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The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review

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The research reported in this monograph was commissioned by the HTA Programme as project number 05/37/01. The contractual start date was in September 2005. The draft report began editorial review in March 2006 and was accepted for publication in January 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review

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Objectives: To assess the clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome (SRNS).
Data sources: Electronic databases from inception to February 2006, bibliographies of studies, and experts in the field.
Review methods: Studies were selected, quality assessed and data were extracted using recognised methods agreed a priori. Meta-analysis was undertaken where appropriate using the random effects model. Where data allowed, subgroup analysis was undertaken according to renal histopathology.
Results: Two systematic reviews and 11 trials were included in the clinical effectiveness review; however, the quality of reporting and methodology of the included studies was generally poor. No economic evaluations were identified. No statistically significant difference in remission rates was found between cyclophosphamide plus prednisone and prednisone alone for all children or those with focal segmental glomerulosclerosis (FSGS), also the time to response was statistically significantly less with cyclophosphamide (38.4 days versus 95.5 days). Remission rates were not statistically significantly different between intravenous and oral cyclophosphamide. Vomiting was common with intravenous cyclophosphamide, while pneumonia and alopecia occurred in the oral group. Ciclosporin statistically significantly increased the number of children with complete remission compared with placebo or supportive treatment, but not for the FSGS subgroup, adverse effects including infection and hypertension differed little between groups. No differences were found between azathioprine and placebo, with about 13% of each group having remission. Complete or partial remission occurred in six out of seven patients on the 18-month methylprednisolone regimen and three out of five patients on the 6-month regimen, for both groups renal function improved and adverse events such as hypertension and frequent infections occurred. Intravenous dexamethasone and methylprednisolone produced similar complete remission rates, partial remission rates, median time to response (about 10 days) and total number of adverse events, with hypertension as the most common. Six-hour urinary albumin and urinary albumin to creatinine ratio decreased statistically significantly with high-dose but not low-dose enalapril. Tuna fish oil was not associated with any statistically significant improvements in proteinuria, creatinine clearance, serum creatinine or lipid profiles compared with placebo. A very limited literature was found on costs associated with SRNS in children. The pharmaceutical cost of treatment varied considerably: an 8-week course of cyclophosphamide cost less than £6, while a course of ciclosporin cost almost £900 per year. Treatment with tacrolimus, an alternative to ciclosporin, was estimated to cost in excess of £3400 per year. Healthcare medical management costs were estimated; varying by treatment strategy, they ranged from £250 to £930 per year in patients not experiencing complications. Other longer term costs may also be incurred. Lack of data meant that cost-effectiveness modelling was not feasible.
Conclusions: The clinical effectiveness literature on treatments for idiopathic SRNS in children is very limited. The available evidence suggests a beneficial effect of ciclosporin on remission rates and of cyclophosphamide on time to remission; however, the strength of the conclusions drawn is limited by the poor quality of the included studies. The other treatments included in this review were each evaluated by only one study, and none found a statistically

significant effect. There is insufficient evidence to determine whether or not there is a clinically significant difference. The available data on costs and outcomes are sparse and do not permit the reliable modelling of the cost-effectiveness of treatments for SRNS at present. A modelling framework is suggested, should more relevant data become available. A well-designed adequately powered randomised controlled trial comparing ciclosporin with other treatments in children with SRNS without genetic mutation is required.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

Glossary

Cellulitis An acute spreading bacterial infection in the deep layers of the skin, characterised by redness, warmth, swelling and pain.

Creatinine A blood and urinary chemical used to estimate overall kidney function. It is produced by the muscles at a regular, predictable rate and excreted by the kidneys. If the filtering of the kidney is deficient, blood levels rise.

Creatinine clearance A method that estimates the glomerular filtration rate of the kidneys. This is the amount of liquid filtered out of the blood that is processed by the kidneys. Creatinine clearance is the amount of creatinine in the urine, divided by the concentration in the blood, over a certain period of time.

Gametogenesis Production of spermatozoa or oocytes.

Hypertrichosis Excessive hair growth.

Immunoglobulin Produced by plasma cells to aid in fighting infection.

Myelotoxic Toxic or destructive to bone marrow.

Nephrotoxic Toxic or destructive to kidney cells.

List of abbreviations

ACE	angiotensin-converting enzyme
CCT	controlled clinical trial
CEA	cost-effectiveness analysis
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DBP	diastolic blood pressure
ESRD	end-stage renal disease
ESRF	end-stage renal failure
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HRQoL	health-related quality of life
IgG	immunoglobulin G
ISKDC	International Study of Kidney Disease in Children
ITT	intention-to-treat

continued

List of abbreviations *continued*

i.v.	intravenous
LDL	low-density lipoprotein
MBGN	membranoproliferative glomerulonephritis
MCNS	minimal change nephrotic syndrome
MPGN	mesangioproliferative glomerulonephritis
NA	not applicable
ns	not significant
NS	nephrotic syndrome
NSAID	non-steroidal anti-inflammatory drug
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SRNS	steroid-resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Nephrotic syndrome is a collection of signs and symptoms, including protein in the urine, low blood protein levels, high cholesterol levels and swelling. First line treatment is with oral corticosteroids, but some children do not respond to this treatment. The optimal treatment of steroid-resistant nephrotic syndrome (SRNS) is uncertain.

Objectives

The objectives of this review were to assess the clinical effectiveness and cost-effectiveness of treatments for children with idiopathic SRNS.

Methods

Data sources

Electronic databases were searched from inception to February 2006. Bibliographies of included studies and related papers were checked for relevant studies. Experts were contacted for advice and peer review and to identify additional studies.

Study selection

Titles and abstracts were screened for eligibility by one reviewer and checked by a second. Inclusion criteria were applied to the full text of selected papers by two reviewers, with differences resolved though discussion. Inclusion criteria were:

- intervention: high-dose steroids, immunosuppressive agents, alkylating agents, plasma exchange therapy, angiotensin-converting enzyme inhibitors or fish oils
- patients: children aged 1–18 years with idiopathic SRNS
- studies: systematic reviews of randomised controlled trials (RCTs), RCTs, controlled clinical trials, prospective cohort studies with concurrent controls and economic evaluations; abstracts were considered if sufficient information was presented; non-English-language studies were excluded
- outcomes: remission rates, relapse rates, renal function, adverse effects, long-term renal survival, quality of life, costs and cost-effectiveness.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second, with differences resolved though discussion. The quality of included studies was assessed using criteria from the NHS Centre for Reviews and Dissemination.

Data synthesis

The clinical effectiveness data were synthesised through a narrative review with full tabulation of results. Meta-analysis was undertaken, where appropriate, using the random effects model. Where data allowed, subgroup analysis was undertaken according to renal histopathology [e.g. minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS)].

Results

Number and quality of studies

Two systematic reviews and 11 trials were included in the systematic review of clinical effectiveness. The quality of reporting and methodology of the included studies was generally poor. No economic evaluations were identified.

Summary of benefits and risks

No statistically significant difference in remission rates was found between cyclophosphamide plus prednisone and prednisone alone for all children [relative risk (RR) 1.15, 95% confidence interval (CI) 0.65 to 2.05] or those with FSGS (RR 1.01, 95% CI 0.43 to 2.37). Time to response was statistically significantly less with cyclophosphamide [38.4 days (range 6–80) versus 95.5 days (range 61–129), $p < 0.05$]. Death occurred in five patients. Remission rates were not statistically significantly different between intravenous and oral cyclophosphamide. Vomiting was common with intravenous cyclophosphamide, while pneumonia and alopecia occurred in the oral group.

Ciclosporin statistically significantly increased the number of children (both MCNS and FSGS included) with complete remission compared with placebo or supportive treatment (RR 7.66, 95% CI 1.06 to 55.34), but not for the FSGS subgroup (RR 5.83, 95% CI 0.75 to 45.09). One trial did not contribute to the summary statistic as no patient in either group had remission. One study reported no major side-effects. Adverse effects including infection and hypertension differed little between groups.

No differences were found between azathioprine and placebo, with about 13% of each group having remission.

Complete or partial remission occurred in six out of seven patients on the 18-month methylprednisolone regimen and three out of five patients on the 6-month regimen. Renal function improved in both groups. Adverse events such as hypertension and frequent infections occurred in both groups. One death occurred.

Intravenous dexamethasone and methylprednisolone produced similar complete remission rates (35.1%, 95% CI 22.9 to 48.9, versus 33.3%, 95% CI 14.6 to 46.9) and partial remission rates (12.3%, 95% CI 5.0 to 23.7 versus 14.3%, 95% CI 3.0 to 36.3). Median time to response (about 10 days) and total number of adverse events were also similar. The most common adverse event was hypertension. There was a statistically significant decrease in median urine to albumin creatinine ratio in both groups.

Six-hour urinary albumin and urinary albumin to creatinine ratio decreased statistically significantly with high-dose but not low-dose enalapril. The difference in the urine albumin to creatinine ratio reduction percentage between the two groups was statistically significant in the period before cross-over only. A small number of patients experienced dry cough.

Tuna fish oil was not associated with any statistically significant improvements in proteinuria, creatinine clearance, serum creatinine or lipid profiles compared with placebo.

Summary of costs

A very limited literature was found on costs associated with SRNS in children. Costs consisted of treatment costs, longer term monitoring and management costs, and longer term costs for patients who progress to end-stage renal failure. The pharmaceutical cost of treatment varied considerably: an 8-week course of cyclophosphamide cost less than £6, while a course of ciclosporin cost almost £900 per year. Treatment with tacrolimus, an alternative to ciclosporin, was estimated to cost in excess of £3400 per year. In addition to pharmaceutical costs, healthcare medical management costs were estimated; varying by treatment strategy, they ranged from £250 to £930 per year in patients not experiencing complications. Other longer term costs may be incurred; these may comprise the cost of care for longer term side-effects and complications, and costs associated with the onset and management of renal failure. Children who fail to respond to treatment are at high risk of developing end-stage renal failure, the costs of which are considerable.

Summary of cost-effectiveness

No published evidence on the cost-effectiveness of treatments for SRNS in children was identified. Subsequent searches were undertaken to identify economic evaluations and economic evidence for SRNS in adults. The current data are sparse and the modelling of the cost-effectiveness of current treatments for SRNS is not feasible at present. It is clear that in future cost-effectiveness analysis it would be inappropriate to compare interventions with a 'no treatment' alternative. It is suggested here that ciclosporin be used as the comparator strategy in future cost-effectiveness analysis, and that the appropriate patient group for analysis may be those patients either not indicated for cyclophosphamide treatment and/or not responding to cyclophosphamide, who would typically be treated with ciclosporin. Where appropriate data on clinical effectiveness were available, a framework for the assessment of the cost-effectiveness of treatment for SRNS was identified in the current review.

Conclusions

Implications for healthcare

The clinical effectiveness literature on treatments for idiopathic SRNS in children is very limited. The available evidence suggests a beneficial effect of ciclosporin on remission rates and of cyclophosphamide on time to remission; however, the strength of the conclusions drawn is limited by the poor quality of the included studies. The other treatments included in this review were each evaluated by only one study, and none found a statistically significant effect. There is insufficient evidence to determine whether or not there is a clinically significant

difference. No economic evaluations were identified. The available data on costs and outcomes are sparse and do not permit the reliable modelling of the cost-effectiveness of treatments for SRNS at present. A modelling framework is suggested, should more relevant data become available.

Recommendation for future research

A well-designed adequately powered RCT comparing ciclosporin with other treatments in children with SRNS without genetic mutation is required.

Chapter 1
Background

Description of health problem

Nephrotic syndrome is a collection of signs and symptoms including proteinuria (protein in urine), hypoalbuminaemia (low blood protein levels), hyperlipidaemia (high cholesterol levels) and oedema (swelling). These symptoms develop from primary alterations in the permselectivity barrier in the kidney glomerular capillary wall, which is no longer able to restrict protein loss to less than 100 mg/m^2 body surface area per day.[1] First line treatment of nephrotic syndrome is with oral corticosteroids. However, it has been estimated that 12–22%[2–5] of patients do not respond after at least 4 weeks of treatment; these patients are described as steroid resistant. Patients who do not initially respond to steroids may remit spontaneously or with repeated courses of corticosteroids over a longer period, although relapses may still occur.[2,6] Of those children who initially respond to steroids, some may develop steroid resistance during subsequent relapses.[6,7]

Idiopathic or primary nephrotic syndrome occurs in the absence of factors known to cause nephrotic syndrome, such as genetic disorders (e.g. Fabry disease, sickle cell disease), infections (e.g. hepatitis, HIV), drugs [e.g. non-steroidal anti-inflammatory drugs (NSAIDs)], immunological or allergic disorders (e.g. food allergens), malignant disease (e.g. lymphoma) or glomerular hyperfiltration (e.g. morbid obesity). While the pathogenesis of idiopathic nephrotic syndrome is unclear, mutations in genes that encode important glomerular epithelial-cell proteins have been identified.[1] In particular, steroid-resistant nephrotic syndromes have been associated with gene mutations, for example, congenital nephrotic syndromes have been associated with NPHS1, NPHS2 and WT-1 mutations. Mutations in the gene ACTN4 are associated with autosomal dominant focal segmental glomerulosclerosis (FSGS), and mutations in the gene NPHS2 which encodes podocin have been associated with familial autosomal recessive steroid-resistant nephrotic syndrome (SRNS)[8] and a significant number of cases of sporadic SRNS. Early diagnosis of mutations in new cases of SRNS could prevent unnecessary treatment with corticosteroid and other immunosuppressive therapy.[9]

Idiopathic nephrotic syndrome is associated with a range of histological features in the kidney, the most common of which include:

- minimal change nephrotic syndrome (MCNS) (minimal change disease or minimal change nephropathy): defined by the absence of any conspicuous glomerular abnormality on light microscopy; in some specimens a very slight increase in mesangial matrix and/or cellularity may be observed
- focal segmental glomerulosclerosis (FSGS): characterised by the presence of at least one glomerulus showing a definite segmental area of sclerosis (with or without accompanying tubular atrophy and interstitial fibrosis), in the absence of any other identifiable cause of glomerular scarring
- mesangioproliferative glomerulonephritis (MPGN): defined by the presence of increased mesangial matrix and moderate to prominent mesangial cell proliferation in the absence of segmentally sclerosed glomeruli or other significant pathologies
- membranoproliferative glomerulonephritis (MBGN) (also known as mesangiocapillary glomerulonephritis): characterised by both diffuse mesangial proliferation and thickening of the glomerular capillary wall due to mesangial cell interposition
- other histological variants, such as membranous nephropathy, which are much less common in children.

These various pathological features carry prognostic significance, but it is not clear whether they represent distinct separate diseases or are simply different morphological patterns of common underlying pathophysiological processes. Most patients with MCNS respond to corticosteroid therapy, with only 2–7%[4,5,10] being steroid resistant. In contrast, most (83%) patients with FSGS are steroid resistant,[5] and studies have reported that 72–90%[4,5,10] of all non-MCNS variants are steroid resistant, ranging from 100% of those with membranous nephropathy to 25% of those with focal global glomerular obsolescence with tubular atrophy.[4] In its early stages, FSGS may be difficult or impossible to distinguish from MCNS, depending on issues of sampling and

extent of involvement. Repeat renal biopsies have demonstrated morphological transition between MCNS, FSGS[11] and diffuse mesangial proliferation,[12] so that these histological variations of idiopathic nephrotic syndrome may be found alone or in any combination on sequential biopsies in the same patient.[13] Children with MCNS differ from those with MBGN in that they are more likely to be younger and male, and less likely to have haematuria. There are overlaps between the characteristics of FSGS patients with both MCNS and MBGN.[14] Only a small percentage of children with MCNS exhibit haematuria (13%) or hypertension (9%), but they account for about one-third of the total who have these additional features.[10]

Untreated nephrotic syndrome is associated with increased risks of life-threatening infection, thromboembolism, lipid abnormalities and malnutrition. Outcome is related to the histopathological features of the disease on renal biopsy, especially the extent of chronic changes such as glomerulosclerosis, tubular atrophy and interstitial fibrosis. The majority of children with FSGS and persistent proteinuria develop chronic renal failure,[2,15] while overall those with MCNS have a generally favourable outcome.[2]

Epidemiology

The incidence of all idiopathic nephrotic syndrome in children under 16 years is estimated at about 2 per 100,000[16,17] to 2.3 per 100,000 [95% confidence interval (CI) 2.0 to 2.6],[3] which equates to about 200–240 children diagnosed in England and Wales per year. The prevalence is reported at 16 per 100,000,[17] which equates to about 1660 children in England and Wales. Nephrotic syndrome is more common in boys than girls, with ratios such as 2:1,[17] 1.6:1[3,10] and 1.5:1[16] reported.

A UK study found the incidence of paediatric SRNS to be 0.3 per 100,000 (95% CI 0.2 to 0.4),[3] or about 30 children diagnosed per year. The male to female ratio for steroid-resistant cases was 1.2:1.

Early reports of the International Study of Kidney Disease in Children (ISKDC) showed that MCNS was the most common histological finding in idiopathic nephrotic syndrome, accounting for approximately 77% of cases,[4,5,14] while 7%[14] to 9.4%[5] of children had FSGS and 5%[5] to 7.5%[14] had MBGN. More recent studies suggest that the pattern is changing and that the incidence of FSGS is increasing, with a reciprocal decline in the incidence of MCNS. One US study found that before 1990, FSGS was diagnosed in 23% of all renal biopsies, but increased to 47% subsequently ($p = 0.02$), and this pattern was observed in all ethnic groups.[18] Srivastava and colleagues, in contrast, reported no significant differences in the frequencies of MCNS and FSGS between the periods 1984–9 and 1990–5, in a study also located in the USA. However, they note that the incidence of FSGS reported among their patients (23%) was much higher than in the earlier studies. Of the remaining patients, 52.7% had MCNS, 12.2% had MPGN, 9.5% had MBGN, 1.9% had membranous glomerulonephritis and 0.7% had focal global glomerulosclerosis. Only 68.9% of these patients underwent renal biopsy; those without biopsy were assumed to have minimal change disease.[19] It has been suggested that renal biopsy findings in recent published series are not representative of the true incidence of the various histopathological categories, as in many centres renal biopsy is only recommended for patients who do not respond to steroids.[13]

The distribution of the histological subtypes is related to gender, age and ethnicity of the population. While more boys have MCNS, the other variants are more common in girls.[10] Children 6 years and under are more likely to have MCNS than other lesions (87% versus 13%).[4] The most common variant among African-American children is FSGS, accounting for 47% of cases with nephrotic syndrome. Moreover, a greater proportion of black or Hispanic children with FSGS reach end-stage renal disease (ESRD) than white children, despite similar treatment.[20] UK studies have demonstrated that the incidence of steroid-sensitive nephrotic syndrome (SSNS) is significantly higher among Asian children.[3,21]

When considering the histology of patients according to their response to steroids, most (92–95%)[2,4,22] steroid-sensitive patients have MCNS, while 25%[4] to 50%[2] of steroid-resistant patients have MCNS and 15%[2] to 25%[4] have FSGS.

Impact of health problem

Nephrotic syndrome has a sudden onset and oedema is the major presenting symptom.[13] Initially, the oedema is mild and is gravity dependent, being periorbital in the early morning and becoming more generalised during the day. More severe oedema can require diuretic therapy.[23] Children can experience abdominal pain due to an accumulation of fluid in the

abdominal cavity (ascites),[13] and fluid around the lungs (pleural effusions) may cause breathlessness and hypoxia. Acute renal failure may arise secondary to hypovolaemia, and peritonitis, pancreatitis, thrombosis, hyperlipidaemia or anaemia can also occur. Children may also experience hypothyroidism secondary to nephrotic syndrome. Bacterial infections, such as peritonitis, meningitis, pneumonitis and cellulitis are common, possibly due to low immunoglobulin G (IgG) levels, urinary loss of factor B and impaired T-lymphocyte function.[13] Patients are also at increased risk of thromboembolic complications, due to the hypercoagulability state, hypovolaemia, immobilisation and infection. Growth can be severely affected in children with persistent nephrotic syndrome.[13] In addition, chicken pox can be very serious in a child taking steroids or other immunosuppressive agents.[23]

Evidence suggests that proteinuria is a cause of progressive renal injury as well as a marker of renal disease, and may also be a long-term risk factor for atherosclerosis in children.[23]

Patients who develop end-stage renal failure (ESRF) secondary to SRNS and undergo renal transplantation are at risk of developing recurrent disease in the graft,[24,25] which is associated with a high risk of acute renal failure, episodes of acute rejection and increased graft loss from rejection.[26] However, this is less common with the forms of SRNS associated with gene mutations.[8]

The burden of SRNS on children and their families can be significant. The child will require regular medical therapy and monitoring of urine. They may also need fluid restriction or a special diet with no added salt, or restrictions of phosphate and potassium where renal impairment is present. Regular hospital attendance is required, and time absent from school is more likely.

Measurement of disease

Nephrotic syndrome is defined as heavy proteinuria (>50 mg/kg/day or >40 mg/m^2/hour determined quantitatively on an overnight collection of urine), accompanied by hypoalbuminaemia ($\leq$2.5 g/dl)[2,14,27] or by spot urinary protein to creatinine ratio higher than 0.25 g protein/mmol creatinine (or >2.0 mg protein/mg creatinine).[1] In severe nephrotic syndrome the urine may contain higher molecular weight proteins as well as albumin, and a selectivity index above 0.15 or 0.20 may be observed. However, the test is of limited clinical value because of its poor specificity.[13] Urinary sodium excretion is low (<5 mmol/24 hours), associated with sodium retention and oedema.[13]

Classification of histopathology is made by percutaneous renal biopsy. This is an invasive procedure, and is not indicated at onset in a child aged 1–8 years with typical symptoms.[28] However, all children who have failed to respond to at least 28 days of therapy and have a clinical diagnosis of SRNS will undergo renal biopsy (Trompeter R: personal communication, 15 November 2005).

Current service provision

In 2003, the British Association for Paediatric Nephrology (BAPN) published 'Review of multi-professional paediatric nephrology services in the UK – towards standards and equity of care'.[29] This publication analysed the current provision and practice, and made recommendations based on evidence. It established benchmarks against which to audit not only the level of services provided, but also clinical and professional practice.

There are 13 paediatric nephrology units in the UK and the population served by each unit ranges from 1.68 to 11.65 million. There is a wide variation in the number of patients seen in the general nephrology clinics in the 13 centres, and at the time of publication of the 2003 review, the annual number of patients varied from 150 to 2067 per service.[29] The enormous variation in the provision of service will depend on local geography and medical labour resources.

It is more than likely that all steroid-resistant cases will be referred to a specialist paediatric nephrology centre for further investigation, whereas most steroid-sensitive patients will be treated by a general paediatrician. Facilities for the examination of renal biopsy will generally be available in all regional centres, although the availability of a consultant paediatric histopathologist with a special interest in renal histopathology will not be generally available in every centre.

Management of SRNS

Dependent upon the severity of the condition, affected children will be seen and managed on an outpatient basis, although occasionally it may be necessary to admit a child as an inpatient for treatment of a complication of the underlying disease.

Optimisation of the general medical condition of the child is important and this will include:

- Growth and diet must be reviewed regularly to ensure maximal nutrition appropriate to the child's age and level of renal function
- Diuretic therapy will be needed to manage a child with severe oedema, but must be used with caution as it may induce intravascular volume depletion with a risk of thromboemboli and acute renal failure as well as severe electrolyte imbalance.[28]
- Antibiotic prophylaxis, e.g. penicillin, has been advocated.[28]
- Immunisation against bacterial and viral disease is generally recommended.[28]
- Replacement therapy with vitamin D and thyroid hormone is generally accepted to be good practice in view of the excessive urinary losses of binding proteins (Trompeter R: personal communication).
- Management of anaemia is required.
- Lipid-lowering agents may be needed.
- Angiotensin-converting enzyme (ACE) inhibitors may be required.

Specific treatment of the glomerular disease

Following a course of treatment with corticosteroid therapy, there is unfortunately no consensus view of what the next course of treatment should be. Historically in the UK, a course of treatment with an alkylating agent, such as oral cyclophosphamide (3 mg/kg body weight per day for 8 weeks), has been advocated for SRNS, particularly with MCNS histology. Precise timing of this regimen in relation to steroid therapy is not clear, but most would advocate a sooner rather than later approach (Trompeter R: personal communication).

Occasionally, a combination of oral cyclophosphamide or chlorambucil (8–12 weeks) and intravenous methylprednisolone (for up to 20 months) has been proposed as a very powerful form of immunosuppression (Mendoza regimen). However, this is associated with considerable adverse side-effects, especially steroid toxicity.[30] Ciclosporin has also been demonstrated to have a favourable effect compared with placebo in the treatment of SRNS.[31] Experience with other immunosuppressive agents, such as vincristine, tacrolimus and mycophenolate mofetil, is limited. Similarly, the use of plasma exchange has been the subject of review, with only variable positive effect.[13] Continuation of alternate-day steroids may be an option, with a proportion of steroid-resistant cases entering remission where such therapy is continued.[32]

Description of technology under assessment

Summary of interventions

A number of interventions may be used to treat idiopathic steroid-resistant nephrotic syndrome in children, including pharmaceutical therapies, plasma-exchange therapy and fish oils. Of the range of potential pharmaceutical therapies used for children who are resistant to steroids (prednisone/prednisolone), some are currently given 'off label', as the indication is unlicensed (*Table 1*).

Corticosteroids: glucocorticoid therapy

High-dose corticosteroids can be used in nephrotic syndrome, but although high doses for prolonged periods may delay relapse, the higher incidence of adverse effects limits the overall benefit.[33] Corticosteroids may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and the severity of these. Side-effects include gastrointestinal, musculoskeletal, endocrine, neuropsychiatric and ophthalmic effects.

Methylprednisolone (Medrone®, Pharmacia; Solu-Medrone®, Pharmacia) is not licensed for use in nephrotic syndrome. It is indicated for inflammatory and allergic disorders, treatment of graft rejection reactions, severe erythema multiforme (Stevens–Johnson syndrome) and lupus nephritis.[33] Rapid intravenous administration of large doses is associated with cardiovascular collapse. High-dose intravenous methylprednisolone can be given in varying regimens with single doses of 10–30 mg/kg or 600 mg/m^2.

Dexamethasone (non-proprietary) is not licensed for use in nephrotic syndrome. It is indicated for inflammatory and allergic disorders, cerebral oedema associated with malignancy, bacterial meningitis and physiological replacement.[33] Dexamethasone is not commonly used for the treatment of nephrotic syndrome, but one study comparing the use of dexamethasone versus methylprednisolone administered dexamethasone at a dose of 5 mg/kg (maximum 150 g).[34]

Deflazacort (Calcort®, Shire Pharmaceuticals) is licensed for nephrotic syndrome in children. The dose is initially 1.5 mg/kg once daily (maximum 120 mg), reduced to the lowest effective dose for maintenance.[33]

TABLE 1 *Potential pharmaceutical therapies and their licence*

BNF classification and drug	Licence
Corticosteroids: glucocorticoid therapy	
Methylprednisolone	Not licensed for nephrotic syndrome
Dexamethasone	Not licensed for nephrotic syndrome
Deflazacort	Licensed for nephrotic syndrome in children
Cytotoxic drugs: alkylating drugs	
Cyclophosphamide	Not licensed for nephrotic syndrome
Chlorambucil	Not licensed for nephrotic syndrome
Cytotoxic drugs: vinca alkaloids and etoposide	
Vincristine sulphate	Not licensed for nephrotic syndrome
Immunosuppressant therapy: antiproliferative immunosuppressants	
Azathioprine	Not licensed for nephrotic syndrome
Mycophenolate mofetil	Not licensed for nephrotic syndrome
Immunosuppressant therapy: corticosteroids and other immunosuppressants	
Ciclosporin	Licensed for nephrotic syndrome in children
Tacrolimus	Not licensed for nephrotic syndrome
Drugs affecting the renin–angiotensin system: ACE inhibitors	
Enalapril maleate	Not licensed for nephrotic syndrome
Antihelmintics: ascaricides	
Levamisole	Not licensed in the UK

BNF, British National Formulary.

Cytotoxic drugs

Alkylating drugs

Alkylating agents are cytotoxic drugs that act by damaging DNA and interfering with cell replication. Problems associated with alkylating agents include an adverse effect on gametogenesis, amenorrhoea, a marked increase in the incidence of secondary tumours and leukaemia, particularly when alkylating drugs are combined with extensive irradiation, fluid retention with oedema and dilutional hyponatraemia in younger children, and urothelial toxicity with intravenous use.[33] However, the dose used in nephrotic syndrome is much less than that used in oncology and expert opinion suggests that the risk of malignancy is very small.

A Cochrane review on non-corticosteroid treatment for SSNS[35] reported side-effects from 16 trials. Both cyclophosphamide and chlorambucil were associated with leucopenia, thrombocytopenia and infections. Hair loss was reported uncommonly and cystitis did not occur with chlorambucil. There were two severe infections reported with cyclophosphamide and three serious viral infections with chlorambucil, the latter reported with a higher dose regimen.

Cyclophosphamide (non-proprietary; Endoxana®, Baxter; Cyclophosphamide tablets, Pharmacia) is not licensed for use in nephrotic syndrome.[33] It is more commonly used in the treatment of chronic lymphocytic leukaemia, the lymphomas and solid tumours. It is given by mouth or intravenously and is inactive until metabolised by the liver. Haemorrhagic cystitis is a rare but very serious complication, and therefore plenty of fluid is required. Local treatment protocols are followed, so dose and administration vary between centres. A dose of 3 mg/kg/day orally as a single dose for 8 weeks with prolonged tapering of prednisolone may be used.

Chlorambucil (Leukeran®, GlaxoSmithKline) is not licensed for use in nephrotic syndrome. It is used to treat chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and Waldenstrom's macroglobulinaemia, and is licensed for Hodgkin's disease in children.[33] It is now uncommon for chlorambucil to be used for nephrotic syndrome.

Vinca alkaloids and etoposide

Vincristine sulphate (Vincristine, non-proprietary; Oncovin®, Clonmel) is not licensed for nephrotic syndrome. It is more commonly used to treat acute leukaemias, lymphomas and paediatric solid tumours. It is given intravenously and local treatment protocols are followed. Neurotoxicity, usually as peripheral or autonomic neuropathy, is a limiting side-effect. It causes negligible myelosuppression, but may cause reversible alopecia.[33]

Immunosuppressants

Immunosuppressants are used to treat a variety of chronic inflammatory and autoimmune diseases as well as to suppress rejection in organ transplant recipients. As the immune responsiveness is impaired, infections can be severe and show atypical features. Corticosteroids may suppress clinical signs of infection and allow diseases such as septicaemia or tuberculosis to reach an advanced stage before being recognised.[33]

Antiproliferative immunosuppressants

Azathioprine (non-proprietary; Imuran®, GlaxoSmithKline) is not licensed for use in nephrotic syndrome. One study has investigated the use of azathioprine in SRNS;[22] however, it is not a common treatment for the condition. It is licensed for use in suppression of transplant rejection and treatment of autoimmune conditions when corticosteroid therapy alone has proved inadequate. Side-effects include hypersensitivity reactions, dose-related bone-marrow suppression, liver impairment, cholestatic jaundice, hair loss and increased susceptibility to infections and colitis (in patients also receiving corticosteroids), nausea, rarely pancreatitis, pneumonitis and hepatic veno-occlusive disease.[33]

Mycophenolate mofetil (CellCept®, Roche Pharmaceutical) is not licensed for nephrotic syndrome and is not commonly used to treat the condition. It is indicated for the prophylaxis of acute transplant rejection in renal transplantation. Expert opinion suggests a dose for nephrotic syndrome of 400 mg/m^2/day in divided doses. The risk of opportunistic infections and the occurrence of blood disorders such as leucopenia may be higher with mycophenolate mofetil than with azathioprine. Children may suffer a high incidence of side-effects, particularly gastrointestinal effects, calling for temporary reduction in dose or interruption of treatment. Other side-effects include cough, influenza-like syndrome, headache, viral, bacterial and fungal infections, increased blood creatinine, leucopenia, anaemia and thrombocytopenia.[33]

Corticosteroids and other immunosuppressants

Ciclosporin (Neoral®, Novartis; Sandimmun®, Novartis) is licensed for use in nephrotic syndrome in children. Ciclosporin is a calcineurin inhibitor. It is a potent immunosuppressant which is virtually non-myelotoxic, but markedly nephrotoxic. The dosage for children is 3 mg/kg twice daily orally and for maintenance treatment it is reduced to the lowest effective dose according to whole-blood ciclosporin concentrations, proteinuria and renal function. Ciclosporin is contraindicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections and malignancy. In long-term management, renal biopsies should be performed every 1–2 years to assess the progression of the renal disease and the extent of any drug-associated changes in the renal morphology that may co-exist. Side-effects include a dose-dependent increase in serum creatinine and urea during the first few weeks, renal structural changes on long-term administration, hypertrichosis, headache, tremor, hypertension, hepatic dysfunction, fatigue and gingival hypertrophy.[33] A Cochrane review of non-corticosteroid treatment for SSNS[35] found that gum hypertrophy and hirsutism were commonly associated with ciclosporin. Elevated creatinine levels and hypertension occurred in 9% and 4% of children, respectively.

Tacrolimus (Prograf®, Fujisawa) is not licensed for use in nephrotic syndrome. It is more commonly used for primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive regimens. Tacrolimus is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity and nephrotoxicity appears to be greater and cardiomyopathy has been reported.[36] Disturbance of glucose metabolism also appears to be significant, although hypertrichosis appears to be less of a problem than with ciclosporin. Side-effects include hepatic dysfunction, tremor, headache, haematological effects, altered acid–base balance and glucose metabolism, altered renal function including increased serum creatinine, and hypophosphataemia.[33]

ACE inhibitors

ACE inhibitors inhibit the conversion of the biologically inactive angiotensin I to active angiotensin II. Angiotensin II causes the contraction of vascular smooth muscle, raising blood pressure and stimulating the release of aldosterone, a steroid hormone that controls salt and water balance in the kidney. ACE inhibitors can cause profound hypotension, renal impairment and a persistent dry cough. Angiotensin II receptor antagonists (e.g. Losartan) have many properties similar to ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus do not appear to cause persistent cough.[33]

Enalapril maleate (Innovace®, Merck Sharp and Dohme) is not licensed for use in nephrotic syndrome. It is used for the treatment of hypertension and symptomatic heart failure. Enalapril maleate is not recommended in children if the creatinine clearance is less than 30 ml/minute/1.73 m^2. Side-effects include palpitations, arrhythmias, chest pain, Raynaud's syndrome, syncope, cerebrovascular accident; anorexia, ileus, stomatitis, hepatic failure; dermatological side-effects including erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and pemphigus; confusion, depression, nervousness, asthenia, drowsiness, insomnia, dream abnormalities, blurred vision, tinnitus, sweating, flushing, impotence, alopecia, dyspnoea, asthma, pulmonary infiltrates and muscle cramps.[33]

Ascaricides

Levamisole is not licensed in the UK and is available from specialist importing companies. It is indicated for use in nephrotic syndrome under specialist supervision, and is also used for roundworm and hookworm. The dosage is 2.5 mg/kg (maximum 150 mg) on alternate days. Side-effects include nausea, vomiting, diarrhoea, dizziness, headache, taste disturbances, insomnia, convulsions, influenza-like syndrome, blood disorders, vasculitis, arthralgia, myalgia and rash.[33]

Plasma-exchange therapy (plasmapheresis)

This is a procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells are retransfused to the patient. It may be used for renal transplant patients with recurrent FSGS, but recommendations are based on evidence from case series.[37] Risks include those relating to central line insertion, bacterial infection and blood-borne virus infection.

Fish oils

Fish oils have been used as an alternative treatment or as adjuvant therapy with corticosteroids.[38]

Anticipated costs associated with intervention

The costs associated with treatment for children with SRNS consist of treatment costs (e.g. medications, management, side-effects and complications), longer term monitoring and management costs (e.g. outpatient attendance, urinalysis, treatment of longer term complications), and longer term costs for patients who progress to ESRF. Children with SRNS are followed up for several years with regular outpatient appointments with a paediatric nephrologist. The pharmaceutical cost of treatment varies considerably.[33] Children who fail to respond to treatment are at a high risk of developing ESRF. The costs associated with ESRF are considerable. One study estimated the cost of dialysis for adults to be £23,504 per year[39] and it is likely to be even more expensive for children. Children with ESRF may receive a renal transplantation graft, which improves their survival and lowers healthcare resource costs to an average of £8500 per year.[39]

Chapter 2

Definition of the decision problem

Decision problem

The treatment of idiopathic SRNS in children remains unsatisfactory.[40] There is uncertainty about the optimal treatment of children, as many of the regimens in current practice have been extrapolated from studies in adults. Owing to the lack of definitive evidence of relative efficacy and lack of consensus on the best form of treatment, current treatment regimens vary considerably. Differences in treatment modes, combinations and dosage regimens are common. The optimal combinations with the least toxicity remain to be determined.

Interventions

The treatments to be considered in this review include high-dose steroids, immunosuppressive agents, alkylating agents, ACE inhibitors, plasma-exchange therapy, fish oils, and combinations of high-dose steroids with immunosuppressive agents or alkylating agents. Comparisons of these treatments with each other or with placebo or standard treatment or with different doses, durations or routes of administration will be included.

Patients

There is currently no consensus on the optimal duration of the initial course of steroid therapy for children with nephrotic syndrome.[23] The definition of steroid resistance differs between studies, with some having defined patients as steroid resistant after 8 weeks of therapy (4 weeks of daily steroids followed by 4 weeks of alternate-day therapy) and others after just 4 weeks of therapy. Moreover, some patients who have not achieved remission after 8 weeks of steroid therapy may do so after continued treatment.[2,6,32] All children defined as steroid resistant will be included in this review and the definition of 'resistance' used by the included studies will be recorded. Children aged less than 1 year with congenital or infantile nephrotic syndrome are not within the scope of this review. Response to treatment and prognosis differs according to the underlying histopathology of nephrotic syndrome, whereby patients with minimal change disease have a better prognosis. Therefore, results will be analysed separately according to histopathological subtype (MCNS and FSGS) where possible.

Outcomes

The primary outcomes of interest are remission rates, relapse rates, renal function, adverse effects, long-term renal survival and quality of life.

Overall aims and objectives of assessment

The aim of this report is to assess the clinical and cost-effectiveness of treatments for children with idiopathic SRNS.

The clinical-effectiveness chapter (Chapter 3) will update and expand on a Cochrane review of interventions for idiopathic SRNS in children, which conducted its most recent searches in April 2002.[31]

The cost-effectiveness chapter (Chapter 4) will involve a systematic search of the literature to identify (1) economic evaluations of the included treatments, (2) studies on the costs and consequences of the condition and subsequent treatment, and (3) studies reporting on methods used to model disease progression and cost-effectiveness analysis. Where appropriate, an economic model will be devised by adapting an existing cost-effectiveness model or constructing a new one using the best available evidence to determine cost-effectiveness in a UK setting.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The a priori methods for systematically reviewing the evidence of clinical effectiveness are described in the research protocol (Appendix 1), which was sent to experts for comment. Although helpful comments were received relating to the general content of the research protocol, none identified specific problems with the methods of the review. However, where the protocol originally stated that NSAIDs and nephrectomy were to be included, it was pointed out that these are only used in congenital idiopathic nephrotic syndrome and are therefore outside the scope of this review. These were subsequently excluded. The protocol stated that searches would be conducted from April 2002 in order to update the searches of a Cochrane review.[31] However, insufficient new randomised controlled trials (RCTs) were identified and therefore searches were extended to database inception to allow the identification of controlled clinical trials (CCTs) and prospective cohort studies, as stated in the protocol.

The methods outlined in the protocol are briefly summarised below.

Search strategy

A sensitive search strategy was developed, tested and refined by an experienced information scientist. Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history. Sources of information, search terms and a flowchart outlining the identification of studies are provided in Appendix 2. The most recent search was carried out in February 2006.

Searches for clinical effectiveness and cost-effectiveness were from database inception to the current date. Electronic databases searched included Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Effectiveness (DARE), Cochrane Library, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), EconLit, Medline, PubMed (previous 6 months), EMBASE, Science Citation Index (SCI), BIOSIS, Inside Information Plus, National Library of Medicine (NLM), Gateway Database, Conference Proceedings Index, PapersFirst, National Research Register (NRR), Current Controlled Trials and Clinical Trials.gov. The searches were restricted to English language. Bibliographies of related papers were screened for relevant studies. Experts were also contacted for advice and peer review, and to identify additional published and unpublished references.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by one reviewer and checked by a second reviewer. The full text of relevant papers was then obtained and inclusion criteria were applied by two reviewers. Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer.

Quality assessment

The quality of included RCTs, CCTs, cohort studies and systematic reviews was assessed using criteria recommended by NHS Centre for Reviews and Dissemination (CRD) (Appendix 3). Quality criteria were applied by one reviewer and checked by a second reviewer.

At each stage, any differences in opinion were resolved through discussion or consultation with a third reviewer.

Inclusion criteria

Interventions

Studies reporting the following interventions were eligible for inclusion:

- high-dose steroids (e.g. methylprednisolone)
- immunosuppressive agents (e.g. ciclosporin, tacrolimus, mycophenolate mofetil)
- alkylating agents (e.g. cyclophosphamide, chlorambucil)
- combinations of high-dose steroids with immunosuppressive agents or alkylating agents
- plasma-exchange therapy
- ACE inhibitors
- fish oils.

Eligible comparators included the above interventions, placebo, standard treatment, or different doses, durations or routes of administration of the above treatments.

Patients

Children aged 1–18 years with idiopathic SRNS were included. Studies of children with SSNS, congenital (birth to 3 months) or infantile (3 months to 1 year) diagnosed genetic disorders, or other renal or systemic forms of nephrotic syndrome were excluded from the review.

Types of study

Systematic reviews and meta-analyses of RCTs and RCTs were included. Systematic reviews were used as a source for RCTs and as a comparator. Initial searches found that no new RCTs had been published since the Cochrane review[31] searches were completed in April 2002 (although one trial published only as an abstract at the time of the Cochrane review had since been published as a full paper[41]); therefore, CCTs and prospective cohort studies with concurrent controls were also considered for inclusion. Studies published only as abstracts were considered if sufficient information was presented to make appropriate decisions about the methodology of the study and the results. Non-English-language studies were excluded.

Outcomes

Studies were included if they reported one or more of the following outcome measures:

- remission rates
- relapse rates
- renal function
- adverse effects
- long-term renal survival
- quality of life
- costs and cost-effectiveness.

Full economic evaluations of the specified interventions were also included. A range of designs for studies on quality of life, epidemiology and natural history was considered.

Data synthesis

Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in Appendices 4 and 5. Where appropriate, studies were combined in a meta-analysis using the random effects model, and results presented as forest plots. Dichotomous results (complete remission or no remission) were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity was analysed using a χ^2 test on $n-1$ degrees of freedom, with $p < 0.1$ used for statistical significance, and by I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Where data allowed, subgroup analysis was undertaken according to renal histopathology.

Results

Quantity and quality of research available

A flowchart outlining the identification of studies is provided in Appendix 2. In total, 1815 references were identified and, of these, two systematic reviews[40,42] and 11 trials met the inclusion criteria for the review. Six were parallel RCTs,[22,32,43–46] three were randomised cross-over trials,[38,41,47] one was a CCT[48] and one was a prospective cohort study with concurrent controls.[34] The following interventions were evaluated:

- cyclosphosphamide: three studies[32,43,44]
- ciclosporin: three studies[45–47]
- azathioprine: one study[22]
- methylprednisolone, 6 months versus 18 months: one study[48]
- dexamethasone versus methylprednisolone: one study[34]
- enalapril: one study[49]
- tuna fish oil: one study.[38]

A summary of the included studies is presented in *Table 2*, and full data extraction tables can be seen in Appendices 4 and 5.

A list of selected excluded studies is given in Appendix 6. No studies available as abstracts only met the inclusion criteria.

Systematic reviews

Of the two systematic reviews included, one was judged to be of good methodological quality,[31] while the other was deemed to be lower quality,[40] only partially searching for all relevant research, inadequately assessing the validity of included studies, and partially presenting sufficient details and appropriately summarising the individual studies (Appendix 4).

RCTs

The quality of reporting and methodology of the included RCTs was generally poor (*Table 3*). The method of randomisation was adequate in just four trials,[22,41,45,46] with concealment of allocation being adequately reported in only one of these.[22]

TABLE 2 *Study characteristics*

Study details and patient characteristics	Treatment
Cyclophosphamide	
ISKDC, 1974,[43] RCT 33 patients, age not reported, inclusion criteria: 12–16 years. Histology: MCNS, FL, MPGN, DPG, MN, unknown	(1) Oral cyclophosphamide 5 mg/kg/day, then 1–3 mg/kg/day plus intermittent prednisone, 90 days (2) Intermittent prednisone 40 mg/m^2/day, 90 days
Tarshish, 1996 (ISKDC),[32] RCT 60 patients, mean age 7.6 years (SEM 0.88), 6.9 years (SEM 0.78) Histology: FSGS	(1) Oral cyclophosphamide 2.5 mg/kg/day, 90 days plus alternate-day prednisone 40 mg/m^2, 12 months (2) Alternate-day prednisone 40 mg/m^2, 12 months
Elhence, 1994,[44] RCT 13 patients, mean age 4.0 years (SD 3.73), 6.08 years (SD 5.5) Histology: MCNS	(1) i.v. pulse cyclophosphamide 500 mg/m^2/month, 6 months plus alternate-day prednisolone, 12 weeks (2) Oral cyclophosphamide 2.5 mg/kg/day, 8 weeks plus alternate-day prednisolone, 12 weeks
Ciclosporin	
Garin, 1988,[47] randomised cross-over 8 patients, mean age 11.4 years (SD 6.4) Histology: MCNS, FSGS	(1) Ciclosporin 5 mg/kg/day, 8 weeks (2) Control, treatment not stated, 8 weeks (1-month washout)
Lieberman, 1996,[46] RCT 24 patients, mean age 11.2 years (SD 4.2), 11.4 years (SD 3.9) Histology: FSGS	(1) Ciclosporin 6 mg/kg/day, 6 months (2) Placebo (vehicle control), 6 months
Ponticelli, 1993,[45] RCT 17 patients, mean age: MCNS 6.8 years (SEM 3.5), 7.5 years (SEM 7.8), FSGS 6.5 years (SEM 4.7), 6.6 years (SEM 1.8)	(1) Ciclosporin 6 mg/kg/day, 12 months (2) Supportive treatment, 12 months
Abramowicz, 1970 (ISKDC),[22] RCT 31 patients, age not reported, inclusion criteria: 12 weeks to 16 years Histology: unknown	(1) Azathioprine 60 mg/m^2/day plus intermittent prednisone, 90 days (2) Placebo, 90 days
Adhikari, 1997,[48] CCT 12 patients, mean age 5.7 years (SD 2.1), 5.5 years (SD 3.2) Histology: focal glomerulosclerosis	(1) 18-month regimen 30 mg/kg i.v. methylprednisolone (2) 6-month regimen 30 mg/kg i.v. methylprednisolone
Hari, 2004,[34] prospective cohort study 81 patients, median age 29 months (95% CI 19.5 to 51.6), 33 months (95% CI 18 to 92.8) Histology: MCNS, FSGS, MPGN	(1) Dexamethasone 5 mg/kg i.v., 2 weeks, plus prednisolone (2) Methylprednisolone 30 mg/kg i.v., 2 weeks, plus prednisolone
Bagga, 2004,[41] randomised cross-over 25 patients, median age 74.2 months (95% CI 21 to 122.3), 61 months (95% CI 19 to 137.4) Histology: MCNS, FSGS, MPGN, MBGN	(1) High-dose enalapril 0.6 mg/kg/day, 8 weeks (2) Low-dose enalapril 0.2 mg/kg/day, 8 weeks (2-week washout)
Chongviriyaphan, 1999,[38] randomised cross-over 5 patients, mean age 13.4 years (SD 3.7) Histology: FSGS, MPGN, unknown	(1) Uni-E® (tuna fish oil), 8 weeks (2) Placebo (olive oil), 8 weeks (6-week washout)

DPG, diffuse proliferative glomerulonephritis; FL, focal lesions; MN, membranous nephropathy.

There is the possibility therefore of selection bias within the trials included in this review. Three of the trials[22,37,43] failed to report adequately whether the comparison groups were similar at baseline. The majority of the RCTs reported eligibility criteria; however, two trials were judged to be inadequate in this respect.[44,47]

None of the trials reported whether the outcome assessor was blinded; however, this is less of a problem when the outcomes are objective, such as proteinuria. The study by Ponticelli and colleagues[45] describes the trial as 'open'. Only one study, by Chongviriyaphan and colleagues,[38] adequately reports the care provider and patient to be blinded.

TABLE 3 *Quality assessment of included RCTs and CCT*

	Adhikari, 1997[48]	**Bagga, 2004[41]**	**Chongviriyaphan, 1999[38]**	**Elhence, 1994[44]**	**Garin, 1988[47]**	**ISKDC, 1970[22]**	**ISKDC, 1974[43]**	**Lieberman, 1996[46]**	**Ponticelli, 1993[45]**	**Tarshish, 1996[32]**
Was the assignment to the treatment groups really random?	NA	Adequate	Unknown	Unknown	Unknown	Adequate	Unknown	Adequate	Adequate	Unknown
Was the treatment allocation concealed?	NA	Unknown	Unknown	Unknown	Unknown	Adequate	Unknown	Unknown	Inadequate	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Reported	Reported	Inadequate	Reported	Reported	Unknown	Unknown	Reported	Reported	Reported
Were the eligibility criteria specified?	Adequate	Adequate	Adequate	Inadequate	Inadequate	Adequate	Adequate	Adequate	Adequate	Adequate
Were outcome assessors blinded to the treatment allocation?	Inadequate	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Inadequate	Unknown
Was the care provider blinded?	Inadequate	Unknown	Adequate	Unknown	Unknown	Partial	Unknown	Partial	Inadequate	Unknown
Was the patient blinded?	Inadequate	Unknown	Adequate	Unknown	Unknown	Partial	Unknown	Partial	Inadequate	Unknown
Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Adequate	Partial	Adequate
Did the analyses include an ITT analysis?	NA	Inadequate	Inadequate	Inadequate	Unknown	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Were withdrawals and dropouts completely described?	Adequate	Adequate	Inadequate	Adequate	Unknown	Adequate	Unknown	Adequate	Adequate	Partial

NA, not applicable.

Six trials[32,38,41,44,46,47] adequately reported the point estimates and measures of variability; however, only Ponticelli and colleagues[45] included an intention-to-treat (ITT) analysis.

Withdrawals and dropouts were completely described in five[22,41,44–46] of the nine RCTs.

In general, appropriate outcomes were used and adequately reported. In the ISKDC (1974) study[43] the outcomes were limited. On a few occasions, more detailed information would have been beneficial (e.g. definition of 'decreased proteinuria'[22] or when, how or by whom the outcomes were assessed[44]).

Study sample sizes were generally small, with variations between the trials. In the six RCTs sample sizes ranged from 13 patients[44] to 60 patients.[32] The three randomised cross-over trials had study sample sizes ranging from only five patients[38] to 25 patients.[41] Four trials reported a higher proportion of male patients than female patients,[38,41,44,47] with Chongviriyaphan and colleagues having only male patients in their small study sample.[38] Two of the ISKDC studies[22,43] included only patients aged 12–16 years.

The two ISKDC studies comparing oral cyclophosphamide with prednisone both had a treatment length of 90 days. In the study by Elhence and colleagues[44] patients receiving intravenous (i.v.) pulse cyclophosphamide had a longer treatment length of 6 months compared with 8 weeks in the oral cyclophosphamide group, although the cumulative dose received was lower (i.v. 90 mg/kg versus oral 150 mg/kg). These would appear to be adequate treatment lengths, with treatment in clinical practice usually lasting for 8 weeks. Treatment duration with ciclosporin in clinical practice is judged to be long term, more than 1 year. The study by Ponticelli and colleagues[45] compared the use of ciclosporin versus supportive treatment over a period of 12 months. However, the remaining two studies, by Garin and colleagues[47] and Lieberman and Tejani,[46] had treatment durations of 8 weeks and 6 months, respectively. The 1970 ISKDC study comparing azathioprine with placebo had a treatment duration of 90 days, which reflects treatment duration with this drug in clinical practice.

The three randomised cross-over trials all had treatment durations of 8 weeks. However, they varied with regard to washout period: Bagga and colleagues[41] had a 2-week washout period, Garin and colleagues[47] used a 1-month washout, and the study of tuna fish oil by Chongviriyaphan and colleagues had the longest washout period of 6 weeks.[38] The duration of the washout period is certainly dependent on the treatment in question, and as such, the included randomised cross-over trials appear to have washout periods of a suitable length. However, variations in individual patient disease pattern, as well as individual reaction to the treatment in question, may cast doubt over any judgements made regarding adequate washout period duration.

CCT

The CCT by Adhikari and colleagues[48] was of moderate quality (*Table 3*). The baseline characteristics of prognostic factors were reported, and the eligibility criteria were specified. Likewise, the point estimates and measure of variability were presented, and withdrawals and dropouts were completely described. However, blinding of the outcome assessor, care provider and patient were inadequate. The trial involved a small sample size of 12 patients (seven in the treatment group and six in the control group). Children had focal glomerulosclerosis and were steroid resistant, with some also resistant to oral cyclophosphamide. Two patients had secondary steroid resistance. The trial compared two treatment lengths, 18 months versus 6 months.

Prospective cohort study

The single prospective cohort study by Hari and colleagues[34] was judged to be of good quality (Appendix 5). There was sufficient description of the groups and the distribution of prognostic factors, and the patients were assembled at a similar point in their disease progression. The groups were comparable on all important confounding factors. It was unknown whether the outcome assessor was blind to the exposure status. Dropout rates and reasons for dropout were similar across intervention and unexposed groups. Treatment duration was short, with patients being treated with either i.v. dexamethasone or i.v. methylprednisolone for 2 weeks.

The trial was limited to children aged 1–14 years with initial or late SRNS (MCNS, FSGS or MPGN), with a sample size of 81 patients (59 patients i.v. dexamethasone, 22 patients i.v. methylprednisolone).

Eligibility criteria for study entry differed between the studies, limiting comparability. Three studies restricted inclusion to patients with FSGS[32,46] or focal glomerulosclerosis.[48] Ponticelli and

colleagues included patients with MCNS or FSGS,[45] while Elhence and colleagues limited inclusion to patients with MCNS.[44] The remaining studies did not restrict inclusion to specific histopathologies,[22,38,43,47] although Hari and colleagues[34] and Bagga and colleagues[41] also included 'early' or 'late' steroid resistance.

Assessment of effectiveness: published systematic reviews

Both systematic reviews assessed interventions for the idiopathic SRNS in children (Appendix 4). The earlier of the two[40] does not present the exact number of studies included in the review, although a table of five large uncontrolled studies is presented. The author concluded that treatment remains unsatisfactory, and that most reports are uncontrolled. The more recent Cochrane review[31] included nine RCTs involving 225 children. Results showed that ciclosporin, when compared with placebo or no treatment, statistically significantly increased the number of children who achieved complete remission (three trials, 49 children: RR for persistent nephrotic syndrome 0.64, 95% CI 0.47 to 0.88). There was no statistically significant difference in the number of children who achieved complete remission between oral cyclophosphamide plus prednisone and prednisone alone (two trials, 91 children: RR 1.01, 95% CI 0.74 to 1.36), between intravenous cyclophosphamide and oral cyclophosphamide (one trial, 11 children: RR 0.09, 95% CI 0.01 to 1.39) or between azathioprine plus prednisone and prednisone alone (one trial, 31 children: RR 1.01, 95% CI 0.77 to 1.32). There was significant heterogeneity between two of the three ciclosporin studies, with one trial showing a greater degree of protective effect (RR 0.05, 95% CI 0.00 to 0.73) than the other (RR 0.40, 95% CI 0.19 to 0.85). Heterogeneity was also demonstrated in the different summary estimates between the random and fixed effects models (fixed effects: RR 0.2, 95% CI 0.08 to 0.49). No economic evaluation was carried out. The authors concluded that further adequately powered and well-designed RCTs are needed to confirm the efficacy of ciclosporin and to evaluate other regimens.

Assessment of effectiveness: results of included trials

Cyclophosphamide

Three RCTs[32,43,44] investigated the use of cyclophosphamide (Appendix 5); two compared oral cyclophosphamide plus prednisone with prednisone alone,[32,43] while Elhence and colleagues compared oral cyclophosphamide with intravenous cyclophosphamide.[44]

Remission

All three RCTs defined remission or absence of proteinuria as proteinuria below 4 mg/m^2/hour, although ISKDC (1974) specified that this should occur on three consecutive days during the course of not more than 7 days,[43] and Elhence and colleagues also required serum albumin above 35 g/l.[44] Of the two RCTs comparing cyclophosphamide plus prednisone with prednisone alone, ISKDC (1974) included patients with nephrotic syndrome[43] and ISKDC (1996) restricted inclusion to patients with FSGS.[32] These studies were combined in a meta-analysis (*Figure 1*). There was no statistically significant difference in the number of children overall (86 children: RR 1.15, 95% CI 0.65 to 2.05) or when limited to those with FSGS (63 children: RR 1.01, 95% CI 0.43 to 2.37) who achieved complete remission after treatment with cyclophosphamide and prednisone compared with prednisone alone. There was no significant heterogeneity between studies for all renal pathologies or for patients with FSGS.

The 1974 ISKDC RCT also reported outcomes for non-FSGS patients, although numbers were small so the histologies were not always represented in each treatment group (*Table 4*). The numbers with complete remission in the cyclophosphamide plus prednisone and prednisone alone groups, respectively, were MCNS: 5/7 (71%) versus 4/7 (57%); and diffuse proliferative glomerulonephritis: 1/2 versus 1/1. Of two patients with MPGN in the cyclophosphamide group (none in the prednisone group), one achieved complete remission. No patients with membranous nephrology were present in the cyclophosphamide group, and neither of two patients in the prednisone group achieved complete remission. Similarly, one of two patients with unknown histology in the prednisone group achieved remission.

The 1996 ISKDC trial[32] reported the number of patients with partial remission, defined as a decrease in proteinuria. Proteinuria was classed as absent (<4 mg/m^2/hour), mild (4–40 mg/m^2/hour), moderate (41–100 mg/m^2/hour) or severe (>100 mg/m^2/hour). An 'increase' or a 'decrease' was based on a change of one class or more. In the treatment group, 25% (8/32) of patients had a decrease in proteinuria, with 28% (6/21) of patients experiencing a decrease in proteinuria in the control group. There was no statistically significant difference between the two groups (*Table 4*).

However, the mean interval between onset of treatment and time to response was statistically

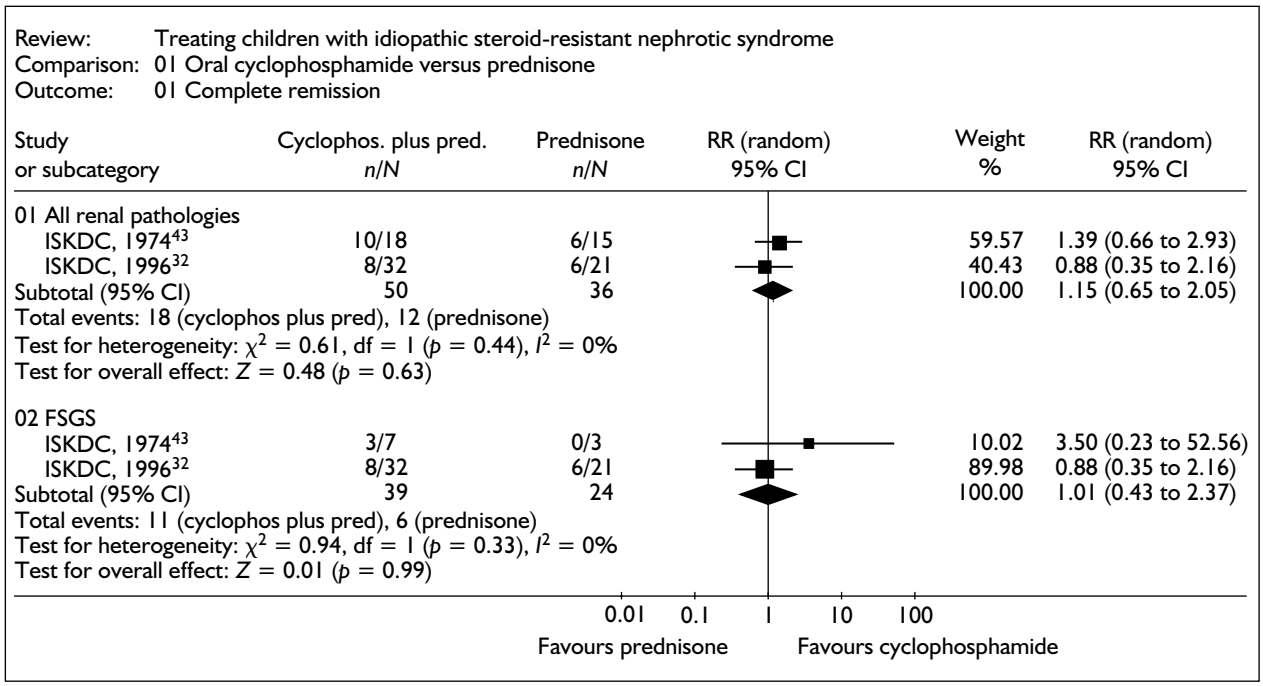

FIGURE 1 *Meta-analysis comparing cyclophosphamide plus prednisone with prednisone*

significantly shorter with cyclophosphamide plus prednisone compared with prednisone alone [38.4 days (range 6–80) versus 95.5 days (range 61–129), $p < 0.05$].[43]

A Kaplan–Meier survival analysis revealed no statistically significant difference between the cyclophosphamide and control group ($Z = 1.06$, $p > 0.25$) in patients with FSGS.[32] The authors report that on the basis of last available biopsy, neither the percentage of glomeruli with global or segmental sclerosis nor the degree of mesangial hypercellularity differed between the experimental and control groups.

The RCT by Elhence and colleagues restricted inclusion to children with MCNS.[44] All seven children in the intravenous cyclophosphamide group achieved complete remission, compared with only one of four children in the oral cyclophosphamide group (*Table 4*). However, no statistically significant difference was demonstrated, possibly owing to the small number of children in the study. Three of the children treated with intravenous cyclophosphamide relapsed after a mean remission of 8.7 months, but subsequently became steroid responsive. The other four patients in this group and one patient in the oral group had sustained remission (no relapse), while the other three patients in the oral group remained unresponsive to treatment. The mean number of protein-free days was 274.3 days (SEM 44.6) in the intravenous group compared with 165 days (SEM 165) in the oral group.

Renal function

None of the studies comparing cyclophosphamide reported measures of renal function such as proteinuria.

Adverse events

One of the three RCTs evaluating cyclophosphamide did not report adverse effects.[43] ISKDC (1996) stated that side-effects were very few; these included one patient with hypertensive seizures in each group and one haemorrhagic cystitis in the cyclophosphamide group (*Table 5*). Death occurred in three patients from the cyclophosphamide plus prednisone group and two in the prednisone group (not statistically significant), owing to sepsis in two patients, cardiorespiratory arrest in one and unknown causes in two. Allocated groups were not specified; however, apart from one patient receiving prednisone at the time of death due to sepsis, the patients were off therapy and in chronic renal failure. None of the patients in the trial experienced tumour development, bone-marrow suppression or aspermia.

Vomiting was common with intravenous cyclophosphamide, occurring in four out of seven patients in this group but in none of the patients with oral cyclophosphamide (*Table 5*). Pneumonia

TABLE 4 *Remission rates*

Study	Treatment	Control
ISKDC, 1974[43] RCT Histology: MCNS, FL, MPGN, DPG, MN, unknown	**Oral cyclophosphamide + intermittent prednisone (*n* = 18)** *Complete remission:* 10/18 (56%) (MCNS 5/7, FL 3/7, MPGN 1/2, DPG 1/2) Interval between onset of treatment and response, mean (range): 38.4 days (6–80)	**Intermittent prednisone (*n* = 15)** *Complete remission:* 6/15 (40%) (MCNS 4/7, FL 0/7, DPG 1/1, MN 0/2, unknown 1/2) Interval between onset of treatment and response, mean (range): 95.5 days (61–129)
Tarshish, 1996 (ISKDC)[32] RCT Histology: FSGS	**Oral cyclosphosphamide + alternate day prednisone (*n* = 32)** *Proteinuria absent:* 8/32 (25%)[a] *Proteinuria decreased:* 8/32 (25%)	**Alternate-day prednisone (*n* = 21)** *Proteinuria absent:* 6/21 (28%) *Proteinuria decreased:* 6/21 (28%)
Elhence, 1994[44] RCT Histology: MCNS	**i.v. Pulse cyclophosphamide (*n* = 7)** *Complete remission:* 7/7 (100%) 4/7 sustained remission (no relapse) 3/7 relapsed after mean 8.7 months, became steroid responsive Mean protein-free days: 274.3 (44.6)	**Oral cyclophosphamide (*n* = 4)** *Complete remission:* 1/4 (25%) 1/4 sustained remission (no relapse) 3/4 remained non-responsive Mean protein-free days: 165 (165)
Garin, 1988[47] random cross-over Histology: MCNS, FSGS	**Ciclosporin (*n* = 8)** *Resolution of proteinuria:* 0/8	**Control (*n* = 8)** *Resolution of proteinuria:* 0/8
Lieberman, 1996[46] RCT Histology: FSGS	**Ciclosporin (*n* = 12)** *Complete remission:* 4/12 *Partial remission:* 8/12 *Time to response:* 4.4 (1.8) weeks	**Placebo (*n* = 12)** *Complete remission:* 0/12 *Partial remission:* 2/12
Ponticelli, 1993[45] RCT Histology: MCNS, FSGS	**Ciclosporin (*n* = 10)** *Complete remission:* 4/10 (1 FSGS, 3 MCD) *Partial remission:* 2/10 (1 FSGS, 1 MCD) Time to response: 61.3 (85.7) days	**Supportive treatment (*n* = 7)** *Complete remission:* 0/7 *Partial remission:* 0/7
Abramowicz, 1970 (ISKDC)[22] RCT Histology: unknown	**Azathioprine + prednisone (*n* = 16)** *Proteinuria eliminated:* 2/16 *Proteinuria decreased:* 2/16	**Placebo (*n* = 15)** *Proteinuria eliminated:* 2/15 *Proteinuria decreased:* 2/15
Adhikari, 1997[48] CCT Histology: FG	**i.v. Methylprednisolone 18-month regimen (*n* = 7)** *Complete remission:* 0/7 *Partial remission:* 6/7 *Relapse:* 1/7	**i.v. Methylprednisolone 6-month regimen (*n* = 5)** *Complete remission:* 2/5 *Partial remission:* 1/5 *Relapse:* 1/5
Hari, 2004[34] Prospective cohort Histology: MCNS, FSGS, MPGN	**i.v. Dexamethasone (*n* = 57)** *Complete remission:* 20/57 (35.1%) 22.9 to 48.9 *Partial remission:* 7/57 (12.3%) 5.0 to 23.7 Median time to remission in patients with complete remission: 9.5 days	**i.v. Methylprednisolone (*n* = 21)** *Complete remission:* 7/21 (33.3%) 14.6 to 56.9 *Partial remission:* 3/21 (14.3%) 3.0 to 36.3 Median time to remission in patients with complete remission: 10 days

[a] One renal failure 14 months later.
FG, focal glomerulosclerosis.

TABLE 5 *Adverse events*

Study details	Adverse event	Treatment	Control
Tarshish, 1996 (ISKDC)[32]		**Oral cyclosphosphamide + alternate-day prednisone (*n* = 32)**	**Alternate-day prednisone (*n* = 21)**
RCT	Hypertensive seizures	1	1
Histology: FSGS	Haemorrhagic cystitis	1	–
	Tumour development	0	0
	Bone-marrow suppression	0	0
	Aspermia	0	0
	Death	3	2
Elhence, 1994[44]		**i.v. Pulse cyclophosphamide (*n* = 7)**	**Oral cyclophosphamide (*n* = 4)**
RCT	Vomiting	4/7	0
Histology: MCNS	Pneumonia	0	1/4
	Alopecia	0	2/4
Garin, 1988[47]		**Ciclosporin (*n* = 8)**	**Control (*n* = 8)**
Random cross-over	Major side-effects	0	–
Histology: MCNS, FSGS	Hypertension	0	0
Lieberman, 1996[46]		**Ciclosporin (*n* = 12)**	**Placebo (*n* = 12)**
RCT	Mild gingival hyperplasia	2/12	–
Histology: FSGS	Worsening hypertension	2/12	2/12
	Intercurrent infection (drug temporarily suspended)	2/12	2/12
	Varicella exposure (drug withheld)	1/12	–
Ponticelli, 1993[45]		**Ciclosporin (*n* = 10)**	**Supportive treatment (*n* = 7)**
RCT	Infections	3/10	3/7
Histology: MCNS, FSGS	Further adverse events were presented, but no specification between adults and children		
Adhikari, 1997[48]		**i.v. Methylprednisolone 18-month regimen (*n* = 7)**	**i.v. Methylprednisolone 6-month regimen (*n* = 5)**
CCT			
Histology: FG	Hypertension	2/7 (treatment discontinued 1)	1/5
	Mild osteopenia	1/7	–
	Frequent infections	2/7	2/5
	Blue discoloration of nails	–	3/5
	Death (septicaemia and systemic candidiasis)	–	1/5
Hari, 2004[34]		**i.v. Dexamethasone (*n* = 57)**	**i.v. Methylprednisolone (*n* = 21)**
Prospective cohort			
Histology: MCNS, FSGS, MPGN	Peritonitis	1/59	1/22
	Septic arthritis	1/59	–
	Transient/worsening of existing hypertension	31/57 (54.4%, 95% CI 40.7 to 67.7)	10/21 (47.6%, 95% CI 25.7 to 70.2)
	Hyperglycaemia	2/57	–
	Any side-effect	66.7% (95% CI 52.9 to 78.6)	61.9% (95% CI 38.4 to 81.9)
Bagga, 2004[41]		**Enalapril low dose then high dose (*n* = 11)**	**Enalapril high dose then low dose (*n* = 14)**
Random cross-over			
Histology: MCNS, FSGS MPGN, MBGN	Dry cough, subsided after stopping treatment	3/25 (low or high dose not specified)	
Chongviriyaphan, 1999[38]		**Tuna fish oil (*n* = 5)**	**Placebo (*n* = 5)**
Random cross-over	Adverse effects	0	0
Histology: FSGS, MPGN, unknown			

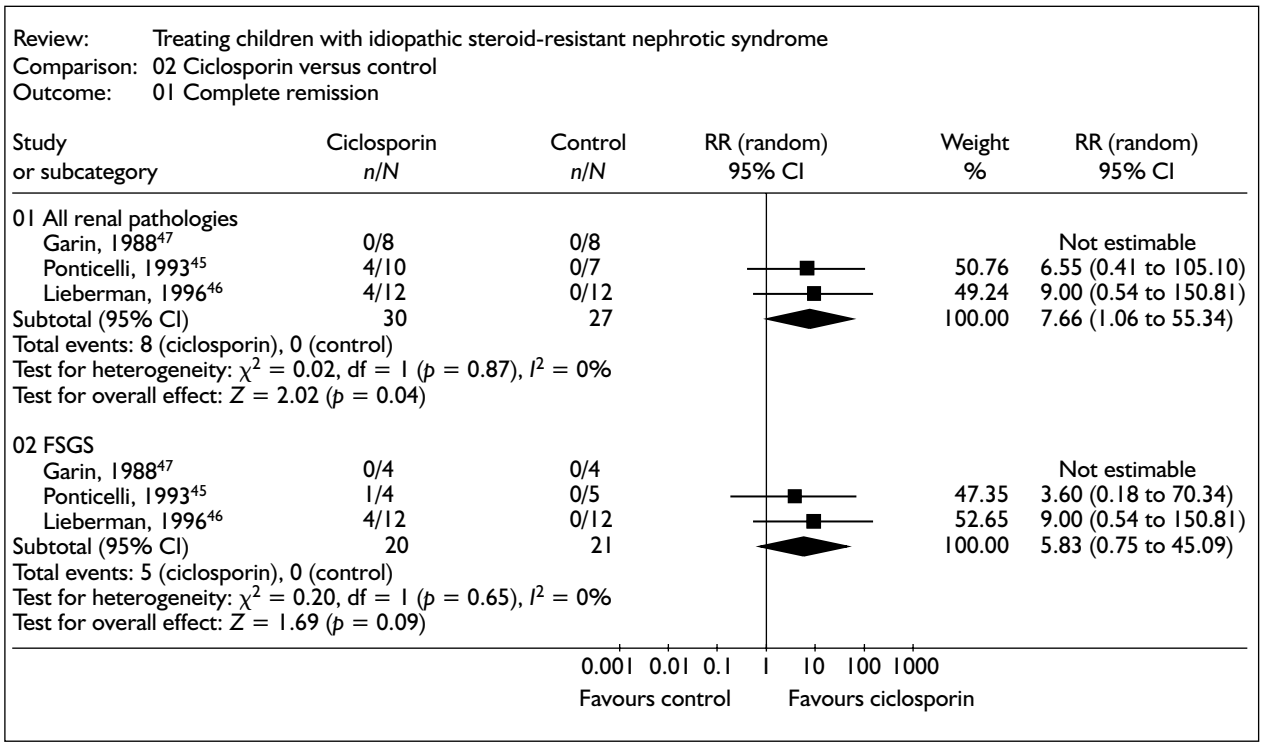

FIGURE 2 *Meta-analysis comparing ciclosporin with control: number of patients with complete remission*

(one patient) and alopecia (two patients) occurred in the oral cyclophosphamide group ($n = 4$).[44]

Ciclosporin

Ciclosporin was compared with placebo,[46] control (no further details)[45] or supportive treatment[47] in three randomised trials, one of which was a cross-over study.[47] Garin and colleagues[47] and Ponticelli and colleagues[45] included patients with MCNS or FSGS, while Lieberman and Tejani restricted inclusion to patients with FSGS.[46]

Remission

Complete remission and partial remission were defined by Lieberman and Tejani as proteinuria declined into the normal range, and a reduction in proteinuria but still remaining in the supranormal range, respectively.[46] Ponticelli and colleagues defined complete remission as proteinuria below 4 mg/m^2/hour on three different non-consecutive days, and partial remission as proteinuria below 40 <4 mg/m^2/hour during three non-consecutive days.[45] Garin and colleagues reported the number of patients with resolution of proteinuria during therapy, with no further details of the definition.[47] The three RCTs were combined in a meta-analysis, although none of the patients had complete remission in the trial by Garin and colleagues,[47] therefore this study did not contribute to the combined summary estimate (*Figure 2*).

Ciclosporin statistically significantly increased the number of children overall with MCNS and FSGS who achieved complete remission compared with placebo or supportive treatment (41 patients: RR 7.66, 95% CI 1.06 to 55.34, $p = 0.04$). Therefore, for MCNS and FSGS combined, remission with ciclosporin is almost eight times more likely than remission without treatment. A meta-analysis of only FSGS patients tended to favour ciclosporin, but this was not statistically significant (33 patients: RR 5.83, 95% CI 0.75 to 45.09). There was no significant heterogeneity between studies with MCNS and FSGS, or with FSGS only.

It should be noted that if the data are treated differently in the meta-analysis, as in the Cochrane review,[31] the FSGS subgroup meta-analysis becomes statistically significant and a different conclusion may be drawn. This occurs if the number of patients 'without complete remission' is entered into the meta-analysis (*Figure 3*), instead of the number of patients 'with complete remission'. In this analysis, ciclosporin statistically significantly reduces the risk of no remission in patients with FSGS by 31% (33 patients: RR 0.69 95% CI 0.50 to 0.96, $p = 0.03$). For MCNS and FSGS combined, the result remains statistically significant (41 patients: RR 0.64, 95% CI 0.47 to 0.88, $p = 0.005$). This will be discussed further in the section 'Other relevant factors' (p. 40).

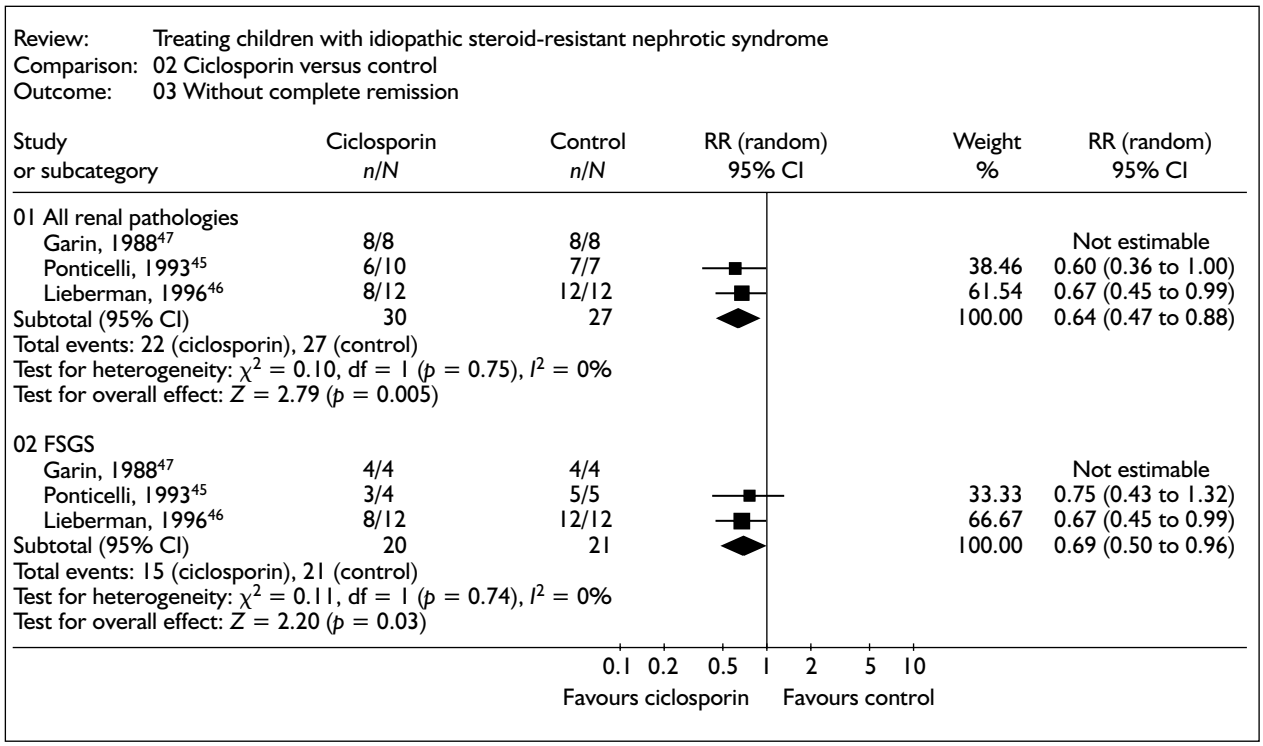

FIGURE 3 *Meta-analysis comparing ciclosporin with control: number of patients* without *complete remission*

The mean time to response for the six patients with FSGS or MCNS who achieved complete or partial remission was 61.3 days (SD 85.7)[45] (*Table 4*). At 1-year follow-up, two of these patients with complete remission had relapsed, one of whom was again in complete remission at 2-year follow-up. Of the other three patients followed for 2 years in this study, one in partial remission had relapsed and two patients had not changed (one still in partial remission and one still with nephrotic syndrome).[45] The time to response (at least a 50% reduction in proteinuria) in the study by Lieberman and Tejani with just FSGS patients was 4.4 (SD 1.8) weeks in the ciclosporin group.[46]

Renal function

Although none of the patients in the trial by Garin and colleagues[47] entered remission, analysis of weekly urinary protein levels found a statistically significant increase in the control group by week 2 of the trial ($p = 0.002$), while there was no change in proteinuria in the ciclosporin group ($p = 0.7$) (*Table 6*). The differences between the ciclosporin and control group were statistically significant ($p = 0.028$). Creatinine clearance decreased in the control group throughout the study ($p = 0.023$ by week 6), but remained unchanged in the ciclosporin group ($p = 0.48$). The difference between groups over the 8-week trial was not statistically significant ($p = 0.24$). There were no statistically significant changes in serum albumin concentration in either group, and no significant difference between groups.

Lieberman and Tejani[46] found a statistically significant reduction in proteinuria from baseline to week 24 in the ciclosporin group but not the placebo group [151.7 (SD 162.4) mg/kg/24 hours to 36.9 (SD 42.3) mg/kg/24 hours, $p < 0.05$, versus 166.9 (SD 137.1) mg/kg/24 hours to 195.4 (SD 173.7) mg/kg/24 hours, p = ns] (*Table 6*). This is a decline of 70.2 ± 19.2% in patients treated with ciclosporin, but an increase of 11.4 ± 29.0% in the placebo group ($p < 0.05$). When factored by the glomerular filtration rate (GFR), proteinuria still statistically significantly declined in the ciclosporin group from 6.0 (SD 7.5) mg/100 ml to 1.7 (SD 2.0) mg/100 ml ($p < 0.05$), and the difference in percentage change between groups was statistically significant (ciclosporin –60.6% (SD 37.7) versus placebo 63.5% (SD 12.8), $p < 0.005$). The GFR declined throughout the study in both groups (ciclosporin $p = 0.05$, placebo $p = 0.06$), but the percentage change was not statistically significantly different between groups [–15.7% (SD 18.4) versus –11.8% (SD 19.0), p = ns].

There were no statistically significant changes in serum biochemical values by the end of the study in the placebo group. However, in the ciclosporin

TABLE 6 *Measures of renal function*

Study	Treatment	Control	Significance
Garin, 1988[47] Random cross-over Histology: MCNS FSGS	**Ciclosporin (*n* = 8)**	**Control (*n* = 8)**	
	Urinary protein excretion values (mg of protein per mg of creatinine), mean (SEM)		
	Week 0: 12.5 (2.1)	Week 0: 11.9 (2.4)	Compared over 8 weeks, urinary protein significantly higher in control group ($p = 0.0286$)
	Week 2: 11.8 (2.3)	Week 2: 15.5 (3.9)	
	Week 4: 11.6 (2.0)	Week 4: 15.1 (2.6)	
	Week 6: 10.9 (2.2)	Week 6: 15.7 (3.7)	
	Week 8: 11.7 (3.1)	Week 8: 17.3 (3.5)	
	Baseline vs 8 weeks, $p = 0.70$	Baseline vs 2 weeks, $p = 0.002$	
	Creatinine clearance values (ml/second/1.73 m^2)		
	Week 0: 1.23 (0.23)	Week 0: 1.50 (0.30)	Compared over 8 weeks, no significant difference in creatinine clearance ($p = 0.2398$)
	Week 2: 1.42 (0.28)	Week 2: 1.13 (0.35)	
	Week 4: 1.42 (0.25)	Week 4: 1.02 (0.20)	
	Week 6: 1.58 (0.48)	Week 6: 0.87 (0.18)	
	Week 8: 1.12 (0.23)	Week 8: 0.87 (0.22)	
	Baseline vs 8 weeks, $p = 0.48$	Baseline vs 6 weeks, $p = 0.023$	
	Serum albumin values (g/l)		
	Week 0: 20 (2)	Week 0: 20 (3)	Compared over 8 weeks, no significant difference in serum albumin level ($p = 0.0824$)
	Week 2: 20 (3)	Week 2: 21 (2)	
	Week 4: 25 (2)	Week 4: 19 (2)	
	Week 6: 24 (3)	Week 6: 17 (2)	
	Week 8: 24 (3)	Week 8: 18 (3)	
	Baseline vs 8 weeks, $p = 0.09$	Baseline vs 8 weeks, $p = 0.27$	
Lieberman, 1996[46] RCT Histology: FSGS	**Ciclosporin (*n* = 12)**	**Placebo (*n* = 12)**	
	Proteinuria (mg/kg/24 hours), mean (SD)		
	Week 0: 151.7 (162.4)	166.9 (137.1)	
	Week 24: 36.9 (42.3)	195.4 (173.7)	
	Week 0 vs week 24 $p < 0.05$	Week 0 vs week 24 p = ns	
	Proteinuria factored by GFR (mg/100 ml)		
	Week 0: 6.0 (7.5)	5.6 (4.4)	
	Week 24: 1.7 (2.0)	9.6 (11.3)	
	Week 0 vs week 24 $p < 0.05$	Week 0 vs week 24 p = ns	
	% Change: –60.6% (37.7)	63.5% (12.8)	$p < 0.005$
	GFR level (ml/minute/1.73 m^2)		
	Week 0: 103.4 (36.7)	86.0 (31.3)	
	Week 24: 82.9 (19.1)	75.1 (30.6)	
	Week 0 vs week 24 $p = 0.05$	Week 0 vs week 24 $p = 0.06$	
	Fractional decline in GFR (% change in poststudy value from prestudy value)		
	–15.7% (18.4)	–11.8% (19.0)	p = ns
	Serum biochemical values (prestudy versus end of study)		
	Albumin (mg/dl)		
	2.8 (1.0) vs 3.5 (0.8), $p < 0.05$	2.5 (1.0) vs 2.7 (1.2), p = ns	
	Potassium (mmol/l)		
	4.1 (0.3) vs 4.6 (0.5), $p < 0.05$	4.0 (0.5) vs 4.1 (0.4), p = ns	
	Uric acid (mg/dl)		
	5.1 (1.0) vs 6.1 (1.5), p = ns	4.8 (1.3) vs 5.0 (1.5), p = ns	
	Magnesium (mg/dl)		
	1.76 (0.12) vs 1.60 (0.22), $p < 0.05$	1.78 (0.20) vs 1.70 (0.18), p = ns	
	SGOT (U/l)		
	26.7 (4.8) vs 31.1 (8.9), p = ns	27.4 (8.3) vs 23.3 (10.1), p = ns	
	Total bilirubin (mg/dl)		
	0.39 (0.17) vs 0.44 (0.17), p = ns	0.38 (0.16) vs 0.41 (0.28), p = ns	

continued

TABLE 6 *Measures of renal function (cont'd)*

Study	Treatment	Control	Significance
	SGPT (U/l) 13.5 (5.7) vs 14.6 (7.2), p = ns	13.8 (4.4) vs 12.7 (4.7), p = ns	
	Creatinine (mg/dl) 0.8 (0.3) vs 1.0 (0.4), $p < 0.05$	0.9 (0.4) vs 1.1 (0.4), p = ns	
	Cholesterol (mg/dl) 397 (237) vs 281 (105), p = ns	348 (162) vs 343 (176), p = ns	
Ponticelli, 1993[45] RCT Histology: MCNS, FSGS	**Ciclosporin (n = 10)**	**Supportive treatment (n = 7)**	
	Proteinuria at response (mg/m^2/hour), mean (SD) (n = 6 with response) 10.8 (15.7)	NA	
Adhikari, 1997[48] CCT Histology: FG	**Methylprednisolone 18-month regimen (n = 7)**	**Methylprednisolone 6-month regimen (n = 5)**	
	Serum creatinine (mmol/l), mean (SD) Before: 145.3 (110.9) After: 55.4 (26.0)	Before: 48.2 (24.7) After: 46.0 (21.6)	
	GFR (ml/minute/1.73 m^2) Before: 63.1 (50.9) After: 155.1 (67.6)	Before: 97.2 (77) After: 164.5 (45.5)	
	Urinary protein/creatinine ratio Before: 2.6 (1.2) After: 0.65 (0.45)	Before: 3.58 (3.32) After: 0.48 (0.35)	
Hari, 2004[34] Prospective cohort Histology: MCNS, FSGS, MPGN	**i.v. Dexamethasone (n = 57)**	**i.v. Methylprednisolone (n = 21)**	
	Median proteinuria (g/24 hours) Pretreatment: 1.9 Post-treatment: 0.7	Pretreatment: 2.2 Post-treatment: 0.2	
	Median urine albumin to creatinine ratio (mg/mg) Pretreatment: 9.2 Post-treatment: 1.5, $p < 0.005$	Pretreatment: 12.1 Post-treatment: 0.7, $p < 0.005$	
	Median reduction in urine albumin to creatinine ratio Post-treatment: 54.1 (95% CI 32.7 to 83.9)	Post-treatment: 63.2 (95% CI 23.5 to 100)	
Bagga, 2004[41] Random cross-over Histology: MCNS, FSGS, MPGN, MBGN	**Enalapril low dose then high dose (n = 11)**	**Enalapril high dose then low dose (n = 14)**	
	6-hour urine albumin (mg), median (95% CI) Baseline: 650 (152.6 to 796.0) 4 weeks low dose: 365 (127.6 to 576.6) 8 weeks low dose: 213 (130.2 to 637.3)	Baseline: 559 (245.8 to 717) 4 weeks high dose: 360 (138.8 to 527.7) 8 weeks high dose: 230.4 (107.9 to 650.2), $p < 0.05$ vs baseline	p = 0.6
	2 weeks washout: 204 (99.6 to 934.7) 4 weeks high dose: 188 (66.3 to 522.4) 8 weeks high dose: 168 (45.4 to 678.9), $p < 0.05$ vs after washout	2 weeks washout: 473.3 (123.0 to 796.3) 4 weeks low dose: 176.5 (92.4 to 646.6) 8 weeks low dose: 144.5 (39.5 to 871.8)	p = 0.6 (end of study)
	Urine albumin to creatinine ratio Baseline: 3.9 (1.9 to 11.6) 4 weeks low dose: 2.5 (1.0 to 14.1) 8 weeks low dose: 2.3 (0.8 to 5.2)	Baseline: 5.2 (2.1 to 10.5) 4 weeks high dose: 3.4 (0.8 to 8.6) 8 weeks low dose: 2.5 (0.8 to 3.3), $p < 0.001$ vs baseline	p = 0.6

continued

TABLE 6 *Measures of renal function (cont'd)*

Study	Treatment	Control	Significance
	2 weeks washout: 2.5 (0.7 to 7.5) 4 weeks high dose: 1.2 (0.4 to 3.9) 8 weeks high dose: 1.1 (0.2 to 4.7) $p < 0.01$vs after washout	2 weeks washout: 3.2 (1.2 to 6.6) 4 weeks low dose: 3.1 (1.1 to 6.3) 8 weeks low dose: 1.8 (0.3 to 9.6)	$p = 0.6$ (end of study)
	Urine albumin to creatinine ratio reduction percentage Low dose: 34.8 (–7.9 to 76.6) High dose: 37.2 (11.3 to 59.8), p = ns vs low dose	High dose: 62.9 (40.6 to 71.6) Low dose: 33.3 (–20 to 58.7) $p < 0.01$ vs high dose	$p < 0.05$
	Albumin (g/dl) Baseline: 3.2 (1.7 to 4.5) 8 weeks low dose: 4.4 (3.9 to 5.5) $p < 0.005$ vs baseline 2 weeks washout: 4.4 (3.7 to 4.9) 8 weeks high dose: 4.5 (2.8 to 5.8)	Baseline: 3.2 (1.6 to 4.4) 8 weeks high dose: 3.5 (2.0 to 4.6) 2 weeks washout: 3.4 (1.6 to 4.4) 8 weeks low dose: 4.1 (3.5 to 5.0)	
	Cholesterol (mg/dl) Baseline: 276 (205 to 405) 8 weeks low dose: 208 (168 to 337) 2 weeks washout: 196 (169 to 279) 8 weeks high dose: 215 (155 to 320)	Baseline: 281 (243 to 390) 8 weeks high dose: 264 (241 to 303) 2 weeks washout: 283 (232 to 364) 8 weeks high dose: 220 (165 to 393)	
	Creatinine (mg/dl) Baseline: 0.6 (0.4 to 0.8) 8 weeks low dose: 0.5 (0.4 to 0.9) 2 weeks washout: 0.6 (0.4 to 1.0) 8 weeks high dose: 0.7 (0.5 to 0.9)	Baseline: 0.5 (0.4 to 0.9) 8 weeks high dose: 0.6 (0.4 to 0.8) 2 weeks washout: 0.5 (0.4 to 0.6) 8 weeks low dose: 0.5 (0.4 to 0.8)	
	Potassium (mEq/l) Baseline: 4.6 (3.7 to 6.3) 8 weeks low dose: 4.5 (4.0 to 6.0) 2 weeks washout: 4.3 (4.0 to 6.0) 8 weeks high dose: 4.5 (3.6 to 6.0)	Baseline: 4.9 (4.2 to 6.5) 8 weeks high dose: 5.0 (4.3 to 6.6) 2 weeks washout: 5.1 (4.4 to 6.6) 8 weeks low dose: 5.1 (4.7 to 6.6)	
Chongviriyaphan 1999[38] Random cross-over Histology: FSGS, MPGN, unknown	**Tuna fish oil ($n = 5$)**	**Placebo ($n = 5$)**	
	Urine protein (g/day), mean (SD) Baseline: 2.68 (3.7) 8 weeks: 1.12 (1.6)	Baseline: 2.71 (3.12) 8 weeks: 3.26 (4.83)	p = ns
	Creatinine clearance (ml/minute/1.73m^2) Baseline: 76.9 (45.8) 8 weeks: 71.22 (41.1)	Baseline: 77.34 (50.6) 8 weeks: 77.21 (46.8)	p = ns
	Serum creatinine (mg/dl) Baseline: 1.4 (0.9) 8 weeks: 1.7 (1.5)	Baseline: 1.6 (1.5) 8 weeks: 1.6 (1.5)	p = ns
	Triglyceride (mg/dl) Baseline: 242 (155.4) 8 weeks: 156 (77)	Baseline: 250 (76.1) 8 weeks: 192 (62.3)	p = ns
	Cholesterol)mg/dl) Baseline: 552 (289.6) 8 weeks: 616 (412.5)	Baseline: 473 (178.1) 8 weeks: 541 (177.4)	p = ns
	HDL-cholesterol (mg/dl) Baseline: 30.5 (10.3) 8 weeks: 38.7 (10.3)	Baseline: 31.4 (8.7) 8 weeks: 34.2 (7.5)	p = ns
	LDL-cholesterol Baseline: 473.5 (266.9) 8 weeks: 546.3 (404.9)	Baseline: 392 (174.8) 8 weeks: 468.2 (171.2)	p = ns

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

group, statistically significant changes were observed in serum albumin, potassium, magnesium and creatinine. There were no statistically significant changes in uric acid, SGOT, total bilirubin, SGPT or cholesterol.

Ponticelli and colleagues[45] did not present data on proteinuria separately for children. However, the authors reported that proteinuria significantly decreased at month 6 ($p < 0.05$) in the ciclosporin group, and was unchanged in the control group. When ciclosporin was reduced gradually, proteinuria tended to return to baseline values. The proteinuria level at response for patients in the treatment group was 10.8 mg/m^2/hour (SD 15.7).

Adverse events
All three RCTs evaluating ciclosporin reported some information regarding adverse effects (*Table 5*). Garin and colleagues[47] stated that no patients from either group suffered from any major side-effects or hypertension. No changes in complete blood cell counts or liver enzyme levels were seen in either group. Ponticelli and colleagues[45] reported infections in three out of ten (30%) patients in the ciclosporin group and three out of seven (43%) patients in the supportive treatment group. Further adverse events were reported in the study, but data for children and adults were combined. All symptoms had disappeared after the first year of observation. There was no difference in blood pressure between the two groups at any time, nor were there any differences between children and adults (data not reported). In the study by Lieberman and Tejani,[46] two of 12 patients in the ciclosporin group experienced mild gingival hyperplasia. Four patients (two from each group) had worsening hypertension that necessitated the initiation of additional antihypertensive agents. Two patients from each group also had an intercurrent infection which resulted in the study drug being temporarily suspended. One patient from the ciclosporin group had the study drug withheld owing to varicella exposure.

Azathioprine
One RCT by Abramowicz and colleagues (ISKDC)[22] investigated the use of the immunosuppressant azathioprine plus prednisone compared with placebo. Patient characteristics were not reported in this study and the proportions of histological diagnoses are unknown. However, the authors do state that no important differences in histological diagnoses existed, either between the azathioprine and placebo groups, or within the groups between those who became protein free and those who did not.

Remission
Two out of 16 patients in the azathioprine group and two of 15 patients in the placebo group became protein free (*Table 4*). Similarly, two patients in each group had a decrease in proteinuria (definition not provided). Patients assigned to azathioprine who did not become protein free were randomly assigned to another 90 days of azathioprine or placebo. Two patients from each group were withdrawn by their physicians while the trial was taking place. Three had not responded (time not stated) and were counted as 'no response', one of whom died; one responded and was counted as a response, but subsequently relapsed and died. Proteinuria disappeared in two out of five azathioprine patients and one out of three placebo group patients.

Renal function
The RCT did not report measures of renal function.[22]

Adverse events
The RCT did not report adverse events.[22]

Methylprednisolone
One CCT by Adhikari and colleagues[48] investigated the use of an 18-month versus a 6-month regimen of 30 mg/kg intravenous methylprednisolone in South African children with focal glomerulosclerosis. Two patients had secondary steroid resistance. Although the study reported adequate outcomes to warrant inclusion in this review, the results were poorly reported and there were several discrepancies between the data in the text and the tables.

Remission
Adhikari and colleagues defined complete remission as no oedema, serum albumin 3 g/l or above, and urinary protein to creatinine ratio <0.2, and partial remission as no oedema, serum albumin 2.5 g/l or above, and urinary protein to creatinine ratio 0.2–1.9.[48] The authors reported that none out of seven patients and two out of five patients had complete remission in the 18-month and 6-month group, respectively (*Table 4*). Partial remission was achieved in six out of seven and one out of five patients, respectively. One patient in each group had a relapse, with the 18-month regimen patient having the initial course of therapy stopped owing to infection. This patient achieved remission following a second course of therapy, but subsequently relapsed after developing a urinary tract infection.

Renal function
Adhikari and colleagues[48] reported an improvement in renal function, as shown by the reduction in proteinuria and serum creatinine and an improvement in estimated GFR. Means and standard deviations were calculated by the reviewer and are presented in *Table 6*. Serum creatinine levels decreased from 145.3 mmol/l (SD 110.9) to 55.4 mmol/l (SD 26.0) and 48.2 mmol/l (SD 24.7) to 46.0 mmol/l (SD 21.6) in the 18-month and 6-month regimens, respectively. Likewise, there was a decrease in urine protein to creatinine ratio from 2.6 (SD 1.2) to 0.65 (SD 0.45) in the 18-month regimen and from 3.58 (SD 3.32) to 0.48 (SD 0.35) in the 6-month regimen. Mean GFR increased from 63.1 ml/minute/1.73 m^2 (SD 50.9) to 155.1 ml/minute/1.73 m^2 (SD 67.6) in the 18-month regimen, and from 97.2 ml/minute/1.73 m^2 (SD 77) to 164.5 ml/minute/1.73 m^2 (SD 45.5) in the 6-month regimen.

Adverse events
Adverse events reported with methylprednisolone on both regimens included hypertension (with treatment discontinued in one patient on the 18-month regimen) and frequent infections (*Table 5*). Mild osteopenia occurred on the 18-month regimen, and for patients on the 6-month regimen there were reports of alopecia and blue discoloration of nails. Death, due to septicaemia and systemic candidiasis, occurred in one patient on the 6-month regimen.[48]

Resource use
Drug costs were shown to be $687 (R2610.80) for 18-month regimen group and $108.9 (R414.14) for the 6-month regimen group. The minimum number of hospital visits was 34 and eight in the 18-month and 6-month groups, respectively

Dexamethasone
Hari and colleagues[34] conducted a prospective cohort study comparing the use of intravenous dexamethasone versus intravenous methylprednisolone. The study included both initial and late steroid-resistant patients, the latter defined as those who responded to therapy initially but failed to respond to prednisolone in a subsequent relapse. Patients in each group had MCNS (36% and 23%), FSGS (47.5% and 59%) and MPGN (17% and 18%).

Remission
Complete remission, defined as urinary protein being nil or trace on at least three consecutive days or urine albumin to creatinine ratio below 0.2, occurred in 20 out of 57 (35.1%, 95% CI 22.9 to 48.9) patients in the dexamethasone group and seven out of 21 (33.3%, 95% CI 14.6 to 56.9) patients in the methylprednisolone group (*Table 4*). Partial remission, defined as urine protein excretion 1+ to 2+, or urine albumin to creatinine ratio between 0.2 and 2 and serum albumin above 2.5 g/dl, occurred in 12.3% (95% CI 5.0 to 23.7) and 14.3% (95% CI 3.0 to 36.3) of patients, respectively.[34]

The median time to complete remission was 9.5 days in patients treated with dexamethasone and 10 days in those treated with methylprednisolone.

Renal function
The median urine albumin to creatinine ratio decreased from 9.2 to 1.5 ($p < 0.005$) in the dexamethasone group and from 12.1 to 0.7 ($p < 0.005$) in the methylprednisolone group (*Table 6*). The median reduction in urine albumin to creatinine ratio was 54.1 (95% CI 32.7 to 83.9) and 63.2 (95% CI 23.5 to 100) in the dexamethasone and methylprednisolone groups, respectively. Median urine protein levels decreased in both groups from pretreatment to post-treatment, from 1.9 to 0.7 g/24 hours in the dexamethasone group and from 2.2 to 0.2 g/24 hours in the methylprednisolone group.[34]

Adverse events
Of those patients in the dexamethasone group, 66.7% (95% CI 52.9 to 78.6) experienced any adverse event (*Table 5*). In the methylprednisolone group this was slightly lower, with 61.9% (95% CI 38.4 to 81.9) experiencing an adverse event. The most common adverse event in both treatment groups was transient hypertension or worsening of existing hypertension, occurring in 54.4% (95% CI 40.7 to 67.7) of patients in the dexamethasone group and 47.6% (95% CI 25.7 to 70.2) of patients in the methylprednisolone group. Other adverse events included peritonitis, septic arthritis and hyperglycaemia. The three patients with peritonitis and septic arthritis (two dexamethasone and one methylprednisolone) could not complete treatment. Electrolyte abnormalities were asymptomatic and included hypokalaemia and hyponatraemia in ten and 11 patients, respectively (group not specified).[34]

Enalapril
One randomised cross-over trial by Bagga and colleagues[41] compared high-dose and low-dose enalapril. Children were randomised to receive either low-dose enalapril then high-dose enalapril after a washout period, or high-dose followed by low-dose enalapril after washout. The study

included patients with both early and late steroid resistance, and the renal histologies in each group were MCNS (1/11 and 3/14), FSGS (4/11 and 5/14), MBGN (4/11 and 3/14) and MPGN (2/11 and 3/14).

Remission
The authors state that 17 of the 25 patients in this trial attained a significant reduction in proteinuria (urine albumin to creatinine ratio percentage reduction >40% at the end of 18 weeks of treatment). However, there is no information about differences between high and low doses.[41]

Renal function
Six-hour urinary albumin decreased statistically significantly from baseline or cross-over to week 8 of treatment with high-dose enalapril but not with low-dose enalapril (*Table 6*). Similarly, high-dose (but not low-dose) enalapril was associated with a statistically significant reduction in urine albumin to creatinine ratio at the end of treatment compared with baseline ($p < 0.001$) or cross-over ($p < 0.01$). At the end of the study, the urine albumin to creatinine ratio was similar in the group who received low-dose then high-dose enalapril and the group who received high-dose then low-dose (1.1, 95% CI 0.2 to 4.7, versus 1.8, 95% CI 0.3 to 9.6, $p = 0.6$). During the first phase of treatment before cross-over, the urine albumin to creatinine ratio reduction percentage was statistically significantly greater with high-dose than with low-dose enalapril (62.9%, 95% CI 40.6 to 71.6, versus 34.8%, 95% CI –7.9 to 76.6, $p < 0.05$); however, the difference was no longer statistically significant between treatments after cross-over (high-dose 37.2%, 95% CI 11.3 to 59.8, versus low-dose 33.3%, 95% CI –20 to 58.7, p = ns). The difference was statistically significant within the group who received high-dose then low-dose enalapril, but not the group who received low-dose then high-dose.

Blood albumin statistically significantly increased with low-dose enalapril in the group that received this treatment first (3.2 g/dl, 95% CI 1.7 to 4.5, versus 4.4 g/dl, 95% CI 3.9 to 5.5, $p < 0.005$); however, the improvements with high-dose enalapril or in the group who received high-dose then low-dose enalapril were not statistically significant (*Table 6*). There were no statistically significant changes in blood cholesterol, creatinine or potassium with either low-dose or high-dose enalapril.[41]

Systolic and diastolic blood pressure (SBP and DBP) decreased in both groups before the washout period, although this was only statistically significant for low-dose enalapril (Appendix 5). Data were not presented for treatments administered after cross-over. However, the authors report that there was a slight increase in blood pressure during the washout period followed by a similar decline during the following 8 weeks of treatment. They also state that the dose of enalapril did not influence the percentage reduction in SBP and DBP, which was similar at cross-over and at the end of study in both groups.[41]

Adverse events
Three patients were reported to have experienced a dry cough that subsided after stopping treatment; however, the dose taken by these patients is not specified (*Table 5*). No further adverse effects were reported.[41]

Tuna fish oil

One small randomised cross-over trial[38] compared tuna fish oil with placebo. It involved five children with nephrotic syndrome, three of whom had FSGS, one had MPGN (IgG deposit) and one was not reported.

Remission
Remission rates were not reported.

Renal function
There was no statistically significant difference in proteinuria or creatinine clearance between the two treatments. Urine protein reduced from 2.68 g per day (SD 3.7) at baseline to 1.12 g per day (SD 1.6) at 8 weeks in patients treated with fish oil, and increased from 2.71 g per day (SD 3.12) at baseline to 3.26 g per day (SD 4.83) in patients treated with placebo. Creatinine clearance decreased slightly from 76.9 ml/minute/1.73 m^2 (SD 45.8) to 71.22 ml/minute/1.73 m^2 (SD 41.1) with fish oil and there was no change with placebo [77.34 ml/minute/1.73 m^2 (SD 50.6) to 77.21 ml/minute/1.73 m^2 (SD 46.8)]. There were no statistically significant differences in serum creatinine and lipid profiles between fish oil and placebo (*Table 6*).

Compliance was good apart from one patient in each group. Calorific intake and dietary composition (protein, fat and carbohydrate as percentage of total calorific intake) were not significantly different between the two treatments.[38]

Adverse events
The authors stated that neither patients nor parents reported any adverse events (*Table 5*).

Summary

Cyclophosphamide

A meta-analysis of two trials comparing cyclophosphamide plus prednisone with prednisone alone found no statistically significant difference in remission rates in children with various histopathologies.[32,43] Similarly, subgroup analysis of patients with FSGS also demonstrated no statistically significant difference. However, response occurred much sooner with cyclophosphamide.[43] Patients in these studies were defined as steroid resistant after 8 weeks of prednisone therapy. The one small study comparing intravenous with oral cyclophosphamide in MCNS found that all seven of the intravenous group had remission, compared with just one of four children in the oral group, but this was not statistically significant. The definition of remission varied slightly between these studies.

In the 1996 ISKDC trial, three deaths occurred in the cyclophosphamide plus prednisone group and two in the prednisone only group; four of these deaths occurred when the patients were off therapy and in chronic renal failure, and one death due to sepsis occurred while taking prednisone.[32] Side-effects were few; hypertensive seizure occurred in both groups and haemorrhagic cystitis occurred in the cyclophosphamide group. Elhence and colleagues reported vomiting with intravenous cyclophosphamide, and pneumonia and alopecia with oral cyclophosphamide.[44]

Ciclosporin

A meta-analysis of three small trials showed that ciclosporin statistically significantly increased the number of children with MCNS and FSGS who achieved complete remission compared with placebo or control.[45–47] However, the trial by Garin and colleagues[47] did not contribute to the summary estimate as no patient in either group had remission. Subgroup analysis of patients with FSGS showed that the improvement in remission rates was not statistically significant.

The poor outcome of patients in the study by Garin and colleagues compared with the other two RCTs may be due in part to differences between the studies. Garin and colleagues defined patients as steroid resistant after 8 weeks of prednisone therapy, compared with just 4 weeks or 5 weeks of therapy in the studies by Lieberman and Ponticelli, respectively. It is therefore possible that the patients in the latter two studies were less resistant to treatment than those in the study by Garin. Moreover, Lieberman and Ponticelli gave slightly higher doses than Garin (6 mg compared with 5 mg/kg/day) and duration of treatment was longer (6 months and 12 months, respectively, compared with 8 weeks). There may be differences between the studies in the definition of remission used, but little detail is provided by Lieberman and Tejani[46] and Garin and colleagues.[47]

Although none of the patients in the trial by Garin and colleagues had remission,[47] urinary protein and creatinine clearance values worsened significantly in the control group throughout the study, while there was no change in these values in the ciclosporin group. The differences between the groups were statistically significant for urinary protein only. There were no statistically significant changes in serum albumin levels.[47] Lieberman and Tejani found a statistically significant decrease in proteinuria with ciclosporin, even when factored by GFR. This study also demonstrated a statistically significant increase in serum albumin, potassium and creatinine, and a decrease in magnesium, but no changes in other serum biochemical values.[46]

Adverse effects were few and differed little between groups. Garin and colleagues reported that no major side-effects or hypertension occurred in either group.[47] Ponticelli and colleagues reported infections in 30% and 43% of the ciclosporin and supportive treatment groups, respectively, but other adverse effects data in children were combined with data from adults in this study.[45] Worsening hypertension and infection occurred in both the ciclosporin and placebo groups in the study by Lieberman and colleagues, while mild gingival hyperplasia occurred in 17% (2/12) of the ciclosporin group.

Azathioprine

One study compared azathioprine plus prednisone with placebo and found that about 13% in each group had complete remission, while proteinuria 'decreased' in a further 13% in each group.[22] However, a definition of 'decreased' proteinuria was not given. Furthermore, the study did not report any patient characteristics, although allocation concealment was judged to be adequate. Adverse events were not reported.

Methylprednisolone

Adhikari and colleagues compared a 6-month and an 18-month regimen of intravenous methylprednisolone in a non-randomised controlled trial of patients with focal glomerulosclerosis.[48] Although no patient in the 18-month regimen had complete remission, six of

seven patients had partial remission. Three-fifths of the 6-month regimen group had complete or partial remission. No statistical comparisons were made in this study. Hari and colleagues found no statistically significant differences in complete or partial remission rates between methylprednisolone and dexamethasone in a prospective cohort study.[34] Dexamethasone[34] and methylprednisolone, regardless of the length of the treatment regimen,[34,48] were both associated with a decrease in protein to creatinine ratio. Hypertension and frequent infections occurred with both the 6-month and 18-month regimens of methylprednisolone; mild osteopenia occurred with the 18-month regimen and alopecia and blue discoloration of nails occurred on the 6-month regimen. One death occurred in this trial.[48] Slightly more patients experienced any adverse event with dexamethasone than with methylprednisolone (67% versus 62%), the most common adverse event being hypertension, which occurred in about half of the patients in each group.[34]

Enalapril

High-dose but not low-dose enalapril was associated with a statistically significant reduction in urinary albumin and albumin to creatinine ratio.[41] The difference in the urine albumin to creatinine ratio reduction percentage between the two groups was statistically significant in the period before cross-over, but not in the following period. The biological importance of these results is not clear. The study was not of good quality and the washout period was just 2 weeks, therefore carry-over effects may have occurred. Blood albumin increased with low-dose enalapril in the group that received this first, but this was not statistically significant with high-dose enalapril or in the group that received low-dose enalapril after cross-over. There were no statistically significant changes in blood cholesterol, creatinine or potassium. A dry cough that subsided after stopping treatment occurred in 12% of patients,[41] but no other adverse effects were reported.

Fish oil

No statistically significant differences in serum creatinine and lipid profiles, urinary protein or creatinine clearance were found between tuna fish oil and placebo.[38] No adverse events were reported by patients or parents. This was a small cross-over study with just five children, four of whom had short stature and one was malnourished, therefore the generalisability of the trial may be questioned. The dosage of the fish oil was described as 'small' and a limitation of the study by the authors. Other limitations suggested by the authors included the small sample size, short duration of supplementation and insufficient washout.

Chapter 4
Economic evidence

Introduction

The aim of this section of the report is to assess the cost-effectiveness of treatments for children with idiopathic SRNS. The assessment comprises a systematic search of the literature on the cost-effectiveness of treatments, and a subsequent review of the literature to inform on the costs and consequences of treatment in this patient group, and on the methods available to model cost-effectiveness analysis (CEA).

Systematic review of the existing cost-effectiveness evidence

The a priori methods for systematically reviewing the cost-effectiveness evidence are described in the research protocol (Appendix 1) and were summarised in the section 'Methods for reviewing effectiveness' (p. 11). Systematic searches were undertaken to identify evidence on (1) economic evaluations, (2) treatment and longer term costs, and (3) the health-related quality of life (HRQoL). These searches found no economic evaluations and a very limited literature on the costs and consequences associated with SRNS in children. Subsequent searches were undertaken to identify economic evaluations and economic evidence in the area of SRNS in adults, and studies that may offer guidance in the modelling of nephrotic syndrome for CEA. See Appendix 2 for the search strategies employed.

Economic evidence on the treatment of SRNS in children

This review has not identified any published evidence (economic evaluations) on the cost-effectiveness of treatments for SRNS in children (or adults). In the absence of this literature, this section of the report considered the broader literature covering SRNS and SSNS. A sparse literature has been identified to inform on individual aspects (costs and benefits) of the cost-effectiveness of treatment for SRNS.

The cost-effectiveness literature for renal disease seems largely to neglect SRNS and SSNS, and to focus quite broadly on renal failure, particularly for ESRF. However, through discussion of the literature identified, the broader literature on renal disease and consultation with clinical experts some commentary is provided on the issues relevant for the cost-effectiveness of treatments for SRNS.

Costs associated with the treatment of SRNS

The costs associated with treatment for children with SRNS consist of treatment costs (e.g. medications, management, side-effects and complications), longer term monitoring and management costs (e.g. outpatient attendance, urinalysis, treatment of longer term complications), and longer term costs for patients who progress to ESRF.

Treatment costs

Table 7 shows the pharmaceutical costs for a range of alternative therapies.[33] For the purposes of these indicative costs the duration of treatment and the relevant dosage data have been taken from regimens reported in clinical trials (see the section 'Results', p. 12) and from advice from clinicians. There is wide variation in the pharmaceutical cost of suggested regimens. For example, the drug cost for a course of cyclosphosphamide is less than £6, whereas longer term therapies such as ciclosporin cost almost £900 per year. Licensing information for these drugs is given in *Table 1* (p. 5).

Consultation and follow-up costs

The consultation and follow-up costs for patients with SRNS vary by treatment strategy and according to the clinical response to treatment. On the basis of expert opinion (R. Trompeter) an estimate of consultation and follow-up cost for typical medical management scenarios is presented in *Table 8*. Each consultation will include routine tests (blood tests and urinalysis). All patients will have their GFR estimated annually. Where indicated, patients have further blood tests for parathyroid hormone, thyroid function tests, lipids and ferritin.

Where patients have condition- or treatment-related complications, a more intensive

TABLE 7 *Pharmaceutical costs for selected treatments for SRNS*

Product	Dosage	Unit cost[33]	Treatment duration	Cost per course of treatment[b]
Steroids				
Methylprednisolone	2 mg/kg/day	30 × 16 mg = £17.17	8 weeks	£95.76
i.v. Methylprednisolone	30 mg/kg	1-g vial = £17.30	18-month regimen[a]	£398.72
i.v. Dexamethasone	5 mg/kg/day	5-ml vial = £16.66	2 weeks	£233.24
Deflazacort	1.5 mg/kg/day	30 × 30 mg = £22.80	8 weeks	£42.56
Alkylating agents				
Chlorambucil	0.15 mg/kg/day	25 × 2 mg = £8.36	8 weeks	£37.52
Cyclophosphamide	2–3 mg/kg/day	20 × 50 mg = £2.12	8 weeks	£5.94
i.v. cyclosphosphamide	500 mg/m^2/month	1-g vial = £5.04	6 months	£13.62
Immunosuppressants				
Ciclosporin	6 mg/kg/day	30 × 25 mg = £12.00	Long-term >1 year	£876 pa
Mycophenolate mofetil	600 mg/m^2 twice a day	50 × 500 mg = 87.33	Long-term >1 year	£1274 pa
Tacrolimus	300 µg/kg/day	50 × 5 mg = £314.84	Long-term >1 year	£3447 pa
Azathioprine	60 mg/m^2/day	56 × 50 mg = £9.97	Long-term >1 year	£16.20 pa
ACE inhibitor				
Enalapril maleate	0.1 mg/kg/day	28 × 2.5 mg = £2.32	Long-term >1 year	£29.20 pa
Ascaricides				
Levamisole	1.25 mg/kg/day	Not available	Long-term >1 year	Not available

[a] Alternate days for six doses, then weekly i.v. injections for 8 weeks, then fortnightly for 8 weeks, then monthly for 12 months.
[b] Cost per course of treatment for a 24-kg or 0.9-m^2 child.

programme of medical management is to be expected. In the more severe cases this can involve weekly consultations with a specialist/nephrologist or inpatient care, or both.

Patients with persistent nephrotic syndrome are monitored according to the severity of their condition. Patients with more stable disease are expected to be seen by a nephrologist every 2–3 months, on an ongoing basis. Where patients progress to ESRF, they will require further, more frequent, consultations and medical management appropriate for their condition.

Longer term treatment costs for SRNS

As well as the ongoing monitoring and medical management costs discussed above, there are other longer term costs relevant for the consideration of SRNS. These comprise the cost of care for longer term side-effects and complications, and costs associated with the onset and management of renal failure, such as dialysis and transplant costs. There is limited clinical effectiveness data on the complications from treatment (see below). As detailed in the following sections, the cost of management of renal failure is considerable.

Dialysis

The cost of dialysis in the UK has been estimated by Gonzalez-Perez and colleagues.[50] Gonzalez-Perez and colleagues[50] measured the healthcare resources used for access surgery/set-up, training, regular dialysis sessions and complications of the dialysis, such as clotting of the fistula or hypotension episodes. Most of the data were derived as part of the European Dialysis and Cost-Effectiveness study (EURODICE), which compared hospital haemodialysis and continuous ambulatory peritoneal dialysis. They estimated that the annual cost of hospital haemodialysis, satellite haemodialysis and home dialysis was between £21,264 and £22,654. A similar value for dialysis cost of £23,504 was used in a recent cost-effectiveness study for new immunosuppressant drugs for renal transplantation.[51]

Transplantation

Woodroffe and colleagues[51] estimated the costs associated with renal transplantation. They estimated the annual drug cost to be £3271 for ciclosporin and £1289 for azathioprine. The cost of the transplant was estimated to be £10,249 and the cost of graft failure was estimated to be between £11,225 and £13,696.

TABLE 8 *Treatment strategy costs*

Treatment	Consultant appointments	Nurse appointments	Blood tests/urinalysis	GFR test	GP appointments	Cost estimate (£)
First year of treatment						
Cyclosphosphamide, chlorambucil						
8-week treatment period	2	8	8[a]		6	704.56
Methylprednisolone, deflazacort, i.v. dexamethasone						
8-week treatment period	2	2	2			254.90
i.v. Cyclophosphamide						
6-month treatment period	3	3	3			382.35
Subsequent treatment (if successful)	2	2	2	1		260.82
i.v. Methylprednisolone						
First year	6	26	6	1		930.62
All drugs except i.v. methylprednisolone and i.v. cyclophosphamide						
First year if treatment successful[b]	4	4	4	1		515.72
All drugs except i.v. methylprednisolone						
First year if treatment is unsuccessful[b]	6	6	6	1		770.62
Long-term treatment						
All drugs except i.v. methylprednisolone						
Years 2–5 if treatment is successful	2	2	2	1		260.82
i.v. Methylprednisolone						
Second year if treatment is successful	4	6	4	1		531.72
All drugs						
After year 5 if treatment is successful	1	1	1	1		133.37

[a] Blood test also includes white blood cell count.
[b] In addition to those costs for the 8-week treatment period for cyclosphosphamide, chlorambucil, methylprednisolone, deflazacort and i.v. dexamethasone.
Unit costs: consultant appointment £84,[52] nurse appointment £8,[53] GP appointment £28,[53] blood test and urinalysis £21.76, white blood cell count £2.62, GFR test £5.92 (estimated by Finance Department of Southampton University Hospitals Trust).

An estimate of the lifetime costs for children with ESRF has been derived (by the current authors) using a model recently developed to consider renal transplantation for children.[39] In children receiving a renal transplant at age 15 years, there would be an estimated lifetime cost of £214,274 (excluding the cost of transplantation), approximating to £8500 per year averaged over their lifetime. The model assumes that they only receive one transplant. Alternatively, if these patients never received a transplant graft, there would be a cost of £228,580 or approximately £21,060 per year. The values used to derive these dialysis costs were for adults; the dialysis cost for children is likely to be higher.

Health-related quality of life

SRNS can have a significant impact on HRQoL, especially in those patients with longer term persistent nephrotic syndrome which may lead to ESRF. A literature search was undertaken to identify studies on the HRQoL in children with nephrotic syndrome (Appendix 2). Only one study was identified.[54]

Ruth and colleagues[54] evaluated quality of life in 45 children with SSNS using the Child Quality of Life Questionnaire (TACQOL). This questionnaire was developed to measure the HRQoL in children with chronic diseases and contains five health status scales: physical complaints, basic motor functioning, autonomy, cognitive and social functioning. There were two additional scales to assess emotional functions. HRQoL was evaluated using the child's own assessment and that of their parents. The study found that the child's self-report was normal for all dimensions except for social functioning, that is, interaction with family members and peers. The parents were more pessimistic and considered their children also to have significant impairment of motor, cognitive and global emotional functioning. The study also assessed the correlation between treatment and illness-related variables and the children's health status. They found that there was a negative correlation between a complicated course of SSNS (steroid dependency and cytotoxic treatment) and social functioning.

As with the cost-effectiveness literature generally, while there is a sparse literature on nephrotic syndrome there are many studies evaluating HRQoL for renal disease in general, especially ESRD. The Cost Effectiveness Analysis Registry from Harvard University (http://www.hsph.harvard.edu/cearegistry/)[55] presents details of studies with preference values for ESRF, but the registry contains no studies on nephrotic syndrome.

Adverse events

Both treatment-related and non-treatment-related complications are expected to impact on patients' HRQoL. Treatment-related complications have been discussed in the section 'Assessment of effectiveness: results of included trials' (p. 16), in the context of findings from clinical trials (see *Table 5*). The most commonly reported side-effects were infection and hypertension. However, few side-effects were reported in the trials and findings reported differed little between the control and treatment groups. As reported in Habashy and colleagues,[42] this may be due to small patient numbers in the trials, short follow-up periods and incomplete reporting. None of the ciclosporin studies reports data on the side-effects that commonly concern patients and clinicians, namely nephrotoxicity and hirsutism.[42] Side-effects from oral and intravenous steroids include behavioural and psychological changes, gastric irritation, fluid retention, hypertension, steroid-induced bone disease and growth retardation.[23] The risk and consequences of complications in SRNS should be an important factor in any economic analysis. However, data from clinical trials are sparse at the present time, and more data are needed on the risk of complications, their prevalence and the related reduction in quality of life associated with complications.

Evidence on the modelling of disease progression in patients with nephrotic syndrome

In literature searches on modelling related to nephrotic syndrome, and renal disease more broadly, seven studies were identified on nephrotic syndrome. None of these studies included cost data in their analyses. Four studies present evaluations of the practice of biopsy prior to steroid treatment for nephrotic syndrome in adults[56–58] and children.[59] One study[60] considers use of prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. Only the studies by Piccoli and colleagues[61,62] have specifically considered decisions over therapy for idiopathic membranous nephropathy (mostly comprising nephrotic syndrome) in adults. These studies are based on a decision-analytic model and an outline of the modelling approach is presented below.

Piccoli and colleagues[61] use a decision-analytic model to investigate the use of three different medical therapies for adults with idiopathic

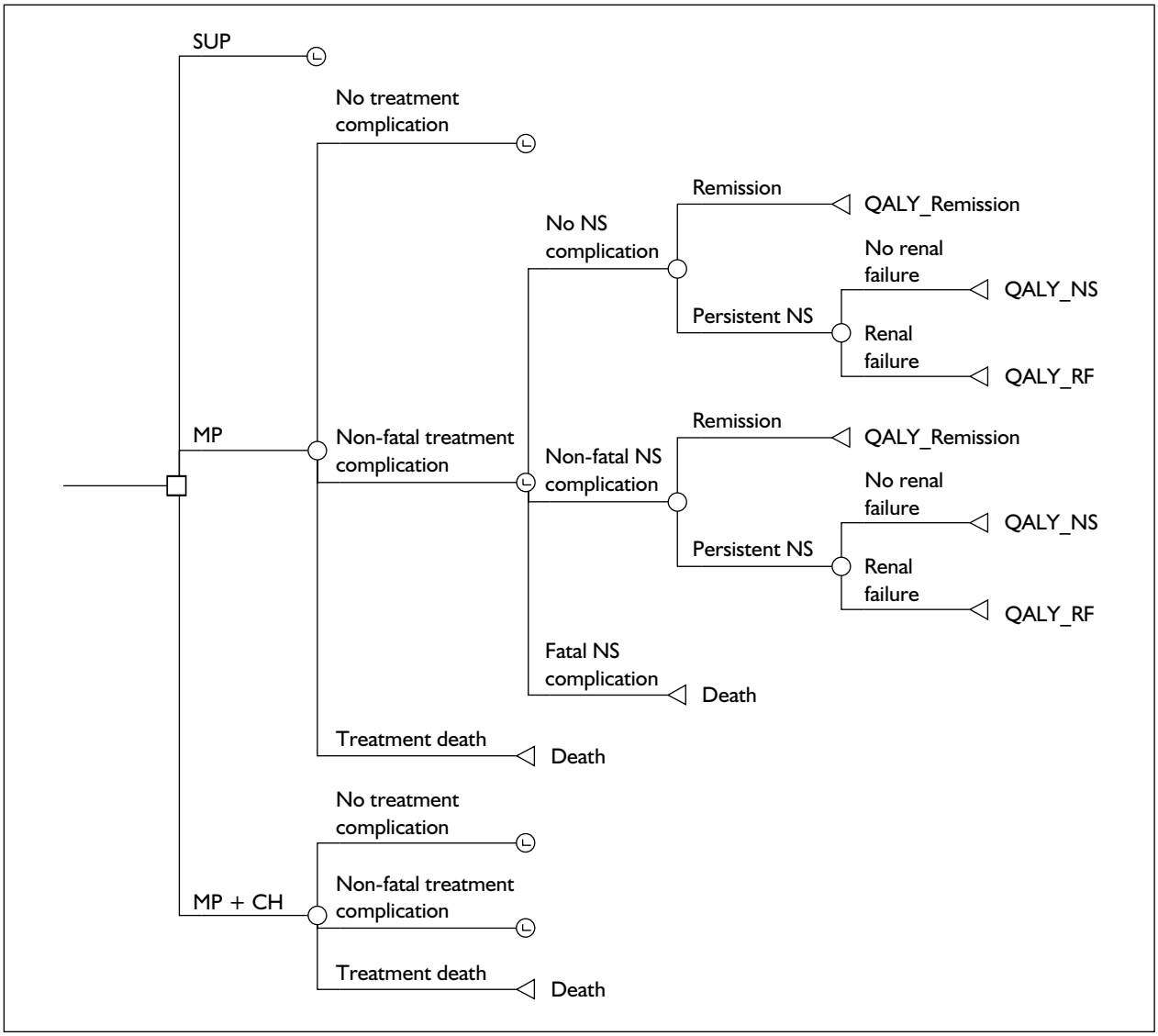

FIGURE 4 *Decision tree for therapy for idiopathic membranous nephropathy (from Picolli and colleagues[61]). MP, methylprednisolone; MP + CH, methylprednisolone and chlorambucil; NS, nephrotic syndrome; RF, renal failure; SUP, supportive treatment.*
Note: patients who do not die after treatment enter the nephrotic syndrome subtree (L).

membranous nephropathy. Idiopathic membranous nephropathy presents most frequently as nephrotic syndrome.[63] The study compared patients who received supportive therapy, methylprednisolone or methylprednisolone and chlorambucil. The analysis was based on evidence from two Italian controlled trials.[64,65]

The model structure (a decision tree) is shown in *Figure 4*. The decision model consists of 28 nodes, including 27 chance nodes and 64 branches, 37 of which are terminal branches. Patients are allocated to supportive treatment (SUP), methylprednisolone (MP) or methylprednisolone and chlorambucil (MP + CH). Patients are exposed to a risk of death, and thereafter they enter the nephrotic syndrome subtree, marked 'L' in *Figure 4*. In this model patients may suffer complications from nephrotic syndrome. They will then either go into remission or have persistent nephrotic syndrome which may result in renal failure. The study used a baseline patient of age 40 years.

Piccoli and colleagues[61] assumed that patients who achieve partial or complete remission within 2 years of the onset do not have long-term complications of nephrotic syndrome and do not develop renal failure. The model uses four outcomes from nephrotic syndrome:

(a) early death due to complications either from nephrotic syndrome or treatment
(b) persistence of nephrotic syndrome with subsequent development of renal failure

TABLE 9 *Piccoli study: baseline assumptions for the decision analysis on treatment of nephrotic syndrome for a 40-year-old nephrotic patient with idiopathic nephropathy*[61]

	Fatal	Non-fatal
Probability of short-term complications related to nephrotic syndrome (%)	0.3%	5%
Probability of short-term complications from treatment (%)		
Supportive	0%	0%
MP	0.3%	15%
MP + Ch	0.9%	45%
Life expectancy for sustained remission (years)	36.4	
Life expectancy at the onset of terminal renal failure (years)	9.7	
Survival until terminal renal failure develops (years)	10	
HRQoL (value) for nephrotic syndrome	0.9	
HRQoL (value) for terminal renal failure	0.75	

(c) persistence of nephrotic syndrome with maintenance of stable renal function
(d) sustained remission of proteinuria within the first 2 years with maintenance of stable renal function thereafter.

The model assigns a life expectancy to each of the health states, and adjusts life expectancy according to HRQoL (health state values). Parameter values used in the model are shown in *Table 9*. The model assumed that patients with complications would have a reduction in HRQoL: with methylprednisolone treatment this was over a 2-week period [0.04 quality-adjusted life-years (QALY)], whereas with methylprednisolone and chlorambucil the reduction in HRQoL was over a 6-week period (0.12 QALY).

Results from the baseline analysis led Picolli and colleagues to recommend the use of methylprednisolone and chlorambucil for nephrotic syndrome. However, in a more recent review,[62] Picolli comments that the earlier recommendations do not appear to have been endorsed by other nephrologists, and alkylating agents such as chlorambucil are recommended only for patients at high risk of progression to renal failure.

Piccoli and colleagues have not explained, in any detail, the rationale for their choice of data, assumptions or model structure. The model developed, and the data used to populate the model, are largely based on previous studies by Levey and colleagues[58] and Kassirer[57] (both of which address research questions over biopsy-tailored treatment).

The model developed by Levey and colleagues[58] was based on the earlier study by Kassirer,[57] but it was further informed by a more extensive review of the literature and further analysis of available data, to inform both parameter values and model structure.

Levey and colleagues[58] assume that membranous nephropathy and MCNS patients are steroid responsive and the other histopathologies are not responsive. They note that the benefit of steroid therapy for patients with membranous nephropathy, based on the literature reviewed, was uncertain, and that conflicting conclusions had been drawn from the seven prospective randomised studies considered. They pooled the data from a number of trials to estimate the transition probabilities used in the model. Few of the clinical studies were longer than 3 years (the longest study was over 6.6 years); therefore, the model is based on assumptions over the long-term progression to renal failure of patients with persistent nephrotic syndrome. The model assumes that the prognosis for survival and preservation of renal function is excellent for MCNS patients, whether or not steroids are prescribed. Their model describes the patient pathway in the short term (less than 8 months), medium term (8 months to 2 years) and long term (after 2 years). After 2 years, patients remain indefinitely in one of the following health states: death, nephrotic syndrome with renal failure or nephrotic syndrome in remission without renal failure. A life expectancy is estimated for each of these health states. Patients who achieve remission within 8 months are assumed to remain in remission indefinitely. Those who do not reach remission in 8 months receive no further treatment, except where treated with empirical sequential therapy (where platelet inhibitor treatment is relevant). Patients who achieve remission within 2 years are assumed to remain in remission indefinitely. Those who do not reach remission in 2 years have

persistent nephrotic syndrome, with a proportion of patients at risk of developing renal failure. The modelled outcome (of nephrotic syndrome) depends on the underlying disease and the specific treatment strategy assigned. The model calculates the expected longer term quality-adjusted life expectancy for each strategy.

Levey and colleagues assumed that all patients have an equal complication risk, regardless of histopathology. Data on complications related to steroid therapy are from the Collaborative Study of Adult Idiopathic Nephrotic Syndrome.[66] Complications from persistent nephrotic syndrome are assumed to impact on quality of life, with a reduction of 10% in quality of life applied in the model. Where patients progress to ESRF, the model assumes a reduction in quality of life of 25%. Levey and colleagues[58] state that these quality of life reductions are based on the literature reviewed, but they do not discuss how these values were extracted from the citations. For general treatment-related complications the model assumes that there will be a short-term QALY loss, but the authors do not discuss how these QALY values have been estimated.

Moxey-Mims and colleagues[59] presented an evaluation that models disease progression for nephrotic syndrome over time. They investigated the clinical need for biopsy-tailored treatment for adolescents with idiopathic nephrotic syndrome. The model and data are largely based on previous analyses by Levey and colleagues[58] (and Kassirer[57]) outlined above.

The challenge of modelling the cost-effectiveness of treatments for SRNS

As outlined above, the literature to inform on the clinical effectiveness and cost-effectiveness of treatments for SRNS is sparse, and there are no clearly presented views in the literature on the relative cost-effectiveness of alternative treatment strategies, or on the modelling of cost-effectiveness in SRNS. As reported in the section 'Results section' (p. 12), there is little or no information on the relative clinical effectiveness of the alternative medical therapies for SRNS in children. The current evidence base on clinical effectiveness offers no basis upon which reliably to consider the cost-effectiveness of treatments. However, based on the review of the available literature, and on discussions with clinical experts, should better quality clinical effectiveness data become available the model structure presented by Picolli and colleagues[61] could be a useful starting point for CEA. The parameter values for such a model (e.g. transition probabilities, complication rates, cost, health state values) should be informed by a thorough review of the available evidence.

Other important considerations for CEA are treatment group and comparator strategy. The section 'Current service provision' (p. 3) has discussed the alternative pharmaceutical therapies in more detail, and considered the issue of current practice, with respect to the expected treatment strategy for SRNS patients. Historically, newly presenting patients (regardless of histology) have typically been prescribed a course of cyclophosphamide (up to 8 weeks). Where patients do not respond to cyclophosphamide they will typically be prescribed ciclosporin. However, it is becoming increasingly common for ciclosporin to be used directly, without prior treatment with cyclophosphamide. In the context of the current review it is suggested that in future cost-effectiveness analysis the treatment eligible patient group should be those patients not indicated for cyclophosphamide treatment and/or those patients not responding to cyclophosphamide, who would typically be treated with ciclosporin.

CEA is concerned with the relative impact of treatment on disease status (i.e. remission from nephrotic syndrome, or persistent nephrotic syndrome with or without renal failure) and the costs and consequences of the respective treatment pathways (by disease status), when compared with the next best alternative treatment. It would seem clear that any treatment having a modifying effect on disease status would prove to be cost-effective when compared with 'no treatment', given the impact of nephrotic syndrome on the health of the patient, and the longer term and extremely serious prospect of renal failure. However, for patients with persistent nephrotic syndrome it is also clear that 'no treatment' is not reflective of current practice. Although there is always going to be variation in the treatments that patients are prescribed, given the small patient group and varied histological presentations of disease, it is suggested here that ciclosporin be used for the comparator strategies in CEA.

Summary

This chapter investigated economic aspects of treatments for children with idiopathic SRNS. A search and review of the literature of treatments for SRNS in children found no economic evaluations and very limited literature on the cost and consequences associated with SRNS in

children. Subsequent searches were undertaken to identify economic evaluations and economic evidence in the area of SRNS in adults, and studies that may be helpful in modelling nephrotic syndrome for cost-effectiveness analyses. One of the aims of the current report was to draw together the best available evidence to estimate the cost-effectiveness of alternative treatments for SRNS in children in a UK setting. The current authors explored the development of an economic model, either adapting an existing cost-effectiveness model or constructing a new one. However, the current data to inform any CEA are very sparse (e.g. clinical effectiveness, cost-effectiveness data, cost and outcome data) and in the authors' opinion do not allow the cost-effectiveness of current treatments for SRNS to be modelled in an appropriate way at present. The limitations in the extent of the evidence on the relative clinical effectiveness of treatments are the main reason for arriving at this conclusion (see Chapter 3). Economic analysis using the comparator of placebo or 'no treatment' is not regarded as appropriate (there is a small number of trials comparing ciclosporin with no treatment) and there is an absence of clinical effectiveness data to model the comparison of other treatment options. However, should better quality and more relevant data become available, the modelling framework presented by Picolli and colleagues[61] is suggested as a useful starting point for CEA (although data inputs would need to be considered from first principles).

Chapter 5
Discussion

Statement of principal findings

Clinical effectiveness

Two published systematic reviews[31,42] and 11 trials were included in this systematic review; these were comprised of six parallel RCTs,[22,32,43–46] three randomised cross-over trials,[38,41,47] one CCT[48] and one prospective cohort study with concurrent controls.[34] The included studies assessed seven different therapies (cyclophosphamide, ciclosporin, azathioprine, methylprednisolone, dexamethasone, enalapril and tuna fish oil), but just two of these drugs (cyclophosphamide and ciclosporin) were assessed by more than one study. The included trials were generally of poor quality, therefore the strength of the evidence and the conclusions that can be drawn are limited.

Of the seven therapies included in this systematic review, only ciclosporin was found to statistically significantly increase remission rates in children with idiopathic SRNS. The children in the three ciclosporin studies had MCNS or FSGS.[45–47] A statistically significant increase in serum albumin, potassium and creatinine, and a decrease in magnesium were also found, but there were no changes in other serum biochemical values. However, the comparator in the RCTs was placebo or 'supportive treatment', which may not be realistic alternatives in current practice. A randomised cross-over trial of ciclosporin that did not contribute to the meta-analysis found no remission with either the drug or the control.[47] Adverse effects were few and differed little between groups, and included infections and hypertension.

There was no difference in remission rates with cyclophosphamide plus prednisone compared with prednisone alone in patients with various histopathologies or in a subgroup with FSGS;[32,43] however, a response occurred much sooner with cyclophosphamide. Deaths occurred in both groups when patients were off therapy and in chronic renal failure, but only one death due to sepsis occurred while taking prednisone. Side-effects in both groups included hypertensive seizure, and haemorrhagic cystitis occurred with cyclophosphamide. No statistically significant difference was found between intravenous and oral cyclophosphamide, although more vomiting occurred with intravenous administration, and pneumonia and alopecia occurred with oral administration.[44]

No statistically significant improvement was found with azathioprine plus prednisone compared with placebo. The histopathology of the patients was not reported. Adverse effects were not reported.[22]

No statistical comparisons were made in the trial comparing a 6-month and an 18-month regimen of methylprednisolone.[48] Three-fifths of the 6-month group had complete or partial remission and six out of seven patients had partial remission in the 18-month group. Hypertension and frequent infections occurred in both groups, and one death occurred. No statistically significant differences in remission rates were found between dexamethasone and methylprednisolone in patients with focal glomerulosclerosis, and adverse event rates were similar (67% versus 62%). The most common adverse event was hypertension.[34]

High-dose but not low-dose enalapril was associated with a statistically significant reduction in urinary albumin and albumin to creatinine ratio in a randomised cross-over study of patients with MCNS, FSGS, MBGN and MPGN.[41] The difference in the urine albumin to creatinine ratio reduction percentage between the two groups was statistically significant in the period before cross-over, but not in the following period. Blood albumin increased with low-dose enalapril in the group that received this first, but this was not statistically significant with high-dose enalapril or the group that received low-dose enalapril after cross-over. Carry-over effects may have occurred in this study. Enalapril was associated with a dry cough that subsided after stopping treatment.

No statistically significant differences in proteinuria, creatinine clearance, serum creatinine or lipid profiles were found between tuna fish oil and placebo in a small study of five patients. Histopathology of the patients was not reported. No adverse events were reported.[38]

The extent of reporting of adverse events varied between the studies, and some of the expected

side-effects were not reported. This may be due to the small number of patients in many of the studies, inadequate length of follow-up or incomplete reporting.

Economic evaluation

The systematic literature search of treatments for SRNS in children found no economic evaluations and a very limited literature on the cost and consequences associated with SRNS in children. Subsequent searches were undertaken to identify economic evaluations and economic evidence in the area of SRNS in adults, and studies that may be helpful in modelling nephrotic syndrome for CEA. Although one of the aims of the report was to inform on the cost-effectiveness of alternative treatments, developing an economic model where appropriate, this has not been possible given the extent of the clinical data available. There are limitations in the evidence available on the relative clinical effectiveness of alternative treatments, and the evidence base does not allow the cost-effectiveness of current treatments for SRNS to be modelled in an appropriate way at present. However, should better quality and more relevant data become available, the modelling framework presented by Picolli and colleagues[61] is suggested as a useful starting point for CEA (although data inputs would need to be considered from first principles).

Strengths and limitations of the assessment

The systematic review has the following strengths:

- It is independent of vested interest.
- The systematic review brings together the evidence on the effectiveness of treatments for children with idiopathic SRNS, applying consistent methods of critical appraisal and presentation.
- A broad and thorough systematic search of the literature has identified all English-language studies with a concurrent control group (not limited to randomised trials) on a number of treatments for idiopathic SRNS in children, and has highlighted gaps in the literature and areas for further research.
- Although the review has not identified any economic evaluations, a thorough systematic search of the literature on the cost-effectiveness of treatments for children with idiopathic SRNS has been undertaken.
- The systematic review was guided by the principles for undertaking a systematic review.
- Before undertaking the review, the methods were set out in a research protocol (Appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations:

- Owing to time constraints, there was a lack of follow-up with authors of the primary studies to clarify methodological details and results. As the quality of reporting was poor in several of the studies, clarification from the authors may have been useful. However, it is unlikely that further details from the authors would have changed the reviewers' conclusions.
- Inclusion was limited to English language owing to time constraints. However, no non-English RCTs were identified by the Cochrane review,[31] which did not limit inclusion.
- The strength of the conclusions drawn is limited by the poor quality of the included studies.

Other relevant factors

- This systematic review updates and expands on a previous systematic review,[31] with broader eligibility criteria allowing the inclusion of additional studies.
- The findings of this review appear to concur broadly with findings of the previous review,[31] despite the inclusion of additional studies. However, differences in the way the data were analysed have led to slightly different results for the subgroup analysis of ciclosporin for patients with FSGS. The authors of the Cochrane review analysed the data using the number of patients 'without remission', rather than the number of patients 'with remission', and found a statistically significant result, in contrast to the non-significant trend found by the current review. As demonstrated here, switching the outcome between events and non-events can make a difference to risk ratios, affecting the effect estimate and its significance, as the precision of a risk ratio estimate differs markedly between situations with low risks of events and situations with high risks of events.[67] By analysing the data as a non-event, as in the Cochrane review, greater precision is achieved.

Switching between events and non-events has little impact on odds ratios (ORs); the new odds ratio is the reciprocal of the original odds ratio. Reanalysing the data using the odds ratio demonstrates a statistically non-significant trend favouring ciclosporin for patients with FSGS, both for numbers 'with remission' (OR 8.44, 95% CI 0.85 to 83.39) and for numbers 'without remission' (OR 0.12, 95% CI 0.01 to 1.17), supporting the present reviewers' conclusion. Discussing the number of patients 'with remission' following treatment rather than the number 'without remission' seems more clinically relevant and the results are therefore presented in this way.

- Apart from ciclosporin and cyclophosphamide, only one eligible study was available for each of the treatments included in this review.
- Where reported, it was apparent that there were some differences between studies in the definition of remission used. The studies also differed in the amount of detail provided when defining remission, so it was not always possible to judge whether the definitions of remission were the same.
- An attempt was made to discuss results according to histopathology where possible, but this is limited by the small number of studies and inadequate description of patients by some studies.
- The studies used different eligibility criteria, with some including all patients with SRNS and others limiting inclusion to patients with specified histopathologies. This may limit generalisability.
- There are emerging data that many cases of SRNS are associated with genetic mutations and that they are less likely to respond to immunosuppressive therapy.[8,9] These cases will have been unknowingly included in all of the eligible studies.

Chapter 6
Conclusions

Implications for service provision

There is an absence of good-quality evidence on the treatment of idiopathic SRNS in children. The identified trials were of generally poor quality and inadequately powered. Cyclophosphamide combined with prednisone decreased the time to remission to approximately 40% of that for patients treated with prednisone alone, but did not increase the number of children with remission. A meta-analysis of two trials found that ciclosporin increased the number of patients with remission compared with placebo or supportive treatment. Other studies included in this review each assessed a different treatment, and none found a statistically significant effect. However, owing to the small sample sizes and poor quality of most of the trials, a beneficial effect cannot be rejected.

Suggested research priorities

New emerging evidence suggests that children with SRNS who have a genetic mutation are much less likely than those without mutations to respond to treatment; therefore, the former patients should be excluded or analysed separately in future trials. A well-designed adequately powered RCT is required comparing ciclosporin with other treatments in children with SRNS without genetic mutations. The comparators may include, but should not necessarily be limited to, tacrolimus or mycophenolate mofetil. Outcomes should include remission rates, renal failure and costs. As this is a rare condition, a multicentre international trial is likely to be required to recruit sufficient numbers. Further well-designed RCTs are required to establish the effectiveness of other treatments that are currently in common use for nephrotic syndrome, such as levamisole.

Steroids may be used to treat 'steroid-resistant' nephrotic syndrome, indicating that a longer course or repeat course was needed. Further research is required to define the point at which further use of prednisone should be abandoned and at what point adverse effects from steroids outweigh the benefits.

The data on prevalence and incidence are poor; therefore, a national UK audit based on histopathology and clinical outcome would be useful.

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Contribution of authors

Jill Colquitt (Senior Research Fellow), Colin Green (Principal Research Fellow), Jo Kirby (Research Fellow) and Richard Trompeter (Consultant in Paediatric Nephrology) developed the protocol. Jill Colquitt, Jo Kirby and Colin Green assisted in the development of the search strategy and carried out the inclusion screening. Jo Kirby and Jill Colquitt were responsible for data extraction/critical appraisal. Colin Green and Keith Cooper (Research Fellow) were responsible for the health economics aspects of the report. All authors contributed to drafting the report. Jill Colquitt was project coordinator.

References

1. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet* 2003;**362**:629–39.
2. Koskimies O, Vilska J, Rapola J, Hallman N. Long-term outcome of primary nephrotic syndrome. *Arch Dis Child* 1982;**57**:544–8.
3. McKinney PA, Feltbower RG, Brocklebank JT, Fitzpatrick MM. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol* 2001;**16**:1040–4.
4. International Study of Kidney Disease in Children. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. *J Pediatr* 1981;**98**:561–4.
5. Churg J, Habib R, White RHR. Pathology of the nephrotic syndrome in children. *Lancet* 1970; **i**:1299–302.
6. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *J Am Soc Nephrol* 1997;**8**:769–76.
7. Kim JS, Bellew CA, Silverstein DM, Aviles DH, Boineau FG, Vehaskari VM. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. *Kidney Int* 2005;**68**:1275–81.
8. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, *et al*. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nature Genet* 2006;**24**:349–54.
9. Ruf RG, Lichtenberger A, Karle SM, Haas JP, Anacleto FE, Schultheiss M, *et al*. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. *J Am Soc Nephrol* 2004;**15**:722–32.
10. White RHR, Glasgow EF, Mills RJ. Clinicopathological study of nephrotic syndrome in childhood. *Lancet* 1970;**i**:1353–9.
11. Ahmad H, Tejani A. Predictive value of repeat renal biopsies in children with nephrotic syndrome. *Nephron* 2000;**84**:342–6.
12. Southwest Pediatric Nephrology Study Group. Focal segmental glomerulosclerosis in children with idiopathic nephrotic syndrome: a report of the Southwest Pediatric Nephrology Study Group. *Kidney Int* 1985;**27**:442–9.
13. Niaudet PA. Steroid-resistant idiopathic nephrotic syndrome in children. In Avner ED, Harmon WE, Niaudet P, editors. *Pediatric nephrology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. pp. 557–73.
14. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 1978; **13**:159–65.
15. Gipson DS, Chin H, Presler DP, Jenette C, Ferris ME, Massengill S, *et al*. Differential risk of remission and ESRD in childhood FSGS. *Pediatr Nephrol* 2006; DOI: 10.1007/s00467-005-2123-2.
16. Arneil GC. 164 children with nephrosis. *Lancet* 1961;**ii**:1103.
17. Schlesinger ER, Sultz HA, Mosher WE, Feldman JG. The nephrotic syndrome. Its incidence and implications for the community. *Am J Dis Child* 1968;**116**:623–32.
18. Bonilla-Felix M, Parra C, Dajani T, Ferris M, Swinford RD, Portman RJ, *et al*. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. *Kidney Int* 1999;**55**:1885–90.
19. Srivastava T, Simon SD, Alon US. High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. *Pediatr Nephrol* 1999; **13**:13–18.
20. Ingulli E, Tejani A. Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. *Pediatr Nephrol* 1991;**5**:393–7.
21. Sharples PM, Poulton J, White RHR. Steroid responsive nephrotic syndrome is more common in Asians. *Arch Dis Child* 1985;**60**:1014–17.
22. Abramowicz M, Barnett HL, Edelmann CM Jr, Greifer I, Kobayashi O, Arneil GC, *et al*. Controlled trial of azathioprine in children with nephrotic syndrome. A report for the International Study of Kidney Disease in Children. *Lancet* 1970;**i**:959–61.
23. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). *Pediatrics* 2000;**105**:1242–9.

24. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis posttransplantation in 42 allografts in children – a single-center experience. *Transplantation* 1991;**51**:401–5.

25. Zhao H-Y, Sun R-P, Dong J-H, Zhen J-H. Relations of nuclear factor-kappa B activity in the kidney of children with primary nephrotic syndrome to clinical manifestations, pathological types, and urinary protein excretion. *Chin Med J* 2005;**118**:854–6.

26. Kim E-M, Striegel J, Kim Y, Matas AJ, Najarian JS, Mauer SM. Recurrence of steroid-resistant nephrotic syndrome in kidney transplants is associated with increased acute renal failure and acute rejection. *Kidney Int* 1994;**45**:1440–5.

27. International Study of Kidney Disease in Children. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. *Kidney International* 1981;**20**:765–71.

28. Niaudet P. Steroid-sensitive idiopathic nephrotic syndrome in children. In Avner ED, Harmon WE, Niaudet P, editors. *Pediatric nephrology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. pp. 543–56.

29. British Association for Paediatric Nephrology. *Review of multi-professional paediatric nephrology services in the UK – Towards standards and equity of care*. Report of a Working Party of the British Association for Paediatric Nephrology. Bristol: Kubiak Creative; 2003.

30. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents. *Pediatr Nephrol* 1990;**4**:303–7.

31. Habashy D, Hodson EM, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev* 2004;(3).

32. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. *Pediatric Nephrology* 1996;**10**:590–3.

33. Paediatric Formulary Committee. *BNF for children 2005*. London: BMJ Publishing Group, Royal Pharmaceutical Society of Great Britain, and RCPCH Publications; 2005.

34. Hari P, Bagga A, Mantan M. Short term efficacy of intravenous dexamethasone and methylprednisolone therapy in steroid resistant nephrotic syndrome. *Indian Pediatr* 2004;**41**:993–1000.

35. Durkan A, Hodson E, Willis N, Craig J. Non-corticosteroid treatment for nephrotic syndrome in children [review]. *Cochrane Database Syst Rev* 2001; (4):CD002290.

36. Joint Formulary Committee. *British National Formulary*. 52nd ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2006.

37. Burgess E. Management of focal segmental glomerulosclerosis: evidence-based recommendations. *Kidney Int Suppl* 1999;**55**(70):25–32.

38. Chongviriyaphan N, Tapaneya-Olarn C, Suthutvoravut U, Karnchanachumpol S, Chantraruksa V. Effects of tuna fish oil on hyperlipidemia and proteinuria in childhood nephrotic syndrome. *J Med Assoc Thail* 1999; **82**(Suppl 1):122–8.

39. Albon E, Yao GL, Milford D, Adi Y, Bayliss S, Ready A, *et al*. *The clinical and cost effectiveness of immunosuppressive therapy for renal transplantation in children*. NICE Report. London: National Institute for Clinical Excellence; 2005.

40. Hodson E. The management of idiopathic nephrotic syndrome in children. *Paediatr Drugs* 2003;**5**:335–49.

41. Bagga A, Mudigoudar BD, Hari P, Vasudev V. Enalapril dosage in steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2004;**19**:45–50.

42. Habashy D, Hodson EM, Craig JC. Interventions for steroid-resistant nephrotic syndrome: a systematic review. *Pediatr Nephrol* 2003;**18**:906–12.

43. International Study of Kidney Disease in Children. Prospective, controlled trial of cyclophosphamide therapy in children with the nephrotic syndrome. *Lancet* 1974;**ii**:423–7.

44. Elhence R, Gulati S, Kher V, Gupta A, Sharma RK. Intravenous pulse cyclophosphamide – a new regime for steroid-resistant minimal change nephrotic syndrome. *Pediatr Nephrol* 1994;**8**:1–3.

45. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, *et al*. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993;**43**:1377–84.

46. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol* 1996;**7**:56–63.

47. Garin EH, Orak JK, Hiott KL, Sutherland SE. Cyclosporine therapy for steroid-resistant nephrotic syndrome. A controlled study. *Am J Dis Child* 1988; **142**:985–8.

48. Adhikari M, Bhimma R, Coovadia HM. Intensive pulse therapies for focal glomerulosclerosis in South African children. *Pediatr Nephrol* 1997;**11**:423–8.

49. Gangakhedkar A, Wong W, Pitcher LA. Cerebral thrombosis in childhood nephrosis. *J Paediatr Child Health* 2005;**41**:221–4.

50. Gonzalez-Perez JG, Vale L, Stearns SC, Wordsworth S. Hemodialysis for end-stage renal disease: a cost-effectiveness analysis of treatment options. *Int J Technol Assess Health Care* 2005; **21**:32–9.

51. Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. *Health Technol Assess* 2005;**9**(21).

52. Department of Health (UK). *NHS reference costs*. 2004. URL: http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en. Accessed January 2006.

53. Netten A, Curtis L. *Unit costs of health and social care*. University of Kent: PSSRU; 2004.

54. Ruth E-M, Landolt MA, Neuhaus TJ, Kemper MJ. Health-related quality of life and psychosocial adjustment in steroid-sensitive nephrotic syndrome. *J Pediatr* 2004;**145**:778–83.

55. Bell CM, Chapman RH, Stone PW, Sandberg EA, Neumann PJ. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost–utility analyses. *Med Decis Making* 2001;**21**:288–94.

56. Hlatky MA. Is renal biopsy necessary in adults with nephrotic syndrome. *Lancet* 1982;**ii**:1264–8.

57. Kassirer JP. Is renal biopsy necessary for optimal management of the idiopathic nephrotic syndrome? *Kidney Int* 1983;**24**:561–75.

58. Levey AS, Lau J, Pauker SG, Kassirer JP. Idiopathic nephrotic syndrome. Puncturing the biopsy myth. *Ann Intern Med* 1987;**107**:697–713.

59. Moxey-Mims MM, Stapleton FB, Feld LG. Applying decision analysis to management of adolescent idiopathic nephrotic syndrome. *Pediatr Nephrol* 1994;**8**:660–4.

60. Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. *Kidney Int* 1994;**45**:578–85.

61. Piccoli A, Pillon L, Passerini P, Ponticelli C. Therapy for idiopathic membranous nephropathy: tailoring the choice by decision analysis. *Kidney Int* 1994; **45**:1193–202.

62. Piccoli A. Elementary clinical decision analysis in evidence-based nephrology. *J Nephrol* 2000;**13**:419–32.

63. Muirhead N. Management of idiopathic membranous nephropathy: evidence-based recommendations. *Kidney Int Suppl* 1999;**70**:S47–55.

64. Ponticelli C, Zucchelli P, Passerini P, Cesana B. Italian Idiopathic Membranous Nephropathy Treatment Study Group. Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 1992;**327**:599–603.

65. Ponticelli C, Zucchelli P, Passerini P, Cagnoli L, Cesana B, Pozzi C, *et al*. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1989; **320**:8–13.

66. Collaborative Study of the Adult Idiopathic Nephrotic Syndrome. A controlled study of short-term prednisone treatment in adults with membranous nephropathy. *N Engl J Med* 1979; **301**:1301–6.

67. Deeks JJ, Higgins J, Altman DG, editors. Analysing and presenting results. In Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.5* [updated May 2005]. URL: http://www.cochrane.org/resources/handbook/hbook.htm. Accessed 20 February 2006.

68. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;**313**:275–83.

69. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

70. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. CRD Report 4. 2nd ed. York: University of York; 2001.

Appendix 1

Protocol

Full title of research question

Treating children with idiopathic steroid-resistant nephrotic syndrome: a systematic review and economic evaluation.

Clarification of research question and scope

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome (SRNS).

The following treatments will be considered. Most of these are given outside the licensed indications of the drug.

- High-dose steroids, e.g. methylprednisolone.
- Immunosuppressive agents, e.g. ciclosporin, Tacrolimus, mycophenolate mofetil.
- Alkylating agents, e.g. cyclophosphamide, chlorambucil.
- Combinations of high-dose steroids with immunosuppressive agents or alkylating agents.
- Plasma-exchange therapy.
- ACE inhibitors.
- Fish oils.
- NSAIDs.
- Surgery, e.g. nephrectomy.

Comparisons of the above treatments will be included. Other comparators may include placebo, standard treatment, or different doses, durations or routes of administration. Primary outcomes include remission rates, relapse rates, renal function, adverse effects, long-term survival, costs and cost-effectiveness.

There are three distinct histological variants of idiopathic nephrotic syndrome; these are minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy, which is rare in children. These will be analysed separately where possible. Children with congenital (birth to 3 months) or infantile (3 months to 1 year) nephrotic syndrome are not within the scope of this review.

The review will focus on randomised controlled trials (RCTS). Controlled clinical trials (CCTs) and cohort studies with concurrent controls will be considered if insufficient RCTs are identified.

Cost-effectiveness will be from an NHS and personal social services perspective (costs and benefits). Estimates of cost-effectiveness will be presented as incremental cost per QALY gained.

Report methods

The review will be undertaken as systematically as time allows following the general principles outlined in NHS CRD Report 4.

The research protocol will be updated as necessary as the research programme progresses. NCCHTA will be notified of any changes in the protocol.

Search strategy

Electronic databases that will be searched include: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Library, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), EconLit, Medline, PubMed (previous 6 months): EMBASE, Science Citation Index (SCI), BIOSIS, Inside Information Plus, NLM (National Library of Medicine) Gateway Databases, Conference Proceedings Index, PapersFirst, National Research Register (NRR), Current Controlled Trials and Clinical Trials.gov.

Searches for clinical effectiveness will be from April 2002 to the current date. Searches for cost-effectiveness will be from database inception to the current date. Searches will be restricted to English language.

Bibliographies of related papers will be assessed for relevant studies.

Experts will be contacted for advice and peer review, and to identify additional published and unpublished references.

Inclusion and exclusion criteria

Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Interventions

Treatments for steroid-resistant nephrotic syndrome:

- high-dose steroids, e.g. methylprednisolone
- immunosuppressive agents, e.g. ciclosporin, tacrolimus, mycophenolate mofetil
- alkylating agents, e.g. cyclophosphamide, chlorambucil
- combinations of high-dose steroids with immunosuppressive agents or alkylating agents
- plasma-exchange therapy
- ACE inhibitors
- fish oils
- NSAIDs
- surgery, e.g. nephrectomy

Comparators:

- comparisons of the above treatments
- different doses, durations or routes of administration of the above treatments
- standard treatment
- placebo

Participants

Children aged between 1 and 18 years with idiopathic SRNS, defined as persistence of proteinuria >3+ on dipstick, urinary protein–creatinine ratio >0.2 g/mmol or >40 mg/m^2/hour after 4 weeks or more of daily corticosteroid.

Studies of children with SRNS, congenital or infantile genetic disorders, congenital infections, or other renal or systemic forms of nephrotic syndrome will be excluded from the review.

Types of study

Systematic reviews of RCTs and RCTs comparing the different drugs with placebo, each other or standard treatment will be included in the review of clinical effectiveness. Systematic reviews will be used as a source for RCTs and as a comparator.

Studies published as abstracts or conference presentations will be assessed for inclusion if sufficient details are presented to make appropriate decisions about the methodology of the study and the results.

If searches show that there are insufficient long-term RCTs to inform the economic model, CCTs or prospective cohort studies with concurrent controls meeting the inclusion criteria may be considered for inclusion. Emphasis will be placed on including studies that use the most rigorous study designs.

Full economic evaluations of the specified interventions in children with idiopathic SRNS will be included.

A range of designs for studies on quality of life, epidemiology and natural history will be considered.

Outcomes

The following outcome measures will be included:

- remission rates
- relapse rates
- renal function, including proteinuria
- adverse effects
- long-term renal survival
- quality of life.

Data extraction strategy

Data will be extracted from the included clinical studies using a standardised template.

Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality assessment strategy

The quality of included systematic reviews and RCTs will be assessed using NHS CRD (University of York) criteria (Appendix 3).

Economic evaluations will be assessed using criteria recommended by Drummond and Jefferson (1996)[68] and/or the format recommended Phillips and colleagues (2004).[69]

Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

Clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.

Where evidence is available, the review will undertake subgroup analyses by histological variants of idiopathic SRNS (MCNS, FSGS).

Data will be combined statistically if of sufficient quantity and quality, and if sufficiently similar, by meta-analysis using Review Manager software.

Methods for estimating cost-effectiveness of interventions

Published cost-effectiveness studies will be reviewed in detail, comprising a narrative review with tabulation of results where appropriate.

Where appropriate, an economic model will be devised by adapting an existing cost-effectiveness model or constructing a new one using the best available evidence to determine cost-effectiveness in a UK setting.

Data on resource use and costs will be from the published literature and NHS sources where appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services. Where costs and resource use related to treatment fall outside this perspective we will report these separately where data are available.

Effectiveness data, in terms of the outcomes described in the above section, will be extracted from published trials and used in association with other relevant data (e.g. resource use, unit costs) to populate the model to obtain measures of cost-effectiveness. If available, quality of life information will be obtained from the literature or other sources to calculate cost–utility estimates in terms of cost per QALY.

The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Competing interests

Nick Webb has received research grants and travel expenses for meetings from Novartis and Fujisawa, both of whom produce drugs which have been used for the treatment of nephrotic syndrome.

Advisory group

Representatives and other potential users of the review from different professional backgrounds and opinions, including academics, clinicians and patient groups, will be invited to provide expert advice.

Appendix 2

Literature search strategies

The databases were searched for published studies and recently completed and ongoing research. All searches were limited to English language only. *Figure 5* shows a flowchart of identification of studies for inclusion.

Clinical effectiveness searches

The following strategy was used to search MEDLINE (OVID), 1966–2005. This was adapted as appropriate to search the other databases listed below.

1 nephrotic syndrome/ 10103 DISPLAY
2 nephrosis lipoid/ 1487 DISPLAY
3 glomerulosclerosis focal/ 2830 DISPLAY
4 FSGS.ti,ab. 678 DISPLAY
5 focal segment$2 glomerulosclerosis.ti,ab. 1413 DISPLAY
6 glomerulonephritis membranoproliferative/ 1458 DISPLAY
7 MCNS.ti,ab. 319 DISPLAY
8 minimal change nephrotic syndrome.ti,ab. 637 DISPLAY
9 MGPN.ti,ab. 4 DISPLAY
10 membranoproliferative glomerulonephritis.ti,ab. 1168 DISPLAY
11 SRNS.ti,ab. 96 DISPLAY
12 (steroid adj5 resistant adj nephrotic syndrome).ti,ab. 215 DISPLAY
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 15434 DISPLAY
14 exp child/ 1051774 DISPLAY
15 adolescent/ 1070037 DISPLAY
16 (adolescent or adolescence).ti,ab. 43758 DISPLAY
17 ("young person" or "young people").ti,ab. 6535 DISPLAY
18 14 or 15 or 16 or 17 1618970 DISPLAY
19 13 and 18 6013 DISPLAY
20 alkylating agents/ 5114 DISPLAY
21 immunosuppressive agents/ 42400 DISPLAY
22 glucocorticoids/ 28814 DISPLAY
23 steroids/dt, tu 3387 DISPLAY
24 corticosteroid$1.ti,ab. 43534 DISPLAY
25 cyclosporine/ 18282 DISPLAY
26 ciclosporin$1.ti,ab. 764 DISPLAY
27 prednisone/ 24911 DISPLAY
28 prednisolone/ 19875 DISPLAY
29 methylprednisolone/ 11177 DISPLAY
30 azathioprine/ 10439 DISPLAY
31 mycophenolic acid/ 2608 DISPLAY
32 mofetil.ti,ab. 2440 DISPLAY
33 MMF.ti,ab. 1256 DISPLAY
34 cyclophosphamide/ 33166 DISPLAY
35 tacrolimus/ 7012 DISPLAY
36 chlorambucil/ 2979 DISPLAY
37 levamisole/ 3603 DISPLAY
38 levamisol$1.ti,ab. 3435 DISPLAY
39 angiotensin converting enzyme inhibitors/ 18866 DISPLAY
40 captopril/ or cilazapril/ or enalapril/ or fosinopril/ or imadapril/ or lisinopril/ or moexipril/ or perindopril.mp. or quinapril/ or ramipril/ or trandolapril/ [mp=title, original title, abstract, name of substance word, subject heading word] 16026 DISPLAY
41 fish oils/ 3697 DISPLAY
42 "tuna fish oil".ti,ab. 17 DISPLAY
43 plasmapheresis/ 6029 DISPLAY
44 plasma exchange/ 3361 DISPLAY
45 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 231335 DISPLAY
46 19 and 45 1826 DISPLAY
47 limit 46 to (humans and English language)

Cost-effectiveness searches

The following strategy was used to search MEDLINE (OVID), 1966–2005, and was adapted as appropriate for the other databases listed below.

1 nephrotic syndrome/ (10135)
2 nephrosis lipoid/ (1491)
3 glomerulosclerosis focal/ (2851)
4 FSGS.ti,ab. (684)
5 focal segment$2 glomerulosclerosis.ti,ab. (1427)
6 glomerulonephritis membranoproliferative/ (1468)
7 MCNS.ti,ab. (321)
8 minimal change nephrotic syndrome.ti,ab. (640)
9 MGPN.ti,ab. (4)
10 membranoproliferative glomerulonephritis.ti,ab. (1176)

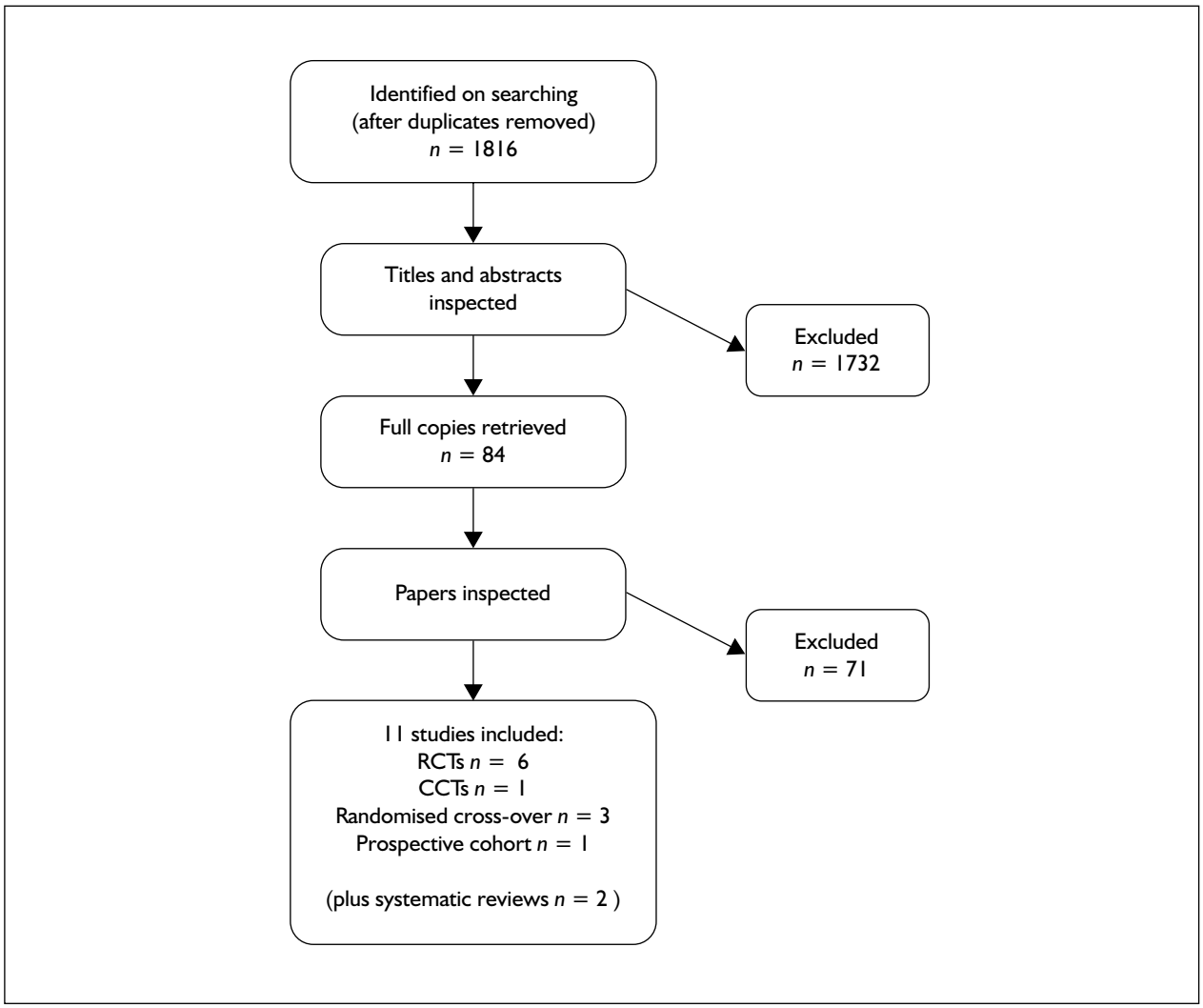

FIGURE 5 *Flowchart of identification of studies for inclusion in the systematic review of clinical effectiveness*

11 SRNS.ti,ab. (97)
12 (steroid adj5 resistant adj nephrotic syndrome).ti,ab. (216)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (15506)
14 exp economics/ (339169)
15 exp economics hospital/ (13492)
16 exp economics pharmaceutical/ (1515)
17 exp economics nursing/ (3666)
18 exp economics medical/ (9687)
19 exp "costs and cost analysis"/ (117766)
20 value of life/ (4528)
21 exp models economic/ (4361)
22 exp fees/ and charges/ (6732)
23 exp budgets/ (8884)
24 (economic$ or price$ or pricing or pharmacoeconomic$ or pharmaeconomic$).tw. (74963)
25 (cost$ or costly or costin$ or costed).tw. (165435)
26 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (12009)
27 (expenditure$ not energy).tw. (9166)
28 (value adj2 (money or monetary)).tw. (536)
29 budget$.tw. (9421)
30 (economic adj2 burden).tw. (1156)
31 "resource use".ti,ab. (21948)
32 "cost effective$".tw. (33431)
33 "economic evaluation$".tw. (2492)
34 or/14-33 (499143)
35 13 and 34 (63)
36 (letter or editorial or comment).pt. (749368)
37 35 not 36 (63)
38 exp child/ (1058482)
39 adolescent/ (1077602)
40 (paediatric$ or pediatric$ or child$).ti,ab. (601329)
41 38 or 39 or 40 (1751259)
42 37 not 41 (29)
43 limit 42 to (humans and english language) (21)

44 from 43 keep 1-21 (21)
45 from 44 keep 1-21 (21)

Modelling search MEDLINE 1966–2005 (59 downloaded, 12 excluded as irrelevant)

1 nephrotic syndrome/ 10168 DISPLAY
2 kidney diseases/ 45055 DISPLAY
3 kidney failure/ 4556 DISPLAY
4 exp models economic/ 4409 DISPLAY
5 *models theoretical/ 18974 DISPLAY
6 *models organizational/ 2477 DISPLAY
7 economic model$.ti,ab. 594 DISPLAY
8 markov chains/ 3200 DISPLAY
9 markov.ti,ab. 3439 DISPLAY
10 monte carlo method/ 7924 DISPLAY
11 monte carlo.ti,ab. 7844 DISPLAY
12 exp decision theory/ 5776 DISPLAY
13 (decision$ adj2 (tree$ or analy$ or model)).ti,ab. 6142 DISPLAY
14 or/4-13 48492 DISPLAY
15 1 and 14 10 DISPLAY
16 14 and (2 or 3) 62 DISPLAY
17 15 or 16 72 DISPLAY
18 limit 17 to (humans and english language) 59 DISPLAY
19 from 18 keep 1-59 59 DISPLAY

Quality of life searches

The following strategy was used to search MEDLINE (OVID), 1966–2005, and was adapted as appropriate to the other databases listed in *Table 10*.

1 nephrotic syndrome/ (7724)
2 nephrosis lipoid/ (1087)
3 glomerulosclerosis focal/ (1555)
4 FSGS.ti,ab. (181)
5 focal segment$2 glomerulosclerosis.ti,ab. (526)
6 glomerulonephritis membranoproliferative/ (687)
7 MCNS.ti,ab. (140)
8 minimal change nephrotic syndrome.ti,ab. (367)
9 MGPN.ti,ab. (2)
10 membranoproliferative glomerulonephritis.ti,ab. (702)
11 SRNS.ti,ab. (36)
12 (steroid adj5 resistant adj nephrotic syndrome).ti,ab. (85)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (10690)
14 exp child/ (728360)
15 adolescent/ (725707)
16 (pediatric$ or paediatric$ or adolesc$ or child$).ti,ab. (382228)
17 14 or 15 or 16 (1174714)
18 13 and 17 (4600)
19 quality adjusted life year/ (111)
20 quality adjusted life.ti,ab. (273)
21 value of life/ (3038)
22 (qaly$ or quald$ or qale$ or qtime$).ti,ab. (249)
23 disability adjusted life.ti,ab. (10)
24 daly$.ti,ab. (66)
25 health status indicators/ (3160)
26 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or shortform thirtysix or short form thirty six).ti,ab. (150)
27 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (366)
28 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (44)
29 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (15)
30 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (117)
31 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (23)
32 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (58)
33 (hye or hyes).ti,ab. (27)
34 health$ year$ equivalen$.ti,ab. (18)
35 health utilit$.ab. (28)
36 (hui or hui1 or hui2 or hui3).ti,ab. (100)
37 disultil$.ti,ab. (0)
38 rosser.ti,ab. (28)
39 quality of well being.ti,ab. (169)
40 quality of wellbeing.ti,ab. (0)
41 qwb.ti,ab. (26)
42 willingness to pay.ti,ab. (102)
43 standard gamble$.ti,ab. (52)
44 time trade off.ti,ab. (50)
45 time tradeoff.ti,ab. (13)
46 tto.ti,ab. (36)
47 or/19-46 (7651)
48 letter.pt. (302855)
49 editorial.pt. (78418)
50 comment.pt. (89901)
51 or/48-50 (387163)
52 47 not 51 (7302)
53 18 and 52 (2)
54 quality of life/ (13816)
55 18 and 54 (1)
56 53 or 55 (2)
57 from 56 keep 1 (1)

Additional databases searched

TABLE 10 *Additional databases*

Databases searched	Date of issue of database searched			
	Clinical effectiveness	**Cost-effectiveness**	**Quality of life**	**Epidemiology**
Cochrane Library	Issue 4, 2005	Issue 4, 2005	Issue 4, 2005	Issue 4, 2005
EMBASE (OVID)	1980–2006	1980–2006	1980–2006	1980–2006
PubMed	February 2006		February 2006	
ISI Web of Knowledge	1990–2006			
Web of Science Proceedings	1990–2006			1990–2006
BIOSIS	Inception to 2006			
DARE	Inception to 2006			
HTA Database	Inception to 2006			
NHS EED			Inception to 2006	
EconLit			Inception to 2006	
NRR	August 2005		August 2005	August 2005
Clinical Trials.gov	August 2005			
Current Controlled Trials	August 2005			

Epidemiology searches

The following strategy was used to search MEDLINE (OVID), 1966–2005, and was adapted as appropriate for the other databases listed in *Table 10*.

1 nephrotic syndrome/ep, et 2004 DISPLAY
2 nephrosis lipoid/ep, et 200 DISPLAY
3 exp child/ 1052397 DISPLAY
4 (paediatric$ or pediatric$ or child$ or adolescen$).tw. 639619 DISPLAY
5 1 or 2 2150 DISPLAY
6 5 and (3 or 4) 627 DISPLAY
7 (infant$ or congenit$ or inherit$ or mutat$ or familial or gene$ or heterogen$).tw. 2057344 DISPLAY
8 infant/ 428296 DISPLAY
9 6 and (7 or 8) 209 DISPLAY
10 6 not 9 418 DISPLAY
11 glomerulonephritis focal/ 2831 DISPLAY
12 FSGS.ti,ab. 678 DISPLAY
13 focal segment$2 glomerulosclerosis.ti,ab. 1415 DISPLAY
14 glomerulonephritis membranoproliferative/ 1460 DISPLAY
15 MCNS.ti,ab. 320 DISPLAY
16 minimal change nephrotic syndrome.ti,ab. 639 DISPLAY
17 MGPN.ti,ab. 4 DISPLAY
18 membranoproliferative glomerulonephritis.ti,ab. 1170 DISPLAY
19 SRNS.ti,ab. 97 DISPLAY
20 (steroid adj5 resistant nephrotic syndrome).ti,ab. 216 DISPLAY
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 5980 DISPLAY
22 21 and (3 or 4) 1628 DISPLAY
23 22 and (7 or 8) 567 DISPLAY
24 22 not 23 1061 DISPLAY
25 exp incidence/ 90520 DISPLAY
26 exp prevalence/ 81350 DISPLAY
27 incidence.ti,ab. 277739 DISPLAY
28 prevalence.ti,ab. 160037 DISPLAY
29 etiolog$.ti,ab. 102391 DISPLAY
30 aetiolog$.ti,ab. 28509 DISPLAY
31 ((natural$ or disease$) adj (progress$ or course$ or histor$)).ti,ab. 46301 DISPLAY
32 *epidemiology/ 3694 DISPLAY
33 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 637645 DISPLAY
34 24 and 33 145 DISPLAY
35 34 not 7 145 DISPLAY
36 10 or 35 548 DISPLAY
37 nephrotic syndrome/ or nephrosis lipoid/ 11194 DISPLAY
38 37 and 33 713 DISPLAY
39 38 and (3 or 4) 319 DISPLAY
40 39 not (7 or 8) 167 DISPLAY
41 36 or 40 623 DISPLAY
42 limit 41 to (humans and english language) 469 DISPLAY
43 from 42 keep 1-469 469 DISPLAY

Additional searching

Bibliographies: all references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Appendix 3

Quality assessment

TABLE 11 *Quality criteria for assessment of experimental studies (NHS CRD[70])*

Item	Judgement[a]
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention-to-treat analysis?	
10. Were withdrawals and dropouts completely described?	

[a] Adequate, inadequate, not reported, unclear.

TABLE 12 *Quality assessment for systematic reviews (NHS CRD DARE criteria)*

Item	Yes/No/Uncertain
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	
2. Is there evidence of a substantial effort to search for all relevant research?	
3. Is the validity of included studies adequately assessed?	
4. Is sufficient detail of the individual studies presented?	
5. Are the primary studies summarised appropriately?	

TABLE 13 *Quality assessment for observational studies (NHS CRD[70])*

	Judgement	Comments
Is there sufficient description of the groups and the distribution of prognostic factors?		
Are the groups assembled at a similar point in their disease progression?		
Is the intervention/treatment reliably ascertained?		
Were the groups comparable on all important confounding factors?		
Was there adequate adjustment for the effects of these confounding variables?		
Was a dose–response relationship between intervention and outcome demonstrated?		
Was outcome assessment blind to exposure status?		
Was follow-up long enough for the outcomes to occur?		
What proportion of the cohort was followed up?		
Were dropout rates and reasons for dropout similar across intervention and unexposed groups?		

Appendix 4

Summary of evidence of clinical effectiveness: systematic reviews

Reference	Methods
Habashy, 2004[31,42] Australia *Funding*: No external or internal sources of support supplied	*Aim/objective*: To evaluate the benefits and harms of all interventions for children with SRNS *Search strategy*: Published and unpublished RCTs identified from the Cochrane Controlled Trials Register, MEDLINE, EMBASE, reference lists or articles and abstracts from conference proceedings *Inclusion criteria* Interventions: All interventions considered. Different immunosuppressive agents or non-immunosuppressive agents with placebo, prednisone or other agent given orally or parenterally Participants: Children aged 3 months to 18 years with SRNS Outcome measures: Complete/partial remission, renal function, adverse effects, duration of remission or partial remission Study design: RCTs and quasi-RCTs *Quality criteria*: Quality of studies assessed independently without blinding to authorship or journal using checklist developed for the Cochrane Renal Group. Quality items assessed were allocation concealment, ITT analysis, completeness of follow-up and blinding of investigators, participants and outcome assessors *Application of methods*: Titles and abstracts screened independently. Reviewers independently assessed retrieved abstracts, and if necessary full text to determine which studies satisfied the inclusion criteria. Data extraction was carried out by the same reviewers independently. Disagreements were resolved in consultation with a third reviewer. *Methods for analysis*: For dichotomous outcomes, results were expressed as relative risk with 95% CI. Data was pooled using the random effects model, but the fixed effects model was analysed to ensure robustness of the model chosen and susceptibility to outliers. For continuous scales, weighted mean difference was used, or the standardised mean difference if different scales were used. Heterogeneity was analysed using a χ^2 test on $n-1$ degrees of freedom. Subgroup analysis was planned to explore possible sources of heterogeneity. Adverse effects were tabulated and assessed with descriptive techniques. If sufficient RCTs were identified, it was planned to examine for publication bias using a funnel plot
Results *Quantity and quality of included studies*: Nine trials were included; 225 children entered in the trials but data on primary outcome evaluated in only 205 Three trials (one cross-over) compared ciclosporin with placebo or no treatment Two trials compared oral cyclophosphamide and prednisone with prednisone alone One trial compared intravenous with oral cyclophosphamide One trial compared azathioprine and prednisone with placebo and prednisone One cross-over trial compared different doses of the ACE inhibitor enalapril with placebo One cross-over trial compared fish oil with placebo *Treatment effect*: Ciclosporin when compared with placebo or no treatment significantly increased the number of children who achieved complete remission. There was no significant difference in the number of children who achieved complete remission between oral cyclophosphamide with prednisone and prednisone alone, between intravenous cyclophosphamide and oral cyclophosphamide, and between azathioprine with prednisone and prednisone alone *Assessment of heterogeneity*: There was significant heterogeneity between two of the three ciclosporin studies, with one trial showing a greater degree of protective effect (RR 0.05, 95% CI 0.00 to 0.73) than the other (RR 0.40, 95% CI 0.19 to 0.85). Heterogeneity was also demonstrated in the difference summary estimates between the random and fixed effects models (fixed effects; RR 0.2 95%, CI 0.08 to 0.49)	

continued

Economic evaluation: No economic evaluation was carried out

Conclusions: Further adequately powered and well-designed RCTs are needed to confirm the efficacy of ciclosporin and to evaluate other regimens for idiopathic SRNS, including high-dose steroids with alkylating agents or ciclosporin

Implications of the review: The review has highlighted how few trials have addressed the efficacy of interventions for SRNS in children. Although ciclosporin may be of some benefit for children with SRNS, the systematic review has demonstrated that RCTs to date are inadequate to confirm this. In addition, the small sample size resulting in large confidence intervals leads to uncertainty in the summary estimates so that a beneficial effect of oral cyclophosphamide cannot be completely excluded in the review. Further adequately powered and well-designed RCTs are needed to assess the benefits and harms of ciclosporin and of regimens of high-dose intravenous steroids with oral or intravenous alkylating agents in treating children with SRNS

Methodological comments
- *Search strategy*: Substantial effort has been made into searching for all relevant research
- *Participants*: Children – broad range of ages (3 months to 18 years)
- *Inclusion/exclusion criteria*: Inclusion and exclusion criteria are precise and well presented
- *Quality assessment of studies*: Quality assessment carried out using established checklist
- *Method of synthesis*: Meta-analysis. Relative risks

General comments
- *Generalisability*: Children aged 3 months to 18 years with idiopathic SRNS
- *Funding*: No external or internal sources of support supplied

Quality assessment for systematic reviews

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Adequate
2. Is there evidence of a substantial effort to search for all relevant research?	Adequate
3. Is the validity of included studies adequately assessed?	Adequate
4. Is sufficient detail of the individual studies presented?	Adequate
5. Are the primary studies summarised appropriately?	Adequate

Reference	Methods
Hodson, 2003[40] Australia *Funding*: Author supported by the National Health and Medical Research Council of Australia, and the Federal Dept of Health and Aging of Australia through grants to the Renal Review Group of the Cochrane Collaboration	*Aim/objective*: To evaluate interventions for the management of idiopathic nephrotic syndrome *Search strategy*: Systematic reviews, RCT and quasi-RCTs were identified from MEDLINE (1966–2000) and Embase (1980–2000), and the Cochrane Controlled Trials Register (Issue 1, 2000), without language restriction. Reference lists of nephrology textbooks, review articles, relevant trials and abstracts of scientific meetings were also searched. Information about unpublished trials and additional data on published trials was sought from trialists. Recent observational studies were identified from MEDLINE and PreMEDLINE (January 2000 to May 2002). Other observational studies were identified from reference lists of review articles and recent observational studies *Inclusion criteria* Interventions: All interventions for idiopathic nephrotic syndrome. Results presented separately for corticosteroid-sensitive and corticosteroid-resistant idiopathic nephrotic syndrome (CRINS) (FSGS and MCNS) Participants: Children (age not specified) with idiopathic nephrotic syndrome (corticosteroid sensitive and resistant) Outcome measures: Proteinuria, renal function, adverse effects Study design: Systematic reviews, RCTs, quasi-RCTs, observational studies *Quality criteria*: No information provided *Application of methods*: No information provided *Methods for analysis*: For systematic reviews of RCTs, a statistical analysis was performed using RevMan. For dichotomous outcomes in the systematic reviews, the relative risks with 95% CI were calculated for individual studies. Data were pooled and summary effect measures were calculated when appropriate using the random effects model, which takes into account the between-study variability, as well as the within-study variability

continued

Results

Quantity and quality of included studies: Exact number of studies included for CRINS not presented. Table presents results for five large, uncontrolled studies (three corticosteroid/alkylating agent regimens; two ciclosporin regimens). Remaining studies reported as narrative. No quality assessment

Treatment effect: High rates of complete remission were achieved with combinations of intravenous 'pulses' of corticosteroids, and oral prednisone with or without alkylating agents. In three of the uncontrolled studies, 48–66% of children with FSGS, and 77% of children with MCNS achieved complete remission

A meta-analysis of three trials showed that ciclosporin increased the number of children who achieved complete remission (RR for not achieving complete remission 0.64; 95% CI 0.47 to 0.88) compared with placebo or no treatment

In two uncontrolled studies on the long-term efficacy of ciclosporin, one resulted in complete remission in 42% of children, and 20% developed ESRF. In the other study 69% children underwent remission with ciclosporin

In one small RCT there was no evidence that azathioprine is effective in CRINS for MCNS or FSGS

Assessment of heterogeneity: None reported

Economic evaluation: None

Conclusions: Author concludes that treatment of corticosteroid-resistant nephrotic syndrome remains unsatisfactory. Most reports are uncontrolled. In most studies, CRINS is defined as failure to achieve complete remission after 4 weeks of daily prednisone, or after 4 weeks of daily prednisone, followed by 4 weeks of alternate-day prednisone. However, CRINS may remit spontaneously or following courses of corticosteroids longer than the standard 2 months, making assessment of the response to treatment in non-randomised studies difficult

Implications of the review: Further elucidation of the causes of FSGS is required to allow appropriate inclusions of patients in RCTs. At present, the aim of the management of CRINS should be to control oedema and its associated morbidities, while limiting the risk of long-term toxicity of available agents

Methodological comments

- *Search strategy*: Effort has been made into searching for all relevant research. Search strategy for observational studies is incomplete and likely to be biased towards studies in prominent English-language publications
- *Participants*: Children with idiopathic nephrotic syndrome (corticosteroid sensitive and resistant). No information provided about age range
- *Inclusion/exclusion criteria*: Not fully reported
- *Quality assessment of studies*: No quality assessment carried out
- *Method of synthesis*: Narrative and tabulated

General comments

- *Generalisability*: Children with idiopathic nephrotic syndrome
- *Funding*: Author supported by the National Health and Medical Research Council of Australia, and the Federal Department of Health and Aging of Australia through grants to the Renal Review Group of the Cochrane Collaboration

Quality assessment for systematic reviews

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Inadequate
2. Is there evidence of a substantial effort to search for all relevant research?	Partial
3. Is the validity of included studies adequately assessed?	Inadequate
4. Is sufficient detail of the individual studies presented?	Partial
5. Are the primary studies summarised appropriately?	Partial

Appendix 5

Summary of evidence of clinical effectiveness: included studies

Reference and design	Intervention	Participants	Outcome measures
Abramowicz, 1970[22] (ISKDC) International (states details elsewhere, but not referenced) RCT Multicentre *Setting*: referred patients[14] *Funding*: US Public Health Service, Kidney Foundation of New York, John Rath Foundation, Lipper Foundation, Burroughs Wellcome & Co., Schering Corporation	(1) Azathioprine, 60 mg/m^2 per day plus intermittent prednisone, 90 days (2) Placebo, 90 days *Other interventions used*: None stated	*Target population*: Nephrotic syndrome (NS) *Number of participants*: 197 with NS, eight lost to follow-up 38 non-responders, seven not included Total 31: (1) Azathioprine + prednisone 16 (2) Placebo 15 *Sample attrition/dropout*: Seven withdrawn, apparently before allocation *Inclusion/exclusion criteria for study entry*: NS defined as serum albumin $\leq$2.5 g/100 ml and urinary protein secretion $\geq$40 mg/m^2 of body surface area per hour in an overnight collection. Age >12 weeks and <16 years at onset of symptoms, no previous treatment with adrenocortical steroids, immunosuppressive or cytotoxic drugs or agents thought to have a similar effect. Patients with certain conditions thought to be a cause of NS were excluded (lupus erythematosus, diabetes mellitus, amyloidosis, syphilis, drug nephropathy, cystinosis or other metabolic errors, malaria, Henoch–Schönlein purpura, sickle-cell anaemia, congenital cyanotic heart disease) Non-responders: did not respond within 8 weeks of initial therapy (prednisone 60 mg/m^2/day in divided doses for 4 weeks, 40 mg/m^2/day given for 3 consecutive days out of 7 for 4 weeks)	*Primary outcome*: Proteinuria *Method of assessing outcome*: Relapse defined by demonstration of proteinuria, >4 mg/m^2/hour for 3 consecutive days within a 7-day period

continued

Characteristics of participants
Not reported

Results

Outcomes	Azathioprine + prednisone (*n* = 16)	Placebo (*n* = 15)	*p*
Proteinuria eliminated	2/16	2/15	
Proteinuria decreased	2/16	2/15	
Proteinuria unchanged	12/16	11/15	

No important differences in histological diagnoses existed, either between the azathioprine and placebo groups or within the groups, between those who became protein free and those who did not

Patients assigned to azathioprine who did not become protein free were randomly assigned to another 90 days of azathioprine or placebo. Two patients from each group were withdrawn by their physicians while trial was in process: three had not responded (time not stated) and are counted as 'no response', one of these died; one responded and is counted as a response, but subsequently relapsed and died
Proteinuria disappeared in two out of five on azathioprine and one out of three on placebo

Methodological comments
- *Allocation to treatment groups*: Reports were sent to a coordinator, who assigned treatment and distributed drugs identified by code numbers to the pharmacists in each clinic. Assignment was centrally derived from a table of random numbers
- *Blinding*: Described as double blind. Patients and families and their physicians did not know treatment allocation
- *Comparability of treatment groups*: Baseline data not reported
- *Method of data analysis*: No statistical analysis; numbers with outcome reported
- *Sample size/power calculation*: Not reported
- *Attrition/dropout*: Of 197 with NS included in survey, eight were lost to follow-up. Of 38 non-responders, seven not included in results: three (all with reduced serum-β_{1c} globulin levels) became corticosteroid toxic during initial therapy and could not be treated according to the protocol; two were incorrectly treated during initial therapy; one died and one moved house before allocation

General comments
- *Generalisability*: Patients with SRNS identified from an international survey, but no details of participants' characteristics. Inclusion criteria limit age to between 12 weeks and 16 years
- *Outcome measures*: Outcomes limited. No definition of 'decreased' proteinuria
- *Intercentre variability*: Not reported
- *Conflict of interests*: Partly funded by the Schering Corporation, manufacturers of azathioprine

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Adequate
2.	Was the treatment allocation concealed?	Adequate
3.	Were the groups similar at baseline in terms of prognostic factors?	Unknown
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Partial
7.	Was the patient blinded?	Partial
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Adhikari, 1997[48] South Africa CTT Single centre *Setting*: Renal clinic *Funding*: Medical Research Council of South Africa	(1) 18-month regimen: 30 mg/kg i.v. methylprednisolone on alternate days for six doses, then weekly i.v. injections for 8 weeks, then biweekly for 8 weeks, then monthly for 12 months Oral prednisone 2 mg/kg on alternate days from third week of treatment Cyclophosphamide 3 mg/kg/day for 8 weeks if patient failed to respond after 10 weeks (2) 6-month regimen: 30 mg/kg i.v. methylprednisolone three daily pulse doses, then monthly pulse i.v. cyclophosphamide 0.5 g/m^2 for six doses and oral prednisone 2 mg/kg on alternate days *Other interventions used*: Standard therapy: Oral prednisone 2 mg/kg/day for 1 month, followed by decreasing doses over the next 2 months and/or cyclophosphamide 3 mg/kg/day for 8 weeks Aggressive antibiotic therapy and conventional antihypertensive drugs for infection and hypertension. Fluid overload managed with diuretics in combination with i.v. albumin or plasma	*Target population*: Focal glomerulosclerosis *Number of participants*: Total: 12 (1) 18-month regimen: 7 (2) 6-month regimen: 5 *Inclusion criteria for study entry*: Age 1–15 years, FSGS on renal biopsy, steroid resistance and/or resistance to oral cyclophosphamide therapy and impaired renal function (rising urea and creatinine corrected for age), GFR below two-thirds normal corrected for body surface area, and unremitting relapses *Exclusion criteria*: Acute or chronic infections, ESRD (GFR <10 ml/m^2/minute), refused parental consent	*Primary outcomes*: Complete remission Partial remission *Secondary outcomes*: Serum creatinine GFR Urine creatinine/protein ratio Side-effects *Method of assessing outcomes*: Monitoring of side-effects included ophthalmological examination for cataracts and radiological examination for bone changes before treatment and every 6 months Clinical signs of cyclophosphamide toxicity checked at each visit, including alopecia, pallor, blue discoloration of the nails and cystitis. Full blood count, urea, electrolytes and creatinine measure before each dose. Height and weight documented at each visit Nephrotic syndrome: heavy proteinuria > 40 mg/m^2/hour, oedema and serum albumin <25 g/l Steroid responsive: respond to prednisone 2 mg/kg/day for 1 month then decreasing doses over 2 months Steroid resistant: persistence of NS despite single or multiple courses as above Response: absence of oedema and clearing of proteinuria for at least 1 week Relapse: presence of the three diagnostic features and a protein creatinine ratio >2.0 Complete remission: no oedema, serum proteinuria ⩾3 g/l, urinary protein/creatinine ratio <0.2 Partial remission: no oedema, serum albumin ⩾2.5 g/l and urinary protein/creatinine ratio 0.2–1.9 Focal glomerulosclerosis, localised or segmental areas of sclerosis in some of the glomerular tufts, unaffected glomeruli appear normal by light microscopy and sclerotic areas often contain rounded eosinophilic areas situated in the capillary loop (hyalinosis) *Length of follow-up*: Treatment 1: 32.6 months (SD 8.4, range 24–42) Treatment 2: 14.6 months (SD 11.7, range 3–34)

continued

Characteristics of participants

Mean	18-month regimen (n = 7)	6-month regimen (n = 5)	p
Age (years)	5.7 (SD 2.1, range 3–8)	5.5 (SD 3.2, range 2.5–9)	
Gender (M:F)	5:2	5:0	
Ethnicity	4 Indian, 3 black	2 Indian, 3 black	
Duration of illness (months)	6.5 (SD 5.2, range 2–15)	13.2 (SD 7.8, range 6–24)	
Secondary steroid resistance	2/7	0/5	

Means and SDs calculated by reviewer from data in table. Several discrepancies between data in table and text. Data taken from table.

Results

Mean (SD)	18-month regimen (n = 7)	6-month regimen (n = 5)	p
Complete remission	0/7	2/5	
Partial remission	6/7	1/5	
Relapse	1/7[a]	1/5	
Died (no response)		1/5	

[a] Initial course of therapy stopped due to infection. Achieved remission following a second course of therapy, subsequently relapsed after developing a urinary tract infection and remains in relapse.

Serum creatinine (mmol/l)	Before: 145.3 (110.9) After: 55.4 (26.0)	Before: 48.2 (24.7) After: 46.0 (21.6)	
GFR (ml/minute/1.73 m^2)	Before: 63.1 (50.9) After: 155.1 (67.6)	Before: 97.2 (77) After: 164.5 (45.5)	
Urinary protein/creatinine ratio	Before: 2.6 (1.2) After: 0.65 (0.45)	Before: 3.58 (3.32) After: 0.48 (0.35)	

Means and SDs calculated by reviewer from data in table.

ESRD and transplant	1/7		
Adverse effects			
Hypertension	2/7 (treatment discontinued in 1)	1/7	
Mild osteopenia	1/7		
Frequent infections	2/7	2/7	
Alopecia		3/7	
Blue discoloration of nails		3/7	
Death (septicaemia and systemic candidiasis)		1/7	
Resource use			
Drug costs	$687 (R2610.80)	$108.9 (R414.14)	
Minimum number of hospital visits	34	8	

Methodological comments

- *Allocation to treatment groups*: Based on discussion with parents, including aspects of travelling distance from the hospital and the number of school days affected
- *Blinding*: None
- *Comparability of treatment groups*: Patients in the 6-month regimen have a longer duration of illness
- *Method of data analysis*: No statistical comparisons made
- *Sample size/power calculation*: None
- *Attrition/dropout*: Treatment discontinued after 12 months in one child due to hypertension (18-month regimen). One patient died after 3 months of therapy, from overwhelming sepsis

General comments

- *Generalisability*: Children with focal glomerulosclerosis. Patients were steroid resistant; some were also resistant to oral cyclophosphamide. Two patients had secondary steroid resistance
- *Outcome measures*: Appropriate
- *Intercentre variability*: NA

continued

- *Conflict of interests*: None stated. Funding from the Medical Research Council of South Africa
- *Other*: There are several discrepancies between data in tables and text

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	NA
2. Was the treatment allocation concealed?	NA
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	NA
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Bagga, 2004[41] India Randomised cross-over Single centre *Setting*: Paediatric nephrology services, hospital *Funding*: Not reported	(1) Low-dose enalapril (0.2 mg/kg/day in two divided doses) (2) High-dose enalapril (0.6 mg/kg/day in two divided doses) (see Results for actual doses received) *Duration of treatment*: 2-week washout before study entry. 8 weeks on each treatment, with 2 weeks washout *Other interventions used*: Alternate-day prednisolone throughout study. Diuretics (furosemide) used if indicated NSAIDs, calcium channel and β-adrenergic blockers were discontinued Salt-restricted diet. Instructed not to change protein intake during study	*Target population*: Idiopathic NS with initial or late steroid resistance *Number of participants*: Total: 25 (1) 11 received low dose first (2) 14 received high dose first *Sample attrition/dropout*: 29 randomised, four excluded *Inclusion criteria for study entry*: Idiopathic NS, aged 1–16 years, initial or late steroid resistance. Initial resistance: no remission of proteinuria despite prednisolone daily 2 mg/kg for 4 weeks then 1.5 mg/kg on alternate days for 4 weeks. Late resistance: responded initially but failed to respond to daily treatment during a subsequent relapse *Exclusion criteria*: Severe hypertension (blood pressure above 99th percentile for age and gender), GFR <70 ml/minute/1.73 m^2, secondary nephrotic syndrome (e.g. systemic lupus erythematosus, Henoch–Schönlein purpura, hepatitis B infection, amyloidosis), single functioning kidney, concurrent or previous treatment with daily or i.v. corticosteroids, alkylating agents, levamisole, ciclosporin or i.v. albumin in the preceding 4 weeks, living >50 km from hospital or unable to come for follow-up visits	*Primary outcomes*: Urine albumin Urine albumin to creatinine ratio *Secondary outcomes*: Blood levels of urea creatinine, electrolytes, albumin, cholesterol Urinary sodium and urea Blood pressure *Method of assessing outcomes*: Remission: urine showing nil or traces of protein by Dipstix on 3 consecutive days Hypertension: blood pressure >95th percentile for age and gender 6-hour urine specimen for albumin, creatinine, sodium, urea Urinary urea and sodium used as markers of dietary protein and sodium intake, respectively Significant reduction defined as a urinary albumin to creatinine ratio reduction of more than 40% at the end of 18 weeks of treatment Baseline measurements taken after initial 2-week washout

continued

Characteristics of participants

Median (95% CI)	Low- then high-dose enalapril (n = 11)	High- then low-dose enalapril (n = 14)	p
Age at onset (months)	74.2 (21 to 122.3)	61 (19 to 137.4)	ns
Age at trial (months)	96 (80.5 to 136.4)	78 (60.0 to 104.7)	ns
Duration of steroid resistance (months)	12 (7.4 to 33.1)	10 (1 to 31.0)	
Initial resistance	8/11	7/14	
Gender (M:F)	9:2	9:5	
Minimal change disease	1/11	3/14	
FSGS	4/11	5/14	
MBGN	4/11	3/14	
MPGN	2/11	3/14	
Hypertension	6/11	5/14	
Height (cm)	121 (108.7 to 140.4)	112 (102.5 to 131)	
Weight (kg)	24 (19.1 to 32.6)	19.3 (16.8 to 29.2)	
SBP (mmHg)	120 (116 to 132)	110 (100 to 126)	
DBP (mmHg)	80 (68 to 84)	70 (66 to 74)	
Serum albumin (g/dl)	3.2 (1.7 to 4.5)	3.2 (1.6 to 4.4)	
Serum creatinine (mg/dl)	0.6 (0.4 to 0.8)	0.5 (0.4 to 0.9)	
Serum cholesterol (mg/dl)	276 (205 to 405)	281 (243 to 390)	
6-hour urine albumin (mg)	650 (152.6 to 796.0)	559 (245.8 to 717)	
Urine albumin to creatinine ratio, after initial washout	3.9 (1.9 to 11.6)	5.2 (2.1 to 10.5)	

Results

Outcomes, median (95% CI)	Low- then high-dose enalapril (n = 11)	High- then low-dose enalapril (n = 14)	p
Dose of enalapril received (mg/kg/day)			
Low dose, mean (SD)	0.21 (0.03) (range 0.16–0.27)	0.23 (0.01) (range 0.18–0.26)	
High dose, mean (SD)	0.62 (0.09) (range 0.54–0.77)	0.61 (0.08) (range 0.53–0.76)	
6-hour urine albumin (mg)			
Baseline	650 (152.6 to 796.0)	559 (245.8 to 717)	0.6
	Low dose:	High dose:	
4 weeks of treatment 1	365 (127.6 to 576.6)	360 (138.8 to 527.7)	
8 weeks of treatment 1	213 (130.2 to 637.3)	230.4 (107.9 to 650.2), $p < 0.05$ vs baseline	
After 2 weeks' washout	204 (99.6 to 934.7)	473.3 (123.0 to 796.3)	
	High dose:	Low dose:	
4 weeks of treatment 2	188 (66.3 to 522.4)	176.5 (92.4 to 646.6)	
8 weeks of treatment 2	168 (45.4 to 678.9), $p < 0.05$ vs after washout	144.5 (39.5 to 871.8)	0.6 (end of study)
Following enalapril therapy (baseline to end of treatment 2), 6-hour urine albumin excretion decreased by 74.2% in each group.			
Urine albumin to creatinine ratio			
Baseline	3.9 (1.9 to 11.6)	5.2 (2.1 to 10.5)	0.6
	Low dose:	High dose:	
4 weeks of treatment 1	2.5 (1.0 to 14.1)	3.4 (0.8 to 8.6)	
8 weeks of treatment 1	2.3 (0.8 to 5.2)	2.5 (0.8 to 3.3), $p < 0.001$ vs baseline	
After 2 weeks' washout	2.5 (0.7 to 7.5)	3.2 (1.2 to 6.6)	
	High dose:	Low dose:	
4 weeks of treatment 2	1.2 (0.4 to 3.9)	3.1 (1.1 to 6.3)	
8 weeks of treatment 2	1.1 (0.2 to 4.7), $p < 0.01$ vs after washout	1.8 (0.3 to 9.6)	0.6 (end of study)

continued

Urine albumin to creatinine ratio reduction (%)	Low dose: 34.8 (–7.9 to 76.6) High dose: 37.2 (11.3 to 59.8), p = ns vs low dose	High dose: 62.9 (40.6 to 71.6) Low dose: 33.3 (–20 to 58.7), $p < 0.01$ vs high dose	<0.05
Blood biochemistry			
Albumin (g/dl)			
Baseline	3.2 (1.7 to 4.5)	3.2 (1.6 to 4.4)	
8 weeks of treatment 1	4.4 (3.9 to 5.5), $p < 0.005$ vs baseline	3.5 (2.0 to 4.6)	
After 2 weeks' washout	4.4 (3.7 to 4.9)	3.4 (1.6 to 4.4)	
8 weeks of treatment 2	4.5 (2.8 to 5.8)	4.1 (3.5 to 5.0)	
Cholesterol (mg/dl)			
Baseline	276 (205 to 405)	281 (243 to 390)	
8 weeks of treatment 1	208 (168 to 337)	264 (241 to 303)	
After 2 weeks' washout	196 (169 to 279)	283 (232 to 364)	
8 weeks of treatment 2	215 (155 to 320)	220 (165 to 393)	
Creatinine (mg/dl)			
Baseline	0.6 (0.4 to 0.8)	0.5 (0.4 to 0.9)	
8 weeks of treatment 1	0.5 (0.4 to 0.9)	0.6 (0.4 to 0.8)	
After 2 weeks' washout	0.6 (0.4 to 1.0)	0.5 (0.4 to 0.6)	
8 weeks of treatment 2	0.7 (0.5 to 0.9)	0.5 (0.4 to 0.8)	
Potassium (mEq/l)			
Baseline	4.6 (3.7 to 6.3)	4.9 (4.2 to 6.5)	
8 weeks of treatment 1	4.5 (4.0 to 6.0)	5.0 (4.3 to 6.6)	
After 2 weeks' washout	4.3 (4.0 to 6.0)	5.1 (4.4 to 6.6)	
8 weeks of treatment 2	4.5 (3.6 to 6.0)	5.1 (4.7 to 6.6)	
All comparisons (other than albumin) p = ns. Blood levels of albumin increased by 46.9% in group with low then high dose (note: this appears incorrect – reviewer calculates increase to be by 40.6%), and by 28.1% in group with high then low dose. Blood levels of cholesterol declined by 22.1% in group with low then high dose, and by 21.7% in group with high then low dose.			
SBP			
Baseline	120 mmHg	110 mmHg	
8 weeks of treatment 1	114.3 mmHg, $p < 0.05$	106 mmHg	
DBP			
Baseline	80 mmHg	70 mmHg	
8 weeks of treatment 1	74.4 mmHg, $p < 0.05$	65.4 mmHg	
There was a slight increase in blood pressure during the washout period, followed by a similar decline during the next 8 weeks. The dose of enalapril did not influence the percentage reduction in SBP and DBP, which was similar at the end of 8 and 18 weeks of treatment in both groups. Data not presented. Urinary levels of urea and sodium remained similar throughout the study period, indicating no effect of dietary protein and sodium on the observed efficacy of enalapril.			
Combined data	**High-dose phase (n = 25)**	**Low-dose phase (n = 25)**	
Urine albumin to creatinine ratio reduction (%)	52% (15.4 to 70.4%)	33% (–10.3 to 72.4%)	<0.05
Determinants of response			
Significant reduction in proteinuria (urine albumin to creatinine ratio reduction >40%)	17 of 25 patients. No differences in age, gender, renal histology, presence of hypertension, change in blood pressure or serum creatinine in patients showing a significant reduction in proteinuria		
Median urine albumin to creatinine ratio reduction (%) after 18 weeks of treatment	Patients with hypertension: Patients without hypertension:	48.1% (20.9 to 78.7%) 46.2% (33.4 to 79.1%), p = 0.08	
Baseline urine albumin to creatinine ratio was higher in patients who showed more than a 40% reduction of proteinuria [median 5.9 (95% CI 2.7 to 12) vs median 3.1 (95% CI 1.3 to 5.0), p = 0.08]			
Adverse effects			
Dry cough, subsided after stopping treatment	3 (dose not specified)		

continued

Methodological comments
- *Allocation to treatment groups*: Computer-generated random numbers were used to allocate randomly patients
- *Blinding*: Not reported
- *Comparability of treatment groups*: Group receiving low dose first were older at onset and start of trial, but not statistically significant
- *Method of data analysis*: χ^2 test, Wilcoxon rank-sum and signed rank tests were applied. $p < 0.05$ considered significant. The 'period effect' was determined to assess whether the severity of NS had altered during the study. The 'carry-over effect' was estimated to examine whether the washout was effective and exclude the effect of previous therapy. $p < 0.1$ considered significant for these tests. No period or carry-over effect was demonstrated ($p > 0.05$)
- *Sample size/power calculation*: Not reported
- *Attrition/dropout*: 29 randomised, four (three low-dose and one high-dose group) did not attend first follow-up and were excluded

General comments
- *Generalisability*: Mainly boys with NS, both initial and late steroid resistance
- *Outcome measures*: Appropriate outcome measures used
- *Intercentre variability*: NA
- *Conflict of interests*: Not reported

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Chongviriyaphan, 1999[38] Thailand Randomised cross-over Single centre *Setting*: Dept of Paediatrics, hospital *Funding*: Supported by Ramathibodi Research Grant No. 25/1996	(1) 8 capsules of Uni-E® [tuna fish oil containing eicosapentaecoic acid (EPA) 230 mg and docosahexaenoic acid (DHA) 1.12 g and 240 IU D-α-tocopheryl acetate] daily (2) Placebo (olive oil) *Duration of treatment*: 8 weeks on each treatment, washout period 6 weeks *Other interventions used*: During study, all patients continued taking medications given by their nephrologists All patients received prednisolone, four dipyridamole, two coumadin, one calcitriol, one aspirin, one hydrochlorothiazide Dietary advice given to reduce dietary fat intake	*Target population*: Children with SRNS *Number of participants*: Total: five patients One started with fish oil Four started with placebo *Sample attrition/dropout*: Six randomised One patient dropped out *Inclusion criteria*: Subjects who did not respond to corticosteroids and cyclophosphamide; also normotension, albustix 3+ or over, fasting serum triglyceride ⩾150 mg/dl and cholesterol ⩾200 mg/dl, serum creatinine ⩽3 mg/dl and creatinine clearance >15 ml/minute/1.73 m^2 *Exclusion criteria*: Severe infection, diarrhoea, haemostatic disorder, taking lipid-lowering drugs	*Primary outcomes*: Urine protein and creatinine clearance Serum creatinine and lipid profiles *Secondary outcomes*: Compliance Side-effects *Method of assessing outcomes*: At the beginning of the study (week 0) and each visit (weeks 4, 8, 14, 18, 32), the physical examinations, weight and height measurements were performed by the same doctor Food frequency questionnaires and 3-day dietary record were collected at each visit Compliance determined by number of capsules remaining in containers Blood drawn for measuring blood urea nitrogen, creatinine, total protein, albumin, triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol 24-hour urine sample for total protein creatinine

continued

Characteristics of participants

	All patients (*n* = 5)	***p***
Age (years), mean (SD)	13.4 (3.7)	
Gender (% male)	100%	
No. patients FSGS	3/5	
Height (cm), mean (SD)	136 (16.8)	
Weight (kg), mean (SD)	35.8 (11.6)	
Height/Age,[a] mean (SD)	–3.15	
Weight/Age,[a] mean (SD)	–1.79	

[a] *Z*-score = (Individual value – Median value of reference population)/SD value of reference population.

Results

Outcomes	**Fish oil (*n* = 5)**	**Placebo (*n* = 5)**	***p*[a]**
Serum creatinine and lipid profiles (md/dl), mean (SD)			
Creatinine			
Baseline	1.4 (0.9)	1.6 (1.5)	ns
8 weeks	1.7 (1.5)	1.6 (1.5)	
Triglyceride			
Baseline	242 (155.4)	250 (76.1)	ns
8 weeks	156 (77)	192 (62.3)	
Cholesterol			
Baseline	552 (289.6)	473 (178.1)	ns
8 weeks	616 (412.5)	541 (177.4)	
HDL-cholesterol			
Baseline	30.5 (10.3)	31.4 (8.7)	ns
8 weeks	38.7 (10.3)	34.2 (7.5)	
LDL-cholesterol			
Baseline	473.5 (266.9)	392 (174.8)	ns
8 weeks	546.3 (404.9)	468.2 (171.2)	
	Fish oil (*n* = 3)	**Placebo (*n* = 3)**	***p*[a]**
Urine protein (g/day)			
Baseline	2.68 (3.7)	2.71 (3.12)	ns
8 weeks	1.12 (1.6)	3.26 (4.83)	
	Fish oil (*n* = 5)	**Placebo (*n* = 5)**	
Creatinine clearance (ml/minute/1.73 m^2)			
Baseline	76.9 (45.8)	77.34 (50.6)	ns
8 weeks	71.22 (41.1)	77.21 (46.8)	

[a] Compared the change in each parameter between placebo and supplemented period.

Compliance

Compliance of most subjects was good (≥80%) except in two patients, one in fish oil (66%) and the other in placebo period (69%), in the second period for each.

Other

Calorific intake, dietary compositions (protein, fat and carbohydrate as % of total calorific intake) were not significantly different between the two periods for each subject.

Adverse effects	**All patients (*n* = 5)**
	0

Both subjects and parents did not report any side-effects

Means and SDs calculated by reviewer from data in table.

continued

Methodological comments

- *Allocation to treatment groups*: States patients were randomly divided. No further information provided
- *Blinding*: The placebo capsules had the same shape and colour as Uni-E®. Neither the doctor nor the subjects knew the type of supplementation until the end of the study
- *Comparability of treatment groups*: Only one patient started with fish oil. The oldest patient had MPGN (IgG deposit)
- *Method of data analysis*: The comparisons of baseline data (week 0, week 14) with post-treatment (week 8, week 32) were performed using the two-tailed paired Student's *t*-test. Significance was considered at $p < 0.05$
- *Sample size/power calculation*: Not reported
- *Attrition/dropout*: One patient dropped out; no further information provided. States that data from some subjects were not analysed owing to incompleteness

General comments

- *Generalisability*: Only five patients with SRNS included, all of whom were male. Patients had also not responded to cyclophosphamide. Duration of steroid treatment before being defined as steroid resistant not reported. Four patients had short stature and one malnourished according to WHO criteria
- *Outcome measures*: Food frequency questionnaires and diary not validated. Other outcomes appropriate. Method of reporting adverse effects not reported
- *Intercentre variability*: NA
- *Conflict of interests*: Capsules provided by Unicord Public Company Ltd
- *Other*: Dosage of fish oil described as 'small' by authors, and a limitation of the study. Other limitations include small sample size, short duration of supplementation and insufficient washout

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Unknown
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Inadequate
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Adequate
7.	Was the patient blinded?	Adequate
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Elhence, 1994[44] India RCT Single centre *Setting*: Not reported *Funding*: Not reported	(1) i.v. pulse cyclophosphamide: 500 mg/m^2 per month for 6 months (2) Oral cyclophosphamide: 2.5 mg/kg per day for 8 weeks *Other interventions used*: Both groups given oral prednisolone 60 mg/m^2 per alternate day for 4 weeks, 40 mg/m^2 per alternate day for 4 weeks, tapered over next 4 weeks	*Target population*: MCNS *Number of participants*: Total 13 (1) i.v. pulse cyclophosphamide: seven (2) Oral cyclophosphamide: six *Sample attrition/dropout*: Two lost to follow-up in oral cyclophosphamide group *Inclusion/exclusion criteria for study entry*: Not explicitly stated. 150 children diagnosed with NS and treated with standard prednisolone therapy. 26 were steroid resistant, 20 continuing non-responders and six subsequent non-responders. 14 had MCNS on renal biopsy, 13 enrolled onto study after informed consent	*Primary outcome*: Remission *Secondary outcomes*: Duration of remission Total proteinuria-free days Side-effects *Method of assessing outcomes*: Complete remission: proteinuria <4 mg/m^2/hour and serum albumin >35 g/l Non-remission: proteinuria >40 mg/m^2/hour *Length of follow-up*: (1) i.v. pulse cyclophosphamide mean 12 months (SD 1.4) (2) Oral cyclophosphamide mean 13 months (SD 3.9)

continued

Characteristics of participants

Mean (SD)	**i.v. pulse cyclophosphamide (*n* = 7)**	**Oral cyclophosphamide (*n* = 6)**	***p***
Age at onset (years)	4.0 (3.73)	6.08 (5.5)	>0.05
Gender (M:F)	6:1	5:1	
Duration of NS (years)	7.14 (4.51)	5.83 (3.47)	>0.05
Continuing non-responders	2/7	3/6	
Subsequent non-responders	5/7	3/6	
Serum protein (g/dl)	4.12 (0.78)	3.9 (0.95)	>0.05
Serum albumin (g/dl)	1.78 (0.45)	1.71 (0.33)	>0.05
Serum creatinine (mg/dl)	0.85 (0.25)	1.03 (0.56)	>0.05
24-hour protein (g/m^2/day)	1.14 (0.14)	1.15 (0.17)	>0.05

Results

Outcomes, mean (SEM)	**i.v. pulse cyclophosphamide (*n* = 7)**	**Oral cyclophosphamide (*n* = 4)**	***p***
Complete remission	7/7 (100%)	1/4 (25%)	
Duration of remission	4/7 sustained remission (no relapse)	1/4 sustained remission (no relapse)	
	3/7 relapsed after a mean remission of 8.7 months. Subsequently became steroid responsive	3/4 remained non-responsive	
Two children received 36 and 45 days of oral cyclophosphamide without remission before loss to follow-up.			
Mean protein-free days	274.3 (44.6)	165 (165)	
Cumulative dose	90 mg/kg	150 mg/kg	
Adverse effects			
Vomiting	4/7	0	
Infection, pneumonia	0	1/4	
Alopecia	0	2/4	

Methodological comments

- *Allocation to treatment groups*: Randomised, method not reported
- *Blinding*: Not reported
- *Comparability of treatment groups*: Oral group on average 2 years older at onset than i.v. group, but not statistically significant ($p > 0.05$). Similar duration of NS, serum protein, serum albumin, serum creatinine and 24-hour protein
- *Method of data analysis*: Not reported. Not ITT analysis. Mean (SD) presented for baseline characteristics, and mean (SEM) reported for results
- *Sample size/power calculation*: Not reported. Sample size small
- *Attrition/dropout*: 2 patients in the oral cyclophosphamide group were lost to follow-up as they moved to another city

General comments

- *Generalisability*: Participants are children with MCNS, mostly boys
- *Outcome measures*: Outcome measures are appropriate, but no details on when, how or by whom they were assessed
- *Conflict of interests*: Not reported
- *Other*: Eligibility criteria not clearly stated. Not clear whether all patients with other causes of NS are excluded

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Unknown
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Inadequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Unknown
7.	Was the patient blinded?	Unknown
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Garin, 1988[47] USA Randomised cross-over Single centre *Setting*: Not reported *Funding*: Not reported	(1) Ciclosporin 5 mg/kg/day in one dose for 8 weeks. Dosage adjusted to keep trough whole-blood level at ⩽200 ng/ml (2) Controls, 8 weeks (no further details) *Duration of treatment*: 8 weeks, 1-month washout *Other interventions used*: Prednisone discontinued at least 1 week before start of trial. No prednisone during trial	*Target population*: Not explicit, but all have MLNS or FSGS *Number of participants*: Total 8 Number undergoing treatment or control first not reported *Sample attrition/dropout*: Not reported, assume none *Inclusion/exclusion criteria for study entry*: Not explicitly stated. Steroid resistance defined as proteinuria >40 mg/m^2/hour or >50 mg/kg/day and low serum albumin levels <25 g/l after 8 weeks of prednisone at 2 mg/kg/day up to 80 mg/day. All had creatinine clearances >0.83 ml/second/1.73 m^2	*Primary outcomes*: Urinary protein excretion Creatinine clearance Serum albumin *Secondary outcomes*: Blood cell counts Liver enzyme levels Adverse effects *Method of assessing outcomes*: 24-hour urine collections. Measurements obtained weekly for ciclosporin and fortnightly for controls Ciclosporin trough level measured at each visit

Characteristics of participants

Mean	All participants (n = 8)
Age (years)	11.4 (SD 6.4, median 12, range 3.25–18.58)[a]
Gender (M:F)	6:2
Age at onset (years)	8.59 (SD 6.47, range 2.08–17)[a]
Duration of NS before ciclosporin therapy (months)	33 (SD 59.55, range 3–176)[a]
Pathological features	Idiopathic minimal lesion nephrotic syndrome (IMLNS): 4 FSGS: 4

[a] Mean, SD and range calculated by reviewer.

Results

Outcomes, mean (SEM)	Ciclosporin period (n = 8)	Control period (n = 8)	p
Urinary protein excretion values (mg protein/mg creatinine)	Week 0: 12.5 (2.1) Week 2: 11.8 (2.3) Week 4: 11.6 (2.0) Week 6: 10.9 (2.2) Week 8: 11.7 (3.1) Baseline vs 8 weeks, p = 0.70	Week 0: 11.9 (2.4) Week 2: 15.5 (3.9) Week 4: 15.1 (2.6) Week 6: 15.7 (3.7) Week 8: 17.3 (3.5) Baseline vs 2 weeks, p = 0.002	Compared over the 8 weeks, urinary protein levels were significantly higher in the control group (p = 0.0286)
Creatinine clearance values (ml/second/1.73 m^2)	Week 0: 1.23 (0.23) Week 2: 1.42 (0.28) Week 4: 1.42 (0.25) Week 6: 1.58 (0.48) Week 8: 1.12 (0.23) Baseline vs 8 weeks, p = 0.48	Week 0: 1.50 (0.30) Week 2: 1.13 (0.35) Week 4: 1.02 (0.20) Week 6: 0.87 (0.18) Week 8: 0.87 (0.22) Baseline vs 6 weeks, p = 0.023	Compared over the 8 weeks, no significant differences in creatinine clearance (p = 0.2398)
Serum albumin values (g/l)	Week 0: 20 (2) Week 2: 20 (3) Week 4: 25 (2) Week 6: 24 (3) Week 8: 24 (3) Baseline vs 8 weeks, p = 0.09	Week 0: 20 (3) Week 2: 21 (2) Week 4: 19 (2) Week 6: 17 (2) Week 8: 18 (3) Baseline vs 8 weeks, p = 0.27	Compared over the 8 weeks, no significant differences in serum albumin level (p = 0.0824)
No. with resolution of proteinuria during therapy	IMLNS: 0 FSGS: 0		
No. with normal serum albumin level during therapy	IMLNS: 0 FSGS: 0		

continued

Adverse effects

Major side-effects	0	
Hypertension	0	0

1/8 ciclosporin group and 2/8 control group had a decrease of >20% of their creatinine clearances at end of trial, which could not be attributed to hypovolaemia. These (all FSGS) all had further deterioration of their GFR.

No changes in complete blood cell counts or liver enzyme levels were seen in either group.

Methodological comments

- *Allocation to treatment groups*: Randomly allocated, but method of randomisation or allocation concealment not reported
- *Blinding*: Not reported
- *Comparability of treatment groups*: States that before therapy began, no statistical difference was found in urinary protein, serum albumin and serum creatinine levels between ciclosporin and control groups. Data not presented, and no other comparisons made
- *Method of data analysis*: One-way analysis of variance for repeated measures. A log transformation was used owing to the nature of the variables observed. Data analysed in a univariate fashion using repeated-measures option in the SAS procedure General Linear Models. Whenever a significant difference was detected, Duncan's multiple range test was used to distinguish the mean differences between the observations within the same group
- *Sample size/power calculation*: States that a pairwise difference in proteinuria of ⩾10 units yields an approximate sample size of five patients, with a power of 90%
- *Attrition/dropout*: Not reported, assume none

General comments

- *Generalisability*: Mainly male children with NS. Not clear whether patients with NS caused by other conditions were excluded
- *Outcome measures*: Appear to be measured appropriately
- *Conflict of interests*: Not reported

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Unknown
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Inadequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Unknown
7.	Was the patient blinded?	Unknown
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Unknown
10.	Were withdrawals and dropouts completely described?	Unknown

Reference and design	Intervention	Participants	Outcome measures
Hari, 2004[34] India Prospective cohort study Single centre *Setting*: Paediatric nephrology service of the hospital. Patients hospitalised for treatment *Funding*: None	(1) i.v. Dexamethasone (5 mg/kg) (maximum 150 g) (2) i.v. Methylprednisolone (30 mg/kg) (maximum 1 g) The drug was infused over a period of 2–3 hours, on alternate days for six doses *Duration of treatment*: 2 weeks *Other interventions used*: Oral prednisolone 2 mg/kg was given on days when i.v. therapy was not administered Enalapril used in 27 patients, started ⩾4 weeks before study started	*Target population*: Initial or late SRNS *Number of participants*: Group 1: 59 patients Group 2: 22 patients *Sample attrition/dropout*: Three patients withdrawn Group 1: 57 Group 2: 21 *Inclusion/exclusion criteria for study entry*: *Inclusion*: Patients aged 1–14 years with initial or late SRNS. NS defined by presence of hypoalbuminaemia (<2.5 d/dl), proteinuria (>40 mg/m^2/hour or urine albumin to creatinine ratio >2) and oedema Initial steroid resistance: failure to respond to treatment with oral prednisolone at a dose of 2 mg/kg daily given for 4 weeks followed by 1.5 mg/kg on alternate days for 4 weeks Late steroid resistance: Responded to therapy initially but failed to respond to daily oral prednisolone in a subsequent relapse *Exclusion*: Renal histopathology other than minimal change disease, FSGS and MPGN; previously received therapy with i.v. steroids or cyclophosphamide; onset of nephritic syndrome <1 year or with persistent renal dysfunction (serum creatinine level >1.5 mg/dl)	*Primary outcomes*: Remission rate Proteinuria *Secondary outcomes*: Urine albumin to creatinine ratio Percentage reduction in urine albumin to creatinine ratio Adverse events *Method of assessing outcomes*: Outcome was assessed at the end of six alternate-day pulses Complete remission: urinary protein being nil or trace on at least 3 consecutive days or urine albumin or creatinine ratio <0.2 Partial remission: urine protein excretion 1+ to 2+, or urine albumin to creatinine ratio between 0.2 and 2 and serum albumin >2.5 g/dl No response: persistence of 3+ to 4+ proteinuria, or urine albumin to creatinine ratio >2 Pulse rate and blood pressure were closely monitored during the corticosteroid infusion, and patients observed for evidence of local or systemic infection. Dipstix examination for urinary protein was done daily, and blood levels of glucose and electrolytes were measured on alternative days before infusion. Blood levels of urea, creatinine, albumin, cholesterol and 24-hour urine albumin were measured at the initiation of therapy and at the end of six alternate-day pulses. GFR was estimated from serum creatinine and height

Characteristics of participants

Characteristic, median (95%CI)	Dexamethasone (n = 59)	Methylprednisolone (n = 22)	p
Age at onset (months)	29 (19.5 to 51.6)	33 (18 to 74.1)	
Age at treatment (months)	38 (36 to 92.8)	42.5 (35.5 to 90.4)	
Gender (M:F)	47:12	12:10	
SBP (mmHg)	110 (100 to 116)	112 (110 to 120)	
DBP (mmHg)	70 (60 to 80.4)	74 (68.9 to 80)	
Hypertension	31 (52%)	10 (47.6%)	
Initial resistance (%)	43 (72.8)	14 (63.6)	
Renal biopsy (%)			
MCNS	21 (35.6)	5 (22.7)	
FSGS	28 (47.5)	13 (59.1)	
MPGN	10 (16.9)	4 (18.2)	

continued

Blood		
Urea (mg/dl)	23 (22 to 42.6)	30 (21.3 to 41.2)
Creatinine (mg/dl)	0.4 (0.4 to 0.6)	0.5 (0.4 to 0.7)
Albumin (g/dl)	1.8 (1.5 to 2.1)	1.8 (1.2 to 2.2)
Cholesterol (mg/dl)	350 (251 to 488)	426 (341 to 494)

Of those patients suffering from hypertension, 22 were receiving treatment with enalapril for 4–20 weeks before inclusion in this study

Results

Outcomes	**Dexamethasone (*n* = 57)**	**Methylprednisolone (*n* = 21)**	***p***
Remission rates, *n* (%) (95% CI) after sixth alternate-day pulse			
Complete remission	20/57 (35.1%) (22.9 to 48.9)	7/21 (33.3%) (14.6 to 56.9)	
Partial remission	7/57 (12.3%) (5.0 to 23.7)	3/21 (14.3%) (3.0 to 36.3)	
No response (post-treatment)	30/57 (52.6%) (38.9 to 66.0)	11/21 (52.4%) (29.9 to 74.3)	
Median time to remission in patients with complete remission (days)	9.5	10	

In the results for no response, there is discrepancy between the table and the text. The table states the 95% CI figures 38.9 and 29.9 for dexamethasone and methylprednisolone, respectively, whereas the text reports 38.8 and 29.8.

Median proteinuria (g/24 hours)		
Pretreatment	1.9	2.2
Post-treatment	0.7	0.2
Median urine albumin to creatinine ratio (mg/mg)		
Pretreatment	9.2	12.1
Post-treatment	1.5, $p < 0.005$	0.7, $p < 0.005$
Median reduction in urine albumin to creatinine ratio		
Post-treatment	54.1 (32.7 to 83.9)	63.2 (23.5 to 100)

Side effects	**Dexamethasone (*n* = 57)**	**Methylprednisolone (*n* = 21)**
Peritonitis	1/59	1/22
Septic arthritis	1/59	
Transient hypertension or worsening of existing hypertension	31/57 (54.4%) (40.7 to 67.7)	10/21 (47.6%) (25.7 to 70.2)
Hyperglycaemia	2/57	
Any side-effect	66.7% (52.9 to 78.6)	61.9% (38.4 to 81.9)

The three patients with peritonitis and septic arthritis could not complete treatment. Electrolyte abnormalities during alternate-day pulse therapy were asymptomatic and included hypokalaemia and hyponatraemia in ten and 11 patients, respectively (group not specified).

Methodological comments

- *Allocation to treatment groups*: Only those patients who paid for methylprednisolone (more expensive) received the drug. The remaining patients were treated with dexamethasone
- *Blinding*:
- *Comparability of treatment groups*: Baseline clinical and biochemical features were not significantly different between the two groups. Allocation depended on ability to afford each drug. Socio-economic status of patients likely to be different, but not reported
- *Method of data analysis*: Outcome within the groups was compared by the Fisher's exact test with two-tailed analysis or by Wilcoxon rank sum test for numeric variables. $p < 0.05$ was taken as significant
- *Sample size/power calculation*: Not reported
- *Attrition/dropout*: Three patients developed serious infections and could not complete intravenous steroid therapy. Excluded from analysis

General comments

- *Generalisability*: Children aged 1–14 years with initial or late SRNS (MCNS, FSGS or MPGN)
- *Outcome measures*: Outcomes appear to be measured appropriately
- *Intercentre variability*: NA
- *Conflict of interests*: none stated

continued

Quality assessment for observational studies

	Judgement	Comments
Is there sufficient description of the groups and the distribution of prognostic factors?	Yes	
Are the groups assembled at a similar point in their disease progression?	Yes	
Is the intervention/treatment reliably ascertained?	Yes	
Were the groups comparable on all important confounding factors?	Yes	But not socio-economic status
Was there adequate adjustment for the effects of these confounding variables?	NA	
Was a dose–response relationship between intervention and outcome demonstrated?	NA	
Was outcome assessment blind to exposure status?	Unknown	
Was follow-up long enough for the outcomes to occur?	Yes	2 weeks
What proportion of the cohort was followed up?	4%	
Were dropout rates and reasons for dropout similar across intervention and unexposed groups?	Yes	

Reference and design	Intervention	Participants	Outcome measures
ISKDC, 1974[43] International (not specified) RCT Multicentre, number not reported *Setting*: Not reported *Funding*: National Institutes of Health Research grant AM 14490-03, Kidney Foundation of New York. Kidney Disease Institute of the State of New York, National Kidney Foundation UK, John Rath Foundation	(1) Cyclophosphamide initially 5 mg/kg/day to induce leukopenia (3000–5000 white blood cells/mm^3), then 1–3 mg/kg/day to keep white blood cell count in range (drug discontinued if count fell below 1000 mm^3 and reintroduced when count rose above 1800 mm^3) Intermittent prednisone (2) Intermittent prednisone, 40 mg/m^2/day in divided doses given on 3 consecutive days of 7 *Duration of treatment*: 90 days *Other interventions used*: Supportive therapy (diuretics, dietary alterations and antibiotics) was given at the discretion of the investigator	*Target population*: NS *Number of participants*: 228 with NS, 33 non-responders Total: 33 (1) Cyclophosphamide plus intermittent prednisone: 18 (2) Intermittent prednisone: 15 *Sample attrition/dropout*: Not explicitly stated, assume none *Inclusion criteria for study entry*: Heavy proteinuria ($\geq$40 mg/m^2/hour by overnight collection) and hypoalbuminaemia ($\leq$2.5 g/100 ml serum), >12 years and <16 years, not been treated with adrenocorticosteroids or other agents thought to have similar effect, no evidence of underlying disease or exposure to agents associated with NS Non-responders: did not respond within 8 weeks of initial therapy (prednisone 60 mg/m^2/day in divided doses for 4 weeks, 40 mg/m^2/day in divided doses given on 3 consecutive days of 7 for 4 weeks)	*Primary outcomes*: Number protein free Interval between start of treatment and response *Method of assessing outcomes*: Condition of patients assessed before admission to study then every 3 months Daily semi-quantitative measurements of protein in the urine were performed by patients or parents throughout study Response defined as demonstration of a protein-free urine on 3 consecutive days during the course of not more than 7 days Protein-free urine defined as containing $\leq$4 mg/m^2/hour determined quantitatively on an overnight collection or semi-quantitatively on the first voided morning specimen

continued

Characteristics of participants

	Cyclophosphamide plus intermittent prednisone (*n* = 18)	**Intermittent prednisone (*n* = 15)**	***p***
Minimal change	7/18	7/15	
Focal lesions	7/18	3/15	
MPGN	2/18	0	
Diffuse proliferative glomerulonephritis	2/18	1/15	
Membranous nephropathy	0	2/15	
Unknown histology	0	2/15	

Other characteristics not reported

Results

Outcomes	**Cyclophosphamide plus intermittent prednisone (*n* = 18)**	**Intermittent prednisone (*n* = 15)**	***p***
Number who became protein-free ('late-responder')			
Minimal change	5/7	4/7	
Focal lesions	3/7	0/3	
MPGN	1/2	–	
Diffuse proliferative glomerulonephritis	1/2	1/1	
Membranous nephropathy	–	0/2	
Unknown histology	–	1/2	
Total	10/18 (56%)	6/15 (40%)	ns
Nine of 16 patients who responded in either group had 'minimal changes'.			
Interval between onset of treatment and time of response, mean (range)	(*n* = 10) 38.4 days (6–80)	(*n* = 6) 95.5 days (61–129)	<0.05

Methodological comments

- *Allocation to treatment groups*: States random but no other details
- *Blinding*: Not reported
- *Comparability of treatment groups*: Age and gender not reported. More focal lesions in cyclophosphamide group than controls
- *Method of data analysis*: Fisher's *t*-test, χ^2 test or the difference between two proportions
- *Sample size/power calculation*: Not reported
- *Attrition/dropout*: Not explicitly stated, assume none

General comments

- *Generalisability*: Patients with SRNS identified from an international survey, but few details of participants' characteristics. Inclusion criteria limit age to between 12 and 16 years
- *Outcome measures*: Outcomes limited
- *Intercentre variability*: Not reported
- *Conflict of interests*: None reported

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Unknown
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Unknown
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Unknown
7.	Was the patient blinded?	Unknown
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Unknown

Reference and design	Intervention	Participants	Outcome measures
Lieberman, 1996[46] USA RCT Number of centres: 8 *Setting*: Not reported *Funding*: Active drug and placebo suspensions were supplied by Sandoz Pharmaceuticals (Hanover, NJ)	(1) Ciclosporin (100 mg/ml suspension) initial dose 0.03 ml/kg (3.0 mg/kg of ciclosporin) twice daily to attain target level of 300–500 ng/ml[a] (2) Placebo (vehicle control) *Duration of treatment*: 6 months *Other interventions used*: Calcium-channel blocking agents were recommended for the treatment of hypertension Strictly contraindicated: other immunosuppressive agents, ACE inhibitors, plasmapheresis. Potentially nephrotoxic drugs and drugs known to interact with ciclosporin to be avoided [a] An unblinded clinical co-ordinator adjusted patients' study drug dose according to a study protocol (reported but not extracted). Each ciclosporin–patient dose-adjustment notification was accompanied by a matched placebo–patient dose adjustment The study drug could be temporarily withheld on the basis of either an intercurrent infection or contact with varicella	*Target population*: Patients with primary FSGS *Number of participants*: 31 randomised: ciclosporin 16, placebo 15 Data presented on: Total: 24 (1) Ciclosporin 12 (2) Placebo 12 *Sample attrition/dropout*: Seven withdrawals/dropouts *Inclusion criteria for study entry*: Between 6 months and 21 years; a biopsy diagnosis of FSGS with significant proteinuria (>4 mg/m^2/hour, random urine protein to creatinine ratio >0.18 in children >2 years or >0.49 in children <2 years); failed to respond fully to a standard course of steroid therapy (prednisone 60 mg/m^2 daily in divided doses for 4 weeks); GFR of ⩾40 ml/minute/1.73 m^2; for sexually mature female patients, a negative pregnancy test at baseline and acceptable birth control throughout the study; patients with any recognised risk factors must have been tested for HIV; written informed consent obtained *Exclusions*: Ciclosporin or other immunosuppressive therapy administered within 3 months of study entry; an identifiable primary aetiology for FSGS lesions; concomitant therapy with a potentially nephrotoxic drug; use of an ACE inhibitor; impaired liver function; inability to understand the protocol or attend regular outpatient clinic sessions; a significant concomitant disease or condition; or pregnancy	*Primary outcomes*: Remission rates Proteinuria *Secondary outcomes*: GFR level Biochemical values Adverse events *Method of assessing outcomes*: Proteinuria was assessed through 24-hour urine collection or the determination of the protein to creatinine ratio in early-morning urine sample GFR calculated from a contemporaneous serum creatinine level. Nuclide disappearance methodology No response: proteinuria did not decline during the course of the study Complete remission: proteinuria declined into the normal range Partial response: a reduction in proteinuria, but still remaining in the supranormal range Total improved: number with complete remission and partial response Outcomes were measured weekly for the first 4 weeks, then monthly Week 0: before the first dose of study dose Week 24: end of study, patient still receiving study drug Week 28: 1 month after patient discontinued the study drug *Length of follow-up*: 6 months treatment plus 1 month follow-up

continued

Characteristics of participants

Mean (SD) (range)	**Ciclosporin (*n* = 16)**	**Placebo (*n* = 15)**	***p***
Age (years)	11.2 (4.2) (2–18)	11.4 (3.9) (3–19)	ns
Gender (M:F)	11:4	10:5	ns
Time from diagnostic biopsy (years)	0.8 (0.7) (0.3–2.2)	1.7 (2.2) (0.3–6)	ns
Hypertensive (*n*)	6/15	5/15	ns
Initial GFR (ml/minute/1.73 m^2)	103.4 (36.7) (57.6–171.2)	86.0 (31.3) (51.1–150.8)	ns
Initial proteinuria (mg/kg/24 hours)	151.7 (162.4) (11.1–566.2)	166.9 (137.1) (38.1–364.5)	ns

Results

	Ciclosporin (*n* = 12)		**Placebo (*n* = 12)**		***p* (prestudy vs end of study) Ciclosporin/ placebo**
Serum biochemical values	**Prestudy**	**End of study**	**Prestudy**	**End of study**	
Albumin (gm/dl)	2.8 (1.0)	3.5 (0.8)	2.5 (1.0)	2.7 (1.2)	<0.05/ns
Potassium (mmol/l)	4.1 (0.3)	4.6 (0.5)	4.0 (0.5)	4.1 (0.4)	<0.05/ns
Uric acid (mg/dl)	5.1 (1.0)	6.1 (1.5)	4.8 (1.3)	5.0 (1.5)	ns/ns
Magnesium (mg/dl)	1.76 (0.12)	1.60 (0.22)	1.78 (0.20)	1.70 (0.18)	<0.05/ns
SGOT (U/l)	26.7 (4.8)	31.1 (8.9)	27.4 (8.3)	23.3 (10.1)	ns/ns
Total bilirubin (mg/dl)	0.39 (0.17)	0.44 (0.17)	0.38 (0.16)	0.41 (0.28)	ns/ns
SGPT (U/l)	13.5 (5.7)	14.6 (7.2)	13.8 (4.4)	12.7 (4.7)	ns/ns
Creatinine (mg/day)	0.8 (0.3)	1.0 (0.4)	0.9 (0.4)	1.1 (0.4)	<0.05/ns
Cholesterol (mg/dl)	397 (237)	281 (105)	348 (162)	343 (176)	ns/ns

Outcomes	**Ciclosporin (*n* = 12)**	**Placebo (*n* = 12)**	***p***
Remission rates			
Complete remission	4/12	0/12	<0.05
Partial response	8/12	2/12	<0.05
Total improved	12/12	2/12	
Renal function (mg/kg/24 hours)			
Week 0 proteinuria	151.7 (162.4)	166.9 (137.1)	
Week 24 proteinuria	36.9 (42.3)	195.4 (173.7)	
	Week 0 vs week, 24, p <0 .05	Week 0 vs week 24, p = ns	

Proteinuria in the ciclosporin group declined by 70.7% (SD 19.2) compared with an increase of 11.4% (SD 29.0) in the placebo group ($p < 0.05$).
When factored by GFR, ciclosporin-group proteinuria still significantly declined from 6.0 (SD 7.5) mg/100 ml glomerular filtrate to 1.7 (SD 2.0) over the course of the study ($p < 0.05$). Placebo-group proteinuria remained not significantly changed when expressed as mg per 100 ml of glomerular filtrate [pre 5.6 (SD 4.4) to end 9.6 (SD 11.3), p = ns]. The difference between the two groups in the percentage changes of proteinuria per 100 ml glomerular filtrate was highly significant [ciclosporin –60.6% (SD 37.7), placebo 63.5% (SD 12.8), $p < 0.005$].

Proteinuria factored by GFR (mg/100 ml)			
Week 0	6.0 (7.5)	5.6 (4.4)	
Week 24	1.7 (2.0)	9.6 (11.3)	
	Week 0 vs week 24, $p < 0.05$	Week 0 vs week 24, p = ns	
% Change	–60.6 (37.7)	63.5 (12.8)	<0.005
Time to response (week) (⩾50% reduction in proteinuria)	4.4 (1.8)		
GFR level			
Week 0 GFR (ml/minute/1.73 m^2)	103.4 (36.7)	86.0 (31.3)	
Week 24 (ml/minute/1.73 m^2)	82.9 (19.1)	75.1 (30.6)	
	Week 0 vs week 24, $p = 0.05$	Week 0 vs week 24, $p = 0.06$	
Fractional decline in GFR (% change in poststudy value from prestudy value)	–15.7 (18.4)	–11.8 (19.0)	ns

% Change in proteinuria over 6 months study and prestudy cholesterol levels ($r = 0.79$, $p < 0.05$).
Average ciclosporin level and proteinuria change ($r = –0.76$, $p < 0.05$)

continued

Adverse effects		
Mild gingival hyperplasia	2/12	
Worsening hypertension that necessitated the initiation of additional antihypertensive agents	2/12	2/12
Intercurrent infection (study drug temporarily suspended)	2/12	2/12
Varicella exposure (study drug withheld)	1/12	
ESRD development within 1–4 years (patients with no further ciclosporin therapy)		
Reached ESRD	3	4
Approaching ESRD	2	2
Remained in remission (patients still on ciclosporin therapy)	5	5

Ciclosporin doses maintained in doses from 6 to 12 mg/kg/day with stable renal function.

Methodological comments

- *Allocation to treatment groups*: Patients were randomised at the time of study entry based on previously computer-generated list of ciclosporin or placebo-group assignments
- *Blinding*: The study states that both the patients and their paediatric nephrologists were blinded as to the administered study treatment. The clinical coordinator was unblinded. Not clear who assessed outcomes
- *Comparability of treatment groups*: There were no significant differences between the ciclosporin and placebo groups at time of randomisation in male to female ratio, age, time from renal biopsy diagnosed as FSGS to study entry, initial GFR, prevalence of hypertension or initial proteinuria. Initial serum albumin cholesterol values not significantly different
- *Method of data analysis*: Data were analysed on a per-protocol basis. Not ITT. Statistical analysis was performed using *t*-test, χ^2, partial correlation analysis and multiple regression analysis. All data are expressed as mean ± SD. Significance was considered to be $p < 0.05$
- *Sample size/power calculation*: None reported
- *Attrition/dropout*: Two patients in each group were withdrawn because of non-compliance with the study protocol. One ciclosporin patient requested withdrawal with no specific reason given. One patient from each group was withdrawn for a progressively rising serum creatinine level not responsive to the protocol-indicated study drug-dose reductions. 12 in each group completed the full 6-month course

General comments

- *Generalisability*: Patients aged between 6 months and 21 years with FSGS treated over a 6-month period. The study was not designed to evaluate the long-term efficacy of ciclosporin, beyond the 6-month treatment period. Patients were defined as steroid responsive after just 4 weeks of prednisone
- *Outcome measures*: Appropriate outcome measures were used and reported
- *Intercentre variability*: Not reported
- *Conflict of interests*: Active drug and placebo suspensions were supplied by Sandoz Pharmaceuticals (Hanover, NJ, USA)

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Adequate
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Partial
7.	Was the patient blinded?	Partial
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Ponticelli, 1993[45] Italy RCT Multicentre, number not reported *Setting*: Not reported *Funding*: Supported in part (drug, organisation, investigators' meeting) by Sandoz PF, Milan, Italy	(1) Ciclosporin 6 mg/kg/day orally (divided in two doses, before breakfast and before supper). Doses then adjusted to maintain the trough blood levels of ciclosporin between 250 and 600 ng/ml (2) Supportive treatment, 1 year *Duration of treatment*: Ciclosporin stopped after 6 months if no response. For responders, given for 6 months, then tapered off over 6 months by 25% every 2 months until complete discontinuation *Other interventions used*: A 'rescue treatment' with corticosteroids was allowed for patients who showed rapidly progressive renal failure or a devastating NS. With the exception of 'rescue treatments', corticosteroid and immunosuppressive agents were forbidden. Clinicians asked not to use erythromycin, cotrimoxazole, aminoglycosides, ACE inhibitors, NSAIDs and/or antiepileptic drugs. Other treatments could be given Patients asked to reduce salt intake. Protein intake was free	*Target population*: MCNS or FSGS *Number of participants*: Total: 17 (1) Ciclosporin: 10 (2) Control: 7 *Sample attrition/dropout*: 20 children randomised. Three withdrawn and data not included; one lost to follow-up *Inclusion criteria*: Study included patients aged 2–65 years. Only results for children (<16 years) have been extracted Children with NS and creatinine clearance >80 ml/minute/1.73 m^2 and with renal biopsies showing either MCNS or FSGS Children who met the eligibility criteria were given 60 mg/m^2/day prednisone for 5 weeks. Only patients who did not have either complete or partial remission of the NS were admitted to the study NS was defined by proteinuria >40 mg/m^2/hour, with variable oedema *Exclusion criteria*: Aged <2 years, nephropathy secondary to a well-identified cause, neoplasia, hereditary angioedema, gastrointestinal malabsorption, concomitant infection or liver dysfunction, pregnancy, non-compliance, drug or alcohol abuse, patients requiring antiepileptic drugs, DBP >95 mmHg if untreated, or >90 mmHg if on antihypertensive treatment, immunosuppressive agents or ciclosporin in previous 12 months. (Some of exclusion criteria more relevant to adult patients)	*Primary outcomes*: Remission Changes in proteinuria Changes in renal function *Secondary outcomes*: Adverse events Biochemical parameters (not reported for children separately) *Method of assessing outcomes*: Partial remission: proteinuria <40 mg/m^2/hour during 3 non-consecutive days Complete remission: proteinuria <4 mg/m^2/hour on 3 different non-consecutive days Time for response: number of days from start of treatment to first day of complete or partial response *Length of follow-up*: Adults and children combined: Ciclosporin: median 18 months (3–24) Control: median 24 months (12–24)

continued

Characteristics of participants

Mean (SEM)	**Ciclosporin (*n* = 10)**		**Control (*n* = 7)**		***p***
Renal biopsy:					
FSGS	4/10		5/7		
MCNS	6/10		2/7		
Age (years)					
FSGS	6.5 (4.7)		6.6 (1.8)		
MCNS	6.8 (3.5)		7.5 (7.8)		
Gender (M:F)	6:4		Not reported		
Duration of disease (years), median					
FSGS	0.5		2.0		
MCNS	2.0		1.0		
	FSGS (*n* = 4)	**MCNS (*n* = 6)**	**FSGS (*n* = 5)**	**MCNS (*n* = 2)**	
Interstitial lesions					
Present	2/4	0/6	3/5	1/2	
Absent	2/4	6/6	2/5	1/2	
Vascular lesions					
Present	1/4	0/6	0/5	0/2	
Absent	3/4	6/6	5/5	2/2	
Obsolescent glomeruli (>50% all glomeruli)					
Present	1/4	1/6	2/5	0/2	
Absent	3/4	5/6	3/5	2/2	
Creatinine clearance (ml/minute/1.73 m^2)	147.95 (100.24)	164.13 (30.09)	121.90 (30.52)	149.60 (52.89)	
Proteinuria (mg/m^2/hour)	220.15 (140.33)	169.85 (109.26)	230.46 (200.88)	113.70 (37.00)	
Hypertension					
Present	0/4	2/6	1/5	0/2	
Absent	4/4	4/6	4/5	2/2	

Results

Outcomes	**Ciclosporin (*n* = 10)**	**Control (*n* = 7)**	***p***
Complete remission	4/10 (1 FSGS, 3 MCNS)	0	
Partial remission	2/10 (1 FSGS, 1 MCNS)	0	
Total complete or partial remission	6/10	0	
Time at response (days), mean (SD)	(*n* = 6) 61.3 (85.7)		
Proteinuria at response (mg/m^2/hour), mean (SD)	(*n* = 6) 10.8 (15.7)		
Outcome at 1 year (treatment tapered after 6 months)	Of six responders, two with complete remission had relapsed		
Outcome at 2 years (only four patients followed)	(*n* = 4) One partial remission relapsed One relapse at 1 year, now complete remission. Two patients no change (one partial remission, one NS)		

Means and SD for time at response and proteinuria at response calculated by reviewer from data in table.
Proteinuria: data not presented separately for children. Reports that proteinuria significantly decreased at month 6 ($p < 0.05$) in the ciclosporin group, and was unchanged in the control group. When ciclosporin was reduced gradually, proteinuria tended to return to baseline values.

continued

Adverse effects		
Infections	3/10	3/7

Further adverse events were presented, but there was no specification between adults and children. These included gum hyperplasia (seven ciclosporin), hypertrichosis (three ciclosporin), transient gastric discomfort (four ciclosporin), a mild increase in bilirubinaemia (one case per group), headache (one case per group), bronchospasm (one case per group); paraesthesia, flushing, epicondylitis, tendonitis, extrasystoles and anaemia (one case per each symptom in control group) occurred sporadically. All symptoms had disappeared after the first year of observation. Blood pressure: no differences between the two groups at any time, nor were there any differences between children and adults (data not shown). Mean trough levels of ciclosporin remained lower than scheduled for children, in spite of increasing doses.

Methodological comments

- *Allocation to treatment groups*: The indication for the therapy was contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers. Randomisation stratified by adults or children. A randomisation stratified by centre was not deemed suitable owing to the small sample size
- *Blinding*: Study described as 'open'
- *Comparability of treatment groups*: Groups were similar at time of randomisation
- *Method of data analysis*: States that patients who did not complete the treatment were included in the analysis according to the ITT principle. However, although data from two such patients (one adult, one child) were included, data from one adult and three children who were withdrawn within 45 days after assignment were not included
- *Sample size/power calculation*: The enrolment of new patients ended when the planned number of 20 patients (including adults and children) in each treatment group was reached. This was considered sufficient to have a power of 0.80 for demonstrating a 0.05 increase in the cumulative proportion of clinical response in the control group versus a 0.40 increase in the ciclosporin group at month 6, using a two-tailed statistical test performed at 0.05 significance level. However, it should be noted that only data on children were extracted from this study (therefore smaller sample size)
- *Attrition/dropout*: One child stopped ciclosporin on day 60 owing to an intercurrent symptomatic urinary tract infection. After recovery, his doctor decided not to restart ciclosporin. The patient was subsequently lost to follow-up. Three children assigned to the control group were withdrawn within 45 days because they did not come for the required visits. Only four of the children were followed for 2 years

General comments

- *Generalisability*: Children aged 2–16 years with FSGS or minimal change disease. Steroid resistance was defined after just 5 weeks of prednisone
- *Outcome measures*: Appropriate outcome measures. Additional outcome measures were reported but not extracted as children and adults were combined
- *Intercentre variability*: States that since the number of patients per centre was small, the 'among-centres' factor was not taken into account in the analysis
- *Conflict of interests*: Supported in part (drug, organisation, investigators' meeting) by Sandoz PF, Milan, Italy

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Adequate
2.	Was the treatment allocation concealed?	Inadequate
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Inadequate
6.	Was the care provider blinded?	Inadequate
7.	Was the patient blinded?	Inadequate
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
9.	Did the analyses include an ITT analysis?	Adequate
10.	Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Tarshish, 1996[32] (ISKDC) International RCT Multicentre *Setting*: Not reported *Funding*: Supported by National Institutes of Health Research, National Kidney Foundation of New York, Kidney Disease Institute of the State of New York, the John Rath Foundation, National Kidney Research Foundation (UK) and the Kidney Foundation of The Netherlands	(1) Cyclophosphamide (2.5 mg/kg) in a single morning dose for 90 days plus prednisone (40 mg/m^2) as below (2) Prednisone (40 mg/m^2) on alternate days in a single morning dose for 12 months *Duration of treatment*: Group 1: 90-day cyclophosphamide plus 12 months of prednisone Group 2: 12 months of prednisone *Other interventions used*: Not reported	*Target population*: Patients with FSGS *Number of participants*: Total: 60 Cyclophosphamide + prednisone: 35 Prednisone: 25 *Sample attrition/dropout*: Five patients died during the duration of the trial. Proteinuria not reported for 3/35 of cyclophosphamide group and 4/25 of prednisone group *Inclusion criteria for study entry*: Renal biopsy performed within 26 weeks of the onset of the NS, showing FSGS; heavy proteinuria ($\geq$40 mg/m^2/hour determined on an overnight collection) despite intensive steroid therapy; hypoalbuminaemia $\leq$2.5 g/dl; age at onset 12 weeks to 18 years; absence of identifiable medical diseases associated with FSGS; no prior treatment with cytotoxic or immunosuppressive agents Patients initially treated as part of ISKDC with daily prednisone regimen of 60 mg/m^2 in three divided doses for 4 weeks, followed by intermittent prednisone for an additional 4 weeks. Or treated outside the ISKDC with a comparable regimen of at least 8 weeks' (max. 26 weeks) steroid therapy Patients suffering deterioration of renal function during the first year of the trial could be withdrawn at the discretion of the investigator	*Primary outcome*: Change in proteinuria *Secondary outcomes*: Treatment failure Adverse events Kaplan–Meier survival analysis *Method of assessing outcomes*: Proteinuria was classified as: Absent <4 mg/m^2/hour Mild 4–40 mg/m^2/hour Moderate 41–100 mg/m^2/hour Severe >100 mg/m^2/hour Described as 'increased' or 'decreased' based on a change of one class or more Treatment failure defined as increase in serum creatinine from baseline of $\geq$30% or >0.4 mg/dl or onset of renal failure as evidenced by serum creatinine >4.0 mg/dl, maintenance on chronic dialysis or having undergone renal transplantation Renal biopsies were obtained before allocation, approximately 1 month after allocation, and at any point of clinical deterioration GFR estimated from serum creatinine and body height *Length of follow-up*: Mean follow-up time from entry: Cyclophosphamide + prednisone: 42.4 months Prednisone: 44.5 months (range 3–102)

continued

Characteristics of participants

Mean (SEM)	**Cyclophosphamide + prednisone (*n* = 35)**	**Prednisone (*n* = 25)**	***p***
Age at diagnosis (years)	7.6 (0.88)	6.9 (0.78)	ns
Age at entrance (years)	8.6 (0.85)	7.4 (0.75)	ns
GFR at entrance (ml/minute/1.73 m^2)	109 (8.7)	118 (8.4)	ns
SBP (mmHg)	114 (3.2)	116 (3.2)	ns
DBP (mmHg)	72 (4.0)	76 (3.7)	ns
Plasma creatinine (mg/dl)	0.81 (0.12)	0.62 (0.05)	ns
Serum albumin (g/dl)	2.1 (0.15)	1.8 (0.16)	ns
Urine protein (mg/m^2/hour)	227 (35)	161 (29)	ns
Global sclerosis (%)	7.1 (2.1)	5.4 (1.6)	ns
Segmental sclerosis (%)	18.8 (2.8)	18.7 (3.1)	ns
% Abnormal with regard to:			
Hyalinosis	21%	28%	ns
Mesangial cells	33%	24%	ns
Mesangial matrix	30%	8%	<0.05
Tubular atrophy and interstitial fibrosis	36%	28%	ns
Hyaline vasculopathy	6%	8%	ns

Results

Outcomes	**Cyclophosphamide + prednisone (*n* = 32)**	**Prednisone (*n* = 21)**	
No. with change in proteinuria (baseline vs final)			$\chi^2 = 0.26$, df = 2, $p = 0.9$
Absent	8/32 (25%)[a]	6/21 (28%)	
Decreased	8/32 (25%)	6/21 (28%)	
Unchanged or increased	16/32 (50%)	9/21 (43%)	

[a] Including one patient who subsequently developed renal failure 14 months later. Others stable at last follow-up. In patients with persistent proteinuria, analysis of change in the rate of proteinuria from baseline to final evaluation revealed no differences between the experimental and control groups.

	Cyclophosphamide + prednisone (*n* = 35)	**Prednisone (*n* = 25)**	
Treatment failure	20/35 (57%)	9/25 (36%)	>0.1

A Kaplan–Meier survival analysis revealed no significant difference between the two groups ($Z = 1.06$, $p > 0.25$).
On the basis of the last available biopsy, neither the percentage of glomeruli with global or segmental sclerosis nor the degree of mesangial hypercellularity differed between the experimental and control groups (data not presented).

Adverse events	**Cyclophosphamide + prednisone (*n* = 35)**	**Prednisone (*n* = 25)**	
Hypertensive seizures	1	1	
Haemorrhagic cystitis	1		
Tumour development	0	0	
Bone-marrow suppression	0	0	
Aspermia	0	0	
Death	3	2	1.0

Side-effects were very few. Causes of death were sepsis in two patients, cardiorespiratory arrest in one and unknown in two. One patient who died from sepsis was receiving prednisone at the time of death. The other patients were off therapy and in chronic renal failure. Allocated groups not specified.

Methodological comments

- *Allocation to treatment groups*: Patients were randomised in one of two central offices according to their geographical location. Two categories of patients: (1) newly diagnosed patients treated as part of ISKDC as described above; (2) patients initially treated outside ISKDC, but with a comparable regimen of steroid therapy. Within each category, children were randomly allocated to either a treated control or an experimental group
- *Blinding*: Histological material was interpreted by the central group of ISKDC pathologists without knowledge of the patient's allocations or course. No further information is provided about blinding

continued

- *Comparability of treatment groups*: Baseline clinical characteristics were equivalent for the two groups. This was also true for histopathological evaluation of the initial biopsy specimens, except for increased mesangial matrix, which was greater in the experimental group ($p < 0.05$)
- *Method of data analysis*: The data were summarised using *t*-tests for the differences of means for quantitative measures, and using Fisher's exact and χ^2 tests and differences of proportions for categorical measures. A Cox proportional hazards regression model was used to compare the two treatment groups with regard to outcome. All significance tests were performed using a two-tailed $\alpha = 0.05$
- *Sample size/power calculation*: The failure rate in the cyclophosphamide-treated group was 21% greater than in the prednisone-treated group. Although not statistically different, the power to detect a difference of this magnitude with 60 subjects is 37%. For a power of 80% to detect differences such as these at the same α, 87 patients per group would be required
- *Attrition/dropout*: 15/75 eligible patients withdrawn before allocation because of retraction of parental consent, development of pancreatitis, lack of clinical data, withdrawal of one centre from the study, or diagnosis of MCNS rather than FSGS when reviewed by central pathologist. Urinary protein excretion data available in 21/25 (84%) of prednisone group and 32/35 (91%) of cyclophosphamide + prednisone group. Reasons not provided. Five patients died during the trial, three in the experimental and two in the control group

General comments

- *Generalisability*: Children aged 12 weeks to 18 years with FSGS
- *Outcome measures*: Outcomes were appropriate and adequately reported
- *Intercentre variability*: Not reported
- *Conflict of interests*: Not reported

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Unknown
2.	Was the treatment allocation concealed?	Unknown
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Unknown
6.	Was the care provider blinded?	Unknown
7.	Was the patient blinded?	Unknown
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and dropouts completely described?	Partial

Appendix 6

List of excluded studies

Arora A, Ahlawat RS, Arora S, Arora N, Mandel AK. Randomised controlled study of enalapril in steroid resistant nephrotic syndrome. *Indian J Nephrol* 2002; **12**(3) [adult patient].

Arumugam R, Watson AR. Nitrogen mustard therapy and nephrotic syndrome. *Pediatr Nephrol* 1996;**10**:130–1 [inappropriate study design].

Beige J, Moosmayer I, Liefeldt L, Neumayer HH, Zidek W, Peters H. Effective and safe treatment of primary nephrotic syndrome with tacrolimus (FK 506). *Nephrol Dial Transplant* 2003;**18**(Suppl 4) [adult patients].

Besbas N, Topaloglu R, Saatci O, Bakkaloglu A. Long-term follow-up in children with steroid-resistant nephrotic syndrome. *Clin Pediatr* 1992;**31**:283–8 [inappropriate study design].

Brocklebank JT, Harcourt RB, Meadow SR. Eye complications of cyclophosphamide and prednisolone therapy in children with idiopathic nephrotic syndrome. *Arch Dis Child* 1980;**55**:491 [unclear whether patients are steroid resistant; inappropriate study design].

Brodehl J, Hoyer PF. Ciclosporin in idiopathic nephrotic syndrome of children. *Am J Nephrol* 1989; **9**(Suppl 1):61–4 [inappropriate study design].

Bullo B, Zdrojewski Z, Rutkowski B. Mycophenolate mofetil (MMF) therapeutic approach in patients with chronic glomerulonephritis (GN). *Kidney Int* 2003; **64**:1139 [adult patients; inappropriate study design].

Butani L, Radsliff E, Makker S. Tacrolimus (T) induces remission in children with steroid-resistant nephrotic syndrome (SRNS). *J Am Soc Nephrol* 2003;14–39A [inappropriate study design].

Callis L, Nieto MDJ, Vila A. Chlorambucil treatment in idiopathic nephrotic syndrome. *Arch Dis Child* 1980; **55**:490 [inappropriate study design].

Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, *et al*. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. *Kidney Int* 1999; **56**:2220–6 [adult patients].

Chon MH, Sohn KH, Jin DK, Choi KE, Lee SH. Efficacy and safety of cyclosporine therapy in children with nephrotic syndrome. *Pharmacotherapy* 2004;**24**:1453 [inappropriate study design].

Donia A, Ammar H, Moustafa F, Sobh M. Long-term efficacy of two unconventional adjunctive therapies in minimal change nephrotic children. *ERA EDTA Congress* 2004;37 [patients steroid resistant].

Dundon S, O'Callaghan U, Raftery J. Stability of remission in minimal lesion nephrotic syndrome after treatment with prednisolone and cyclophosphamide. *Int J Pediatr Nephrol* 1980;**1**:22–5 [patients steroid sensitive].

Duzova A. Cyclophosphamide (CYC) and cyclosporin-A (CsA) in the treatment of primary MPGN in children. *Nephrol Dial Transplant* 2001;(6):A67 [inappropriate study design].

El-Husseini A, El-Basuony F, Mahmoud I, Donia A, Hassan N, Sayed-Ahmed N, *et al*. Effect of concomitant administration of cyclosporine and ketoconazole in children with focal segmental glomerulosclerosis. *Am J Nephrol* 2004;**24**:301–6 [results for steroid-resistant patients not reported separately; inappropriate study design].

El-Husseini A, El-Basuony F, Donia A, Mahmoud I, Hassan N, Sayed-Ahmad N, *et al*. Co-administration of cyclosporine and ketoconazole in children with minimal change nephrotic syndrome. *Nephron Clin Pract* 2005; **100**(2):c27–32 [results for steroid resistant patients not reported separately; inappropriate study design].

Filler G. Treatment of nephrotic syndrome in children and controlled trials. *Nephrol Dial Transplant* 2003; **18**(Suppl 6):vi75–8 [patients steroid responsive].

Ghose S, Kumar M, Kundu B, Bindal S. Long term follow up of steroid and cyclophosphamide therapy in nephrosis. *Indian Pediatr* 1977;**14**:885–9 [patients not SRNS].

Grunwald HW, Rossner F, Mallick NP. Cyclophosphamide for minimal change nephropathy in children. *N Engl J Med* 1984;**311**:126–7 [letter].

Guigonis V, Audat F, Lefrere F, Jouvet P, Bensman A, Deschenes G. Remission of cyclosporine-steroid-resistant nephrotic syndrome using multiple immunosuppression. *J Am Soc Nephrol* 2002;(13):679–80A [inappropriate study design].

Gulati S, Gupta AK. Reversal of steroid resistance in nephrotic syndrome secondary to idiopathic FSGS with intravenous pulse cyclophosphamide. *Nephrol Dial Transplant* 2001; **16**(6):A61 [inappropriate study design].

Hall AS, Thorley G, Houtman PN. The effects of corticosteroids on behavior in children with nephrotic syndrome. *Pediatr Nephrol* 2003;**18**:1220–3 [patients steroid sensitive; inappropriate outcomes and study design].

Hari P, Bagga A, Jindal N, Srivastava RN. Treatment of focal glomerulosclerosis with pulse steroids and oral cyclophosphamide. *Pediatr Nephrol* 2001;**16**:901–5 [inappropriate study design].

Heering P, Braun N, Müllejans R, Ivens K, Zäuner I, Fünfstück R, *et al*. Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. *Am J Kidney Dis* 2004;**43**:10–18 [adult patients].

Honda M. Nephrotic syndrome and mizoribine in children. *Pediatr Int* 2002;**44**:210–16 [review of mixture of patients, ages and disease; inappropriate study design].

Igarashi Y, Moro Y, Kondo Y, Inoue CN. Steroid-sparing effect of mizoribine in long-term nephrotic syndrome of children. *Pediatr Nephrol* 1994;**8**:396–7 [inappropriate study design].

Imbasciati E, Gusmano R, Edefonti A, Zucchelli P, Pozzi C, Grassi C, *et al*. Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. *BMJ* 1985;**291**:1305–8 [patients not steroid resistant].

International Study of Kidney Disease in Children (ISKDC). A controlled therapeutic trial of cyclophosphamide plus prednisone versus prednisone alone in children with focal segmental glomerulosclerosis (FSGS). *Pediatr Res* 1980;**14**:1006 [unclear disease histology].

James RW, Burke JR, Petrie JJB, Rigby RJ, Williams M. Cyclosporin A in the treatment of childhood glomerulonephritis. *Aust N Z J Med* 1989;**19**:198–201 [inappropriate study design].

Jones G, Juszczak M, Kingdon E, Harber M, Sweny P, Burns A. Treatment of idiopathic membranoproliferative glomerulonephritis with mycophenolate mofetil and steroids. *Nephrol Dial Transplant* 2004;**19**:3160–4 [adult patients; inappropriate study design].

Krasnova T, Tareyeva I, Avdokhine A, Krasnova E. Efficiency of CyA treatment and the role of its predictors in patients with glomerulonephritis (GN) and nephrotic syndrome (NS). *Nephrol Dial Transplant* 2001;(6):A69 [adult patients; inappropriate study design].

Kumar NS, Singh AK, Mishra RN, Prakash J. Comparative study of angiotensin converting enzyme inhibitor and calcium channel blocker in the treatment of steroid-resistant idiopathic nephrotic syndrome. *J Assoc Physicians India* 2004;**52**:454–8 [children not analysed separately].

Lemire J, De Chadarevian JP, Kaplan BS. Treatment of focal glomerulosclerosis (FGS) with alkylating agents. *Pediatr Res* 1981;**15**(4) [inappropriate study design].

McCauley J, Shapiro R, Scantlebury V, Gilboa N, Jordan M, Jensen C, *et al*. FK 506 in the management of transplant-related nephrotic syndrome and steroid-resistant nephrotic syndrome. *Transplant Proc* 1991; **23**:3354–6 [adult patients; inappropriate study design].

Martinelli R, Okumura AS, Pereira LJ, Rocha H. Primary focal segmental glomerulosclerosis in children: prognostic factors. *Pediatr Nephrol* 2001;**16**:658–61 [not all patients steroid resistant; inappropriate study design].

Martinelli R, Pereira LJ, Silva OM, Okumura AS, Rocha H. Cyclophosphamide in the treatment of focal segmental glomerulosclerosis. *Braz J Med Biol Res* 2004; **37**:1365–72 [children not analysed separately].

Michail S, Filiopoulos V, Kosmadakis G, Tentolouris N, Georgoulias C, Gobou A, *et al*. Comparison of three regimens in patients with idiopathic membranous nephropathy (IMN) associated with nephrotic syndrome (NS). *ERA EDTA Congress* 2004;34 [adult patients].

Mocan H, Erduran E, Karaguzel G. High dose methylprednisolone therapy in nephrotic syndrome. *Indian J Pediatr* 1999;**66**:171–4 [patients with first episode of nephrotic syndrome; not SRNS].

Na KY, Han JS, Kim YS, Ahn C, Kim S, Lee JS, *et al*. Does albumin preinfusion potentiate diuretic action of furosemide in patients with nephrotic syndrome? *J Korean Med Sci* 2001;**16**:448–54 [adult patients].

Ni ZH, Qian JQ, Lin AW, Mu S, Zhu ML, Fang W. A controlled, prospective study of efficacy of leflunomide in patients with nephrotic syndrome. *J Am Soc Nephrol* 2003;**14**(Abstracts):524A [patients not all idiopathic SRNS].

Niaudet P. Steroid-resistant idiopathic nephrotic syndrome and ciclosporin. French Club of Pediatric Nephrology. *Nephron* 1991;**57**:481 [inappropriate study design].

Niaudet P, Tete M-J, Broyer M, Habib R. Cyclosporine and childhood idiopathic nephrosis. *Transplant Proc* 1988;**20**(3 Suppl 4) [steroid-resistant patients not reported separately; inappropriate study design]

Oemar B, Brodehl J. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. *Arch Dis Child* 1991;**66**:751 [letter].

Panzarino V, Ramirez F, Bunchman T. Effects of tacrolimus and alternate day steroids on lipid and glucose metabolism in children with nephrotic syndrome. *J Am Soc Nephrol* 2002;**13**:704–5A [disease histology unclear; inappropriate study design].

Pascual JF, Molina M, Lopez J. Long-term assessment of chlorambucil in children with nephrotic syndrome who fail to respond adequately to corticosteroids. *Contrib Nephrol* 1981;**27**:65–74 [inappropriate study design].

Perrone L, Sinisi AA, Del GR, Del GD, Bellastella A, Faggiano M. Late effects of cyclophosphamide on testicular function in prepubertal boys and adults. *J Pediatr Endocrinol* 1989;**3**:105–8 [patients not steroid resistant and frequent relapse].

Ponticelli C, Rivolta E. Ciclosporin in minimal-change glomerulopathy and in focal segmental glomerular sclerosis. *Am J Nephrol* 1990;**10** (Suppl 1):105–9 [results for children not reported separately].

Ponticelli C, Imbasciati E, Case N, Zucchelli P, Cagnoli L, Pasquali S. Intravenous methylprednisolone in minimal change nephrotic syndrome. *BMJ* 1980;**280**:685 [patients not steroid resistant; inappropriate study design].

Ponticelli C, Zucchelli P, Passerini P, Cesana B. Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. The Italian Idiopathic Membranous Nephropathy Treatment Study Group. *N Engl J Med* 1992;**327**:599–603 [adult patients with idiopathic membranous nephropathy].

Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, *et al*. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 1998;**9**:444–50 [patients not steroid resistant].

Prasad R, Dayal RS, Srivastava VK, Bhatnagar AK, Jain S, Kapur S. A clinicopathological study of nephrotic syndrome and role of immunosuppressive therapy. *Indian Pediatr* 1980;**17**:923–9 [inappropriate study design].

Qiu WQ, Li MJ, Du CL, Zhou LL. Clinical observation of treatment of refractory nephrotic syndrome by cyclophosphamide. *Chinese Journal of Primary Medicine and Pharmacy* 2002;**9**:490–1 [non-English language].

Roberti M, Reisman L. Use of tacrolimus versus cyclosporine for the treatment of severe nephrosis in pediatric patients: a comparative analysis. *J Am Soc Nephrol* 2002;(13):666A [inappropriate study design].

Sa GA, Luis JP, Mendonca E, Almeida M, Rosa FC. Treatment of childhood steroid-resistant nephrotic syndrome with pulse methylprednisolone and cyclophosphamide. *Pediatr Nephrol* 1996;**10**:250 [inappropriate study design].

Shibasaki T, Koyama A, Hishida A, Muso E, Osawa G, Yamabe H, *et al*. A randomized open-label comparative study of conventional therapy versus mizoribine only therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clin Exp Nephrol* 2004;**8**:117–26 [adult patients].

Tejani A, Suthanthiran M, Pomrantz A. A randomized controlled trial of low-dose prednisone and ciclosporin versus high-dose prednisone in nephrotic syndrome of children. *Nephron* 1991;**59**:96–9 [patients not steroid resistant].

Toz H, Ok E, Unsal A, Asci G, Basdemir G, Basci A. Effectiveness of pulse cyclophosphamide plus oral steroid therapy in idiopathic membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 1997; **12**:1081–2 [age group 15–45 years; inappropriate study design].

Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long-term follow-up. *Clin Nephrol* 1995;**43**:84–8 [inappropriate study design].

Walker RG, Kincaid-Smith P. The effect of treatment of corticosteroid-resistant idiopathic (primary) focal and segmental hyalinosis and sclerosis (focal glomerulosclerosis) with ciclosporin. *Nephron* 1990; **54**:117–21 [adult patients].

Wila W, Alatas H, Tambunan T, Khow LP, Ramelan W. The effect of cyclophosphamide on children with steroid resistant nephrotic syndrome and its side effect upon the gonadal tissue. *Paediatrica Indonesiana* 1976; **16**:291–8 [inappropriate study design].

Wyszynska T, Ksiazek J, Uszycka-Karcz M, Kobierska-Szczepanska A, Morawska Z, Zoch-Zwierz W. Evaluation of prednisolone pulse therapy in steroid-resistant nephrotic syndrome. A multicenter collaborative study. *Contrib Nephrol* 1988;**67**:229–32 [inappropriate study design].

Yiu VN, Gowrishankar M, Loeffler K. Tacrolimus therapy in pediatric patients with treatment resistant forms of nephrotic syndrome. *J Am Soc Nephrol* 2003; **14**:525A [inappropriate study design].

List of 'unclear' excluded abstracts

Bhatti S, Ahmed E, Akhtar F, Naqvi A, Rizvi A. Response to immunosuppressive drugs in steroid resistant nephrotic syndrome in children. *J Am Soc Nephrol* 2002;(13):678A [insufficient information about study design].

Bizo A, Aldea C, Delean D, Marian M, Miu N. Cyclosporine vs corticotherapy in children with nephrotic syndrome. *ERA EDTA Congress* 2004;38 [insufficient information].

El-Husseini A, El-Basuony F, Donia A, Mahmoud I, Sobh M. Concomitant administration of cyclosporine and ketoconazole in children with idiopathic nephrotic syndrome. *ERA EDTA Congress* 2004;37 [insufficient information].

Hui LZ, Wen YZ. Clinical study of fosinopril in children with steroid resistant nephrotic syndrome. *Pediatr Nephrol* 2001;C114 [insufficient information].

Panzarino VM. A multi-center trial of tacrolimus in childhood nephrotic syndrome. *Paediatr Res* 2003; **53**:523–4A [insufficient information about disease histology].

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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