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Interventions for minimal change disease in adults with nephrotic syndrome (Review)

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[Intervention Review]

Interventions for minimal change disease in adults with nephrotic syndrome

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A B S T R A C T

Background

Steroids have been used widely since the early 1970s for the treatment of adult-onset minimal change disease. The response rates to immunosuppressive agents in adult minimal change disease, especially steroids, are more variable than in children. The optimal agent, dose, and duration of treatment for the first episode of nephrotic syndrome, or for disease relapse(s) has not been determined.

Objectives

To determine the benefits and harms of interventions for the nephrotic syndrome in adults caused by minimal change disease.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference articles and abstracts from conference proceedings, without language restriction.
Search date: January 2007.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs of any intervention for minimal change disease in adults over 18 years with the nephrotic syndrome were included. Studies comparing different routes, frequencies, and duration of immunosuppressive agents were selected. Studies comparing non-immunosuppressive agents were also assessed.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random effects model and results were expressed as a risk ratio (RR) for dichotomous outcomes, or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Main results

Three RCTs (68 participants) were identified. All treatment comparisons contained only one study. No significant difference was found between prednisone compared with placebo for complete (RR 1.44, CI 0.95 to 2.19) and partial remission (RR 1.00, CI 0.07 to 14.45) of the nephrotic syndrome due to minimal change disease. There was no difference between intravenous methylprednisolone plus oral prednisone compared with oral prednisone alone for complete remission (RR 0.74, CI 0.50 to 1.08). Prednisone, compared with short-course intravenous methylprednisolone, increased the number of subjects who achieved complete remission (RR 4.95, CI 1.15 to 21.26). The lack of statistical evidence of efficacy associated with prednisone therapy was based on data derived from a single study that compared

'alternate-day prednisone' to no immunosuppression' with only a small number of participants in each group. No RCTs were identified comparing regimens in adults with a steroid-dependent or relapsing disease course or comparing treatments comprising alkylating agents, cyclosporine, tacrolimus, levamisole, or mycophenolate mofetil.

Authors' conclusions

Further comparative studies are required to examine the efficacy of immunosuppressive agents for achievement of sustained remission of nephrotic syndrome caused by minimal change disease. Studies are also needed to evaluate treatments for adults with steroid-dependent or relapsing disease.

PLAIN LANGUAGE SUMMARY

Interventions for minimal change disease in adults with nephrotic syndrome

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. Minimal change disease is the third most common primary kidney disease in adults with unexplained nephrotic syndrome (10% to 15%). Steroids have been used widely since the early 1970s for the treatment of adult-onset minimal change disease, however the optimal agent, dose and duration has not been determined. This review identified three small studies (68 participants) comparing: 1) intravenous plus oral steroid treatment versus oral sterids; 2) oral versus short-course intravenous steroid treatment; and 3) oral steroid treatment versus placebo. Only oral steroid treatment (compared to short-course intravenous steroid treatment) showed an increase in the number of patients who achieved complete remission. However, the lack of available studies leaves important treatment questions unanswered; what is the optimal dose and duration of steroid treatment in new-onset adult minimal change disease; how are relapses following steroid-induced remission prevented and treated; and what are the appropriate treatments for steroid-dependent or treatment-resistant minimal change disease?

BACKGROUND

Nephrotic syndrome is a clinical condition where the glomeruli of the kidney leak protein from the blood into the urine. It is characterised by often severe generalised oedema and hypoproteinaemia and, if untreated, is associated with considerable morbidity. The causes of nephrotic syndrome are either a primary renal process, or a result of injury to the kidney through systemic diseases, most commonly diabetes mellitus. Minimal change disease is the third most common primary kidney disease in adults with unexplained nephrotic syndrome (10% to 15%) (Haas 1995; Korbet 1996), after membranous nephropathy (30% to 40%) and segmental sclerosing glomerular disorders (20% to 30%) (Haas 1997). In fact, minimal change disease may be diagnosed in cases of focal and segmental glomerulosclerosis due to sampling errors in the kidney biopsy process. The incidence of minimal change disease varies depending on the population studied and is reported as 1/1,000,000 in the UK compared with 27/1,000,000 in the USA (Johnson 2003). Adult-onset minimal change disease is associated with kidney failure in 33% of patients, hypertension in 35%, microscopic haematuria in 47%, and hypercholesterolaemia in 96% (Nakayama 2002). Kidney biopsy is mandatory for a diagnosis of minimal change disease in adults with the nephrotic syndrome.

The kidney biopsy in minimal change disease reveals no, or only minor, changes on light microscopy. The abnormality is the fusion of the foot processes of the podocyte cell which normally forms an impermeable barrier to protein as part of the glomerular membrane that controls the urinary filtrate. While the precise pathogenesis of minimal change disease is yet to be clarified there is increasing evidence that T lymphocytes, and probably other immune cells, are involved in the disease and may produce cytokines that alter the normal glomerular filtration membrane that prevents proteinuria (Grimbert 2003).

The response rates to immunosuppressive agents in adult minimal change disease, especially steroids, are more variable than in children. Uncontrolled studies have suggested that the response rates to steroids in adults is "delayed" by 8 to 16 weeks compared to that demonstrated in children and the reasons for this delay are poorly understood. The development of minimal change disease in those older than 40 years may be characterised by increased rates of kidney impairment and hypertension, although these features may simply reflect age-related changes (Tse 2003). The most efficacious treatment to achieve sustained remission of proteinuria in adults is less well defined than for children. Relapse of the nephrotic syndrome after remission may occur and refers to the recurrence of an abnormal urine protein excretion rate, with or without oedema. Spontaneous remission is infrequent, although prior to the widespread use of corticosteroids a spontaneous rate of remission was reported in over half of patients in the first two years after diagnosis (Black 1970). Steroids have been used widely since the early 1970s for the treatment of adult-onset minimal change disease (Nolasco 1986). The response rate to corticosteroids is slower in adults than in children where remission can be achieved in 37% to 50% within four weeks, 51% to 76% within eight weeks, and 76% to 97% within 16 weeks. However, up to 10% of patients may fail to achieve complete remission with corticosteroid therapy alone and require additional immunosuppression. After an initial complete response, up to two-thirds of adults treated with steroids alone will relapse on one or more occasions, and approximately

25% become frequent relapsers (Nakayama 2002). Many patients develop steroid dependency. Older patients may have different remission rates to corticosteroids (Korbet 1996; Nakayama 2002).

Other agents active against the immune system have been employed to prolong periods of remission or reduce corticosteroid exposure. In adults, alkylating agents (cyclophosphamide and chlorambucil) (Al Khader 1979; Mak 1996) have been tested for the treatment of glomerular diseases. More recently, agents used in transplantation including cyclosporine, (Matsumoto 2004; Meyrier 1991; Woo 2001), tacrolimus (Patel 2005; Schweda 1997), sirolimus (Patel 2005), and mycophenolate mofetil (MMF) (Briggs 1998; Day 2002; Mogyorosi 2002) have all been reported in patients with either steroid-resistant or frequently relapsing nephrotic syndrome. Adverse effects from immunosuppression may be considerable, depending on the agent used, and include infection, malignancy, peptic ulceration, diabetes mellitus, infertility, kidney failure, bone marrow suppression, hypertrichosis, and alopecia. Other nonspecific supportive treatments to reduce proteinuria and ameliorate the morbidity of the nephrotic syndrome are reported, including angiotensin-converting enzyme (ACE) inhibitors (Arora 2002; Dilek 1999), non-steroid anti-inflammatory drugs (NSAIDs), heparinoids, and hydroxymethylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (Deighan 2001; Olbricht 1999).

The treatment of adult-onset minimal change disease appears to have developed without consensus and the most effective second-line immunosuppressive agent to treat steroid-resistant nephrotic syndrome or frequently relapsing disease appears uncertain. Initial therapy is most commonly in the form of corticosteroids alone but strong evidence is lacking for the treatment of steroid-resistant, relapsing or steroid-dependent subjects. This systematic review examined the existing randomised controlled trials (RCTs) for the benefits and harms of interventions for the nephrotic syndrome caused by minimal change disease in adults to identify areas that require further research. The incidence and nature of treatment related toxicity were emphasised.

OBJECTIVES

- To evaluate the benefits and harms of different agents, including both immunosuppressive and non-immunosuppressive agents, in adults with minimal change disease causing the nephrotic syndrome.
- To evaluate the efficacy of interventions on 'time-to-remission' of nephrotic syndrome, in adults with minimal change disease causing the nephrotic syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at any intervention for minimal change disease in adults with the nephrotic syndrome were included. Immunosuppressive agents included corticosteroids, cyclophosphamide, chlorambucil, azathioprine, cyclosporine, tacrolimus (FK-506), sirolimus (target of rapamycin inhibitors (TOR-I; sirolimus and everolimus), and MMF. Non-immunosuppressive agents included NSAIDs, ACE inhibitors,

angiotensin-receptor antagonists, heparinoids, parenteral albumin and HMG Co-A reductase inhibitors. The first period of randomised cross-over studies were included.

Types of participants

Inclusion criteria

RCTs enrolling adults (> 18 years) with the nephrotic syndrome and biopsy-proven minimal change disease were included. Nephrotic syndrome was defined as proteinuria >3.0 g/24 h, oedema and hypercholesterolaemia.

Exclusion criteria

Studies enrolling paediatric patients were excluded as these were the subject of previously published reviews (Durkan 2005; Hodson 2006; Hodson 2007). Studies enrolling patients who had any type of segmental sclerosing abnormality on kidney biopsy (focal and segmental glomerulosclerosis (FSGS), collapsing variant of FSGS) were excluded. Any RCT enrolling patients with secondary minimal change nephropathy (e.g. related to drug therapy) were excluded.

Types of interventions

All immunosuppressive agents were considered and included the following:

- Corticosteroid agent versus placebo or no treatment.
- Different doses and/or durations and routes of administration of corticosteroid treatments.
- Non-corticosteroid immunosuppressive agent (with or without concomitant corticosteroid treatment) versus corticosteroid agent alone. These non-corticosteroid agents included azathioprine, cyclophosphamide, chlorambucil, cyclosporine, tacrolimus, sirolimus, levamisole and mycophenolate mofetil.
- Comparisons between two different non-corticosteroid agents (with or without concomitant steroid agent).
- Different doses, durations, and routes of the same non-corticosteroid immunosuppressive agent (with or without concomitant use of corticosteroid agent).

All studies where participants were randomised to a non-immunosuppressive agent were included. These included:

- Non-immunosuppressive agent versus placebo or no treatment.
- Immunosuppressive agent versus non-immunosuppressive agent.
- Comparisons between two different non-immunosuppressive agents.

Types of outcome measures

Primary outcome measure

- Number of patients who achieved complete remission during and following therapy (i.e. oedema free and proteinuria < 1+ (on dipstick), or protein:creatinine < 0.03 g/mmol or complete remission as defined by the investigators).

Secondary outcome measures

- Number of patients who achieve partial remission with reduction in proteinuria (i.e. proteinuria < 2+ on dipstick, urine protein:creatinine ratio < 0.3 g/mmol, protein excretion < 3 g/d or partial remission as defined by the triallists).

- End of treatment increase in serum albumin ≥ 30 g/L.
- End of treatment loss of oedema.
- Time to remission (days) of nephrotic syndrome.
- End of treatment reduction in total cholesterol to ≤ 5.5 mmol/L.
- Doubling of serum creatinine.
- End stage kidney disease (GFR ≤ 15 mL/min or requiring renal replacement therapy).
- One or more episodes of thrombosis.
- All-cause mortality.
- Fatal and non-fatal cardiovascular events (myocardial infarction, stroke, revascularisation).
- Adverse events including major infection requiring parenteral antibiosis or hospitalisation, all-cause infection, hypertension, malignancy, kidney failure (as defined by the triallists or a rise in the plasma creatinine > 0.03 mmol/L or a rise in the estimated glomerular filtration rate > 25%), diabetes mellitus/impaired glucose tolerance, gonadal failure (sustained amenorrhoea or infertility), bone toxicity (avascular necrosis or fracture), bone marrow toxicity, bladder toxicity (haemorrhagic cystitis), hypertrichosis, gingival hyperplasia, alopecia, peptic ulceration.

The following continuous variables were analysed:

- End of treatment mean serum creatinine (mmol/L).
- End of treatment mean protein excretion rate (g/24 h) or protein:creatinine ratio (g/mmol).
- End of treatment mean serum albumin (g/L).
- End of treatment mean serum total cholesterol (mmol/L).
- End of treatment mean serum LDL cholesterol/HDL cholesterol/ triglycerides (all mmol/L) and HDL:LDL cholesterol ratio.
- Protein excretion rate at 6, 12 and 24 months (g/24 h) after treatment.
- Duration of complete remission or partial remission (months).

Search methods for identification of studies

Relevant studies were obtained from the following sources without language restriction (Appendix 1 - *Electronic search strategies*):

1. The Cochrane Renal Group's specialised register (January 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* issue 1, 2007). CENTRAL and the Renal Group's specialised register contain the hand searched 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).

2. MEDLINE (1966 to January 2007) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific strategy developed with input from the Cochrane Renal Group Trials Search Coordinators.

3. EMBASE (1980 to January 2007) 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 developed with input from the Cochrane Renal Group Trials Search Coordinators.

4. Reference lists of nephrology textbooks, review articles and relevant studies.

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

Data collection and analysis

Included and excluded studies

The review was undertaken independently by three authors (SCP, KN, GFMS). The search strategy was used to obtain titles and abstracts of studies that might be relevant to the review. The titles and abstracts were screened independently by (SCP) and (KN), who discarded studies that were not applicable. Studies and reviews that might include relevant data or information on studies were retained initially. Reviewers (SCP) and (KN) independently assessed retrieved abstracts and, if necessary, the full text of these studies, to determine which studies satisfied the inclusion criteria. Data extraction was carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Any further information to clarify study reporting or to request additional information from the original author was be requested by written correspondence and any relevant information obtained in this manner was be included in the review. Disagreements were resolved in consultation with (GFMS).

Study quality

The quality of studies included was assessed independently by (SCP) and (KN) without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion with GFMS. The quality items assessed were allocation concealment, blinding (participants, investigators, outcome assessors and data analysis), intention-to-treat analysis and completeness of follow-up.

Quality checklist

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

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

The above 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 stated but confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated

Completeness of follow-up

Per cent of participants excluded or lost to follow-up.

Statistical assessment

For dichotomous outcomes (complete remission, partial remission, doubling of serum creatinine or end-stage kidney disease, adverse events) results were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Data were pooled using the Der Simonian Laird random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (proteinuria, kidney outcomes, duration of remission), the mean difference (MD) was used. Heterogeneity was analysed, where applicable, using a chi squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003).

Subgroup analysis was planned to explore any possible sources of heterogeneity (e.g. participants, treatments and study quality). Heterogeneity among participants could have been related to; age (dichotomised to between 18-40 years and greater than 40 years), kidney function, evidence of glomerulosclerosis on biopsy, haematuria, hypertension, response to corticosteroids, characteristics of clinical course (partial remission, frequently relapsing disease, steroid dependence, duration of NS), severity of NS, severity of hyperlipidaemia. Heterogeneity in treatments could have been related to prior agent(s) used and the agent, dose and duration of therapy. Adverse effects were tabulated and assessed with descriptive techniques, as they were likely to be different for the various agents used (Table 1). Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent.

Insufficient RCTs were identified to enable examination for publication bias using a funnel plot (Egger 1997).

R E S U L T S

Description of studies

Figure 1- *Flow chart of study identification and selection)* details the progress through the phases of this systematic review. From the Cochrane Renal Group's specialised register and CENTRAL, 91 citations were received; from MEDLINE 697 citations, and from EMBASE 3057 citations. Of these 3845 potentially eligible publications 3781 were excluded after title and abstract review. The primary reasons for exclusion of citations were a non-randomised design, not minimal change disease, or a paediatric study

population. Full-text analysis of the remaining 64 publications found three RCTs for inclusion in this review (Coggins 1985; Imbasciati 1985; Yeung 1983). The total number of adult patients randomised in the included studies was 68. No authors responded to our written requests for unpublished study data. Study characteristics are presented in the table *Characteristics of included studies*.

Figure 1.   Flow chart of study identification and selection

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┌─────────────────────────────┐
│ Databases (n = 3845)        │
│   MEDLINE (n = 697)         │
│   EMBASE (n = 3057)         │
│   CENTRAL (n = 12)          │
└─────────────────────────────┘
               │                          ┌──────────────────────────────────────────┐
               │─────────────────────────▶│ Excluded (n = 3781)                        │
               │                          │   Search overlap (n = 236)                 │
               │                          │   Not RCT, or not adult minimal change     │
               ▼                          │   disease (n = 3481)                       │
┌─────────────────────────────┐          └──────────────────────────────────────────┘
│ Full text analysis (n = 64) │
│   MEDLINE (n = 43)          │
│   EMBASE (n = 35)           │
│   CENTRAL (n = 27)          │
└─────────────────────────────┘
               │                          ┌──────────────────────────────────────────┐
               │─────────────────────────▶│ Excluded (61)                              │
               │                          │   Not RCT 20)                              │
               │                          │   Review articles (4)                      │
               │                          │   Mixed aetiology of nephrotic syndrome    │
               │                          │   (8)                                      │
               │                          │   Not minimal change disease (15)          │
               ▼                          │   Paediatric studies (7)                   │
┌─────────────────────────────┐          │   Duplicate or abstract publication (7)    │
│ Included (n = 3, 3 publications)         └──────────────────────────────────────────┘
│ MEDLINE (n = 3)             │
│ EMBASE (n = 2)              │
│ CENTRAL (n = 3)             │
│                             │
│ 68 patients                 │
└─────────────────────────────┘
               │
               ▼
┌───────────────────────────────────────────────────────────┐
│ Number of studies by outcome:                             │
│   All-cause mortality (1 study, 22 patients)              │
│   Complete remission (3 studies, 68 patients)             │
│   Partial remission (1 study, 28 patients)                │
│   Sustained remission during follow-up (2 studies, 50 patients)│
│   Doubling plasma creatinine (1 study, 28 patients)       │
│   Time to complete remission (1 study, 18 patients)       │
│   Protein excretion rate (1 study, 28 patients)           │
│                                                           │
│ Adverse events:                                           │
│   Avascular necrosis (1 study, 28 patients)               │
│   Peptic ulcer disease (1 study, 18 patients)             │
│   Renal failure (1 study, 28 patients)                    │
│   Thrombosis (1 study, 22 patients)                       │
└───────────────────────────────────────────────────────────┘
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A number of studies comparing treatment regimens containing cyclosporine, cyclophosphamide and high dose steroids for primary disease, and poorly responsive or relapsing disease were excluded because they were observational, included children, or included heterogenous causes of the nephrotic syndrome. The details of these are presented in the table *Characteristics of excluded studies.*

Interventions

Coggins 1985 (28 participants) compared oral prednisone (125 mg alternate daily) with no treatment, Yeung 1983 (18 participants) compared intravenous bolus methylprednisolone alone with oral prednisone, and Imbasciati 1985 (22 participants) compared intravenous methylprednisolone followed by oral prednisone with oral prednisone alone.

Diagnoses

The three included studies were published over 20 years prior to this review. Yeung 1983 randomised people with a first episode of biopsy-proven minimal change disease. Imbasciati 1985 enrolled adults with the nephrotic syndrome, persisting for at least two weeks. Patients in this study included those with previous episodes of the nephrotic syndrome who were included only when they had achieved a complete remission with steroids at least one year previously. In Coggins 1985 patients had experienced the nephrotic syndrome for a mean of two months, although it was unclear whether participants were enrolled during their first or subsequent episodes of nephrotic syndrome.

Outcomes

Coggins 1985 reported a pretreatment mean level of proteinuria of 9.8 g/d, whereas the degree of proteinuria prior to randomisation was unclear for Imbasciati 1985 and Yeung 1983. The reporting of biopsy data prior to enrolment was poor and participants with sclerosing lesions were included in the studies. Imbasciati 1985 reported evidence of focal glomerular obsolescence in 2/22 participants. Yeung 1983 reported a single repeat kidney biopsy showing focal and segmental glomerulosclerosis following a poor response to intervention (oral prednisone) despite an entry biopsy showing normal glomeruli. Coggins 1985 did not detail biopsy findings. The age of participants was 30 years in Coggins 1985 and ranged up to 56 years in Imbasciati 1985 and Yeung 1983. Complete remission events were reported in all studies. Relapses and non-response to treatment were described inconsistently. Imbasciati 1985 and Yeung 1983 detailed one or more episodes of relapse (including time to relapse) and non-responders to treatment, while Coggins 1985 reported the non-responders to intervention, however the number of patients who experienced relapse of the nephrotic syndrome during follow up was unclear. This study also reported patients continuing to have 1 g or more proteinuria during months of follow up (Coggins 1985). Follow-up was up to 840 days (Yeung 1983), 52.5 months (Imbasciati 1985) and 24 months (Coggins 1985).

Cointerventions

Cointerventions included diuretics (Coggins 1985; Imbasciati 1985; Yeung 1983), a low-salt diet (Imbasciati 1985) and antihypertensive treatment (Imbasciati 1985).

Risk of bias in included studies

The quality of studies was difficult to assess because many details such as methods of allocation concealment, the use of intention-to-treat analysis, methods of blinding and the number of patients lost to follow-up were difficult to ascertain or were not provided. In general, study quality was variable and reporting of study method details was unsatisfactory or incomplete. Of note, all included studies preceded the CONSORT guidelines for reporting of RCTs (Begg 1996).

Allocation concealment

Allocation concealment was unclear in all three studies.

Blinding

Blinding of participants and investigators was not used in Imbasciati 1985 or Yeung 1983, and was unclear in Coggins 1985. Blinding of outcome assessors was not described in any study.

Intention-to-treat analysis

Intention-to-treat analysis was used in Imbasciati 1985, not stated in Coggins 1985, and not used in Yeung 1983.

Completeness of follow-up

No participants were lost to follow-up in Coggins 1985 or Imbasciati 1985, and the loss to follow-up was not stated in Yeung 1983.

Effects of interventions

The identified treatment comparisons were steroid versus no treatment (*comparison 01*), intravenous steroid plus oral steroid versus oral steroid alone (*comparison 02*) and intravenous steroid versus oral steroid (*comparison 03*). No other treatment modalities were assessed. Each treatment comparison contained a single study, and therefore no meta-analyses were possible.

Steroid versus placebo or no treatment

Coggins 1985 compared alternate daily oral prednisone 125 mg with no treatment. Treatment was continued for two months. Prednisone did not increase the number of patients who achieved complete remission compared with no treatment (Analysis 1.1: RR 1.44, 95% CI 0.95 to 2.19). No difference was found between treatment groups for the achievement of partial remission (Analysis 1.2: RR 1.00, 95% CI 0.07 to 14.45) or sustained remission (Analysis 1.3: RR 2.50, 95% CI 0.58 to 10.80). The likelihood of resolution of oedema was similar between the two treatment groups (Analysis 1.4: RR 1.21, 95% CI 0.89 to 1.66). The incidence of adverse events (Analysis 1.5) was similar for each treatment group including for avascular necrosis (RR 3.00, 95%CI 0.13 to 67.91), doubling of serum creatinine (RR 0.11, 95% CI 0.01 to 1.89), and renal failure (RR 0.33, 95% CI 0.01 to 7.55). The four patients who experienced doubling of serum creatinine were randomised to no treatment and three achieved subsequent remission with steroid treatment. The number of patients in each group who relapsed during the follow-up period was unclear.

Intravenous and oral steroid versus oral steroid alone

Imbasciati 1985 randomly assigned participants to either methylprednisolone 20 mg/kg/d for three days then oral prednisone 0.5 mg/kg/d for four weeks, 0.5 and 0.25 mg/kg alternate days for four weeks, then 0.5 mg/alternate days for four

months, or treatment with oral prednisone 1 mg/kg/d for four weeks, then 1 mg/kg/alternate days for four weeks, then 0.5 mg/kg on alternate days for four months. Relapses during treatment were treated according to the initial treatment allocation. No significant difference was seen following treatment with intravenous and oral steroid compared with steroid alone for complete remission (Analysis 2.1: RR 0.73, 95% CI 0.50 to 1.08), sustained remission during follow up (Analysis 2.2: RR 0.50, 95% CI 0.11 to 2.19), all-cause mortality Analysis 2.3: RR 0.33, 95% CI 0.02 to 7.39) or adverse events (thrombosis) (Analysis 2.4.1: RR 2.00, 95% CI 0.21 to 18.98). Six patients in the intravenous plus oral steroid group experienced 13 relapses compared with seven patients who developed 11 relapses in the steroid alone group (Analysis 2.5; RR 1.18, 95% CI 0.65 to 2.15).

Intravenous steroid versus oral steroid

Yeung 1983 randomised participants to either intravenous methylprednisolone 20 mg/kg/d on three consecutive days or to oral prednisone 1 mg/kg/d given for four to six weeks. Patients in the intravenous methylprednisolone group were administered oral prednisone if they failed to respond to initial treatment within two weeks. Oral prednisone was associated with a significant increase in episodes of complete remission (Analysis 3.1: RR 4.95, 95%CI 1.15 to 21.26). Four of the six participants (all randomised to intravenous methylprednisolone) who did not achieve complete remission within two weeks, and were subsequently administered oral prednisone, experienced complete remission 14 to 31 days after commencing oral prednisone. One of the non-responders demonstrated FSGS on a follow up biopsy. Time to complete remission (days) was similar between study groups (Analysis 3.2: MD 3.17, 95% CI -9.21 to 15.55). No adverse events were reported for adult participants during follow-up.

Subgroup analyses or assessment for publication bias were not possible. No ongoing studies were identified.

Adverse events

Adverse events for all treatment regimens are detailed in Table 1 - *Adverse events*.

DISCUSSION

All available RCTs in adults with minimal change disease evaluate treatment of recent onset nephrotic syndrome and compare prednisone with another steroid regime or with no treatment. The review identified three vastly different RCTs performed over two decades, on small numbers of participants without adequate power to detect differences in therapeutic efficacy. This suggests these original studies have little relevance to contemporary treatment of minimal change disease in adults. RCT data for treatment of relapsing disease or steroid-resistant disease are absent. The likelihood of achieving remission within two months of presentation did not differ between alternate-day prednisone and no immunosuppression in one study, or between intravenous steroid followed by oral prednisone and oral prednisone alone in another study. The lack of superior efficacy for prednisone over placebo for achievement of remission is surprising and probably explained by the spontaneous remission rate in the small group (N = 14) prescribed no treatment, such that there was no difference in complete remission between groups at the end of the study (Coggins 1985). In children, studies of steroid-sensitive nephrotic syndrome using either higher doses of steroid or an increased

duration of steroid therapy lead to prolonged remission from the nephrotic syndrome (Hodson 2007). This is echoed by the finding in this review of a single RCT in adults where continuous oral prednisone induced complete remission better than short-course (three day) intravenous steroids, although the small patient numbers could not exclude the possibility that this treatment advantage was due to chance alone.

Adult minimal change disease is steroid-responsive in approximately 80% of cases (Meyrier 1988) although up to two-thirds of adults undergo a relapsing course, and steroid-sensitive forms may become steroid-dependent. In such cases, repeated or continuous courses of corticosteroid treatment increases the likelihood of glucocorticoid toxicity. In relapsing paediatric nephrotic syndrome, daily prednisone treatment, cyclophosphamide, chlorambucil, levamisole, and cyclosporine all significantly reduce the risk of subsequent relapse (Durkan 2005). No RCT data are available to guide similar treatment for adults, particularly for those who experience relapse during or after initial treatment, for those who frequently relapse, or for those who develop steroid dependency. Agents such as cyclosporine (Matsumoto 2004), tacrolimus (Westhoff 2006) cyclophosphamide, and mycophenolate mofetil (Mogyorosi 2002) are evaluated in uncontrolled studies of adult nephrotic syndrome, and may be associated with significant toxicity, including kidney impairment (Ponticelli 1993; Sharpstone 1969; Tejani 1988; Uldall 1972). The lack of available studies leaves important treatment questions unanswered; what is the optimal dose and duration of steroid treatment in new-onset adult minimal change disease; how are relapses following steroid-induced remission prevented and treated; and what are the appropriate treatments for steroid-dependent or treatment-resistant minimal change disease?

The absence of evidence to guide management of adults with the nephrotic syndrome due to minimal change disease is in direct contrast to the available data for children with the nephrotic syndrome, summarised in three separate Cochrane systematic reviews (Durkan 2005; Hodson 2006; Hodson 2007). Adult minimal change disease is a rarer condition and this rarity has presented a vital barrier to the conduct of adequately powered studies for this population. The incidence of (all-cause) nephrotic syndrome in children approaches 2/100,000, probably an order of magnitude more frequent than the condition in adults (Arneil 1961). Moreover, studies in adults with minimal change disease, published in the 1970's, showed an "early and dramatic" decrease in proteinuria following prednisone therapy (Black 1970; Gulati 1973). This profound "before and after" evidence to support the use of steroids in adult minimal change disease lead to the widespread adoption of this empirical approach. No subsequent adequately powered studies to examine the efficacy and toxicity of steroids were conducted. The low incidence of the disease in adults has also prevented adequate RCTs to evaluate treatment for steroid-dependent or relapsing disease

The combination of causes for nephrotic syndrome together into RCTs has commonly occurred for adults. Frequently adults with minimal change disease have been combined in interventional studies with adults with focal and segmental glomerulosclerosis (Lee 1995; Meyrier 1988; Ponticelli 1993), membranous nephropathy (Black 1970; Mansy 1989), and membrano-proliferative disease (Gulati 1973). In order to maximise recruitment previous studies have also enrolled both adults and

children with minimal change disease into the same study. This approach is problematic as the study populations are necessarily heterogenous and the applicability of such research findings to individuals with adult minimal change disease is limited. This is particularly true where adults are enrolled in studies with children, and where patients with sclerosing glomerular lesions are combined with patients with minimal change disease. The heterogenous response of these different populations to treatment demands that any future studies enrol adults with biopsy-proven minimal change disease alone.

An international collaborative group to organise multicentre studies of therapy in adult glomerular disease would facilitate the conduct of such studies. The funding of the European Vasculitis Study Group in 1993 is such an example of a collaborative international network coordinated with a central secretariat to ensure appropriate studies of rare diseases are conducted in vasculitis (EUVAS 2006). This group has published a large body of well-conducted research to guide therapy for vasculitis. For primary glomerulopathies a similar collaborative network could facilitate international studies of treatments that have previously been shown to be efficacious in children and in observational studies in adults. In adults with new-onset nephrotic syndrome comparisons of different durations and doses of corticosteroids should be considered. Non-corticosteroid based immunosuppression should be assessed in steroid-dependent, steroid-resistant, and relapsing disease, focusing on the duration of remission, kidney outcomes, and treatment-related toxicity.

AUTHORS' CONCLUSIONS

Implications for practice

This review has generated no evidence to support the efficacy of any agent for induction or prolongation of remission for adults with the nephrotic syndrome caused by minimal change disease. The lack of statistical evidence of efficacy associated with prednisone therapy was based on data derived from a single study that compared 'alternate-day prednisone' to no immunosuppression' with only a small number of participants in each group. The results should be treated with caution due to the small numbers of studies available. No information is available to guide the use of non-steroid immunosuppression either following the first presentation of nephrotic syndrome or relapsing or steroid-resistant adult minimal change disease. There are insufficient data to determine whether 'time-to-remission' was significantly influenced by any treatments in this review.

Implications for research

Future adequately powered RCTs are required to compare the benefits and harms of;

- Prednisone for the first episode of minimal change disease, comparing different doses and durations of treatment.
- Cyclosporine, tacrolimus, or alkylating agents for relapsing disease or steroid-resistant disease, with a focus on duration on remission, kidney outcomes, and toxicity.

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mofetil. *American Journal of Nephrology* 2002;**22**(5-6):569-72. [MEDLINE: 12381961]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Coggins 1985

Methods	Country: United States Setting/Design: Collaborative placebo-controlled RCT Time Frame: NS Randomisation method: NS Blinding - Participants: NS

Coggins 1985 *(Continued)*

	- Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat: NS Follow-up period: 77 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Idiopathic nephrotic syndrome of minimal change disease GROUP 1 (prednisone) Number: 14 Age: 29 years GROUP 2 (no treatment) Number: 14 Age: 32 years
Interventions	GROUP 1 Prednisone 125 mg PO given in alternate-day doses for 2 months. Relapses were re-treated. GROUP 2 No treatment. If patient reached "stop points" (including doubling of admission creatinine) they were withdrawn from the placebo group and treated with steroids. COINTERVENTIONS: NS
Outcomes	1. Complete remission prior to "Stop Point" (doubling of admission creatinine, severe steroid toxicity, and undefined other bad outcomes) 2. Complete remission 3. Partial remission 4. Time to remission (months) 5. Doubling of serum creatinine 6. Kidney failure 7. Steroid-related toxicity (avascular necrosis) 8. Mean end of treatment serum creatinine
Notes	Exclusions post-randomisation but pre-intervention: NS Additional data requested from authors: Method of randomisation, allocation concealment COMPLETENESS OF FOLLOW-UP Eligible/considered for inclusion = NS; Enrolled/randomised = 28; Analysed = 28 ; Percent followed = 100

Risk of bias

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

Imbasciati 1985

Methods	Country: Italy Setting/Design: Multicentre RCT Time Frame: June 1980 to June 1983

Imbasciati 1985 *(Continued)*

	Randomisation method: Table of random numbers kept in one centre
	Blinding
	- Participants: No
	- Investigators: No
	- Outcome assessors: NS
	- Data analyses: NS
	Intention-to-treat: Yes
	Follow-up period: 12-24 months
	Loss to follow-up: 0%

Participants	INCLUSION CRITERIA
	1. Proteinuria > 3.5 g/24 h persisting for at least 2 weeks and plasma albumin concentration < 25 g/L.
	2. No secondary cause for nephrotic syndrome.
	3. Not been treated with steroids or cytotoxic agents for at least one year before admission.
	4. Kidney biopsy shows clear histological picture consistent with MCD.
	GROUP 1 (Methylprednisone + prednisone)
	Number: 11
	Age: NS
	GROUP 2 (Prednisone alone)
	Number: 11
	Age: NS

Interventions	GROUP 1
	Methylprednisone 20 mg/kg/d IV for 3 days; then prednisone 0.5 mg/kg/d for 4 weeks PO; then 0.25-0.5 mg/kg/alternate days PO for 4 weeks; then 0.5 mg/kg/alternate days PO for 4 months.
	GROUP 2
	Prednisone 1 mg/kg/d for 4 weeks; then 1 mg/kg/alternate days for 4 weeks; then 0.5 mg/kg on alternate days 4 months.
	COINTERVENTIONS
	Low salt diet, diuretics, anti-hypertensive changes as needed.

Outcomes	
	1. Complete remission within 8 weeks of treatment
	2. Time to remission (days)
	3. Relapse of nephrotic syndrome during follow-up
	4. Number of relapses/patient/year follow-up
	5. Proportion of patients remaining in remission
	6. Treatment-related toxicity
	7. Nephrotic syndrome-related adverse events

Notes	Exclusions post-randomisation but pre-intervention: 0
	Additional data requested from authors: Allocation concealment, age of participants, mean time to remission
	COMPLETENESS OF FOLLOW-UP
	Eligible/considered for inclusion = NS; Enrolled/randomised = 89; Analysed = 89; Percent followed = 100

Risk of bias

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

Yeung 1983

Methods	Country: Hong Kong Setting/Design:Single university centre RCT Time Frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analyses: NS Intention-to-treat: No Follow-up period: Up to 750 days Loss to follow-up: NS
Participants	INCLUSION CRITERIA Biopsy-proven minimal change nephrotic syndrome, first episode GROUP 1 (methylprednisolone) Number: 10 (1 F) Age: mean 29.0 y GROUP 2 (prednisone) Number: 8 (3 F) Age: mean 22.4 y
Interventions	GROUP 1 Methylprednisolone 20 mg/kg/d IV on three consecutive days; then prednisone 1-2 mg/kg/d 2 weeks after methylprednisolone dose as maintenance if response to methylprednisolone. If no response within 2 weeks re-allocated to oral prednisone. GROUP 2 Prednisone 1 mg/kg/d for 4-6 weeks COINTERVENTIONS Diuretics
Outcomes	1. Complete remission 2. Time to complete remission (days) 3. Duration of first remission 4. Treatment related toxicity
Notes	Exclusions post-randomisation but pre-intervention: NS Additional data requested from authors: Study quality data COMPLETENESS OF FOLLOW-UP Eligible/considered for inclusion = NS; Enrolled/randomised = 18; Analysed = 18 ; Percent followed = 100

Risk of bias

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

MCD - minimal change disease; NS - not stated

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

Study	Reason for exclusion
Abaigar 1993	Individuals with NS caused by non-MCD comparing two levels of dietary protein intake. (Not MCD)
Arora 2002	Case control study of patients with idiopathic nephrotic syndrome (N = 15) receiving either ACE inhibitor or supportive treatment. No patient had MCD. (Not MCD)
Bagga 1997	RCT in children comparing two regimens for prednisone treatment of childhood NS. (Not adult NS)
Bagga 1999	Study in childhood NS. (Not adult NS)
Bargman 1999	Review article of treatment for MCD in adults and children. (Not RCT)
Beige 2003	Abstract of pilot observational study of tacrolimus to treat adults (N = 7) with steroid-resistant or relapsing NS. Three individuals had MCD. (Not RCT)
Black 1970	Multicentre RCT of oral prednisone compared with no treatment in 125 people (aged 15 years and over), with the NS. Causes of the syndrome were MCD, membranous nephropathy, and proliferative glomerulonephritis. Unable to interpret outcomes in MCD category due to inadequate baseline data.
Broyer 1995	RCT in paediatric NS. (Not adult NS)
Choi 2002	Retrospective analysis of mycophenolate mofetil in biopsy proven glomerular disease complicated by NS and/or kidney failure. (Not RCT)
Cole 1994	Commentary regarding need for collaborative study in childhood NS caused by MCD. (Not RCT)
Deighan 2001	RCT cross-over design study of adults with proteinuria >3 g/d, biopsy proven glomerulonephritis comparing cerivastatin with fenofibrate. Two out of 12 patients had MCD. (Not MCD)
Dilek 1999	Controlled prospective study comparing enalapril with losartan in NS. Single patient had MCD. (Not MCD)
Don 1989	RCT in 12 individuals with NS comparing reduction in dietary protein intake with enalapril. No patients had MCD. (Not MCD)
El-Reshaid 1995	Observational study of cyclosporine in refractory adult nephrotic syndrome > 4 months. (Not RCT)
Gentile 1993	RCT comparing vegetarian soy diet with or without fish oil supplements. Not all participants had NS. No patient had biopsy-proven MCD. (Not NS, not MCD)
Groggel 1989	RCT comparing gemfibrozil with no treatment in adult NS (N = 11). No participant had MCD. (Not MCD)
Gulati 1973	Patients between 13 and 56 years with NS and biopsy-proven glomerular disease. Randomised study comparing prednisolone with placebo. Fourteen of 42 participants with MCD. (Not MCD)
Ishikawa 1982	Not MCD.
Koike 2002	Observational study. (Not RCT)
Kumar 2004	RCT comparing ramipril with verapamil in adults with idiopathic NS not showing reduction in proteinuria despite 12 weeks of oral prednisone 2 mg/kg on alternate days. No patient had biopsy-proven MCD. (Not MCD)
Lee 1995	Observational study of the efficacy and tolerability of cyclosporine in 30 patients with adult NS. Rate of relapse after withdrawal was assessed after treatment. (Not RCT)

Study	Reason for exclusion
Leisti 1978	Paediatric study. (Not adult NS)
Mansy 1989	RCT cross-over study of 3 levels of protein intake in patients with NS. Two of 12 patients had biopsy proven MCD. (Not MCD)
Martins 1994	Observational single-arm study. Open prospective 2-year study of lovastatin in biopsy-proven primary NS. (Not RCT)
Matl 1997	Quasi-RCT of 30 patients with chronic glomerular disease proven by biopsy and protein excretion rate higher than 3 g/d randomised to either cyclosporine (5 mg/kg/d) or cyclophosphamide (1.5 mg/kg/d) for 6 months or until remission. Combined aetiology for NS. (Non MCD)
Matsubara 2002	Correspondence describing 2 case reports of combined therapy with camostat mesilate and glycyrrhin for steroid-dependent NS. (Not RCT)
Matsumoto 2004	Prospective non-randomised study of methylprednisolone + cyclosporine versus cyclosporine versus prednisone in 36 adults with biopsy-proven MCD and NS. (Not RCT)
Matzkies 1999	Observational study of fluvastatin (N = 10) in adults with all-cause NS. (Not RCT)
Meyrier 1988	Observational study of cyclosporine treatment in 56 participants over 14 years of age with NS, MCD in 23. (Not RCT)
Meyrier 1991	Two single arm observational studies in patients with NS (either cyclosporine monotherapy or cyclosporine and prednisone). (Not RCT)
Meyrier 1994	Longitudinal follow up study of cyclosporine in 36 adults with steroid-dependent or steroid-resistant idiopathic NS. (Not RCT)
Meyrier 1996	Review article of the utility of cyclosporine treatment for NS in adults. (Not RCT)
Mocan 1997	Paediatric participants. (Not adult NS)
Naigui 1997	RCT for cyclosporine versus prednisone and cyclophosphamide versus prednisone in nephrotic syndrome. Undefined numbers of patients had NS caused by MCD, focal and segmental glomerulosclerosis, membranous nephropathy and membranoproliferative glomerulonephritis. (Not MCD)
Ni 2003	Unclear whether RCT. Comparison of leflunomide and prednisone with cyclophosphamide and prednisone in 41 patients with NS (MCD=12). (Not RCT, not MCD)
Niaudet 1994	Review article. (Not RCT)
Olbricht 1999	RCT of simvastatin versus placebo in 56 patients with NS. No patient had MCD. (Not MCD)
Pecoraro 2003	Paediatric study. (Not adult NS)
Piccoli 1993	RCT comparing deflazacort and prednisone for adults with NS. No patients with MCD were enrolled. (Non-MCD)
Pirisi 1998	Observational study of immunosuppression in NS (No patient with MCD was enrolled). (Not MCD, not RCT)
Ponticelli 1993	Multicentre RCT of 73 patients (adults and children) comparing cyclophosphamide with cyclosporine in steroid dependent or frequently relapsing idiopathic NS. Included people with a kidney biopsy showing focal and segmental glomerulosclerosis.

Study	Reason for exclusion
Ponticelli 1993A	RCT of cyclosporine in steroid-resistant idiopathic NS. Included people with either MCD or focal segmental glomerulosclerosis.
Rabelink 1988	RCT of simvastatin versus cholestyramine in NS. No patient had MCD. (Not MCD)
Reichert 1999	Pharmacokinetic observational study of prednisone in all-cause NS. No patient had MCD. (Not RCT)
Sharpstone 1969	RCT of 8-week courses of prednisone with or without azathioprine. Patients entering study with MCD were not randomised. (Not RCT)
Shibasaki 2004	Comparative study of mizoribine versus standard care in steroid resistant NS. 28/175 had NS caused by MCD or focal and segmental glomerulosclerosis (combine histological category). (Not MCD)
Spitalewitz 1993	Prospective double-blind placebo-controlled study of pravastatin versus placebo in patients with NS. No patient had MCD. (Not MCD)
Sural 2001	RCT of levamisole versus steroid and cyclophosphamide in childhood NS. (Not adult NS)
Tejani 1988	Children (1-18 years) with NS > 1 year randomised to high-dose prednisone versus cyclosporine and low-dose prednisone. (Not adult NS)
Thomas 1993	Patients with sub-nephrotic range proteinuria, steroid-responsive MCD was an exclusion criteria. (Not MCD, Not NS)
Toto 2000	RCT of adults with NS from any glomerular cause (not described in detail) dichotomised into those with hypercholesterolaemia or mixed dyslipidaemia. (Not MCD)
Uldall 1972	Observational study of cyclophosphamide in 10 individuals with NS due to MCD. (Not RCT)
Wyszynska 1988	Single arm study in children. (Not RCT)
Ye 1993	Cause of NS not defined. RCT comparing short duration prednisone (< 8 weeks) versus longer duration (> 8 weeks). (Not MCD)
Yoshikawa 1995	Observational study in children. (Not RCT)

MCD - minimal change disease; NS - nephrotic syndrome
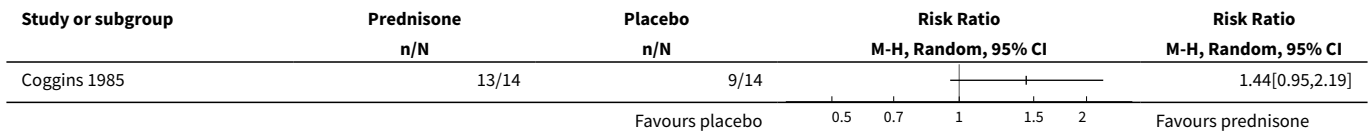
DATA AND ANALYSES

Comparison 1. Steroid versus placebo or no treatment

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

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
3 Sustained remission during fol- low-up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Loss of oedema	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Avascular necrosis	1		Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 67.91]
5.2 Doubling serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.89]
5.3 Kidney failure	1		Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.55]

Analysis 1.1. Comparison 1 Steroid versus placebo or no treatment, Outcome 1 Complete remission.

Study or subgroup	Prednisone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1985	13/14	9/14		1.44[0.95,2.19]

Favours placebo 0.5 0.7 1 1.5 2 Favours prednisone

Analysis 1.2. Comparison 1 Steroid versus placebo or no treatment, Outcome 2 Partial remission.

Study or subgroup	Prednisone n/N	Placebo/No treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1985	1/14	1/14		1[0.07,14.45]

Favours placebo 0.01 0.1 1 10 100 Favours prednisone
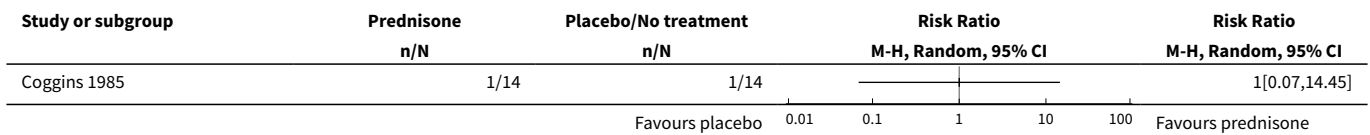
Analysis 1.3. Comparison 1 Steroid versus placebo or no treatment, Outcome 3 Sustained remission during follow-up.

Study or subgroup	Prednisone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1985	5/14	2/14		2.5[0.58,10.8]

Favours placebo 0.01 0.1 1 10 100 Favours prednisone
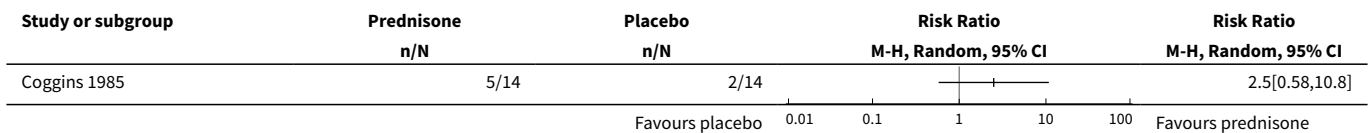
Analysis 1.4. Comparison 1 Steroid versus placebo or no treatment, Outcome 4 Loss of oedema.

Study or subgroup	Prednisone n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1985	12/12	9/11		1.21[0.89,1.66]

Favours prednisone 0.5 0.7 1 1.5 2 Favours no treatment

![Cochrane Library logo] Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews
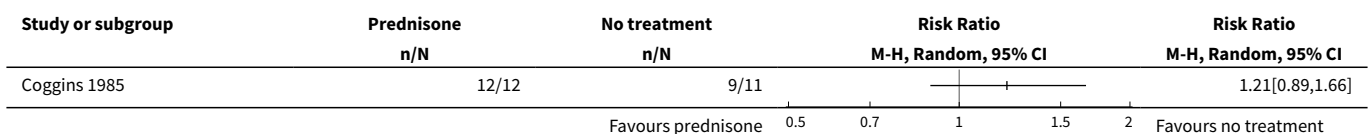
Analysis 1.5. Comparison 1 Steroid versus placebo or no treatment, Outcome 5 Adverse events.
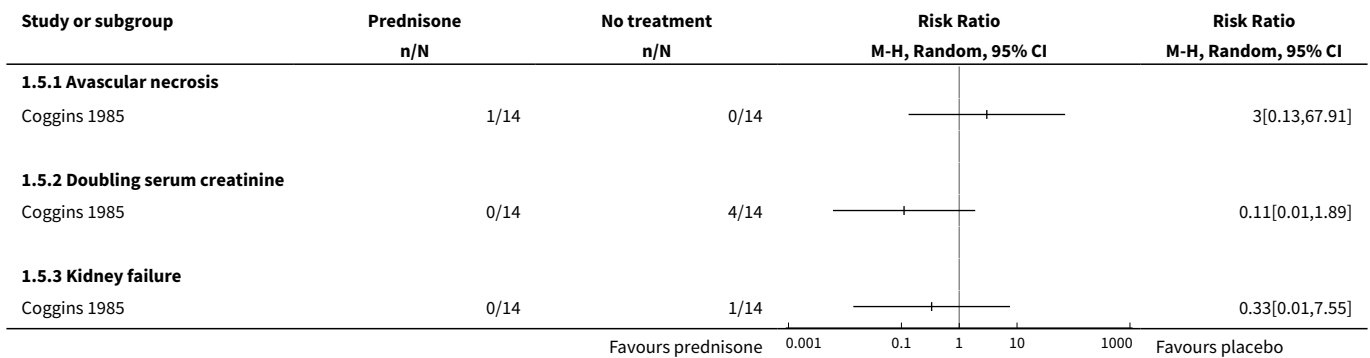
Study or subgroup	Prednisone n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.5.1 Avascular necrosis				
Coggins 1985	1/14	0/14		3[0.13,67.91]
1.5.2 Doubling serum creatinine				
Coggins 1985	0/14	4/14		0.11[0.01,1.89]
1.5.3 Kidney failure				
Coggins 1985	0/14	1/14		0.33[0.01,7.55]

Favours prednisone 0.001 0.1 1 10 1000 Favours placebo
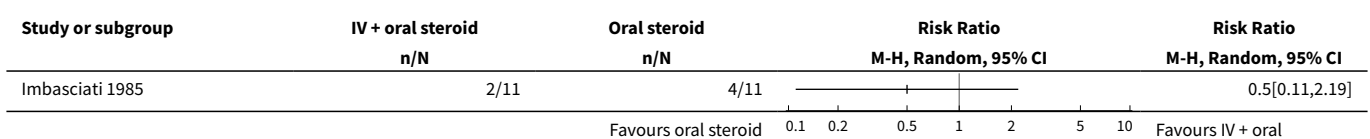
Comparison 2.   Intravenous + oral steroid versus oral steroid

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Sustained remission during fol-low-up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Thrombosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Relapse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1.   Comparison 2 Intravenous + oral steroid versus oral steroid, Outcome 1 Complete remission.

Study or subgroup	IV + oral steroid n/N	Oral steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Imbasciati 1985	8/11	11/11		0.74[0.5,1.08]

Favours oral steriod 0.5 0.7 1 1.5 2 Favours IV + oral
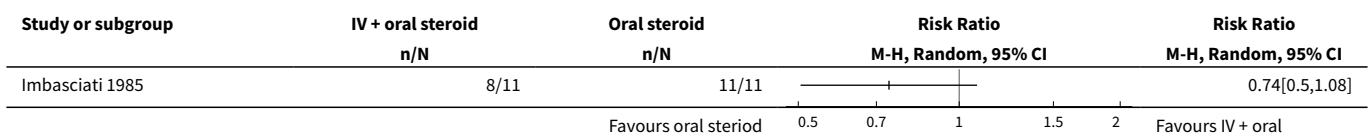
Analysis 2.2.   Comparison 2 Intravenous + oral steroid versus oral steroid, Outcome 2 Sustained remission during follow-up.

Study or subgroup	IV + oral steroid n/N	Oral steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Imbasciati 1985	2/11	4/11		0.5[0.11,2.19]

Favours oral steroid 0.1 0.2 0.5 1 2 5 10 Favours IV + oral

Analysis 2.3.   Comparison 2 Intravenous + oral steroid versus oral steroid, Outcome 3 All-cause mortality.

Study or subgroup	IV + oral steroid n/N	Oral steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Imbasciati 1985	0/11	1/11		0.33[0.02,7.39]

Favours IV + oral 0.01 0.1 1 10 100 Favours oral steroid
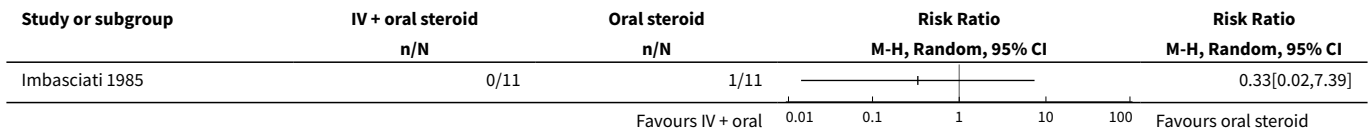
Analysis 2.4.   Comparison 2 Intravenous + oral steroid versus oral steroid, Outcome 4 Adverse events.

Study or subgroup	IV + oral steroid n/N	Oral steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.4.1 Thrombosis				
Imbasciati 1985	2/11	1/11		2[0.21,18.98]

Favours IV + oral 0.01 0.1 1 10 100 Favours oral steroid

Analysis 2.5.   Comparison 2 Intravenous + oral steroid versus oral steroid, Outcome 5 Relapse.

Study or subgroup	IV + oral steroid n/N	Oral steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Imbasciati 1985	6/8	7/11		1.18[0.65,2.15]

Favours IV + oral 0.2 0.5 1 2 5 Favours oral steroid

Comparison 3.   Intravenous steroid versus oral steroid

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Time to complete remission (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

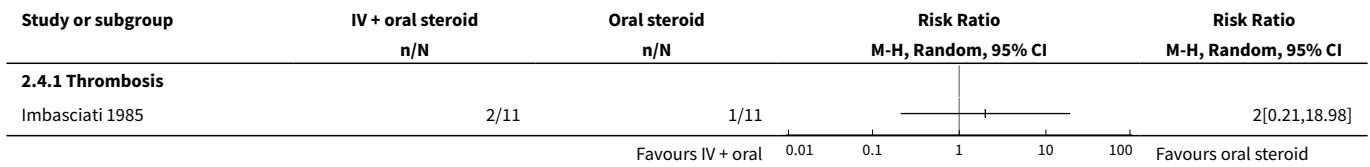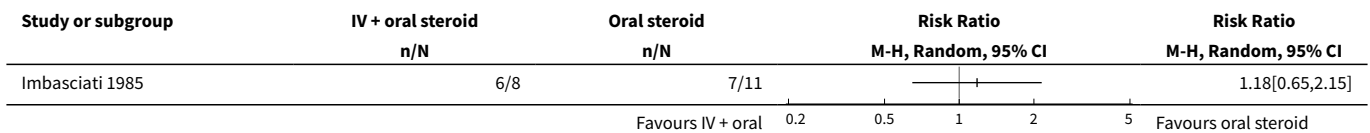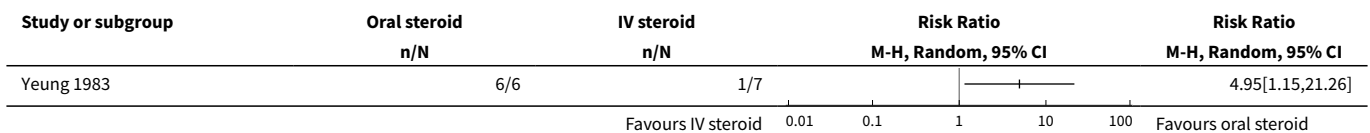### Analysis 3.1.   Comparison 3 Intravenous steroid versus oral steroid, Outcome 1 Complete remission.

Study or subgroup	Oral steroid n/N	IV steroid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Yeung 1983	6/6	1/7		4.95[1.15,21.26]

Favours IV steroid 0.01 0.1 1 10 100 Favours oral steroid

Analysis 3.2. Comparison 3 Intravenous steroid versus oral steroid, Outcome 2 Time to complete remission (days).

Study or subgroup	IV steroid		Oral steroid		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Yeung 1983	5	20 (10.2)	6	16.8 (10.7)		3.17[-9.21,15.55]

Favours IV steroid -20 -10 0 10 20 Favours oral steroid

ADDITIONAL TABLES

Table 1. Adverse events

Study	Treatment Group	Number of participants	Adverse events
Coggins 1985	Prednisone	14	Psychosis (1); avascular necrosis (1)
Coggins 1985	No treatment	14	Doubling of serum creatinine (3); renal replacement therapy (1)
Imbasciati 1985	Prednisone	11	Thrombosis (1); death (1)
Imbasciati 1985	Methylprednisone and prednisone	11	Pulmonary embolism (1)
Yeung 1983	Methylprednisone	10	-
Yeung 1983	Prednisone	8	Gastroenteric bleed (1)

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
EMBASE	1. exp clinical trial/ 2. comparative study/ 3. drug comparison/ 4. major clinical study/ 5. randomisation/ 6. crossover procedure/ 7. double blind procedure/ 8. single blind procedure/ 9. placebo/ 10. prospective study/ 11. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab. 12. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab. 13. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab. 14. (cross?over$ or (cross adj1 over$)).ti,ab. 15. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).ti,ab.

(Continued)

16. or/1-10
17. or/11-15
18. 16 or 17
19. minimal change glomerulonephritis/
20. Lipoid Nephrosis/
21. minimal change disease.tw.
22. minimal change glomerulonephritis.tw.
23. minimal change nephr$.tw.
24. nil disease.tw.
25. lipoid nephrosis.tw.
26. idiopathic nephrotic syndrome.tw.
27. or/19-26 1. exp clinical trial/
2. comparative study/
3. drug comparison/
4. major clinical study/
5. randomisation/
6. crossover procedure/
7. double blind procedure/
8. single blind procedure/
9. placebo/
10. prospective study/
11. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab.
12. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab.
14. (cross?over$ or (cross adj1 over$)).ti,ab.
15. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).ti,ab.
16. or/1-10
17. or/11-15
18. 16 or 17
19. minimal change glomerulonephritis/
20. Lipoid Nephrosis/
21. minimal change disease.tw.
22. minimal change glomerulonephritis.tw.
23. minimal change nephr$.tw.
24. nil disease.tw.
25. lipoid nephrosis.tw.
26. idiopathic nephrotic syndrome.tw.
27. or/19-26

CENTRAL	#1 Nephrosis, Lipoid, this term only in MeSH products #2 lipoid next nephrosis in All Fields #3 minimal next change next disease in All Fields #4 minimal next change next glomerul* in All Fields #5 minimal next change next nephr* in All Fields #6 nil next disease in All Fields #7 idiopathic next nephrotic next syndrome in All Fields #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
MEDLINE	1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trials/ 4. random allocation/ 5. double blind method/ 6. single blind method/ 7. or/1-7 8. animals/ not (animals/ and human/) 9. 7 not 8 10. clinical trial.pt.

(Continued)

> 11. exp clinical trials/
> 12. (clinic$ adj25 trial$).ti,ab.
> 13. cross-over studies/
> 14. (crossover or cross-over or cross over).tw.
> 15. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
> 16. placebos/
> 17. placebo$.ti,ab.
> 18. random$.ti,ab.
> 19. research design/
> 20. or/10-19
> 21. 20 not 8
> 22. 9 or 21
> 23. Nephrosis Lipoid/
> 24. minimal change disease.tw.
> 25. minimal change glomerulonephritis.tw.
> 26. minimal change nephro$.tw.
> 27. nil disease.tw.
> 28. lipoid nephrosis.tw.
> 29. idiopathic nephrotic syndrome.tw.
> 30. or/23-29

WHAT'S NEW

Date	Event	Description
13 August 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 1, 2008

Date	Event	Description
14 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review - SCP, KN, GFMS
Screening of titles and abstracts - SCP, KN
Assessment for inclusion - SCP, KN
Quality assessment - SCP, KN
Data extraction - SCP, KN
Data entry into RevMan - SCP, KN
Data analysis - SCP, KN
Disagreement resolution - SCP, KN, GFMS

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Methylprednisolone [therapeutic use]; Nephrosis, Lipoid [complications] [*drug therapy]; Nephrotic Syndrome [*drug therapy] [etiology]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Adult; Humans