenolate mofetil with prednisone.
- RCT comparing levamisole with prednisone.
- RCT comparing levamisole with cyclophosphamide.
- RCT comparing tacrolimus with cyclosporin particularly in terms of adverse effects.

In these studies 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]*

Abeyagunawardena 2006a

Methods	Country: Sri Lanka Setting/Design: Tertiary centre, parallel groups Time frame: 2002-2005 Randomisation method: Sealed envelopes Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS previously in stable remission on levamisole and alternate day prednisone for 2 years. TREATMENT GROUP Number: 42 Age: Median 9.2 years (range 2.1-13.4) Sex (M/F): 25/17 CONTROL GROUP Number: 34 Age: Median 8.3 years (range 1.7-12.6) Sex (M/F): 20/14 EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral levamisole 2.5 mg/kg/dose on alternate days for 1 year. CONTROL GROUP No treatment. CO-INTERVENTIONS None reported. Prednisone for relapses.

Abeyagunawardena 2006a *(Continued)*

Outcomes	STUDY OUTCOMES 1. Number in relapse at completion of 12 months of therapy/no treatment (relapse: 3+ proteinuria on 3 consecutive days). 2. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on allocation concealment, ages, sex. obtained from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Abeyagunawardena 2006b

Methods	Country: Sri Lanka Setting/Design: Tertiary centre, parallel groups Time frame: 2002-2005 Randomisation method: Sealed envelopes Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS TREATMENT GROUP Number: 15 Age: Median 6.6 years (range 1.8 - 13.1) Sex (M/F): 11/4 CONTROL GROUP Number: 21 Age: Median 5.8 years (range 1.4-12.5) Sex (M/F): 15/6 EXCLUSIONS: NS
Interventions	TREATMENT GROUP IV cyclophosphamide 500 mg/m^2/dose 4 wkly x 6 months (total dose 132 mg/kg). CONTROL GROUP Oral cyclophosphamide 3 mg/kg/d x 8 weeks (total dose 187 mg/kg). CO-INTERVENTIONS None reported. Prednisone for relapses.
Outcomes	STUDY OUTCOMES 1. Mean relapse rate at 6 months and 1 year follow up from beginning of treatment.

Abeyagunawardena 2006b *(Continued)*

	2. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on allocation concealment, ages and sexes of participants and on results obtained from author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2 relapses in any 6 months); age 12 weeks - 15.9 years. TREATMENT GROUP Number: 18 Age: NS Sex (M/F): NS CONTROL GROUP Number: 18 Age: NS Sex (M/F): NS EXCLUSIONS Previous treatment with prednisone, immunosuppressive or cytotoxic drugs.
Interventions	TREATMENT GROUP Oral azathioprine 60 mg/m^2/d for 26 weeks with "maintenance'" prednisone. CONTROL GROUP Placebo for 26 weeks with "maintenance" prednisone. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (defined as proteinuria > 4 mg/m^2/d 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.

Abramowicz 1970 *(Continued)*

STOP OR END POINT/S: NS
ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Al-Saran 2006

Methods	Country: Saudi Arabia Setting/Design: Single tertiary centre, parallel groups Time frame: January 1, 2001 to December 31, 2003 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD or FR SSNS (ISKDC definitions); age < 14 years TREATMENT GROUP Number: 32 Age: Mean about 6.5 years Sex (M/F): 20/12 CONTROL GROUP Number: 24 Age: Mean about 7.1 years Sex (M/F): 15/9 EXCLUSIONS Previous treatment with immunosuppressive or cytotoxic drugs; patients on levamisole < 3 months; steroid resistant patients; secondary nephrotic syndrome.
Interventions	TREATMENT GROUP Levamisole 2.5 mg/kg on alternate days for 1 year started when child in remission. CONTROL GROUP Low dose (<0.5 mg/kg/d) prednisone on alternate days after achieving remission. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 12 months (not defined). 2. Mean relapse/pt/mo over 12 months. 3. Need for another second line medication for nephrotic syndrome. 4. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: Unclear how many excluded from analysis because levamisole given for less than 3 months. STOP OR END POINT/S: NS

Al-Saran 2006 *(Continued)*

	ADDITIONAL DATA REQUESTED FROM AUTHORS: Data on quality items and clarification of treatment regimens sought but no response obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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 months & 11 to 1 year. Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2 relapses in 6 months or 4 relapses in 1 year) Age: 12 weeks - 15.9 years TREATMENT GROUP Number: 11 Age: 6.95 ± 2.82 years Sex (M/F): 8/3 CONTROL GROUP Number: 9 Age: 8.56 ± 2.17 years Sex (M/F): 7/2 EXCLUSIONS Secondary nephrotic syndrome.
Interventions	TREATMENT GROUP Oral chlorambucil 0.3 mg/kg/d and prednisone 40 mg/m^2/d for 8 weeks. CONTROL GROUP Placebo and prednisone 40 mg/m^2/d for 8 weeks. CO-INTERVENTIONS All treated with prednisone 60 mg/m^2/d till remission and then randomised.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (definition NS.) 2. Number in relapse at 12 months. 3. Mean relapse rate/patient.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Alatas 1978 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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 years Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2+ relapses in 6 months or 4+ in 1 year). SD SSNS (relapsed on alternate day prednisone or within 14 days of ceasing). CYCLOPHOSPHAMIDE GROUP Number: 26 Age: 2-16 years Sex (M/F): 14/12 CHLORAMBUCIL GROUP Number: 24 Age: 2-16 years Sex (M/F): 17/7 EXCLUSIONS Previous treatment with cytotoxic agents.
Interventions	CYCLOPHOSPHAMIDE GROUP Oral CPA 2 mg/kg/d for 8 weeks and prednisone for 4 weeks. CHLORAMBUCIL GROUP Oral chlorambucil 0.15 mg/kg/d for 8 weeks and prednisone for 4 weeks. CO-INTERVENTIONS All treated with prednisone 60 mg/m^2/d till remission and then randomised.
Outcomes	STUDY OUTCOMES 1. Number with relapse at 12 months (ISKDC definition). 2. Number with relapse at 24 months. 3. Number with relapse in FR compared with SD patients regardless of treatment (Post hoc analysis).
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on relapse rates in groups according to medication given and for adverse effects requested and provided.

APN 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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 months (stable dose) 1); 27.2 months (increasing dose). Loss to follow-up: 0% at 1 year.
Participants	INCLUSION CRITERIA FR SSNS (ISKDC criteria). CHLORAMBUCIL STABLE DOSE GROUP Number: 10 Age: Average 7 years 8 months (3.5-14 years) Sex (M/F): NS CHLORAMBUCIL INCREASING DOSE GROUP Number: 11 Age: Average 8 years 9 months (5-15 years) Sex (M/F): NS EXCLUSIONS: NS
Interventions	CHLORAMBUCIL STABLE DOSE GROUP Oral chlorambucil 0.2 mg/kg/d for 8 weeks. CHLORAMBUCIL INCREASING DOSE GROUP Oral chlorambucil 0.2 mg/kg/d increasing by about 0.1 mg/kg every 2 weeks for 6-11 weeks till leucopenia. CO-INTERVENTIONS Prednisone 60 mg/m^2/d till urine protein-free for 5-7 days. Prednisone 60 mg/m^2 on alternate days until WCC > 4000 in both groups.
Outcomes	STUDY OUTCOMES 1. Number with relapse at 6 months (no definition provided). 2. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Baluarte 1978 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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 - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 28 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (relapse on prednisolone > 0.5 mg/kg on alternate days). TREATMENT GROUP Number: 31 Age: 8.3 ± 3.6 years Sex (M/F): 21/10 CONTROL GROUP Number: 30 Age: 8.8 ± 3.7 years Sex (M/F): 20/10 EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral levamisole 2.5 mg/kg on alternate days for 16 weeks. CONTROL GROUP Placebo on alternate days for 16 weeks. CO-INTERVENTIONS Prednisone 2 mg/kg/d till remission; prednisone 1 mg/kg on alternate days for 28 days, reduced by 0.25 mg/kg every 14 days & ceased at 8 weeks.
Outcomes	STUDY OUTCOMES 1. Relapse at end of treatment (defined as 3+ proteinuria for 3 consecutive days, confirmed on albumin/creatinine ratio > 2 mg/mg or protein/creatinine ratio > 200 mg/mmol). 2. Relapse at 6 months. 3. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on allocation concealment requested and obtained.
Risk of bias	

BAPN 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses in at least 6 months). Age: < 14 years. TREATMENT GROUP Number: 15 Age: 3.7-12.5 years Sex (M/F): NS CONTROL GROUP Number: 15 Age: 2.9-12.9 years Sex (M/F): NS EXCLUSIONS Children unable to tolerate 8 weeks prednisone.
Interventions	TREATMENT GROUP Oral CPA 3 mg/kg/d for 8 weeks. Prednisone for 8 weeks and reduced over 8 weeks. CONTROL GROUP Reducing dose of prednisone for 8 weeks. CO-INTERVENTIONS Penicillin 125 mg twice day to week 16.
Outcomes	STUDY OUTCOMES 1. Relapse at 6 months (defined as oedema & albumin/creatinine ratio >1.0 or Albustix 3+ or 4+ on 2 days). 2. Relapse at 12 months. 3. Relapse at 2 years.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None
Risk of bias	

Barratt 1970 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Barratt 1973

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: No Follow-up period: 20-104 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses in at least 6 months). Age: < 14 years SHORT CPA GROUP Number: 16 Age: 3.7-13.8 years Sex (M/F): NS STANDARD CPA GROUP Number: 16 Age: 4.1-12.9 years Sex (M/F): NS EXCLUSIONS Children unable to tolerate 8 weeks prednisone.
Interventions	SHORT CPA GROUP Oral CPA 3 mg/kg/d for 2 weeks. STANDARD CPA GROUP Oral CPA 3 mg/kg/d for 8 weeks. CO-INTERVENTIONS Maintenance prednisone for 8 weeks; taper for 8 weeks after CPA completed.
Outcomes	STUDY OUTCOMES 1. Relapse at 6 months (defined as albumin/creatinine ratio > 1.0). 2. Relapse at 12 months. 3. Need to cease CPA because of leucopenia.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 3 excluded from Short CPA group STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement

Barratt 1973 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Barratt 1977

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: 32 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (previous relapse on at least 0.2 mg/kg of prednisone on alternate days). Age: < 14 years. TREATMENT GROUP Number: 12 Age: < 14 years Sex (M/F): NS CONTROL GROUP Number: 12 Age: < 14 years Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral azathioprine 2 mg/kg/d for 8 weeks. Prednisone for 8 weeks, tapered over next 8 weeks (total 16 weeks). CONTROL GROUP Prednisone for 8 weeks, tapered over next 8 weeks (total 16 weeks). CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 32 weeks (defined as urine albumin/creatinine > 1.0 in 2 specimens).
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS 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?	Unclear risk	B - Unclear

Cerkauskiene 2005

Methods	Country: Lithuania Setting/Design: Tertiary centre, crossover study Time frame: May 1992 to March 1994 Randomisation method: Envelopes Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: Unclear Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS in relapse (oedema, proteinuria > 50 mg/kg/d, total protein < 50 g/L, ESR> 20, high lipids). Age: 1-15 years TOTAL GROUP Number: 18 Age: 1.3-13.2 years Sex (M/F): 12/6 Results from 14 courses of fusidic acid/prednisone compared with 17 courses of prednisone alone. EXCLUSIONS Age < 1 or > 15 years, hypertension, abnormal renal function, secondary NS, steroid sparing agents at entry, contraindication to study drugs.
Interventions	FUSIDIC ACID/PREDNISONE GROUP Fusidic acid 0.5-1.5 g/d according to age orally in 3-4 divided doses for 2 months. Prednisone 1.5-2 mg/kg/d till remission (negative urine on 3 consecutive days), alternate day dose tapered over next 6 weeks. PREDNISONE ALONE GROUP Prednisone 1.5-2 mg/kg/d till remission (negative urine on 3 consecutive days), alternate day dose tapered over next 6 weeks. CO-INTERVENTIONS Diuretics, vitamins, antimicrobial agents as required.
Outcomes	STUDY OUTCOMES 1. Mean time to remission. 2. Mean time to relapse. 3. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chiu 1973

Methods	Country: Canada Setting/Design: Multicentre tertiary institutions, parallel groups Time frame: September 1967 to 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) months in control group. 25.7 (14-39) months in treatment group 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 (2 years 11 months - 15 years 10 months). Sex (M/F): 4/8 CONTROL GROUP Number: 11 Age: 9 years 7 months (6 years 2 months - 9 years 11 months). Sex (M/F): 7/4 EXCLUSIONS Absence of definite history of varicella regarded as relative contraindication.
Interventions	TREATMENT GROUP Oral CPA 75 mg/m^2/d for 16 weeks. Prednisone 60 mg/m^2/d till urine protein free for 2 weeks, then same dose on alternate days, total 16 weeks. CONTROL GROUP Prednisone 60 mg/m^2/d till urine protein free for 2 weeks, then same dose on alternate days, total 16 weeks. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 10 months (proteinuria > 2 g/m^2/d). 2. Number in relapse at 20 months.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dayal 1994

Methods	Country: India

Dayal 1994 *(Continued)*

	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 months in treatment group, 10.5 months 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). Age: 65.5 ± 30.9 months Sex (M/F): 19/4 CONTROL GROUP (Relapsing SSNS only) Number: 14 Age: 60.1± 37.2 months Sex (M/F): 10/4 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 weeks. CONTROL GROUP No treatment for 52 weeks. CO-INTERVENTIONS Prednisolone 60 mg/m^2/d for 4 weeks, prednisolone 40 mg/m^2 on alternate days for weeks to achieve initial remission and for relapse.
Outcomes	STUDY OUTCOMES 1. Number in relapse at end of treatment (12 months) (defined as oedema, urine protein >1 g/m^2/d and serum albumin < 2.5 g/100 mL). 2. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported. Consecutive enrolment of children. STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Donia 2005

Methods	Country: Egypt Setting/Design: Single tertiary centre, parallel groups Time frame: NS Randomisation method: Table of random numbers. Patients withdrawn before treatment were replaced in that group by next enrolled patient. Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 2 years Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA 40 consecutive patients with SD SSNS recruited in relapse, allocated after remission. All had MCD on biopsy. LEVAMISOLE GROUP Number: 20 Age: 7.4 (2.89 SD) years Sex (M/F): 16/4 CYCLOPHOSPHAMIDE GROUP Number: 20 Age: 7.38 (2.44 SD) years Sex (M/F): 15/5 EXCLUSIONS: NS
Interventions	LEVAMISOLE GROUP Oral levamisole 2.5 mg/kg on alternate days for 6 months. Prednisone 1 mg/kg on alternate days x 14 days, reduce by 0.25 mg/kg every 14 days. Total 2 months. CYCLOPHOSPHAMIDE GROUP IV cyclophosphamide 500 mg/m^2/dose monthly for 6 months Prednisone 1 mg/kg on alternate days x 14 days, reduce by 0.25 mg/kg every 14 days. Total 2 months. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at end of treatment (6 months), 6 months, 12 months, 24 months after the end of therapy (relapse: 3+ proteinuria for 3 consecutive days/protein excretion > 50 mg/kg/d). 2. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 2 children from levamisole group and one from IV cyclophosphamide group excluded before intervention and replaced by next enrolled patient STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on patient numbers, randomisation, allocation concealment and loss to follow-up obtained from the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dorresteijn 2007

Methods	Country: Netherlands enrolled 1/2003 to 6/2005 Setting/Design: Multicentre tertiary institutions, parallel groups Time frame: One year Randomisation method: Sealed envelopes Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR or SD SSNS (definition not provided) in remission. Age <18 years. Biopsy proven MCD. TREATMENT GROUP Number: 12 Age: NS Sex (M/F): NS CONTROL GROUP Number: 12 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral mycophenolate mofetil 1200 mg/m^2 /d in 2 divided doses for 1 year. CONTROL GROUP Cyclosporin 4-5 mg/kg/d in 2 divided doses for 1 year. CO-INTERVENTIONS Prednisolone for relapses.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 12 months. 2. Relapse rate/year. 3. Calculated GFR at 3, 6, 12 months. 4. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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) months in treatment group; 20.0 (12-33) months in control group. Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses/year). SD SSNS (Prednisone required for 6 months + to maintain remission). TREATMENT GROUP Number: 10 Age: 11.0 (3-15.5) years Sex (M/F): 6/4 CONTROL GROUP Number: 11 Age: 7.0 (3.3-12) years Sex (M/F): 7/4 EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral chlorambucil started at 0.1-0.2 mg/kg/d and increased every 2 weeks (average maximum dose 0.33 mg/kg/d, range 0.26-0.41) until WCC fell (average 9.7 weeks, range 6-12 weeks). Total average dose 16.9 mg/kg (range 9.5-23.7 mg/kg). Prednisone 80-120 mg on alternate days for 2 months, taper over 4-6 weeks. Prednisone given till WCC > 5000. CONTROL GROUP Prednisone 80-120 mg on alternate days for 2 months, taper over 4-6 weeks. CO-INTERVENTIONS To induce remission, both groups given prednisone 40-60 mg/d till urine protein free for 2 weeks.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (defined as urine protein 100 mg/24 h for > 10 days). 2. Number in relapse at 12 months. 3. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ISKDC 1974

Methods	Country: International Setting/Design: Multicentre tertiary institutions, parallel groups Time frame: April 1970 - June 1972 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 1.8 years in treatment group, 1.7 years in control group. Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2 relapses within 6 months of initial response, 4 relapses in any 1 year). TREATMENT GROUP Number: 27 Age: NS Sex (M/F): NS CONTROL GROUP Number: 26 Age: NS Sex (M/F): NS EXCLUSIONS: NS
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 weeks. Prednisone 10 mg/m^2/d for 10 days. CONTROL GROUP Prednisone 40 mg/m^2 on 3 out of 7 days for 26 weeks. CO-INTERVENTIONS None
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (defined as urine protein > 4 mg/m^2/h on 3 out of 7 days). 2. Mean relapse rate/patient. 3. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 10 patients excluded STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McCrory 1973

Methods	Country: USA Setting/Design: Single tertiary centre, parallel groups

McCrory 1973 *(Continued)*

	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 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2+ relapses in 6 months). HIGH DOSE CPA GROUP Number: 6 Age: 41 months - 14 years Sex (M/F): NS LOW DOSE CPA GROUP Number: 8 Age: 41 months - 14 years Sex (M/F): NS EXCLUSIONS: NS
Interventions	HIGH DOSE CPA GROUP Oral CPA 5 mg/kg/d for 45 days. Prednisone 1.5 mg/kg on alternate days for 45 days. LOW DOSE CPA GROUP Oral CPA 2.5 mg/kg/d for 90 days. Prednisone 1.5 mg/kg on alternate days for 90 days. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6, 12 and 18 months (defined as urine protein > 4 mg/m^2/h on 3 out of 7 days). 2. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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

Niaudet 1992 *(Continued)*

	- Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 2-3 years 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 <50 mL/min/1.73 m^2, abnormal liver function tests, uncontrolled hypertension. Previous cytotoxic therapy.
Interventions	CYCLOSPORIN GROUP Oral CSA 6 mg/kg/d for 3 months and then tapered over 3 months. Dose adjusted to trough CSA level of 50-150 ng/mL. CHLORAMBUCIL GROUP Oral Chlorambucil 0.2 mg/kg/d for 40 days (cumulative dose 8 mg/kg). CO-INTERVENTIONS For relapse prednisone 30-60 mg/m^2 till remission, then same dose on alternate days and tapered over 3 months.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 6 months (Relapse criteria not defined). 2. Number in relapse at 12 months. 3. Number in relapse at 24 months.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ponticelli 1993

Methods	Country: Italy Setting/Design: Multicentre tertiary institutions, parallel groups Time frame: NS Randomisation method: NS Blinding

Ponticelli 1993 *(Continued)*

	- Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 3 months-2 years Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (2+ relapses in 6 months or 3+ in 1 year). SD SSNS (Relapse within 2 weeks of discontinuation or reduction in prednisone). Children 2-15 years. Adults > 16 years. CYCLOSPORIN GROUP Number: 30 children; 6 adults Age: Median 10.5 year Sex (M/F): 24/12 CYCLOPHOSPHAMIDE GROUP Number: 25 children. 5 adults Age: Median 10.0 years Sex (M/F): 24/6 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 months (dose adjusted for trough level 200-600 ng/mL), reducing over next 3 months (total duration 12 months). CYCLOPHOSPHAMIDE GROUP Oral CPA 2.5 mg/kg/d for 8 weeks. CO-INTERVENTIONS For relapse prednisone 60 mg/m^2/d till remission, prednisone 40 mg/m^2 on alternate days for 4 weeks.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 9 months (defined as urine protein > 4 mg/m^2/h for 2 weeks). 2. Number in relapse at 24 months. 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: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Detailed paediatric data requested but not obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Prasad 2004

Methods	Country: India Setting/Design: Single tertiary care centre, parallel groups Time frame: NS

Prasad 2004 *(Continued)*

	Randomisation method: Random numbers Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: NS Intention-to-treat: Yes Follow-up period: Median 24 months (treatment group); 21 months (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 months before study entry). Age: 1-16 years Steroid toxicity (2 + of severe cushingoid appearance, hypertension, growth suppression, cataract. diabetes mellitus, glaucoma, psychosis). IV CYCLOPHOSPHAMIDE GROUP Number: 26 Age: 4.7 ± 4.4 years Sex (M/F): 22/4 ORAL CYCLOPHOSPHAMIDE GROUP Number: 21 Age: 7.6 ± 5.3 years Sex (M/F): 18/3 EXCLUSIONS Previous use of cytotoxic therapy.
Interventions	IV CYCLOPHOSPHAMIDE GROUP IV CPA 500 mg/m^2 monthly for 6 doses (total dose 100 mg/kg) . ORAL CYCLOPHOSPHAMIDE GROUP Oral CPA 2 mg/kg/d for 12 weeks (total dose 180 mg/kg). CO-INTERVENTIONS Prednisone 60 mg/m^2 till remission for 3 days, 40 mg/m^2 on alternate days for 4 weeks, 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 months) or SD SSNS. 3. Median protein free days (± SE). 4. Adverse effects (leucopenia, cystitis, hair loss, all infections, nausea and vomiting).
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: Consecutive recruitment of patients reported and no exclusions post randomisation STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	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 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA FR SSNS (ISKDC definition) SD SSNS (ISKDC definition) TREATMENT GROUP Number: 20 Age: Average 8 years Sex (M/F): 13/7 CONTROL GROUP Number: 20 Age: Average 6 years Sex (M/F): 14/6 EXCLUSIONS: NS
Interventions	TREATMENT GROUP Oral levamisole 2.5 mg/kg on alternate days for 26 weeks. Prednisone 2 mg/kg/d for 2 weeks, 1 mg/kg/d for 4-6 weeks, tapering dose to 6 months (total duration 6 months). CONTROL GROUP Prednisone 2 mg/kg/d for 2 weeks, 1 mg/kg/d for 4-6 weeks, tapering dose to 6 months (total duration 6 months). 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 weeks).
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Ueda 1990

Methods	Country: Japan Setting/Design: Multicentre tertiary institutions, parallel groups

Ueda 1990 *(Continued)*

	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 weeks CPA group 66.2 (50.6) months; 12 weeks CPA group 63.1 (33.7) months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA SD SSNS (relapse during reducing prednisone dose or within 2 weeks 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) years Sex (M/F): 26/6 12 WEEK CYCLOPHOSPHAMIDE GROUP Number: 41 Age: 7.8 (3.7) years Sex (M/F): 28/13 EXCLUSIONS Patients in relapse.
Interventions	8 WEEK CYCLOPHOSPHAMIDE GROUP Oral CPA 2 mg/kg/d for 8 weeks (total dose 112 mg/kg). 12 WEEK CYCLOPHOSPHAMIDE GROUP CPA 2 mg/kg/d for 12 weeks (total dose 168 mg/kg). CO-INTERVENTIONS Relapses treated with prednisone 60 mg/m^2/d for 4 weeks, then taper by 5-10 mg/m^2 over 3-4 months.
Outcomes	STUDY OUTCOMES 1. Number in relapse at 12 months (defined as urine protein >40 mg/m^2/h for 3 consecutive days). 2. Number in relapse at 24 months. 3. Mean relapse rate/patient. 4. Adverse effects.
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Weiss 1993

Methods	Country: USA Setting/Design: Multicentre tertiary institutions, parallel groups

Weiss 1993 *(Continued)*

	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 months Loss to follow-up: 2%
Participants	INCLUSION CRITERIA: FR SSNS: 2+ relapses on alt day prednisone within 6 months of initial episode or 4+ relapses in an year. SD SSNS: 2 consecutive relapses on alt day prednisone of within 2 weeks of ceasing or 4 relapses in a year while on alt day prednisone or within 2 weeks of ceasing. TREATMENT GROUP Number: 23 Age: 7.3 ± 4.4 years Sex (M/F): 19/4 CONTROL GROUP Number: 26 Age: 7.5 ± 3.8 years Sex (M/F): 19/7 EXCLUSIONS Other immunosuppressive agents in previous 6 months, post menarchal girls, WCC < 4000, abnormal liver function tests, creatinine clearance < 90 mL/min/1.73 m^2, complement C3 < 50 mg/dL, co-existent medical condition likely to interfere with procedures or results.
Interventions	TREATMENT GROUP Levamisole oral suspension 2.5 mg/kg orally twice weekly (Saturday, Sunday) for 6 months. CONTROL GROUP Placebo oral suspension twice weekly (Saturday, Sunday) for 6 months. CO-INTERVENTIONS Relapses treated with prednisone 60 mg/m^2/d till remission and then 40 mg/m^2 on alternate days for 28 days (ISKDC protocol).
Outcomes	STUDY OUTCOMES 1. Mean relapse rate/patient by 6 months (defined as > 1+ proteinuria on 3 consecutive first morning urine). 2. Mean time to next relapse. 3. Mean number of days/month of prednisone treatment. 4. Number with relapse at end of treatment. 5. Number with relapse at 6 months 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: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Draft manuscript of trial obtained from author.

Risk of bias

Bias	Authors' judgement	Support for judgement

Weiss 1993 *(Continued)*

Allocation concealment?	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 months Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA FR SSNS (3+ relapses in 12 months or 2+ in 6 months). Age >2-17.9 years. TREATMENT GROUP Number: 99 Age: Age 2-17.9 years Sex (M/F): 72/27 CONTROL GROUP Number: 98 Age: 2-17.9 years Sex (M/F): 70/28 EXCLUSIONS Immunosuppressive treatment in previous 6 months, creatinine clearance < 50 ml/min/1.73 m^2, secondary nephrotic syndrome.
Interventions	TREATMENT GROUP Oral mizoribine 4 mg/kg/d for 48 weeks. Prednisone 1-2 mg/kg/d for 4 weeks, then reducing dose and ceased at 12 weeks. CONTROL GROUP Placebo for 48 weeks. Prednisone 1-2 mg/kg/d for 4 weeks, then reducing dose & ceased at 12 weeks. CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. No. of relapses/patient.month of study (defined as urinary protein >100 mg/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: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Information on numbers relapsing sought but not obtained.

Yoshioka 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

CPA = cyclophosphamide; CSA = cyclosporin; SSNS = steroid sensitive nephrotic syndrome; FR = frequent relapsing; SD = steroid dependent; MCD = Minimal change disease; NS = Not stated; WCC = white cell count

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

Study	Reason for exclusion
Anonymous 1968	Not RCT.
Beige 2003	Adult patients.
Bizo 2004	Not RCT.
Davin 2005	Not RCT.
El-Husseini 2004	Not RCT.
Fu 2004	Not RCT.
Gellermann 2004	Not RCT.
Gong 1997	Cannot separate children from adults and treatments not fully specified.
Goto 2006	Not RCT.
Hafeez 2006	Not RCT.
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.
Li 1994	Does not evaluated non-corticosteroid therapy.
Liu 1995	Not RCT.
Martinelli 2004	Not RCT.
Mendizabal 2004	Not RCT.
Moudgil 2005	Review article.
Naigui 1997	Data from children and adults could not be separated.
Pecoraro 2003	RCT of corticosteroids not non-corticosteroid therapy.
Raafat 2004	Not RCT.
Sancewicz-Pach 1995	Children with steroid resistant nephrotic syndrome.

Study	Reason for exclusion
	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.
Wang 2005	Includes children with nephrotic syndrome associated with nephritic features including hypocomplementaemia.
Wingen 1990	Not RCT.
Yamashita 1971	Does not evaluated non-corticosteroid therapy.
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.

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

Gruppen 2006

Trial name or title	Levamisole in steroid-sensitive nephrotic syndrome (SSNS): an international multicenter double-blind randomized trial
Methods	
Participants	100 children with SSNS
Interventions	Levamisole
Outcomes	1) Relapse 2) Long-term efficacy 3) Side effects
Starting date	October 2006
Contact information	Dr Gruppen (m.p.gruppne@amc.nl) Dr Davin (j.c.davin@amc.nl)
Notes	Funding: Dutch Kidney Foundation. The study will be performed in collaboration with ACE Pharmaceuticals

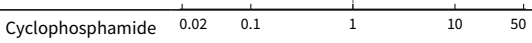
DATA AND ANALYSES

Comparison 1. Cyclophosphamide versus prednisone

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

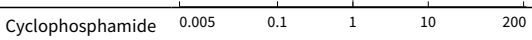
Analysis 1.1. Comparison 1 Cyclophosphamide versus prednisone, Outcome 1 Relapse at 6-12 months.

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 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)					

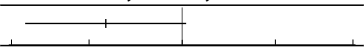


Comparison 2. Cyclophosphamide: 8 weeks versus 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

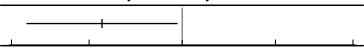
Analysis 2.1. Comparison 2 Cyclophosphamide: 8 weeks versus 2 weeks, Outcome 1 Relapse at 6 months.

Study or subgroup	8 weeks n/N	2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Barratt 1973	2/15	7/14		0.27[0.07,1.07]



Analysis 2.2. Comparison 2 Cyclophosphamide: 8 weeks versus 2 weeks, Outcome 2 Relapse at 12 months.

Study or subgroup	8 weeks n/N	2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Barratt 1973	2/11	8/11		0.25[0.07,0.92]

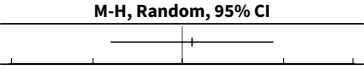


Comparison 3. Cyclophosphamide: 12 weeks versus 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

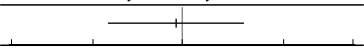
Analysis 3.1. Comparison 3 Cyclophosphamide: 12 weeks versus 8 weeks, Outcome 1 Relapse at 12 months.

Study or subgroup	12 weeks n/N	8 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ueda 1990	28/41	21/32		1.04[0.75,1.44]



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

Study or subgroup	12 weeks n/N	8 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ueda 1990	30/41	24/32		0.98[0.74,1.28]

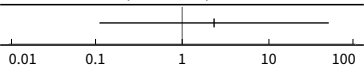


Comparison 4. Cyclophosphamide: different doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Leukopenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Lymphopenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Alopecia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Gastrointestinal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Genitourinary	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

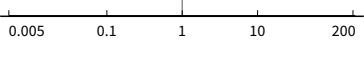
Analysis 4.1. Comparison 4 Cyclophosphamide: different doses, Outcome 1 Relapse at 12 months.

Study or subgroup	2.5 mg/kg/d n/N	5 mg/kg/d n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
McCrory 1973	1/8	0/6		2.33[0.11,48.99]



Analysis 4.2. Comparison 4 Cyclophosphamide: different doses, Outcome 2 Adverse effects.

Study or subgroup	2.5 mg/kg/d n/N	5 mg/kg/d n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 Leukopenia				
McCrory 1973	2/8	5/6		0.3[0.09,1.05]
4.2.2 Lymphopenia				
McCrory 1973	5/8	6/6		0.66[0.38,1.15]
4.2.3 Alopecia				
McCrory 1973	0/8	4/6		0.09[0.01,1.35]
4.2.4 Gastrointestinal				
McCrory 1973	1/8	3/6		0.25[0.03,1.85]
4.2.5 Genitourinary				
McCrory 1973	1/8	3/6		0.25[0.03,1.85]

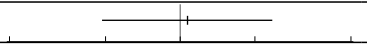


Comparison 5. Cyclophosphamide versus cyclosporin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 9 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Cyclophosphamide versus cyclosporin, Outcome 1 Relapse at 9 months.

Study or subgroup	Cyclophosphamide n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 1993	8/25	9/30		1.07[0.48,2.35]



Analysis 5.2. Comparison 5 Cyclophosphamide versus cyclosporin, Outcome 2 Relapse at 24 months.

Study or subgroup	Cyclophosphamide n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 1993	8/25	24/30		0.4[0.22,0.73]

Comparison 6. Cyclophosphamide versus chlorambucil

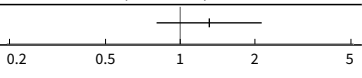
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Cyclophosphamide versus chlorambucil, Outcome 1 Relapse at 12 months.

Study or subgroup	Cyclophosphamide n/N	Chlorambucil n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1982	15/26	12/24		1.15[0.69,1.94]

Analysis 6.2. Comparison 6 Cyclophosphamide versus chlorambucil, Outcome 2 Relapse at 24 months.

Study or subgroup	Cyclophosphamide n/N	Chlorambucil n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1982	17/26	12/24		1.31[0.8,2.13]

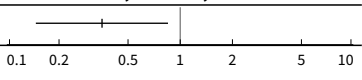


Comparison 7. Cyclophosphamide & chlorambucil in frequently relapsing & steroid dependent patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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

Study or subgroup	Frequent relapsers n/N	Steriod dependent n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 1982	4/16	24/34		0.35[0.15,0.85]

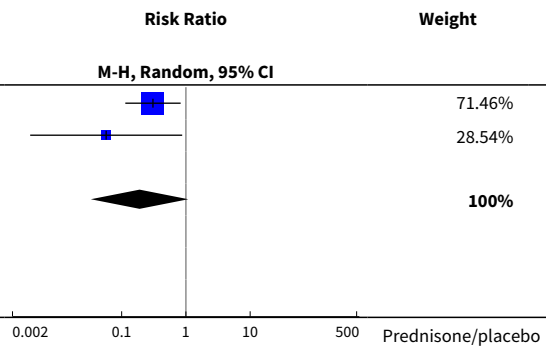


Comparison 8. Chlorambucil versus prednisone/placebo

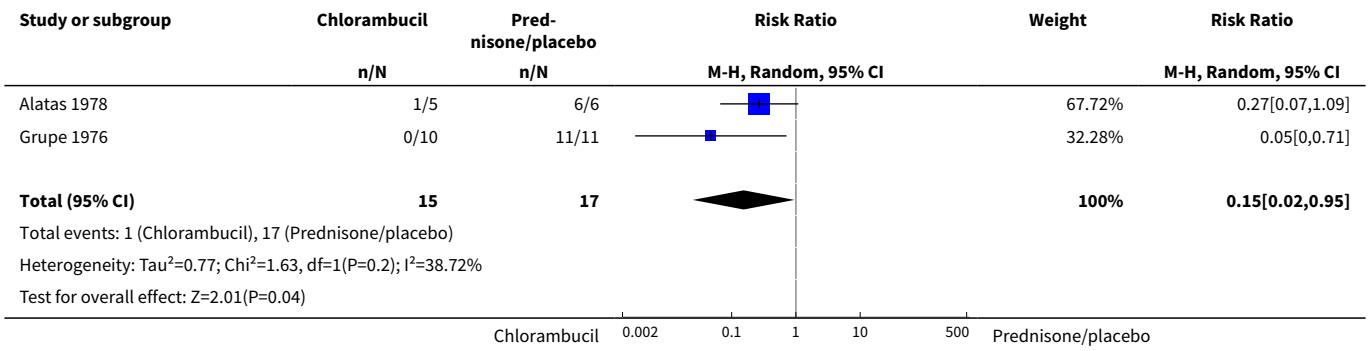
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 6 months	2	41	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.09]
2 Relapse at 12 months	2	32	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 0.95]

Analysis 8.1. Comparison 8 Chlorambucil versus prednisone/placebo, Outcome 1 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)					



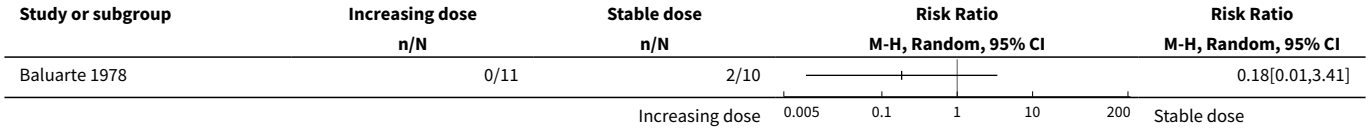
Analysis 8.2. Comparison 8 Chlorambucil versus prednisone/placebo, Outcome 2 Relapse at 12 months.



Comparison 9. Chlorambucil: stable dose versus increasing dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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

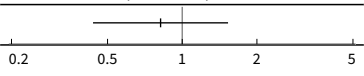


Comparison 10. Chlorambucil versus cyclosporin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapse at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Relapse at 24 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

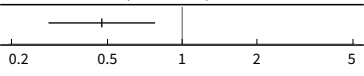
Analysis 10.1. Comparison 10 Chlorambucil versus cyclosporin, Outcome 1 Relapse at 6 months.

Study or subgroup	Chlorambucil n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Niaudet 1992	9/20	11/20		0.82[0.44,1.53]



Analysis 10.2. Comparison 10 Chlorambucil versus cyclosporin, Outcome 2 Relapse at 12 months.

Study or subgroup	Chlorambucil n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Niaudet 1992	9/20	19/20		0.47[0.29,0.78]



Analysis 10.3. Comparison 10 Chlorambucil versus cyclosporin, Outcome 3 Relapse at 24 months.

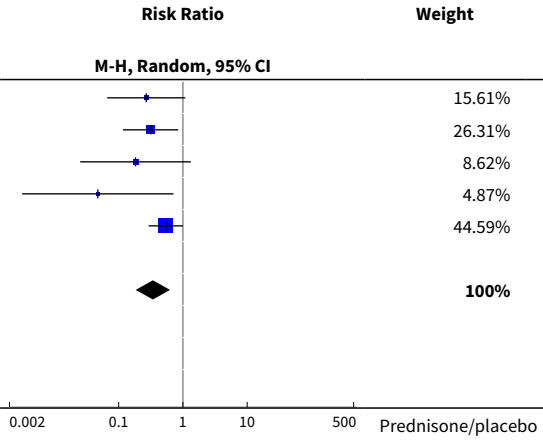
Study or subgroup	Chlorambucil n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Niaudet 1992	14/20	19/20		0.74[0.54,1]

Comparison 11. Alkylating agents versus prednisone/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 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 Relapse at 6-12 months.

Study or subgroup	Alkylating agent 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		15.61%	0.27[0.07,1.09]
Barratt 1970	3/11	13/15		26.31%	0.31[0.12,0.84]
Chiu 1973	1/12	5/11		8.62%	0.18[0.03,1.33]
Grupe 1976	0/10	11/11		4.87%	0.05[0,0.71]
ISKDC 1974	9/27	16/26		44.59%	0.54[0.29,1]
Total (95% CI)	**65**	**69**		**100%**	**0.34[0.18,0.63]**
Total events: 14 (Alkylating agent), 51 (Prednisone/placebo)					
Heterogeneity: Tau^2=0.12; Chi^2=5.31, df=4(P=0.26); I^2=24.64%					
Test for overall effect: Z=3.42(P=0)					

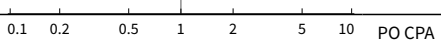


Comparison 12. Intravenous versus oral cyclophosphamide

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Relapse at 6 months	2	83	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.34, 0.88]
2 Relapse at end of study	2	83	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.29]
3 Continuing frequently relapsing or steroid dependent SSNS at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Leucopenia	2	83	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.51]
4.2 Hair loss	2	83	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.04, 1.03]
4.3 All infections	2	83	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.03, 0.72]
4.4 Nausea and vomiting	1	47	Risk Ratio (M-H, Random, 95% CI)	4.07 [0.21, 80.51]

Analysis 12.1. Comparison 12 Intravenous versus oral cyclophosphamide, Outcome 1 Relapse at 6 months.

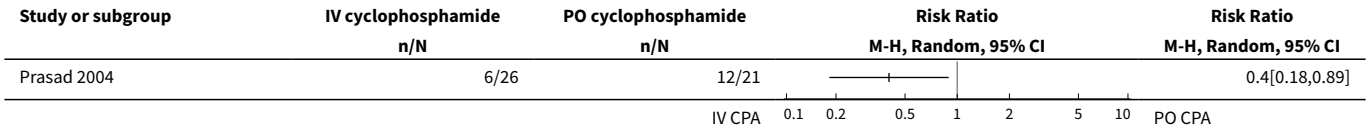
Study or subgroup	IV cyclophos-phamide n/N	PO cyclophos-phamide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Abeyagunawardena 2006b	2/15	6/21		10.86%	0.47[0.11,2]
Prasad 2004	11/26	16/21		89.14%	0.56[0.33,0.92]
Total (95% CI)	**41**	**42**		**100%**	**0.54[0.34,0.88]**
Total events: 13 (IV cyclophosphamide), 22 (PO cyclophosphamide)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=2.48(P=0.01)					



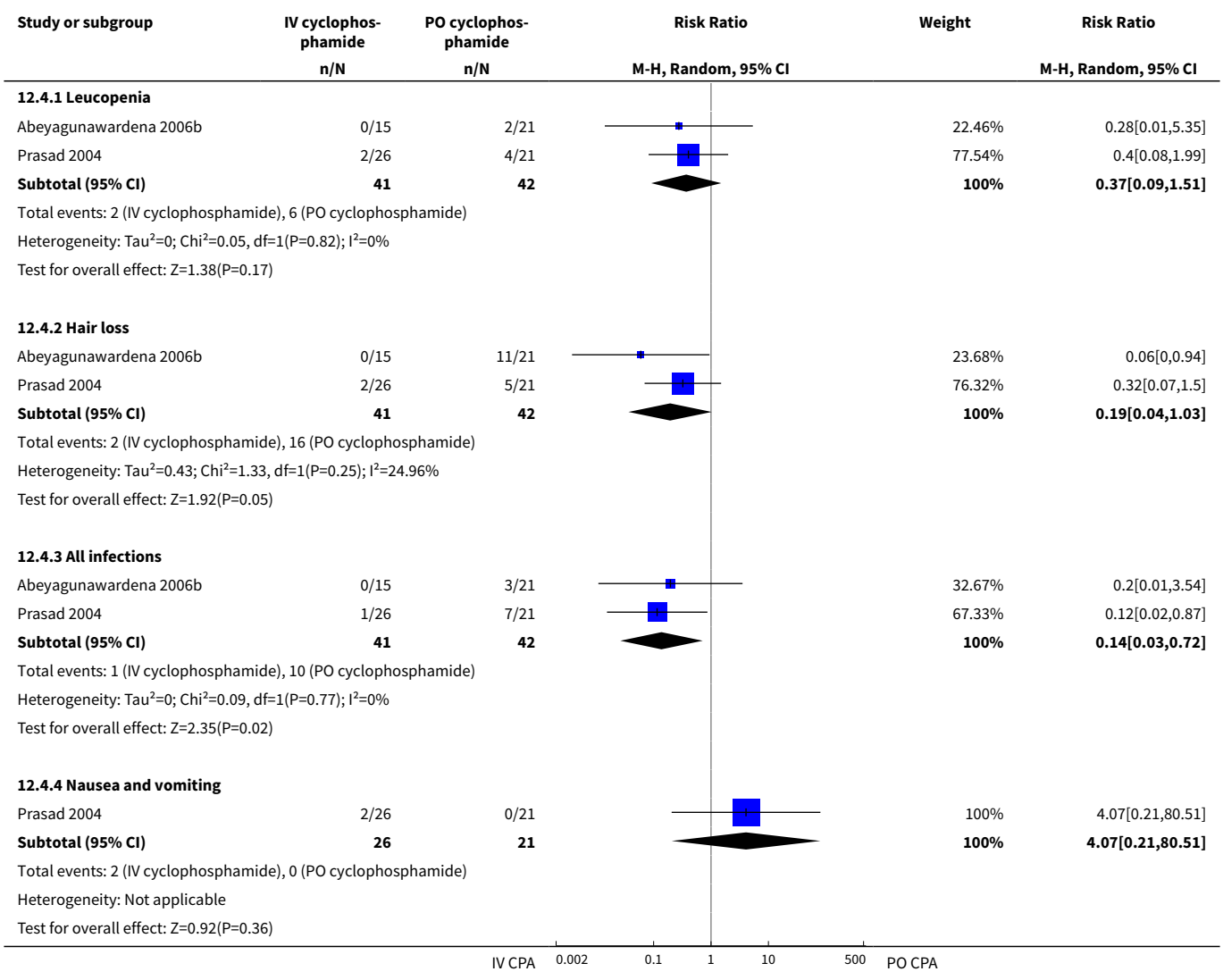
Analysis 12.2. Comparison 12 Intravenous versus oral cyclophosphamide, Outcome 2 Relapse at end of study.

Study or subgroup	IV cyclophos-phamide n/N	PO cyclophos-phamide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Abeyagunawardena 2006b	6/15	9/21		11.08%	0.93[0.42,2.06]
Prasad 2004	21/26	17/21		88.92%	1[0.75,1.32]
Total (95% CI)	**41**	**42**		**100%**	**0.99[0.76,1.29]**
Total events: 27 (IV cyclophosphamide), 26 (PO cyclophosphamide)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					

Analysis 12.3. Comparison 12 Intravenous versus oral cyclophosphamide, Outcome 3 Continuing frequently relapsing or steroid dependent SSNS at 6 months.



Analysis 12.4. Comparison 12 Intravenous versus oral cyclophosphamide, Outcome 4 Adverse events.

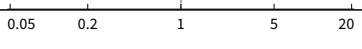


Comparison 13. Levamisole versus placebo, low dose prednisone or no specific treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse during treatment (4-12 months)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Including Weiss 1993	6	317	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.25, 0.99]
1.2 Excluding Weiss 1993	5	269	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.68]
2 Relapse at 6-12 months	6	305	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.38, 0.96]
3 Mean relapse rate/patient/month	2	90	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.20]

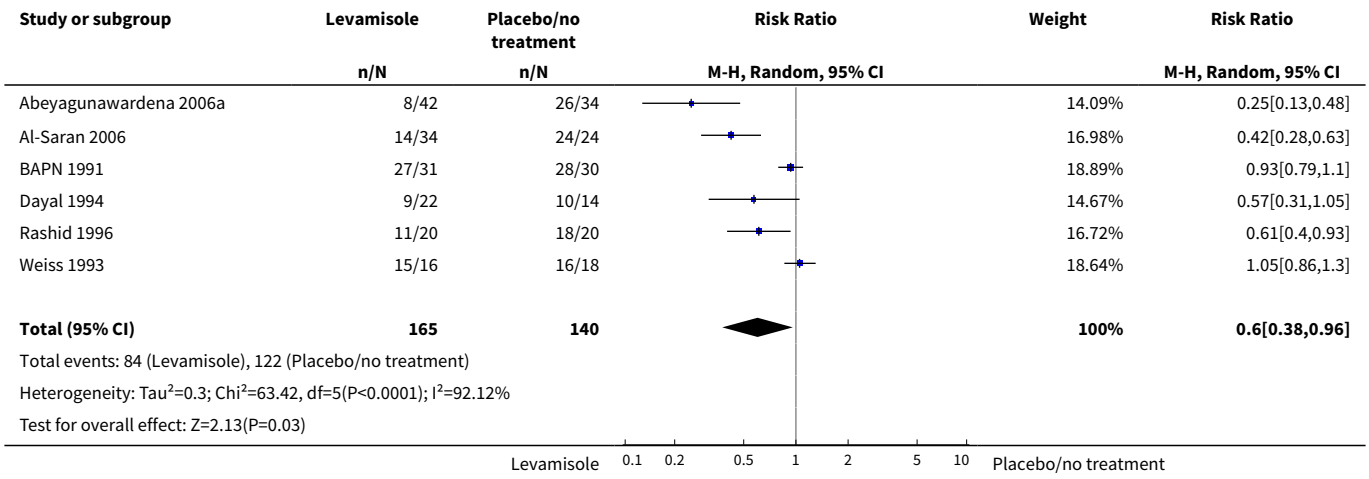
Analysis 13.1. Comparison 13 Levamisole versus placebo, low dose prednisone or no specific treatment, Outcome 1 Relapse during treatment (4-12 months).

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
13.1.1 Including Weiss 1993					
Abeyagunawardena 2006a	8/42	26/34		16.56%	0.25[0.13,0.48]
Al-Saran 2006	3/32	12/24		11.79%	0.19[0.06,0.59]
BAPN 1991	17/31	26/30		19.16%	0.63[0.45,0.9]
Dayal 1994	9/22	10/14		17.03%	0.57[0.31,1.05]
Rashid 1996	6/20	12/20		15.49%	0.5[0.23,1.07]
Weiss 1993	21/22	21/26		19.98%	1.18[0.96,1.46]
Subtotal (95% CI)	**169**	**148**		**100%**	**0.5[0.25,0.99]**
Total events: 64 (Levamisole), 107 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.63; Chi^2=60.63, df=5(P<0.0001); I^2=91.75%					
Test for overall effect: Z=2(P=0.05)					
13.1.2 Excluding Weiss 1993					
Abeyagunawardena 2006a	8/42	26/34		20.69%	0.25[0.13,0.48]
Al-Saran 2006	3/32	12/24		14.73%	0.19[0.06,0.59]
BAPN 1991	17/31	26/30		23.94%	0.63[0.45,0.9]
Dayal 1994	9/22	10/14		21.28%	0.57[0.31,1.05]
Rashid 1996	6/20	12/20		19.36%	0.5[0.23,1.07]
Subtotal (95% CI)	**147**	**122**		**100%**	**0.43[0.27,0.68]**
Total events: 43 (Levamisole), 86 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.17; Chi^2=10.71, df=4(P=0.03); I^2=62.66%					
Test for overall effect: Z=3.56(P=0)					

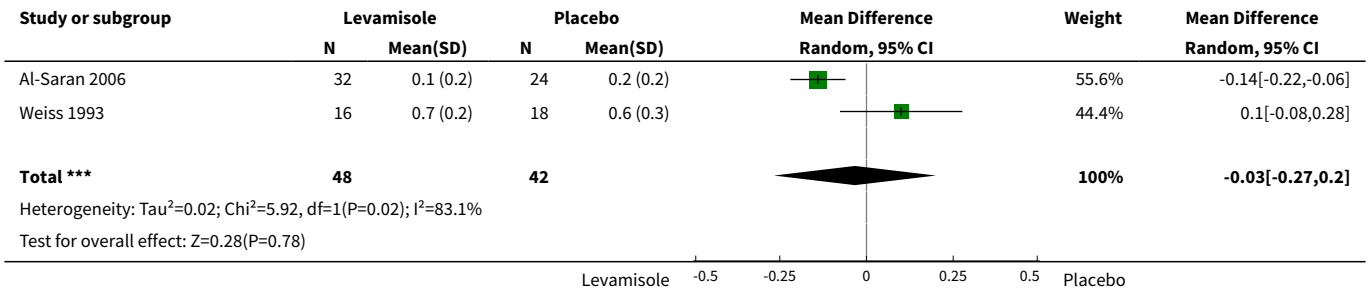


Levamisole — Placebo/no treatment

Analysis 13.2. Comparison 13 Levamisole versus placebo, low dose prednisone or no specific treatment, Outcome 2 Relapse at 6-12 months.



Analysis 13.3. Comparison 13 Levamisole versus placebo, low dose prednisone or no specific treatment, Outcome 3 Mean relapse rate/patient/month.

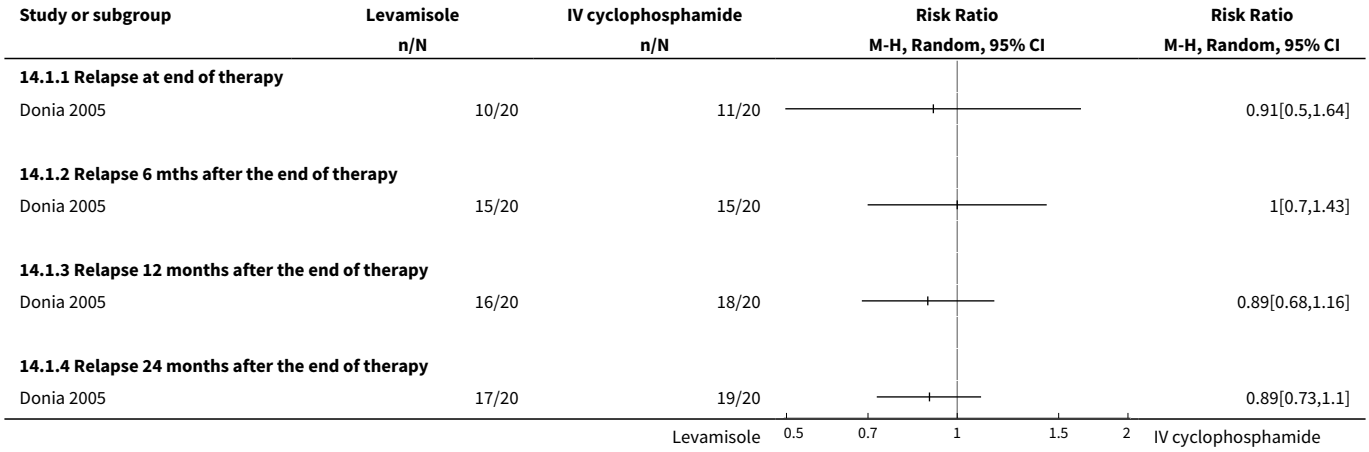


Comparison 14. Levamisole compared with intravenous cyclophosphamide

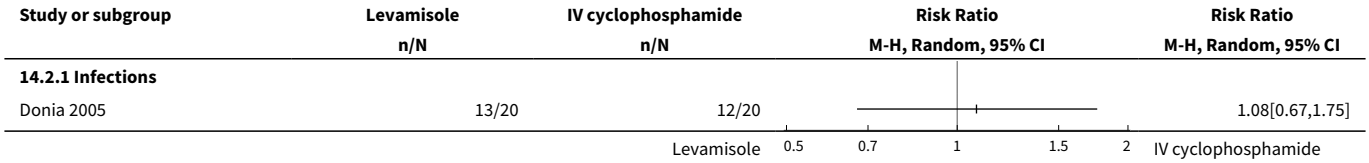
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Relapse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Relapse at end of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Relapse 6 mths after the end of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Relapse 12 months after the end of thera-py	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Relapse 24 months after the end of thera-py	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 Levamisole compared with intravenous cyclophosphamide, Outcome 1 Relapse.



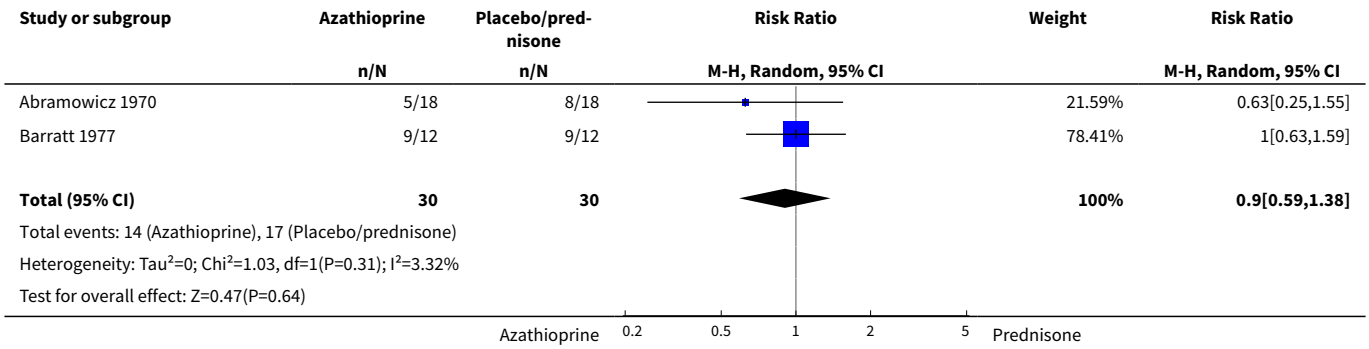
Analysis 14.2. Comparison 14 Levamisole compared with intravenous cyclophosphamide, Outcome 2 Adverse effects.



Comparison 15. Azathioprine versus placebo/prednisone

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

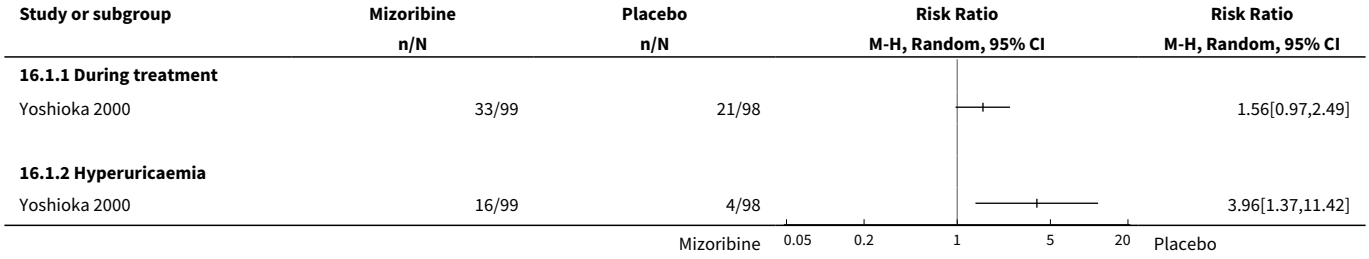
Analysis 15.1. Comparison 15 Azathioprine versus placebo/prednisone, Outcome 1 Relapse at 6 months.



Comparison 16. Mizoribine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 During treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Hyperuricaemia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 16.1. Comparison 16 Mizoribine versus placebo, Outcome 1 Adverse effects.

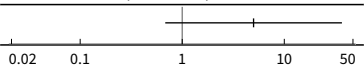


Comparison 17. Mycophenolate mofetil versus cyclosporin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

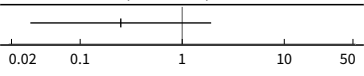
Analysis 17.1. Comparison 17 Mycophenolate mofetil versus cyclosporin, Outcome 1 Relapse by 12 months.

Study or subgroup	Mycophenolate n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dorresteijn 2007	5/12	1/12		5[0.68,36.66]



Analysis 17.2. Comparison 17 Mycophenolate mofetil versus cyclosporin, Outcome 2 Hypertension.

Study or subgroup	Mycophenolate n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dorresteijn 2007	1/12	4/12		0.25[0.03,1.92]



ADDITIONAL TABLES

Table 1. Electonic search strategies

Databases	Search terms
CENTRAL	#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	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

Table 1. Electonic search strategies *(Continued)*

	27 21 and 24
EMBASE	1 exp controlled study/ or controlled study.ti,ab,hw,tn,mf. 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 concealment	Blinding: participants	Blinding: investigators	Blinding: assessors	Intention-to-treat	Loss to follow-up
Abeyagunawardena 2006a	Adequate	No	No	NS	Yes	0%
Abeyagunawardena 2006b	Adequate	No	No	NS	Yes	0%
Abramowicz 1970	Adequate	Yes	Yes	NS	No	0%
Alatas 1978	Unclear	Yes	Yes	NS	Unclear	0%
Al-Saran 2006	Unclear	No	No	NS	No	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%
Cerkauskiene 2005	Unclear	No	No	NS	Unclear	0%
Chiu 1973	Adequate	No	No	NS	Unclear	0%
Dayal 1994	Unclear	No	No	NS	Yes	3%
Donia 2005	Adequate	No	No	NS	No	0%
Dorresteijn 2007	Adequate	No	No	NS	Yes	0%

Table 2. Methodological quality assessment *(Continued)*

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%
Weiss 1993	Adequate	Yes	Yes	NS	No	2%
Yoshioka 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 to 3.5)	5	3/97	3% (0.6 to 8.8)			
Leucopenia < 5000 mm^3	6	57/176	32% (26 to 39)	4	14/76	18% (10 to 29)			
Medication ceased due to leucopenia	6	17/132	9% (6 to 15)	3	3/52	6% (1.2 to 15)			
Thrombocytopenia	4	3/143	2% (0.4 to 5.7)	4	8/86	9% (4.1 to 18)			
Hair loss	4	26/188	14% (9 to 19)	4	3/86	3% (0.7 to 10)			
Cystitis	4	7/188	4% (1.5 to 7.5)	4	0/86	0% (0 to 4.2)			
Gum hypertrophy							2	13/56	28% (33 to 60)
Hirsutism							2	19/56	34% (22 to 48)
Hypertension							2	2/56	4% (0.4 to 12)
Elevated creatinine level							2	5/56	9% (3 to 20)

CPA = cyclophosphamide; CHL = chlorambucil; CSA = cyclosporin

WHAT'S NEW

Date	Event	Description
18 March 2010	Amended	Contact details updated.

HISTORY

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

Date	Event	Description
13 May 2009	Amended	Contact details updated.
14 October 2008	Amended	Converted to new review format.
8 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Initial review and updates

- EM Hodson: Wrote the protocol, assessment of eligibility and quality, data extraction, data synthesis, wrote the review, review update
- NS Willis: Literature searching, data synthesis, review update
- JC Craig: wrote the review, review update.

Initial review

- AM Durkan: Wrote the protocol, literature searching, assessment for eligibility and quality, data extraction, data synthesis, 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