Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for idiopathic steroid-resistant nephrotic syndrome in children (Review)

Hodson EM, Willis NS, Craig JC

Hodson EM, Willis NS, Craig JC.
Interventions for idiopathic steroid-resistant nephrotic syndrome in children.
Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003594.
DOI: 10.1002/14651858.CD003594.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

Elisabeth M Hodson[1], Narelle S Willis[2], Jonathan C Craig[2]

[1]a) Centre for Kidney Research, The Children's Hospital at Westmead, b) Sydney School of Public Health, The University of Sydney, Westmead, Australia. [2]a) Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, b) Sydney School of Public Health, The University of Sydney, Sydney, Australia

Contact address: Elisabeth M Hodson, Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Australia. Elisah@chw.edu.au.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: Edited (conclusions changed), published in Issue 11, 2010.

Citation: Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD003594. DOI: 10.1002/14651858.CD003594.pub4.

ABSTRACT

Background

The majority of children who present with their first episode of nephrotic syndrome achieve remission with corticosteroid therapy. Children who fail to respond may be treated with immunosuppressive agents including calcineurin inhibitors (cyclosporin or tacrolimus) and with non-immunosuppressive agents such as angiotensin-converting enzyme inhibitors (ACEi). Optimal combinations of these agents with the least toxicity remain to be determined.

Objectives

To evaluate the benefits and harms of interventions used to treat idiopathic steroid-resistant nephrotic syndrome (SRNS) in children.

Search methods

Randomised controlled trials (RCTs) were identified from the Cochrane Renal Group's specialised register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles.

Selection criteria

RCTs and quasi-RCTs were included if they compared different immunosuppressive agents or non-immunosuppressive agents with placebo, prednisone or other agent given orally or parenterally in children aged three months to 18 years with SRNS.

Data collection and analysis

Two authors independently searched the literature, determined study eligibility, assessed quality and extracted data. For dichotomous outcomes, results were expressed as risk ratios (RR) and 95% confidence intervals (CI). Data were pooled using the random effects model.

Main results

Fourteen RCTs (449 children) were included. Cyclosporin when compared with placebo or no treatment significantly increased the number of children who achieved complete remission (three studies, 49 children: RR 7.66, 95% CI 1.06 to 55.34). Cyclosporin significantly increased the number with complete or partial remission compared with IV cyclophosphamide (one study, 32 children: RR 3.40, 95% CI 1.12 to 10.28). There was no significant difference in the number who achieved complete remission between oral cyclophosphamide with prednisone versus prednisone alone (two studies, 91 children: RR 1.06, 95% CI 0.61 to 1.87), IV versus oral cyclophosphamide (one study, 11 children: RR 3.13, 95% CI 0.81 to 12.06), IV cyclophosphamide versus oral cyclophosphamide with IV dexamethasone (one study, 49 children: RR 1.13, 95% CI 0.65 to 1.96), tacrolimus versus cyclosporin (one study, 41 children: RR 0.86, 95% CI 0.44 to 1.66) and azathioprine with prednisone

versus prednisone alone (one study, 31 children: RR 0.94, 95% CI 0.15 to 5.84). ACEi significantly reduced proteinuria (two studies, 70 children). No studies were identified comparing high dose steroids and cyclosporin with single agents, placebo or no treatment.

Authors' conclusions

Further adequately powered, well designed RCTs are needed to confirm the efficacy of cyclosporin and to evaluate other regimens for idiopathic SRNS including high dose steroids with cyclosporin.

PLAIN LANGUAGE SUMMARY

Cyclosporin may increase the number of children who achieve complete remission in steroid-resistant nephrotic syndrome. Angiotensin converting enzyme (ACE) inhibitors significantly reduce the degree of proteinuria

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. Corticosteroids are used in the first instance to achieve remission. Some children do not respond to this treatment and other agents such as cyclophosphamide, chlorambucil, cyclosporin or ACE inhibitors may be used. This review found that when cyclosporin was compared to placebo or no treatment there was a significant increase in the number of children who achieved complete remission. Cyclosporin also significantly increased the number of children, who achieved complete or partial remission compared with IV cyclophosphamide. There was no improvement with other immunosuppressive agents. However the number of studies was small. More research is needed.

Summary of findings for the main comparison. Cyclosporin versus placebo/no treatment for idiopathic steroid-resistant nephrotic syndrome in children

Cyclosporin versus placebo/no treatment for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary services
Intervention: Cyclosporin
Comparison: Placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Cyclosporin				
Number of patients with complete remission - All renal pathologies Urine protein excretion Follow-up: 3-12 months	**Study population**		**RR 7.66** (1.06 to 55.34)	49 (3 studies)	⊕⊕⊝⊝ **low**[1,2]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Number of patients with complete remission - FSGS urine protein excretion Follow-up: 6-12 months	**Study population**		**RR 5.83** (0.75 to 45.09)	33 (2 studies)	⊕⊕⊝⊝ **low**[1]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Number of patients with complete or partial remission - All renal pathologies Follow-up: 3-12 months	**Study population**		**RR 5.48** (1.95 to 15.44)	49 (3 studies)	⊕⊕⊝⊝ **low**[1,2,3]	
	87 per 1000	**477 per 1000** (170 to 1000)				

	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Number of patients with complete or partial remission - FSGS Urine protein excretion Follow-up: mean 6 months	**Study population**		**RR 5** (1.63 to 15.31)	24 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	167 per 1000	**835 per 1000** (272 to 1000)				
	Medium risk population					
	167 per 1000	**835 per 1000** (272 to 1000)				
Adverse effects Follow-up: 6-12 months	**Study population**		See comment	41 (2)		Risks were calculated from pooled risk differences
	263 per 1000	**0 per 1000** (-79 to 79)				
	Medium risk population					
	298 per 1000	**0 per 1000** (-89 to 89)				
Adverse effects - Worsening of hypertension Blood pressure measurement Follow-up: mean 6 months	See comment	See comment	Not estimable	24 (1 study)	⊕⊕⊝⊝ **low**[1]	Risks were calculated from pooled risk differences
Adverse effects - Infection Patient report Follow-up: mean 12 months	See comment	See comment	Not estimable	17 (1 study)	⊕⊕⊝⊝ **low**[1]	Risks were calculated from pooled risk differences

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Small patient numbers
[2] No intention-to-treat analysis
[3] No blinding

Summary of findings 2. Cyclosporin versus IV cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

Cyclosporin versus IV cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary health settings
Intervention: Cyclosporin
Comparison: IV cyclophosphamide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV cyclophosphamide	Cyclosporin				
Number achieving complete remission at 12 weeks Urinary protein excretion Follow-up: mean 12 weeks	**Study population**		**RR 1.13** (0.18 to 7.09)	32 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	118 per 1000	**133 per 1000** (21 to 837)				
	Medium risk population					
	118 per 1000	**133 per 1000** (21 to 837)				
Number achieving complete or partial remission at 12 weeks urine protein excretion Follow-up: mean 12 weeks	**Study population**		**RR 3.4** (1.12 to 10.28)	32 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	176 per 1000	**598 per 1000** (197 to 1000)				
	Medium risk population					
	177 per 1000	**602 per 1000** (198 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Follow-up for only 12 weeks
[2] Small numbers of patients

Summary of findings 3. Tacrolimus versus cyclosporin for idiopathic steroid-resistant nephrotic syndrome in children

Tacrolimus versus cyclosporin for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary health services
Intervention: Tacrolimus
Comparison: Cyclosporin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cyclosporin	Tacrolimus				
Treatment response at 6 months - Complete remission Urinary protein excretion Follow-up: mean 12 months	**Study population**		**RR 0.86** (0.44 to 1.66)	41 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	500 per 1000	**430 per 1000** (220 to 830)				
	Medium risk population					
	500 per 1000	**430 per 1000** (220 to 830)				
Treatment response at 6 months - Complete and partial remission Urine protein excretion Follow-up: mean 12 months	**Study population**		**RR 1.07** (0.81 to 1.42)	41 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	800 per 1000	**856 per 1000** (648 to 1000)				
	Medium risk population					

	800 per 1000	**856 per 1000** (648 to 1000)				
Treatment response at 12 months - Complete remission Follow-up: mean 12 months	**Study population**		**RR 0.87** (0.48 to 1.58)	41 (1 study)	⊕⊕⊝⊝ **low**[2,3]	
	550 per 1000	**478 per 1000** (264 to 869)				
	Medium risk population					
	550 per 1000	**478 per 1000** (264 to 869)				
Treatment response at 12 months - Complete and partial remission Urinary protein excretion Follow-up: mean 12 months	**Study population**		**RR 1.14** (0.84 to 1.55)	41 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	750 per 1000	**855 per 1000** (630 to 1000)				
	Medium risk population					
	750 per 1000	**855 per 1000** (630 to 1000)				
Number with relapse following complete or partial remission Urine protein excretion Follow-up: mean 12 months	**Study population**		**RR 0.22** (0.06 to 0.9)	34 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	500 per 1000	**110 per 1000** (30 to 450)				
	Medium risk population					
	500 per 1000	**110 per 1000** (30 to 450)				
Change in estimated GFR over 12 months Follow-up: mean 12 months		The mean Change in estimated GFR over 12 months in the intervention groups was **0.7 lower** (16.71 lower to 15.31 higher)		35 (1 study)	⊕⊕⊝⊝ **low**[2,3]	
Adverse effects - Reversible nephrotoxicity Serum creatinine Follow-up: mean 12 months	See comment	See comment	Not estimable	41 (1 study)	⊕⊕⊝⊝ **low**[1,2,4]	Risks were calculated from pooled risk differences

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No blinding
[2] Small patient numbers
[3] No explanation was provided
[4] Small event rates

Summary of findings 4. Oral cyclophosphamide versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children

Oral cyclophosphamide versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary paediatric nephrology services
Intervention: Oral cyclophosphamide
Comparison: Prednisone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prednisone	Oral cyclophosphamide				
Number of patients with complete remission - All renal pathologies clinical assessment Follow-up: 3-102 months	**Study population**		**RR 1.06** (0.61 to 1.87)	84 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	
	353 per 1000	**374 per 1000** (215 to 660)				
	Medium risk population					
	374 per 1000	**396 per 1000** (228 to 699)				
Number of patients with complete remission - FSGS	**Study population**		**RR 1.01** (0.43 to 2.37)	63 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	

urine testing Follow-up: 3-102 months	**250 per 1000**	**252 per 1000** (108 to 592)				
	Medium risk population					
	143 per 1000	**144 per 1000** (61 to 339)				
Number of patients with complete or partial remission clinical assessment Follow-up: 3=102 months	See comment	See comment	Not estimable	53 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
Number of patients with complete or partial remission - FSGS urine testing Follow-up: 3-102 months	**Study population**		**RR 0.88** (0.53 to 1.45)	53 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
	571 per 1000	**502 per 1000** (303 to 828)				
	Medium risk population					
	571 per 1000	**502 per 1000** (303 to 828)				
Adverse events - All cause mortality	**Study population**		See comment	60 (1 study)	⊕⊝⊝⊝ **very low**[1,2,3]	Risks were calculated from pooled risk differences
	80 per 1000	**86 per 1000** (-60 to 230)				
	Medium risk population					
	80 per 1000	**86 per 1000** (-60 to 230)				
Adverse events - Bone marrow suppression clinical assessment Follow-up: 3-102 months	**Study population**		See comment	60 (1 study)	⊕⊝⊝⊝ **very low**[1,2,3]	Risks were calculated from pooled risk differences
	See comment	See comment				
	Medium risk population					
	0 per 1000	**-2147483648 per 1000** (0 to 0)				
Treatment failure	**Study population**		**RR 1.59**	60	⊕⊝⊝⊝	

clinical assessment Follow-up: 3-102 months	**360 per 1000**	**572 per 1000** (313 to 1000)	(0.87 to 2.88)	(1 study)	**very low**[1,2,3]
	Medium risk population				
	360 per 1000	**572 per 1000** (313 to 1000)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No blinding. Unclear timing of end points
[2] Small patient numbers
[3] Small number of events

Summary of findings 5. IV versus oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

IV versus oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary paediatric service
Intervention: Intravenous cyclophosphamide
Comparison: Oral cyclophosphamide

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Oral cyclophosphamide	**Intravenous cyclophosphamide**				
Number of patients with complete remission clinical assessment Follow-up: mean 12 months	**Study population**		**RR 3.12** (0.81 to 12.06)	11 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	
	250 per 1000	**780 per 1000** (203 to 1000)				

	Medium risk population					
	250 per 1000	**780 per 1000** (203 to 1000)				
Adverse effects - Bacterial infection clinical assessment Follow-up: mean 12 months	**Study population**		See comment	11 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	Risks were calculated from pooled risk differences
	250 per 1000	**0 per 1000** (-440 to 440)				
	Medium risk population					
	250 per 1000	**0 per 1000** (-440 to 440)				
Adverse effects - Vomiting clinical assessment Follow-up: mean 12 months	**Study population**		See comment	11 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	Risks were calculated from pooled risk differences
	0 per 1000	**-2147483648 per 1000** (0 to 0)				
	Medium risk population					
	0 per 1000	**-2147483648 per 1000** (0 to 0)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Large loss to follow-up
[2] Very small numbers included

Summary of findings 6. IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings:
Intervention: IV cyclophosphamide
Comparison: IV dexamethasone and oral cyclophosphamide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV dexamethasone and oral cyclophosphamide	IV cyclophosphamide				
Treatment response at 6 months - Complete remission clinical assessment Follow-up: 18 months	**Study population**		**RR 1.13** (0.65 to 1.96)	49 (1 study)	⊕⊕⊝⊝ **low**[1]	
	478 per 1000	**540 per 1000** (311 to 937)				
	Medium risk population					
	478 per 1000	**540 per 1000** (311 to 937)				
Treatment response at 6 months - Complete or partial remission Clinical assessment Follow-up: 18 months	**Study population**		**RR 1.09** (0.68 to 1.74)	49 (1 study)	⊕⊕⊝⊝ **low**[2]	
	565 per 1000	**616 per 1000** (384 to 983)				
	Medium risk population					
	565 per 1000	**616 per 1000** (384 to 983)				
Treatment response at 18 months - Sustained remission/steroid sensitive relapses Clinical assessment Follow-up: 18 months	**Study population**		**RR 1.27** (0.72 to 2.26)	52 (1 study)	⊕⊕⊝⊝ **low**[2]	
	423 per 1000	**537 per 1000** (305 to 956)				
	Medium risk population					
	423 per 1000	**537 per 1000** (305 to 956)				
Treatment response at 18 months - CKD	**Study population**		**RR 0.88** (0.06 to 13.35)	49 (1 study)	⊕⊕⊝⊝ **low**[1,2]	

clinical assessment Follow-up: 18 months	**43 per 1000**	**38 per 1000** (3 to 574)				
	Medium risk population					
	44 per 1000	**39 per 1000** (3 to 587)				
Complete or partial resistance in sub-groups - Initial SRNS clinical assessment Follow-up: 18 months	**Study population**		**RR 0.96** (0.46 to 2.01)	18 (1 study)	⊕⊕⊝⊝ **low**[2]	
	625 per 1000	**600 per 1000** (288 to 1000)				
	Medium risk population					
	625 per 1000	**600 per 1000** (288 to 1000)				
Complete or partial resistance in sub-groups - Late SRNS clinical assessment Follow-up: 18 months	**Study population**		**RR 1.17** (0.64 to 2.15)	31 (1 study)	⊕⊕⊝⊝ **low**[2]	
	533 per 1000	**624 per 1000** (341 to 1000)				
	Medium risk population					
	533 per 1000	**624 per 1000** (341 to 1000)				
Adverse events - Bacterial infections clinical assessment Follow-up: mean 18 months	**Study population**		See comment	49 (1 study)	⊕⊕⊝⊝ **low**[1,2]	Risks were calculated from pooled risk differences
	348 per 1000	**-42 per 1000** (-129 to 49)				
	Medium risk population					
	348 per 1000	**-42 per 1000** (-129 to 49)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small numbers of events
[2] Small numbers of patients

Summary of findings 7. Chlorambucil versus indomethacin for idiopathic steroid-resistant nephrotic syndrome in children

Chlorambucil versus indomethacin for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary paediatric service
Intervention: Chlorambucil
Comparison: Indomethacin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Indomethacin	Chlorambucil				
Number with complete remission clinical assessment Follow-up: mean 6 months	**Study population**		**RR 1** (0.42 to 2.4)	30 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	400 per 1000	**400 per 1000** (168 to 960)				
	Medium risk population					
	400 per 1000	**400 per 1000** (168 to 960)				
Number with end stage renal failure clinical assessment Follow-up: mean 6 months	**Study population**		**RR 0.2** (0.01 to 3.85)	30 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	133 per 1000	**27 per 1000** (1 to 512)				
	Medium risk population					
	133 per 1000	**27 per 1000** (1 to 512)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Insufficient patients entered study

Summary of findings 8. Azathioprine versus placebo for idiopathic steroid-resistant nephrotic syndrome in children

Azathioprine versus placebo for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary paediatric nephrology services
Intervention: Azathioprine
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Azathioprine				
Number of patients with complete remission - All renal pathologies clinical assessment Follow-up: 24 months	**Study population**		**RR 0.94** (0.15 to 5.84)	31 (1 study)	⊕⊕⊝⊝ **low**[1]	
	133 per 1000	**125 per 1000** (20 to 777)				
	Medium risk population					
	133 per 1000	**125 per 1000** (20 to 777)				
Number of patients with complete or partial remission - All renal pathologies clinical assessment Follow-up: 24 months	**Study population**		**RR 0.94** (0.28 to 3.09)	31 (1 study)	⊕⊕⊝⊝ **low**[1]	
	267 per 1000	**251 per 1000** (75 to 825)				

Medium risk population		
267 per 1000	**251 per 1000** (75 to 825)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small numbers of patients

Summary of findings 9. Fosinopril and prednisone versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children

Fosinopril and prednisone versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: patients with idiopathic steroid-resistant nephrotic syndrome in children
Settings: Tertiary paediatric service
Intervention: Fosinopril and prednisone
Comparison: Prednisone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prednisone	Fosinopril and prednisone				
Proteinuria - After 12 weeks of treatment Follow-up: mean 12 weeks		The mean Proteinuria - After 12 weeks of treatment in the intervention groups was **0.95 lower** (1.21 to 0.69 lower)		45 (1 study)	⊕⊕⊝⊝ **low**[1,2]	
Serum albumin (end study) Follow-up: mean 12 weeks		The mean Serum albumin (end study) in the intervention groups was **0 higher** (0 to 0 higher)		45 (1 study)	⊕⊕⊝⊝ **low**[1,2]	

Creatinine clearance (end study) Follow-up: mean 12 weeks		The mean Creatinine clearance (end study) in the intervention groups was **0 higher** (0 to 0 higher)	45 (1 study)	⊕⊕⊝⊝ **low**[1,2]
Serum potassium (end study) Follow-up: mean 12 weeks		The mean Serum potassium (end study) in the intervention groups was **0.2 higher** (0.34 lower to 0.74 higher)	45 (1 study)	⊕⊕⊝⊝ **low**[1,2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Short duration of follow-up
[2] Small numbers of patients in single study

BACKGROUND

Nephrotic syndrome is a condition in which the glomeruli of the kidney leak protein from the blood into the urine. It results in hypoproteinaemia and generalised oedema. In children, the incidence of nephrotic syndrome in Europe and North America is 2/100,000 children (Arneil 1961; Schlesinger 1968). The majority of children have minimal change disease (MCD), in which changes on light microscopy are minor or absent. The cause of minimal change nephrotic syndrome is unknown. Oral corticosteroids are the first-line treatment for a child presenting with idiopathic nephrotic syndrome. For children who present with their first episode of nephrotic syndrome, about 90% will achieve remission with corticosteroid therapy (Koskimies 1982). Of those who respond, about 95% will have responded after four weeks of daily corticosteroid therapy and 98% will have responded after eight weeks of corticosteroid therapy (ISKDC 1981a). Children with untreated nephrotic syndrome are at increased risk of bacterial infection, characteristically resulting in peritonitis, cellulitis or septicaemia, of thromboembolic phenomena and protein calorie malnutrition.

In children who fail to respond to corticosteroids, renal biopsy is carried out to determine renal pathology. The majority will have MCD, mesangioproliferative glomerulonephritis (MesPGN) or focal segmental glomerulosclerosis (FSGS). Children who fail to respond to corticosteroids may be treated with immunosuppressive agents such as cyclophosphamide, chlorambucil or cyclosporin. Observational studies have found that about one third of children go into remission with cyclosporin (Niaudet 1994). However, the relapse rate is high after tapering or discontinuing the drug. Other observational studies have reported remission rates of up to 60% with combinations of IV methylprednisolone and cyclophosphamide (Tune 1996). Other non-immunosuppressive agents including angiotensin-converting enzyme inhibitors (ACEi) and fish oil have also been used in steroid-resistant nephrotic syndrome (SRNS).

There is, however, considerable diversity in the use of these agents with differences in treatment modes, combinations and dosage regimens. Optimal combinations with least toxicity remain to be determined. The aims of this systematic review were to assess the benefits and harms of interventions used to treat idiopathic SRNS in children.

OBJECTIVES

To evaluate the benefits and harms of different interventions used in children with idiopathic nephrotic syndrome, who do not achieve remission following four weeks or more of daily corticosteroid therapy.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs, in which different agents are used in the treatment of children (aged three months to 18 years) with idiopathic SRNS were included.

Types of participants

Inclusion criteria

Children aged three months to 18 years with SRNS (i.e. persistence of proteinuria > 3+ on dipstick, urinary protein-creatinine ratio (PCR) > 0.2 g/mmol or > 40 mg/m^2/h after four weeks or more of daily corticosteroid agent). Where a renal biopsy was performed, only children with biopsy diagnoses of MCD, MesPGN or FSGS were included.

Exclusion criteria

Children with steroid-sensitive nephrotic syndrome, children with congenital nephrotic syndrome and children with other renal or systemic forms of nephrotic syndrome defined on renal biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schönlein nephritis, systemic lupus erythematosus, membranous glomerulopathy or mesangiocapillary glomerulonephritis) were excluded.

Types of interventions

All interventions were potentially eligible. Interventions considered:

1. IV corticosteroid agent versus oral corticosteroid agent, placebo or no intervention.
2. Different doses and/or durations of IV corticosteroid agent.
3. Non-corticosteroid immunosuppressive agent (with or without concomitant use of corticosteroid agent) versus corticosteroid agent alone.
4. Two different non-corticosteroid agents (with or without concomitant use of corticosteroid agent).
5. Different doses, durations and routes of administration of the same non-corticosteroid agent (with or without concomitant use of corticosteroid agent).
6. Other non-immunosuppressive agents such as ACEi or fish oil used with or without corticosteroid or non-corticosteroid immunosuppressive agents.

Types of outcome measures

Primary outcomes

- Number in complete remission during and following therapy (i.e. the child became oedema free and his/her urine protein was < 1+ on dipstick, urinary PCR < 0.02 g/mmol or < 4 mg/m^2/h for three or more consecutive days).
- Number in partial remission with reduction in proteinuria (i.e. proteinuria < 2+ , urinary PCR < 0.2 g/mmol or < 40 mg/m^2/h) and an increase in serum albumin levels.
- Number reaching end-stage kidney disease (ESKD)

Secondary outcomes

- Changes in kidney function (serum creatinine (SCr); creatinine clearance (CrCl)
- Adverse effects of therapy
- Duration of remission or partial remission
- Reduction in proteinuria

Search methods for identification of studies

Initial search

Relevant studies were obtained from the following sources (Appendix 1).

1. Cochrane Renal Group's specialised register
2. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 2, 2002)
3. MEDLINE (1966 to April 2002) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy for nephrotic syndrome in children developed with the Cochrane Renal Group Trial Search Coordinators.
4. EMBASE (1980 to April 2002) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy for nephrotic syndrome in children developed with the Cochrane Renal Group Trial Search Coordinators.
5. Reference lists of nephrology textbooks, review articles and relevant studies.
6. Reference lists of abstracts from nephrology scientific meetings.
7. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Updated review

For this update the Cochrane Renal Group's specialised register and CENTRAL (in *The Cochrane Library*) were searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (http://www.cochrane.us/masterlist.asp). Please refer to The Cochrane Renal Review Group's Module (Renal Group 2010) for the complete list of nephrology conference proceedings searched.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. Disagreements were resolved in consultation with a third author.

Data extraction and management

Data extraction was carried out by the same authors independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and only the publication with the most complete data was used in the analyses. Disagreements were resolved in consultation with JC.

Assessment of risk of bias in included studies

Studies to be included were assessed independently by two authors without blinding to authorship or journal. Discrepancies were resolved by discussion with a third author.

The following items were assessed using the risk of bias assessment tool (Higgins 2008) (*see* Appendix 2).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. remission or no remission) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. protein excretion), the mean difference (MD) was to be used, or the standardised MD (SMD) if different scales were to be used.

Adverse events were tabulated and assessed with descriptive techniques if they could not be included in meta-analyses.

Dealing with missing data

Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 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 (Higgins 2003).

Data synthesis

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.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore possible sources of heterogeneity (e.g. participants, treatments and study quality). Heterogeneity among participants could be related to age and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy.

RESULTS

Description of studies

Initially, of the 1744 titles and abstracts screened, 10 RCTs involving children with SRNS were identified. There was no disagreement between the authors over study inclusion. One study was excluded because 31/36 children had nephrotic syndrome considered

secondary to *Plasmodium malariae* (Adeniyi 1979) so nine RCTs were included in the review. Three studies were crossover studies (Bagga 2004; Chongviriyaphan 1999; Garin 1988) and data from the first part of the studies were included. One study available in abstract form only for the initial review has now been published in full (Bagga 2004). A further literature search in June 2005 identified four additional studies (Kano 2005; Kleinknecht 1979; Shibasaki 2004; Yi 2006) of which two were subsequently excluded: one because paediatric data could not be separated from adult data (Shibasaki 2004) and one because it involved patients who had moderate proteinuria but not nephrotic syndrome (Kano 2005). The two additional included studies were available in abstract form only. Eleven studies were included in the updated review; 312 children were entered in the studies but data on the primary outcome were evaluated in only 280 children. A further search of the Cochrane Renal Group's specialised register in April 2009 identified three additional studies (APN 2008; Choudhry 2009; Mantan 2008) and the full publication of one study previously available as an abstract (Yi 2006). Therefore 14 studies were included in the 2010 update; 494 children entered the studies and 449 were evaluated.

Study characteristics are shown in the Characteristics of included studies. Three studies (one crossover) compared cyclosporin with placebo or no treatment (49 children) (Garin 1988; Lieberman 1996; Ponticelli 1993a). Two studies (Garin 1988; Ponticelli 1993a) included children with MCD and FSGS while the third study (Lieberman 1996) included only children with FSGS. None of these studies specified whether children were initial or late non-responders to steroids. Children with previous treatment with cyclosporin or alkylating agents in the previous three months (Lieberman 1996) or 12 months (Ponticelli 1993b) were excluded; this information was not reported in the third study (Garin 1988). Two studies compared oral cyclophosphamide and prednisone with prednisone alone (91 children) (ISKDC 1974; ISKDC 1996). One study (ISKDC 1974) included children with MCD, FSGS and MesPGN. The other study (ISKDC 1996) included only children with FSGS. Only children with initial non-response to steroids were included in these studies and none had received prior treatment with cytotoxic or immunosuppressive agents. One study of children with MCD, who failed to respond to the initial course of prednisone, compared IV with oral cyclophosphamide (11 children) (Elhence 1994); pre-study treatment other than with steroids was not reported. One study compared azathioprine (AZA) and prednisone with placebo and prednisone (31 children) (ISKDC 1970). All were initial non-responders to steroids and had received no other therapies. The study included children with MCD (5), FSGS (10), MesPGN (15) and unknown pathology (3). Crossover studies compared different doses of the ACEi, enalapril, (25 children; 15 initial non-responders and 10 late non-responders) (Bagga 2004) and fish oil with placebo (5 children) (Chongviriyaphan 1999). One study compared the ACEi, fosinopril, and prednisone with prednisone alone (Yi 2006); 48 children were initial non-responders to prednisone and 7 were late non-responders. One study compared chlorambucil with indomethacin (Kleinknecht 1979). This study did not report whether patients were initial or late non-responders to steroids.

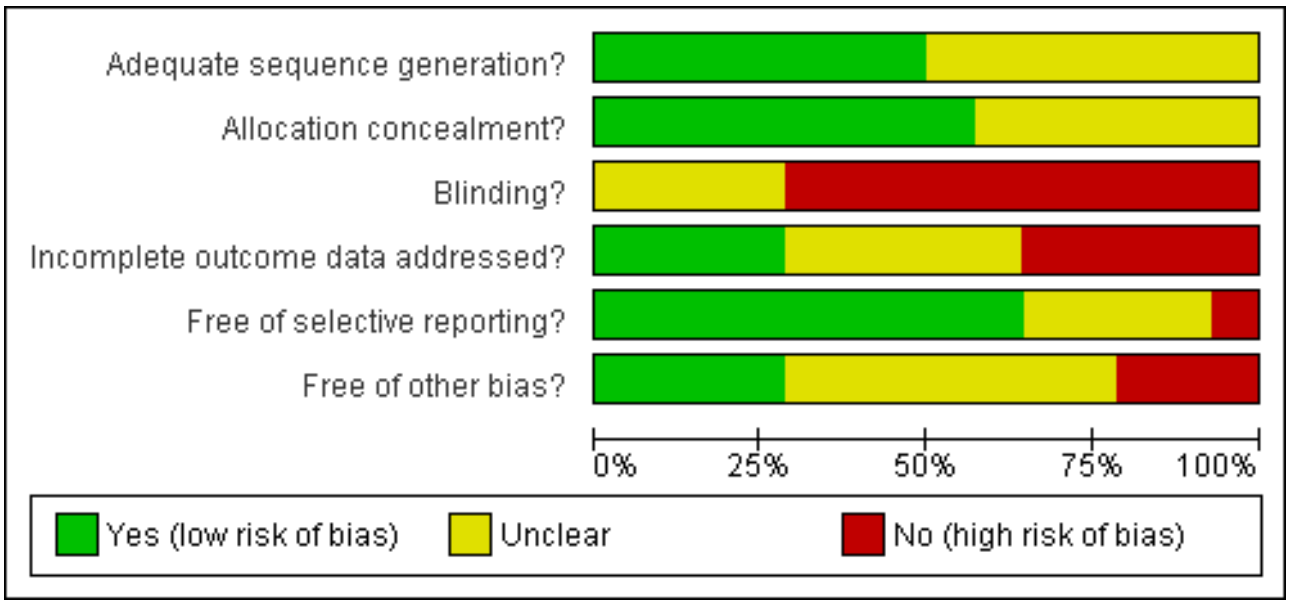
The additional studies in the 2010 update compared oral cyclosporin with IV cyclophosphamide (APN 2008; 32 patients), oral cyclosporin with oral tacrolimus (Choudhry 2009; 41 children) and IV cyclophosphamide with oral cyclophosphamide and IV dexamethasone (Mantan 2008; 52 children). The three studies included children with MCD, FSGS and MesPGN. One study (APN 2008) included only children with initial non-response to prednisone while the other two included both initial and late non-responders (Choudhry 2009; Mantan 2008).

No studies comparing high dose steroids with cyclosporin with other treatment regimens, placebo or no treatment were found.

Risk of bias in included studies

Figure 1

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



The definition of steroid resistance varied between studies. Six studies defined steroid resistance as persistent proteinuria of > 4 mg/m²/h after four weeks (Lieberman 1996), five weeks (Kleinknecht 1979), six weeks (APN 2008) or eight weeks of prednisone (Bagga 2004; ISKDC 1970; ISKDC 1974). Three studies defined steroid resistance as persistent proteinuria > 40 mg/m²/h after five (Ponticelli 1993a) or eight weeks of prednisone (Garin 1988; ISKDC 1996). Two studies defined persistent proteinuria as above 2g/g (Choudhry 2009) or above 1 g/m²/d (Mantan 2008) after four weeks of daily prednisone. One study defined steroid resistance as no response after eight weeks of prednisone (Yi 2006) but did not define the degree of proteinuria. Two studies did not define steroid resistance (Chongviriyaphan 1999; Elhence 1994).

Allocation

Sequence generation was satisfactory in eight studies (APN 2008, Bagga 2004; Choudhry 2009; ISKDC 1970; Lieberman 1996; Mantan 2008; Ponticelli 1993a; Yi 2006) and unclear in the remaining six studies.

Allocation concealment was adequate in eight studies (APN 2008; Bagga 2004; Choudhry 2009; ISKDC 1970; Lieberman 1996; Mantan 2008; Ponticelli 1993a) and unclear in the remaining six studies.

Blinding

No study reported blinding of participants, investigators, outcome assessors or data assessors. Blinding was unclear (usually reported as "blinded" without detail of which groups were blinded) in four studies (Chongviriyaphan 1999; Choudhry 2009; ISKDC 1970; Lieberman 1996). In the remaining 10 studies there was no blinding.

Incomplete outcome data

Four studies were considered to have provided complete outcome data (Choudhry 2009; Garin 1988; ISKDC 1970; Mantan 2008) while five studies did not provide complete outcome data (APN 2008; Elhence 1994; Lieberman 1996; Ponticelli 1993a; Yi 2006). In the remaining five studies it was unclear whether complete outcome data was provided.

Selective reporting

Nine studies were considered to be free of selective reporting (APN 2008; Bagga 2004; Chongviriyaphan 1999; Choudhry 2009; Elhence 1994; ISKDC 1996; Lieberman 1996; Mantan 2008; Yi 2006). One study was considered to have reported outcomes selectively (Ponticelli 1993a) as results for adverse events in children and adults were not reported separately unlike efficacy outcomes. In the remaining four studies it was unclear whether there was selective reporting.

Other potential sources of bias

Four studies reported funding by university or government agencies and were considered free of other potential sources of bias (Chongviriyaphan 1999; ISKDC 1974; ISKDC 1996; Yi 2006). Three studies reported funding from pharmaceutical companies and were considered at risk of potential bias (APN 2008; ISKDC 1970; Ponticelli 1993a). Other potential sources of bias were unclear in the remaining seven studies as none reported on support.

These items have been summarised in Table 1.

Effects of interventions

See: **Summary of findings for the main comparison** Cyclosporin versus placebo/no treatment for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 2** Cyclosporin versus IV cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 3** Tacrolimus versus cyclosporin for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 4** Oral cyclophosphamide versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 5** IV versus oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 6** IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 7** Chlorambucil versus indomethacin for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 8** Azathioprine versus placebo for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 9** Fosinopril and prednisone versus prednisone for idiopathic steroid-resistant nephrotic syndrome in children

Cyclosporin versus placebo/no specific treatment

Remission

Cyclosporin significantly increased the number of children with SRNS who achieved complete remission compared with placebo or no treatment, irrespective of renal pathology (Analysis 1.1.1 (3 studies, 49 patients): RR 7.66, 95% CI 1.06 to 55.34). The number who achieved complete or partial remission also was significantly increased with cyclosporin (Analysis 1.2.1 (3 studies, 49 patients): RR 5.48, 95% CI 1.95 to 15.44). While included in the meta-analysis, no child in either group achieved complete or partial remission in Garin 1988 so did not contribute any events to the combined summary estimates. When treatment with cyclosporin was compared with placebo/no treatment In the subgroup of children with FSGS, the summary estimate (Analysis 1.1.2 (2 studies, 33 patients): RR 5.83, 95% CI 0.75 to 45.09) was similar to that for the analysis for all renal pathologies (Analysis 1.1.1). Although the 95% CI crossed 1, a significant benefit of cyclosporin on complete remission in FSGS cannot be excluded because of the imprecision resulting from small patient numbers. In addition children treated with cyclosporin achieved complete or partial remission (Analysis 1.2.2 (1 study, 24 patients): RR 5.00, 95% CI 1.63 to 15.31) significantly more frequently than children treated with placebo or no treatment (Lieberman 1996; Ponticelli 1993a). Relapse was reported in 2/6 children, who achieved partial or complete remission, by the end of 12 months of cyclosporin treatment (Ponticelli 1993a). Subgroup analysis, other than for renal pathology, was not possible because of small patient numbers.

Adverse events

There was no significant difference in the number of children with worsening hypertension (Analysis 1.3.1 (1 study, 24 patients): RD 0.00, 95% CI -0.30 to 0.30) or in the number of children with bacterial infections (Analysis 1.3.2 (1 study, 17 patients): RD -0.13, 95% CI -0.59 to 0.34). The study including children and adults did not report adverse events (except bacterial infections) separately in children and adults (Ponticelli 1993a). In the crossover study, no child was reported to develop hypertension in either the cyclosporin or

control group while one child developed renal dysfunction while receiving cyclosporin and two developed renal dysfunction while in the control group (Garin 1988).

Cyclophosphamide versus prednisone/placebo

Remission

There was no significant difference in the overall number of children (Analysis 2.1.1 (2 studies, 84 children): RR 1.06, 95% CI 0.61 to 1.87) or in those with FSGS (Analysis 2.1.2 (2 studies, 63 children): RR 1.01, 95% CI 0.43 to 2.37) who achieved complete remission after treatment with oral cyclophosphamide and prednisone compared with prednisone alone. The number of children who achieved complete or partial remission did not differ significantly between treatment groups (Analysis 2.2 (1 study, 53 children): RR 0.88, 95% CI 0.53 to 1.45). Subgroup analysis, other than for renal pathology, was not possible because of small patient numbers.

Treatment failure (increase in creatinine by ≥ 30%, creatinine > 4 mg/dL, dialysis or transplant) occurred in 36% (9/25) of the control group and 57% (20/35) of the treatment group (Analysis 2.3 (1 study, 60 patients); RR 1.59, 95% CI 0.87 to 2.88).

Adverse events

The number of children who had hypertension with seizures, cystitis or bone marrow suppression did not differ between the treatment groups (Analysis 2.4).Three children treated with cyclophosphamide and two with prednisone died (ISKDC 1996) (Analysis 2.4.1 (1 study, 60 patients): RD 0.01, 95% CI -0.14 to 0.15). Deaths were related to sepsis, cardiorespiratory arrest and unknown factors. Adverse events in the second study were not reported separately for steroid-sensitive and steroid-resistant patients (ISKDC 1974).

IV versus oral cyclophosphamide

Remission

Although all seven children with MCD who received IV cyclophosphamide achieved complete remission compared with 1/4 children given oral cyclophosphamide, no significant difference was demonstrated because of the small numbers of children studied (Analysis 3.1.1 (1 study, 11 children): RR 3.13, 95% CI 0.81 to 12.06) (Elhence 1994). Two children treated with IV cyclophosphamide subsequently relapsed at 12 months.

Adverse events

Vomiting was significantly more common in children treated with IV cyclophosphamide (Analysis 3.2.1 (1 study, 11 patients): RD 0.57, 95% CI 0.14 to 1.00) but the numbers with bacterial infections (Analysis 3.2.2 (1 study, 11 patients): RD -0.25, 95% CI -0.69 to 0.19) did not differ between treatment groups.

Azathioprine versus placebo

There was no significant difference in the number of children who achieved complete remission (Analysis 4.1.1 (1 study, 31 children): RR 0.94, 95% CI 0.15 to 5.84) or complete or partial remission (Analysis 4.2.1 (1 study, 31 patients): RR 0.94, 95% CI 0.28 to 3.09) after treatment with azathioprine and prednisone compared with placebo and prednisone.

Adverse events of azathioprine were not reported.

Chlorambucil versus indomethacin

There was no significant difference between chlorambucil and indomethacin in the number who achieved complete remission (Analysis 5.1 (1 study; 30 children): RR 1.00, 95% CI 0.42 to 2.40) and in the number reaching ESKD (Analysis 5.2 (1 study, 30 patients): RR 0.20, 95% CI 0.01 to 3.85) (Kleinknecht 1979).

Adverse events of chlorambucil or indomethacin were not reported.

Enalapril (high versus low dose)

Bagga 2004 reported that low dose enalapril (0.2 mg/kg/d) reduced median urinary albumin/creatinine ratio from 3.9 (5th to 95th percentiles 1.9 to 11.6) to 2.3 (5th to 95th percentiles 0.8 to 5.2) but the difference was not significant. High dose enalapril (0.6 mg/kg/d) reduced median urinary albumin/creatinine ratio significantly from 5.2 (5th to 95th percentiles 2.1 to 10.5) to 2.5 (5th to 95th percentiles 0.8 to 3.3). In addition, the urinary albumin/creatinine reduction between the beginning and end of treatment was significantly lower with low dose enalapril (median 34.8, 95% CI -7.9 to 76.6) compared with high dose enalapril (median 62.9, 95% CI 40.6 to 71.6). These results were not able to be meta-analysed.

SCr and potassium levels were unchanged by enalapril. Three children ceased enalapril because of a dry cough.

Fosinopril and prednisone versus prednisone alone

In a single study of 45 children, fosinopril and prednisone (Yi 2006) significantly reduced the 24 hour urinary protein excretion at four weeks (Analysis 6.1.1 (1 study, 45 patients): MD -1.27 g/d, 95% CI -1.62 to -0.92), eight weeks (Analysis 6.1.2 (1 study, 45 patients): MD -1.26 g/d, 95% CI -1.47 to -1.05) and 12 weeks of treatment (Analysis 6.1.3 (1 study, 45 patients): MD -0.95 g/d, 95% CI -1.21 to -0.69) compared with prednisone alone. In addition, there were significant reductions in the tubular proteins, retinol binding protein (Analysis 6.2.1 (1 study, 45 patients): MD -0.21 mg/L, 95% CI -0.33 to -0.09) and beta-2 microglobulin (Analysis 6.2.2 (1 study, 45 patients): MD -0.17 mg/L, 95% CI -0.27 to -0.07). Serum albumin at study end did not differ significantly between study groups (Analysis 6.3 (1 study, 45 patients): MD 1.20 g/L, 95% CI -6.58 to 8.98).

No changes were reported in systolic blood pressure (Analysis 6.4 (1 study, 45 patients): MD -0.87 mm Hg, 95% CI -3.33 to 1.59), CrCl (Analysis 6.5 (1 study, 45 patients): MD -5.28 mL/min, 95% CI -9.66 to -0.90) or serum potassium (Analysis 6.6 (1 study, 45 patients): MD 0.20 mmol/L, 95% CI -0.34 to 0.74).

Tuna fish oil versus placebo

In one small crossover study involving five children, there was no significant change in the degree of proteinuria or in CrCl after fish oil compared with placebo (Chongviriyaphan 1999). The results from each part of the crossover study were combined so that the RR and 95% CI could not be calculated.

Adverse events were not reported.

Cyclosporin versus IV cyclophosphamide

Remission

In a single study of 32 children (APN 2008) with initial steroid unresponsive nephrotic syndrome (initial SRNS), cyclosporin significantly increased the number of children who achieved complete or partial remission at 12 weeks compared with IV cyclophosphamide (Analysis 7.1 (1 study, 32 patients): RR 3.40, 95% CI 1.12 to 10.28) but there was no significant difference between treatment groups in the number who achieved complete remission at 12 weeks (Analysis 7.2 (1 study, 32 patients): RR 2.27, 95% CI 0.23 to 22.56). Because patients without response to treatment at 12 weeks could be treated with a non-responder protocol, it was not possible to analyse results at a later time period.

Adverse events

In this study, 76 adverse events were reported during the initial treatment with cyclosporin (number/month/patient 1.22 ± 1.08 SD) and 66 adverse events were reported during initial treatment with IV cyclophosphamide (number/month/patient 1.61 ± 1.04 SD). In both arms the most frequent adverse events were Infection, hypertension and Cushing syndrome. As expected hirsutism and gum hypertrophy occurred almost exclusively with cyclosporin treatment.

Tacrolimus versus cyclosporin

Remission

After six months of treatment in a single study of 41 children (Choudhry 2009) with either initial SRNS or late steroid unresponsive nephrotic syndrome (late SRNS), there was no significant differences between tacrolimus and cyclosporin treatment in the numbers of children who achieved complete remission (Analysis 8.1.1 (1 study, 41 patients): RR 0.86, 95% CI 0.44 to 1.66), achieved partial remission (Analysis 8.1.2 (1 study, 41 patients): RR 1.43, 95% CI 0.62 to 3.28) or achieved complete or partial remission (Analysis 8.1.3 (1 study, 41 patients): RR 1.07, 95% CI 0.81 to 1.42). Similarly there were no significant differences in these outcomes at 12 months (Analysis 8.2). Significantly fewer children relapsed following treatment with tacrolimus compared with cyclosporin (Analysis 8.3 (1 study, 34 patients): RR 0.22, 95% CI 0.06 to 0.90). In a post hoc analysis, there were no significant differences between tacrolimus and cyclosporin therapy in the numbers of children with initial non-response and late non-response to steroids, who achieved complete remission or complete or partial remission (Analysis 8.4).

Adverse events

There was no significant difference between medications in change in GFR during treatment. With both treatments GFR fell by approximately 12 mL/min/1.73 m^2 during one year. Hypertrichosis (Analysis 8.7.6 (1 study, 41 patients): RD -0.95, 95% CI -1.08 to -0.82) and gingival hypertrophy (Analysis 8.7.7 (1 study, 41 patients): RD -0.55, 95% CI -0.79 to -0.32) were significantly less common with tacrolimus compared with cyclosporin while diarrhoea was significantly more common with tacrolimus compared with cyclosporin (Analysis 8.7.9 (1 study, 41 patients): RD 0.24, 95% CI 0.02 to 0.45). Other reported adverse events (Analysis 8.7) including persistent and reversibility nephrotoxicity and worsening of hypertension did not differ significantly between treatments. No children with new onset hypertension were reported.

IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide

Remission

In a single study of children (Mantan 2008) with initial or late SRNS, there were no significant differences in the number of children who achieved complete remission (Analysis 9.1.1 (1 study, 49 patients): RR 1.13, 95% CI 0.65 to 1.96), partial remission (Analysis 9.1.2 (1 study, 49 patients): RR 0.88, 95% CI 0.14 to 5.79) or complete or partial remission (Analysis 9.1.3 (1 study, 49 patients): RR 1.09, 95% CI 0.68 to 1.74) after six months of treatment. Similarly there were no significant differences in the number of children, who had sustained remission or steroid sensitive relapses after 18 months of follow-up (Analysis 9.2.1 (1 study, 49 patients): RR 1.13, 95% CI 0.65 to 1.96). Chronic kidney disease (CKD) developed in one patient in each treatment group during 18 months of follow-up (Analysis 9.2.2 (1 study, 49 patients): RR 0.88, 95% CI 0.06 to 13.35). Study entry was stratified for children with initial SRNS and for those with late SRNS but not for renal pathology. There was no significant difference between treatments in the numbers who achieved complete or partial remission among children with initial SRNS (Analysis 9.3.1 (1 study, 18 patients): RR 0.96, 95% CI 0.46 to 2.01) or late SRNS (Analysis 9.3.2 (1 study, 31 patients): RR 1.17, 95% CI 0.64 to 2.15) though CI were wide due to small patient numbers. Similarly there was no significant differences between treatments in the numbers, who achieved complete or partial remission, among children with MCD (Analysis 9.3.3 (1 study, 24 patients): RR 1.09, 95% CI 0.61 to 1.93) or among children with FSGS or MesPGN (Analysis 9.3.4 (1 study, 25 patients): RR 1.08, 95% CI 0.51 to 2.30).

Adverse events

Hypertension (Analysis 9.4.1 (1 study, 49 patients): RD -0.43, 95% CI -0.64 to -0.23) and hypokalaemia (Analysis 9.4.7 (1 study, 49 patients): RD -0.30, 95% CI -0.50 to -0.11) were significantly less common while hair loss (Analysis 9.4.9 (1 study, 49 patients): RD 0.18, 95% CI -0.02 to 0.39) was slightly but not significantly more common in children treated with IV cyclophosphamide. The other reported adverse events (cataracts/ glaucoma, leucopenia, cushingoid features, cystitis, bacterial infections, steroid encephalopathy) were not significantly different between treatment groups (Analysis 9.4).

DISCUSSION

Summary of main results

In this 2010 update, this systematic review now includes 14 studies involving 449 evaluable patients. These studies examined nine therapeutic regimens for SRNS.

Five studies examined the efficacy of calcineurin inhibitors. A meta-analysis of three small studies (Garin 1988; Lieberman 1996; Ponticelli 1993a) showed that cyclosporin increased the number of children with SRNS, who achieved complete remission or complete and partial remission. Although In children with FSGS, a significant difference in the number achieving complete remission with cyclosporin was not identified in a meta-analysis of two studies, the number achieving complete or partial remission following cyclosporin was significantly higher than placebo in one study. These data support previously published data from a large case series of 65 children with initial non-response to steroids in which 46% of children with MCD (21/45) and 30%

with FSGS (6/20) achieved complete remission with cyclosporin (Niaudet 1994). There were no data presented in these studies on the effect of cyclosporin on long term renal function. Since the studies did not specify whether initial and late non-responders were included in the studies, no information can be provided on whether cyclosporin achieves different responses in these patient groups. The quality of the evidence was considered to be low because of small numbers (Summary of findings for the main comparison).

Children treated with oral cyclosporin were significantly more likely to achieve partial remission compared with IV cyclophosphamide though there was no significant difference in the numbers achieving complete remission in a study of only 32 children (APN 2008). However results were only interpretable to 12 weeks as children without response at 12 weeks were entered into a non-responder protocol thus breaking the randomisation. The quality of the evidence was considered to be low because of small patient numbers, a single study and the short follow-up period (Summary of findings 2). Further larger studies with longer follow-up are required to investigate this possible difference in efficacy. No significant differences in efficacy were demonstrated between tacrolimus and cyclosporin with 86% of patients in the tacrolimus group and 80% in the cyclosporin group achieving complete or partial remission (Choudhry 2009). Among those who relapsed, subsequent response to corticosteroids was significantly more common in tacrolimus treated patients. The quality of the evidence was considered low because of small patient numbers in a single study (Summary of findings 3).

Five studies investigated the efficacy of oral or IV alkylating agents. No statistically significant differences in remission rates or prevention of renal functional deterioration were demonstrated with oral cyclophosphamide compared with prednisone alone (ISKDC 1974; ISKDC 1996). However a beneficial effect of cyclophosphamide cannot be completely excluded because of residual imprecision due to inadequate patient numbers resulting in wide confidence intervals. Time to response was shorter in the cyclophosphamide treated group (mean 38.4 days) compared with the prednisone treated group (mean 95.5 days) in ISKDC 1996. The quality of the evidence for the outcome of complete remission was considered low due to low patient numbers and limitations in study design (Summary of findings 4). Elhence 1994 compared IV cyclophosphamide with oral cyclophosphamide and Mantan 2008 compared IV cyclophosphamide with oral cyclophosphamide and IV pulse dexamethasone. In Elhence 1994, patient numbers were too small to exclude the possibility that the apparent beneficial effect of IV cyclophosphamide was due to chance so the quality of the evidence was considered very low (Summary of findings 5). Mantan 2008 found no significant differences in efficacy between treatment groups and no difference in treatment response between children with initial or late non-response to corticosteroids. The quality of the evidence was considered to be low because of small patient numbers (Summary of findings 6). The final study found no significant differences between chlorambucil and indomethacin in the number who achieved remission or developed ESKD (Kleinknecht 1979). Because of low patient numbers the quality of the study was considered to be very low (Summary of findings 7).

The single studies of azathioprine (ISKDC 1970) and tuna fish oil (Chongviriyaphan 1999) showed no evidence of benefit. For the azathioprine study, the quality of the evidence was considered to be low because of small patient numbers in a single study (Summary of findings 8).

Two studies (Bagga 2004; Yi 2006) found that the ACEi, enalapril and fosinopril reduced proteinuria significantly in children with SRNS. However the studies were too short to provide data on whether ACE inhibition provides long term reduction in proteinuria and protects against deterioration in renal function. The quality of the evidence in the fosinopril studies was considered to be low because of small patient numbers and short follow-up in a single study (Summary of findings 9).

Overall completeness and applicability of evidence

Currently cyclosporin and cyclophosphamide are commonly used to treat SRNS. Information from RCTs about these treatments for SRNS in children is limited. Only 10 small studies were identified examining these interventions. Only one study has compared cyclophosphamide and cyclosporin with cyclosporin appearing to be more effective. However results could only be assessed at 12 weeks because children, who failed to respond, entered non-responder protocols at that stage.

Cyclosporin is known to be effective in children with steroid-sensitive nephrotic syndrome (Ponticelli 1993b). Some study participants may have responded to steroids had they been treated with prednisone for longer than the four to five weeks used to define steroid resistance (Lieberman 1996; Ponticelli 1993a). Though the majority of children who eventually respond to prednisone therapy do so within eight weeks regardless of underlying pathology (ISKDC 1981a), additional children may enter remission after longer periods of treatment (Cattran 1998; ISKDC 1981b). It has been suggested that patients should receive up to six months of prednisone before determining that the patient has SRNS (Burgess 1999; Cattran 1998). Also no study was identified which compared cyclosporin and prednisone with prednisone alone so it remains uncertain whether cyclosporin is more effective than prednisone. Therefore there remains doubt about the efficacy of cyclosporin in children with SRNS. Ideally a further adequately powered and well designed RCT is required to confirm the efficacy of cyclosporin compared with prednisone using renal function and complete remission as endpoints. However paediatric nephrologists are unlikely to be willing to consider further RCTs comparing cyclosporin with prednisone and are likely only to consider studies comparing two therapies thought to be potentially effective.

We hypothesised that the different pathologies in SRNS would influence the response to immunosuppressive agents and that children with MCD would be more likely to respond to treatment than children with FSGS as suggested by some non-randomised studies (Niaudet 1994; Ehrich 2007) though others have identified little difference (Chua 2009). However no difference in efficacy in children with MCD or FSGS could be demonstrated for cyclosporin or cyclophosphamide from the data available from these small studies.

No RCTs were identified which examined the benefits or harms of high dose steroids with alkylating agents or cyclosporin with prednisone alone compared with placebo, prednisone or no specific therapy although these regimens are now widely used in children with SRNS. Uncontrolled studies of regimens of alkylating agents and high dose steroids have reported complete remission in

32% to 65% of children (Hari 2001; Tune 1995; Tune 1996) though adverse events of these regimens are significant. A retrospective analysis of children with non-genetic FSGS found that the cumulative proportion of children achieving complete remission after treatment with IV methylprednisolone, oral cyclosporin and oral prednisone was 84% and significantly higher than the 64% of children, who achieved complete remission with oral cyclosporin and oral prednisone alone (Ehrich 2007).

Most studies have not taken into account the recently available information that a proportion of patients with FSGS have mutations in the podocin gene and are unlikely to respond to therapy (Ehrich 2007). Two studies included information about genetic studies (APN 2008; Choudhry 2009). This may explain some of the variation in response to therapy between studies. In addition many studies have included children with initial non-responsiveness to steroids and children with late non-responsiveness. An observational study (Ehrich 2007) and post hoc analysis in one RCT (Choudhry 2009) suggests that the response to cyclosporin but not tacrolimus is better in children with late non-responsiveness.

The incidence of reported adverse events during treatment was low but could be underestimated because of small patient numbers, short follow-up periods and incomplete reporting. None of the three studies comparing cyclosporin with placebo/no treatment reported on nephrotoxicity though nephrotoxicity occurs in 9% of treated children (Niaudet 1992; Niaudet 1994; Ponticelli 1993b). The numbers with persistent or reversible nephrotoxicity did not differ between cyclosporin and tacrolimus. Similar number of children developed or suffered worsening of hypertension during treatments with cyclosporin or IV cyclophosphamide and with cyclosporin or tacrolimus. Episode of Infection were common with alkylating agents and cyclosporin. A review of cyclophosphamide treatment in 866 children with frequently relapsing nephrotic syndrome, who received 902 courses of cyclophosphamide, found that leucopenia, severe bacterial infections and death occurred in 32%, 1.5% and 0.8% of patients respectively (Latta 2001).

No subgroup analyses could be undertaken because of the paucity of data. Also funnel plots (Egger 1997) could not be used because of the limited number of studies for each intervention.

Quality of the evidence

Studies included in this systematic review were small, often of poor quality and addressed several different therapeutic regimens, which limited the opportunities for meta-analysis. The quality of data for each outcome for each therapeutic regimen was considered to be low or very low because of small patient numbers often in single studies. Study quality can affect study results (Schulz 1995) and combining poor quality studies in meta-analyses can provide erroneous information on the benefits of therapy (Moher 1998). Of 59 randomised patients included in the meta-analysis comparing cyclosporin with placebo/no treatment, 10 were excluded from the analysis after randomisation. Studies without an intention-to-treat analysis can exaggerate the efficacy of the experimental treatment (Hollis 1999). All 14 studies were small with 494 children enrolled and 449 evaluated. The largest study enrolled only 60 children and most studies enrolled 20 or fewer children in each group. Other than the three studies examining cyclosporin compared with placebo/no treatment and the two studies comparing cyclophosphamide with no treatment, each study of immunosuppressive agents examined a different therapeutic regimen. The two studies examining ACEi could not be combined in meta-analyses.

Potential biases in the review process

This review identified 14 studies of which one was available only as an abstract. Additional information was provided by the authors from two studies. The literature search is likely to identify all relevant published studies. However 40% of study reports in the Cochrane Renal Group's trials register have been identified by handsearching of conference proceedings so it remains possible that further studies of therapy for SRNS will be identified as conference proceedings from different congresses are searched.

Agreements and disagreements with other studies or reviews

The treatment of SRNS in children has been comprehensively reviewed recently by Chua 2009 and Colquitt 2007. Colquitt 2007 included nine RCTs (all included in this review), one controlled clinical trial (comparing 6 months with 18 months of IV methylprednisolone) and one prospective cohort study comparing IV methylprednisolone with IV dexamethasone. They concluded that while the available evidence suggested a beneficial effect of cyclosporin on remission rates and of cyclophosphamide on time to remission, the strength of the conclusions was limited by the poor quality of included studies. Chua 2009 assessed observational studies, which evaluated complete or partial remission in 494 children treated with cyclosporin or tacrolimus, 192 treated with oral alkylating agents, 71 treated with IV cyclophosphamide and 204 treated with IV pulse corticosteroid with cyclophosphamide or cyclosporin. Overall these observational studies indicated that one third to a half of patients with SRNS achieve complete remission with cyclosporin, cyclophosphamide and/or IV methylprednisolone. RCTs indicate that patients treated with cyclosporin are significantly more likely to achieve complete or partial remission when compared with placebo or no specific therapy or with IV cyclophosphamide.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has highlighted how few studies have addressed the efficacy of interventions for SRNS in children. The studies were generally small and of variable quality. Most studies did not provide data on the duration of remission, on renal dysfunction including the number progressing to end stage renal failure or on mortality although these are important patient centred outcomes. Though calcineurin inhibitors appear to be of some benefit for children with SRNS, this systematic review has demonstrated that RCTs to date are inadequate in size and quality to confidently confirm this. A single small study has demonstrated a benefit of cyclosporin compared with IV cyclophosphamide. In addition, the small sample size resulting in large CI leads to uncertainty in the summary estimates so that a beneficial effect of oral cyclophosphamide cannot be completely excluded in this review. ACEi significantly reduce proteinuria in children with SRNS but there are no data on whether they significantly reduce the risk for long term renal dysfunction and the need for dialysis and transplantation.

Implications for research

Further adequately powered and well designed RCTs are needed to assess the benefits and harms of calcineurin inhibitors (cyclosporin and tacrolimus) with/without corticosteroids compared with regimens of oral or IV alkylating agents with corticosteroids in treating children with SRNS. These studies should be of sufficient duration to assess complete remission rates, relapse rates, renal function and adverse events. Some children with mutations in the gene coding for podocin may respond to therapy. To assess differences in response to therapy between children with and without mutations, children entering RCTs should be screened for mutations in the podocin genes and the studies should be large enough to allow separate analysis of outcomes in children with and without mutations. Mycophenolate mofetil (MMF) is also used to treat SRNS with variable results. The results of the NIH sponsored study comparing MMF and IV methylprednisolone with cyclosporin in children and adults with FSGS are awaited.

Well designed RCTs with longer follow-up periods are required to confirm the efficacy of ACEi compared with placebo on the reduction of proteinuria and to determine the effect on renal dysfunction.

Since cyclosporin and ACEi appear to be effective when used alone, further studies should examine the efficacy of combination therapy with an ACEi and cyclosporin compared with an ACEi alone and with cyclosporin alone.

The anti CD-20 monoclonal antibody, rituximab, has been used in some children with SRNS and FSGS resistant to other therapies with variable results (Prytula 2010). The efficacy of this medication, which has significant adverse events, should be formally assessed in RCTs in comparison with calcineurin inhibitors.

ACKNOWLEDGEMENTS

We are grateful to Dr Doaa Habashy who contributed to the original iterations of this review (Habashy 2001; Habashy 2003; Habashy 2004; Habashy 2006), contributing to the design, quality assessment, data collection, entry, analysis and interpretation, and writing.

This work was presented at the Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, Sydney, Australia, 2-4 September, 2002 and published in abstract form in *Nephrology* in 2002. The authors would like to thank Dr Arvind Bagga for providing additional study data. The authors wish to thank Ms Ruth Mitchell, Trials Search Co-ordinator of the Cochrane Renal Group, for her help with this study.

REFERENCES

References to studies included in this review

APN 2008 *{published data only}*

* Plank C, Kalb V, Hinkes B, Hildebrandt F, Gefeller O, Rascher W for Arbeitgemeinschaft für Pädiatrische Nephrologie. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome-a randomized controlled multicentre trial by the Arbeitgemeinschaft für Pädiatrische Nephrologie. *Pediatric Nephrology* 2008;**23**(9):1483-93. [MEDLINE: 18481113]

Bagga 2004 *{published data only}*

* Bagga A, Mudigoudar BD, Hari P, Vasudev V. Enalapril dosage in steroid-resistant nephrotic syndrome. *Pediatric Nephrology* 2004;**19**(1):45-50. [MEDLINE: 14648339]

Bagga A, Mudigoudar BD, Vasudev V, Hari P. Low (LD) versus high dose (HD) enalapril therapy in steroid resistant nephrotic syndrome (SRNS). Seventh Asian Congress of Pediatric Nephrology; 2000 Nov 4-6; Singapore. 2000. [CENTRAL: CN-00583291]

Chongviriyaphan 1999 *{published data only}*

* Chongviriyaphan N, Tapaneya-Olarn C, Suthutvoravut U, Karnchanachumpol S, Chantraruksa V. Effects of tuna fish oil on hyperlipidemia and proteinuria in childhood nephrotic syndrome. *Journal of the Medical Association of Thailand* 1999;**82 Suppl**(1):122-8. [MEDLINE: 10730531]

Choudhry 2009 *{published data only}*

* Choudhry S, Bagga A, Hari P, Sharma S, Kalaivani M, Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. *American Journal of Kidney Diseases* 2009;**53**(5):760-9. [MEDLINE: 19268410]

Elhence 1994 *{published data only}*

* Elhence R, Gulati S, Kher V, Gupta A, Sharma RK. Intravenous pulse cyclophosphamide - a new regime for steroid-resistant minimal change nephrotic syndrome. *Pediatric Nephrology* 1994;**8**(1):1-3. [MEDLINE: 8142205]

Garin 1988 *{published data only}*

* Garin EH, Orak JK, Hiott KL, Sutherland SE. Cyclosporine therapy for steroid-resistant nephrotic syndrome. A controlled study. *American Journal of Diseases of Children* 1988;**142**(9):985-8. [MEDLINE: 3046332]

ISKDC 1970 *{published data only}*

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

ISKDC 1974 *{published data only}*

* Anonymous. Prospective, controlled trial of cyclophosphamide therapy in children with the nephrotic syndrome. Report of the International Study of Kidney Disease in Children. *Lancet* 1974;**2**(7878):423-7. [MEDLINE: 4137139]

ISKDC 1996 *{published data only}*

* 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**(5):590-3. [MEDLINE: 8897562]

Kleinknecht 1979 *{published data only}*

* Kleinknecht C, Broyer M, Palcoux JB, Gubler MC. Irreversible renal failure after indomethacin in steroid resistant nephrosis. Kidney International. 1979; Vol. 302, issue 12:961. [MEDLINE: 6986554]

Lieberman 1996 *{published data only}*

* Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *Journal of the American Society of Nephrology* 1996;**7**(1):56-63. [MEDLINE: 8808110]

Mantan 2008 *{published data only}*

Mantan M, Bagga A, Hari P. Efficacy of IV pulse cyclophosphamide (CP) vs IV steroids and oral CP for steroid resistant nephrotic syndrome [abstract]. *Pediatric Nephrology* 2004;**19**(9):C75. [CENTRAL: CN-00653731]

* Mantan M, Sriram CS, Hari P, Dinda A, Bagga A. Efficacy of intravenous pulse cyclophosphamide treatment versus combination of intravenous dexamethasone and oral cyclophosphamide treatment in steroid-resistant nephrotic syndrome. *Pediatric Nephrology* 2008;**23**(9):1495-502. [MEDLINE: 18566839]

Ponticelli 1993a *{published data only}*

* 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 International* 1993;**43**(6):1377-84. [MEDLINE: 8315953]

Yi 2006 *{published data only}*

Li Z, Yi Z. Clinical study of fosinopril in children with steroid resistant nephrotic syndrome [abstract]. *Pediatric Nephrology* 2001;**16**:C114.

Li ZH, Yi ZW. Clinical study of fosinopril in children with steroid resistant nephrotic syndrome [abstract]. 23rd International Congress of Paediatrics; 2001 Sep 9-14; Beijing (China). 2001. [CENTRAL: CN-00445802]

* Yi Z, Li Z, Wu XC, He QN, Dang XQ, He XJ. Effect of fosinopril in children with steroid-resistant idiopathic nephrotic syndrome. *Pediatric Nephrology* 2006;**21**(7):967-72. [MEDLINE: 16773409]

References to studies excluded from this review

Adeniyi 1979 *{published data only}*

Adeniyi A, Hendrickse RG, Soothill JF. A controlled trial of cyclophosphamide and azathioprine in Nigerian children with the nephrotic syndrome and poorly selective proteinuria. *Archives of Disease in Childhood* 1979;**54**(3):204-7. [MEDLINE: 373645]

Bhaumik 2002 *{published data only}*

Bhaumik SK, Barman SC. Comparison of pulse methyl prednisolone vs cyclosporin based therapy in steroid resistant focal segmental glomerulosclerosis [abstract]. *Indian Journal of Nephrology* 2002;**12**(4):190. [CENTRAL: CN-00460392]

Buyukcelik 2002 *{published data only}*

Buyukcelik M, Anarat A, Bayazit AK, Noyan A, Ozel A, Anarat R, et al. The effects of gemfibrozil on hyperlipidemia in children with persistent nephrotic syndrome. *Turkish Journal of Pediatrics* 2002;**44**(1):40-4. [CENTRAL: CN-00420817]

Jung 1990 *{published data only}*

Jung A. Immunomodulatory treatment in children with steroid-dependent/steroid-resistant nephrotic syndrome [abstract]. *European Journal of Clinical Investigation* 1990;**20 (2 Pt II)**:A 33. [CENTRAL: CN-00253605]

Kano 2005 *{published data only}*

Kano K, Nishikura K, Yamada Y, Arisaka O. No effect of fluvastatin on the bone mineral density of children with minimal change glomerulonephritis and some focal mesangial cell proliferation, other than an ameliorating effect on their proteinuria. *Clinical Nephrology* 2005;**63**(2):74-9. [MEDLINE: 15730048]

Kumar 2001 *{published data only}*

Kumar NS, Mishra RN, Singh AK, Prakash J. Effect of Ace Inhibitor And Calcium Channel Blocker On Proteinuria In Subjects With Steroid Resistant Idiopathic Nephrotic Syndrome [abstract]. *Indian Journal of Nephrology* 2001;**11**(3):110-1. [CENTRAL: CN-00461120]

Shibasaki 2004 *{published data only}*

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 onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clinical & Experimental Nephrology* 2004;**8**(2):117-26. [MEDLINE: 15235928]

Additional references

Arneil 1961

Arneil GC. 164 children with nephrosis. *Lancet* 1961;**2**:1103. [MEDLINE: 13862397]

Burgess 1999

Burgess E. Management of focal segmental glomerulosclerosis: evidence-based recommendations. *Kidney International - Supplement* 1999;**55**(70):25-32. [MEDLINE: 10369192]

Cattran 1998

Cattran DC, Rao P. Long-term outcome in children and adults with classic focal and segmental glomerulosclerosis. *American Journal of Kidney Diseases* 1998;**32**(1):72-9. [MEDLINE: 9669427]

Chua 2009

Chua A, Yorgin P. Steroid-resistant Nephrotic Syndrome. In: Molony DA, Craig JC editor(s). Evidence-based Nephrology. Wiley-Blackwell, 2009.

Colquitt 2007

Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS. The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review. *Health Technology Assessment (Winchester, England)* 2007;**11**(21):1-93. [MEDLINE: 17537341]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 7718048]

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315**(7109):629-34. [MEDLINE: 9310563]

Ehrich 2007

Ehrich JHH, Geerlings C, Zivicnjak M, Franke D, Geerlings H, Gellerman J. Steroid-resistant idiopathic childhood nephrosis: overdiagnosed and undertreated. *Nephrology Dialysis Transplantation* 2007;**22**(8):2183-93. [MEDLINE: 17504846]

Hari 2001

Hari P, Bagga A, Jindal N, Srivastava RN. Treatment of focal glomerulosclerosis with pulse steroids and oral cyclophosphamide. *Pediatric Nephrology* 2001;**16**(11):901-5. [MEDLINE: 11685598]

Higgins 2003

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

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. 2008. Available from www.cochrane-handbook.org.

Hollis 1999

Hollis S, Cambell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**(7211):670-4. [MEDLINE: 10480822]

ISKDC 1981a

Anonymous. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *Journal of Pediatrics* 1981;**98**(4):561-4. [MEDLINE: 7205481]

ISKDC 1981b

Anonymous. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. *Kidney International* 1981;**20**(6):765-71. [MEDLINE: 7334749]

Koskimies 1982

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

Latta 2001

Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatric Nephrology* 2001;**16**(3):271-82. [MEDLINE: 11322378]

Lefebvre 1996

Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Fourth International Cochrane Colloquium; 1996 Oct 20-24; Adelaide (Australia). 1996.

Moher 1998

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

Niaudet 1992

Niaudet P. Comparison of cyclosporin and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: A multicentre randomized controlled trial. *Pediatric Nephrology* 1992;**6**(1):1-3. [MEDLINE: 1536727]

Niaudet 1994

Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. *Journal of Pediatrics* 1994;**125**(6 Pt 1):981-6. [MEDLINE: 7996374]

Ponticelli 1993b

Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. *Nephrology Dialysis Transplantation* 1993;**8**(12):1326-32. [MEDLINE: 8159300]

Prytula 2010

Prytula A, Iijima K, Kamei K, Geary D, Gottlich E, Majeed A, et al. Rituximab in refractory nephrotic syndrome. *Pediatric Nephrology* 2010;**25**(3):461-8. [MEDLINE: 20033225]

Renal Group 2010

Willis NS, Mitchell R, Higgins GY, Webster AC, Craig JC. Cochrane Renal Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2010, Issue 9. Art. No.: RENAL (accessed September 2010).

Schlesinger 1968

Schlesinger ER, Sultz HA, Mosher WE, Feldman JG. The nephrotic syndrome. Its incidence and implications for the community. *American Journal of Diseases of Children* 1968;**116**(6):623-32. [MEDLINE: 5697193]

Schulz 1995

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

Tune 1995

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. *Clinical Nephrology* 1995;**43**(2):84-8. [MEDLINE: 7736683]

Tune 1996

Tune BM, Lieberman E, Mendoza SA. Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease. *Pediatric Nephrology* 1996;**10**(6):772-8. [MEDLINE: 8971906]

References to other published versions of this review

Habashy 2001

Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003594]

Habashy 2003

Habashy D, Hodson EM, Craig JC. Interventions for steroid-resistant nephrotic syndrome: a systematic review. *Pediatric Nephrology* 2003;**18**(9):906-12. [MEDLINE: 12836096]

Habashy 2004

Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD003594.pub2]

Habashy 2006

Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003594.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

APN 2008

Methods	• Study design: parallel RCT
	• Time frame: 1/2001 to 11/2004
	• Follow-up period: 48 weeks for whole study
	• Loss to follow-up: Complete follow-up to 12 weeks.
	  * 5/15 CSA group withdrawn from 12 weeks onwards (4 treated with non-responder protocol of high dose CSA)
	  * 14/17 CPA group withdrawn from 12 weeks onwards (7 treated with non-responder protocol of pulse methylprednisolone)

Participants	Inclusion criteria
	• Setting: Tertiary, multicentre study
	• Country: Germany, Austria. Study by the Arbeitsgemeinschaft fur Pädiatrische Nephrologie
	• SRNS: Initial non-responder; absence of complete remission (proteinuria < 4 mg/m^2/h) 14 days after ≥ 4 weeks of prednisone (60 mg/m^2/d) and 3 methylprednisone pulses (500 mg/m^2); FSGS, MCD or MesPGN on biopsy. Normal C3, CrCl > 70 mL/min/1.73m^2.
	• Number
	  * CSA group: 15 (MCD 6, FSGS 8, MP 1)
	  * CPA group: 17 (MCD 4, FSGS 13, MP 0)
	• Age (mean ± SD)
	  * CSA group: 6.99 ± 5.48 years
	  * CPA group: 6.84 ± 3.90 years
	• Sex (M/F)
	  * CSA group: 11/4
	  * CPA group: 8/9
	Exclusion criteria
	• Hereditary, syndromic and secondary nephrotic syndrome; pre-treatment with immunosuppressive therapy other than prednisone; prednisone regimen other than APN or ISKDC

Interventions	CSA group • Oral CS 150 mg/m^2/d in 2 divided doses aiming for trough levels of 120-180 ng/mL for 24 weeks and then CSA to achieve trough level of 80-120 ng/mL for 24 weeks CPA group • IV CPA starting at 500 mg/m^2 over 4 hours every 4 weeks for 7 doses. Dose increased or decreased by 250 mg/m^2 according to WCC. Maximum dose 1 g/m^2 Co-interventions • Tapering dose of alternate day prednisone to week 48
Outcomes	• Complete remission (proteinuria < 4 mg/m^2/h) within 24 weeks but non-responder treatment offered from 12 weeks so results only interpretable to 12 weeks • Partial remission (resolution of oedema, albumin > 35 g/L, proteinuria 4-40 mg/m^2/h at 24 weeks) at 12 weeks • Adverse events
Notes	• Exclusions post randomisation but pre-intervention: None

APN 2008 *(Continued)*

- Stop or end points/s: Study to be discontinued if number of patients achieving complete/partial remission by 12 weeks was significantly greater with one treatment. Patients failing to respond were offered non-responder protocol after 12 weeks therapy.
- Additional data requested from authors: None
- Other: More patients with FSGS in cyclophosphamide group. Six patients in cyclophosphamide group had heterozygous mutations or sequence variations of NPHS2 gene
- Inclusion criteria allowed inclusion of patients with partial response to prednisone (proteinuria > 4mg/m^2/h but < 40 mg/m^2/h)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated random lists, stratified by centre
Allocation concealment?	Low risk	Central allocation by study coordinator.
Blinding? All outcomes	High risk	No blinding of participants or investigators; blinding of outcome or data assessors not stated
Incomplete outcome data addressed? All outcomes	High risk	Complete follow-up to 12 weeks. Then non-responders could be withdrawn to enter non-responder protocol
Free of selective reporting?	Low risk	Complete or partial remission reported at 12 weeks
Free of other bias?	High risk	Funded in part by a grant of Novartis Pharma

Bagga 2004

Methods

- Study design: Crossover study
- Time frame: NS
- Follow-up period: 20 weeks. First part of crossover included so outcome at 8 weeks used
- Loss to follow-up: 0%

Participants

Inclusion criteria

- Setting: Tertiary centre
- Country: India
- SRNS (no remission after 8 weeks of prednisone). Patients with initial SRNS or late SRNS following response to prednisone.
- Number (high dose/low dose): 14/11
- Age (range)
  - High dose: 78 months (60-104.7)
  - Low dose: 96 months (80.5-136.4)
- Sex (M/F)
  - High dose: 9/5
  - Low dose: 9/2
- Histology
  - High dose: MCD (3); FSGS (5); MCGN (3); MesPGN (3)
  - Low dose: MCD (1); FSGS (4); MCGN (4)

Exclusion criteria

Bagga 2004 *(Continued)*

	• Severe hypertension (SBP or DBP > 99th percentile); GFR < 70 mL/min/1.73m^2; secondary nephrotic syndrome (SLE, HSP, Hepatitis B, amyloidosis); single functioning kidney; treatment with daily prednisone, IV steroids, alkylating agents, levamisole, cyclosporin, IV albumin in previous 4 weeks; patients unable to attend 4 weekly visits; age < 1 year or > 16 years.
Interventions	High dose enalapril • 0.6 mg/kg/d for 8 weeks in 2 doses Low dose enalapril • 0.2 mg/kg/d for 8 weeks in 2 doses Co-interventions • Alternate day prednisone, frusemide
Outcomes	• Urine albumin/creatinine ratios (median, 95% CI) after 8 weeks • Urine albumin/creatinine reduction (median, 95% CI) after 8 weeks • Levels of creatinine, albumin, cholesterol, potassium, blood pressure • Adverse events: Cough
Notes	• Exclusions post randomisation but pre-intervention: 4 (1 high dose group, 3 low dose group) excluded after randomisation and before treatment • Stop or end points/s: NS • Additional data requested from authors: Information on allocation concealment, study characteristics and results received from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated random numbers
Allocation concealment?	Low risk	Sealed opaque envelopes opened by investigator, who did not manage the patients (information from author)
Blinding? All outcomes	High risk	No blinding of participants or investigators. Not stated for outcome assessors or data assessors.
Incomplete outcome data addressed? All outcomes	Unclear risk	Numbers not reported for end of study data
Free of selective reporting?	Low risk	Outcomes reported (urinary albumin excretion, renal function, adverse events)
Free of other bias?	Unclear risk	Funding source not stated

Chongviriyaphan 1999

Methods	• Study design: crossover study • Time frame: NS • Follow-up period: 32 weeks but outcome data provided at 8 weeks • Loss to follow-up: 17%: 1 lost to follow-up and excluded from analysis

Chongviriyaphan 1999 *(Continued)*

Participants	Inclusion criteria • Setting: Tertiary centre • Country: Thailand • SRNS, no response to cyclophosphamide, normotension, Cr < 3 mg/dL, GFR > 15 mL/min/1.73 m^2 • Number: 5 • Age range: 7-17 years • Sex (M/F): All male • Histology (4 patients): FSGS 3; MesPGN 1 Exclusion criteria • Severe infection; diarrhoea; haemostatic disorder; on lipid lowering drugs
Interventions	Treatment • Tuna fish oil (EPA 230 mg, DHA 1.12 g, 240 IU D-a-tocopheryl acetate) 8 capsules/d for 8 weeks Control • Placebo (olive oil) 8 capsules/d for 8 weeks Co-interventions: NS
Outcomes	• Urine protein excretion at 8 weeks • CrCl at 8 weeks • SCr and lipids at 8 weeks
Notes	• Exclusions post randomisation but pre-intervention: NS • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	Unclear risk	Blinding of participants/investigators. Outcome and data assessors not reported
Incomplete outcome data addressed? All outcomes	Unclear risk	Crossover study of 6 patients, I patient did not complete the study with no reason provided
Free of selective reporting?	Low risk	Outcomes (urine protein excretion, CrCl) reported
Free of other bias?	Low risk	Study supported by Ramathibodi Research Grant No.25/1996, Mahidol University, Bangkok

Choudhry 2009

Methods	• Study design: Parallel • Time frame: Aug 2005 to Jul 2007 • Follow-up period: 12 months • Loss to follow-up: 0%

Participants	Inclusion criteria
	• Setting: Tertiary centre
	• Country: India
	• SRNS (UP/UCr > 2 g/g, albumin <2.5 mg/dL, oedema) despite prednisone for 4 weeks at 2 mg/kg/d, initial and late non-responders with MCD, FSGS, MesPGN
	• Number (TAC/CSA): 21/21
	• Age
	  * TAC group: 75 (95% CI 53 to 97) months
	  * CSA group: 62.6 (95% CI 43.1 to 82.1) months
	• Sex (M/F)
	  * TAC group: 14/7
	  * CSA group: 11/9
	• Early/late resistance
	  * TAC group: 12/9
	  * CSA group: 11/9
	Exclusion criteria
	• Immunosuppression other than prednisone in previous 12 weeks; secondary SRNS; Cr >1.5 mg/dL; eGFR < 60mL/min/1.73m^2; history of DM or liver disease; time between onset of SRNS and study > 24 months

Interventions	TAC group • TAC 0.1-0.2 mg/kg/d in 2 divided doses for 12 months • Trough levels 5-8 ng/mL CSA group • CSA 5-6 mg/kg/d in 2 divided doses for 12 months • Trough levels 100-150 ng/mL Co-interventions • Alternate day prednisone (1 mg/kg for 6 months and 0.5 mg/kg for 6 months); enalapril 0.3 mg/kg/d; atorvastatin 5-10 mg/d for cholesterol > 200 mg/dL; calcium and vitamin D supplements
Outcomes	• Complete (UP/UCr < 0.2 g/g, albumin > 2.5 g/dL) or partial remission (UP/UCr 0.2-2 g/g, albumin > 2.5 g/dL) at 6 and 12 months • Treatment failure: Non-response (UP/UCr > 2g/g, albumin < 2.5 g/dL) after 6 months and 12 months or persistent nephrotoxicity (Cr increased by 50% from baseline with no resolution after reducing dose by 50% for 15 days) or death • Frequency of relapses • Adverse events: nephrotoxicity (persistent or reversible); worsening of hypertension; neurological; hypertrichosis; gingival hyperplasia; acne; diarrhoea; severe infection
Notes	• All underwent molecular analyses of *NPHS2* and exons 8 and 9 of *WT1* genes in 2 laboratories • Exclusions post randomisation but pre-intervention: NS • Stop or end points/s: NS • Additional data requested from authors: Numbers with response related to early/late resistance

Choudhry 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated randomisation list were generated off site by colleague not involved in the study
Allocation concealment?	Low risk	Sealed opaque serially numbered envelopes opened at randomisation
Blinding? All outcomes	Unclear risk	No blinding of participants/investigators. Blinding of outcome assessors, who assessed gum hypertrophy and hirsutism. Blinding of data assessors not reported.
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up
Free of selective reporting?	Low risk	Outcomes (complete remission, partial remission, relapse, adverse events) reported
Free of other bias?	Unclear risk	Study medications provided by Pancea Biotec, India

Elhence 1994

Methods	• Study design: parallel RCT • Time frame: 1990 to 1991 • Follow-up period: 12 months • Loss to follow-up: 15%; 2 from control group lost to follow-up and excluded from analysis

Participants	Inclusion criteria
	• Setting: Tertiary centre
	• Country: India
	• SRNS, initial and late non-responders with MCNS
	• Number (IV/oral): 7/6
	• Age (IV/Oral): 3-16 years/9-14.5 years
	• Sex (M/F)
	  * IV CPA: 6/1
	  * Oral CPA: 5/1
	Exclusion criteria: NS

Interventions	IV CPA group • IV CPA: 500 mg/m^2/mo for 6 weeks • Prednisone: 60 mg/m^2/d for 4 weeks; 40 mg/m^2 alternate days for 4 weeks and taper Oral CPA group • Oral CPA: 2.5 mg/kg/d for 8 weeks • Prednisone: 60 mg/m^2/d for 4 weeks; 40 mg/m^2 alternate days for 4 weeks and taper Co-interventions: NS
Outcomes	• Remission: proteinuria < 4 mg/m^2/h and albumin > 35 g/L at 6 months

Elhence 1994 *(Continued)*

	• Adverse events
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome and data assessors not reported.
Incomplete outcome data addressed? All outcomes	High risk	2 patients lost to follow-up from control group and results not incorporated
Free of selective reporting?	Low risk	Outcome (complete remission) reported
Free of other bias?	Unclear risk	Funding source not stated

Garin 1988

Methods	• Study design: crossover study • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	Inclusion criteria • Setting: Tertiary centre • Country: USA • SRNS: Defined as proteinuria 40 mg/m^2/h, or > 50 mg/kg/d and serum albumin < 25 g/L after 8 weeks of prednisone (2 mg/kg/d) • Number: 8 • Age: 3-18 years • Sex (M/F): 6/2 • Histology: MCD 4, FSGS 4 Exclusion criteria: NS
Interventions	CSA group • Cyclosporin 5 mg/kg/d for 8 weeks adjusted to level ≤ 200 ng/mL No treatment group • No treatment for 8 weeks Co-interventions

Garin 1988 *(Continued)*

	• NS; no patient on prednisone during study
Outcomes	• Complete remission at 8 weeks: Not defined • Partial remission at 8 weeks: Not defined
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	High risk	Participants/investigators not blinded. Blinding of outcome and data assessors not reported
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up and accounted for
Free of selective reporting?	Unclear risk	Complete/partial remission reported but no definitions provided
Free of other bias?	Unclear risk	Funding source not stated

ISKDC 1970

Methods	• Study design: parallel RCT • Time frame: Jan 1967 to Dec 1969 • Follow-up period: 3 months; non-responders at 90 days randomised to 2nd course of 90 days of AZA • Loss to follow-up: 0%
Participants	Inclusion criteria • Setting: Tertiary, multicentre • Country: Europe, USA, Japan, Mexico • SRNS: absence of 3 consecutive days without proteinuria (≤ 4 mg/m^2/h) within 8 weeks of therapy; aged 12 weeks to 16 years at onset of nephrotic syndrome; no previous treatment with cytotoxic or immunosuppressive agents. • Histology: MCD (5); FSGS (10); MesPGN (15); unknown (3) • Number (AZA/placebo): 16/15 • Age: NS • Sex (M/F): NS Exclusion criteria • Secondary nephrotic syndrome (SLE, diabetes, amyloidosis, syphilis, HSP, malaria)
Interventions	AZA group

ISKDC 1970 *(Continued)*

	• AZA 60 mg/m²/d + intermittent prednisone for 90 days Placebo group • Placebo + intermittent prednisone for 90 days Co-interventions: NS
Outcomes	• Complete remission at 90 days: proteinuria ≤ 4 mg/m²/h for 3 consecutive days • Partial remission at 90 days
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Centrally derived table of random numbers
Allocation concealment?	Low risk	"Reports were sent to a co-ordinator, who assigned treatment and distributed drugs identified by code numbers to pharmacists at each clinic"
Blinding? All outcomes	Unclear risk	Blinding of participants/investigators. Blinding of outcome or data assessors not stated.
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up
Free of selective reporting?	Unclear risk	Outcomes of complete or partial remission but definition of partial remission not stated
Free of other bias?	High risk	Help with planning of study provided by employees of Wellcome Foundation and Burroughs Welcome

ISKDC 1974

Methods	• Study design: parallel RCT • Time frame: Apr 1970 to Jun 1972 • Follow-up period: 24 months • Loss to follow-up: 0%

Participants	Inclusion criteria
	
	• Setting: Tertiary, multicentre
	• Country: Europe, USA, Mexico, Hong Kong, Japan
	• SRNS: Failure to achieve remission (proteinuria ≤ 4 mL/m²/h) after 8 weeks of prednisone (60 mg/m²/d for 4 weeks then 40 mg/m²/d for 3 consecutive days out of 7); aged 12 weeks to 16 years at onset of nephrotic syndrome.
	• Number
	  * CPA-prednisone group: 18
	  * Prednisone group: 13 (2 patients with MNS excluded)
	• Age: NS

ISKDC 1974 *(Continued)*

	• Sex (M/F): NS
	• Histology
	  * CPA-prednisone group: MCD (7); FSGS (7); MesPGN (2); diffuse proliferative GN (2)
	  * Prednisone group: MCNS (7); FSGS (3); diffuse proliferative GN (1); unknown (2)
	
	Exclusion criteria: NS

Interventions	CPA-prednisone group • Oral CPA 5 mg/kg/d till WCC < 5000 then 1-3 mg/kg/d • Intermittent prednisone for 90 days Prednisone group • Intermittent prednisone for 90 days Co-interventions: NS
Outcomes	• Complete remission: proteinuria ≤ 4 mg/m^2/h for 3 consecutive days at about 3-4 months but unclear • Partial remission
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported
Allocation concealment?	Unclear risk	Not reported
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome/data assessors not reported
Incomplete outcome data addressed? All outcomes	Unclear risk	All patients followed up
Free of selective reporting?	Unclear risk	Complete and partial remission reported but no definition for partial remission provided
Free of other bias?	Low risk	Support from NIH AM 14490-93, National Kidney Foundation, Kidney Foundation of New York, John Rath Foundation

ISKDC 1996

Methods	• Study design: parallel RCT • Time frame: Sep 1974 to Jun 1980 • Follow-up period: 3-102 months • Loss to follow-up: 0%
Participants	Inclusion criteria

ISKDC 1996 *(Continued)*

- Setting: Tertiary, multicentre
- Country: Europe, USA, Canada
- SRNS: Proteinuria 40 mg/m²/h after prednisone (60 mg/m²/h for 4 weeks and then intermittent prednisone for 4 weeks); biopsy showing FSGS within 26 weeks of onset of nephrotic syndrome; heavy proteinuria > 40 mg/m²/h; albumin < 2.5 g/dL; age of onset of nephrotic syndrome 12 weeks to 16 years; no medical disease associated with FSGS; no prior treatment with cytotoxic or immunosuppressive agents.
- Number
  - CPA-prednisone group: 35
  - Prednisone group: 25
- Mean age (± SEM)
  - CPA-prednisone group: 8.6 ± 0.85 years
  - Prednisone group: 7.4 ± 0.75 years
- Sex (M/F): NS
- Histology: All FSGS (both groups)

Exclusion criteria

- MCD on biopsy

Interventions	CPA-prednisone group • Oral CPA 2.5 mg/kg/d for 90 days • Alternate day prednisone 40 mg/m² for 12 months Prednisone group • Alternate day prednisone for 12 months Co-interventions: NS
Outcomes	• Complete remission during study: Proteinuria < 4 mg/m²/h • Partial remission • Treatment failure: increased SCr from baseline ≥ 30% or > 4 mg/dL or onset of kidney failure (Cr > 4 mg/dL, maintenance on chronic dialysis or undergoing kidney transplantation) • Death • Adverse events
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None • CPA-prednisone group: 32/35 could be analysed • Prednisone group: 21/25 could be analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome and data assessors not reported
Incomplete outcome data addressed?	Unclear risk	32/35 in treatment group and 21/25 in control group analysed for complete/partial remission and unclear why these patients not included

ISKDC 1996 *(Continued)*

All outcomes

Free of selective reporting?	Low risk	Outcomes of complete and partial remission, adverse events, renal function included
Free of other bias?	Low risk	Supported by NIH Grant 1 RO1 AM18234 and multiple other not for profit agencies in USA, UK, Netherlands

Kleinknecht 1979

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: greater than 6 months • Loss to follow-up: 0%

Participants	Inclusion criteria
	• Setting: Tertiary centre
	• Country: France
	• Children with SRNS (persistent nephrotic syndrome after 5 weeks or more of prednisone at 2 mg/kg/d)
	• Number (chlorambucil/indomethacin): 15/15
	• Age: NS
	• Sex (M/F): NS
	• Histology
	  * Chlorambucil group: MCD (5); FSGS (6); FSGS with mesangial proliferation (4)
	  * Indomethacin group: MCD (4); FSGS (8); FSGS with mesangial proliferation (2)
	Exclusion criteria
	• Steroid responsive NS

Interventions	Chlorambucil group • Chlorambucil 0.2 mg/kg/d for 6 months Indomethacin group • Indomethacin 3 mg/kg/d for 6 months Co-interventions: NS
Outcomes	• Remission of nephrotic syndrome: definition NS after at least 6 months • End-stage kidney failure
Notes	• Exclusions post randomisation but pre-intervention: NS • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided

Kleinknecht 1979 *(Continued)*

Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	High risk	No blinding of investigators/participants. Blinding of outcome or data assessors not reported
Incomplete outcome data addressed? All outcomes	Unclear risk	Data only available from conference proceedings
Free of selective reporting?	Unclear risk	Complete remission (no definition provided), end stage renal failure. Data from conference proceedings
Free of other bias?	Unclear risk	Funding source not stated. Data from conference proceedings.

Lieberman 1996

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%

Participants	Inclusion criteria
	• Setting: Tertiary, multicentre
	• Country: USA
	• Age 6 months to 12 years; FSGS on biopsy; proteinuria > 4 mg/m^2/h or UP/UCr of > 0.18 in > 2 years and > 0.49 in < 2 years; failure to achieve proteinuria ≤ 4 mg/m^2/h after 4 weeks of prednisone (60 mg/m^2/d); GFR > 40 mL/min/1.73m^2; adequate contraception
	• CYCLOSPORIN GROUP
	• Number
	  * CSA group: 12/16 analysed. Excluded for non compliance (2); rising Cr (1); unknown reason (1)
	  * Placebo group: 12/15 analysed. Excluded for non compliance (2); rising Cr (1)
	• Mean age (± SD)
	  * CSA group 11.2 ± 4.2 years
	  * Placebo group: 11.4 ± 3.9 years
	• Sex (M/F)
	  * CSA group: 11/4
	  * Placebo group: 10/5
	Exclusion criteria
	• CSA or other immunosuppressive agent in previous 3 months; primary cause for FSGS; other significant disease; pregnancy; impaired LFTs; concomitant therapy with nephrotoxic agents including ACEi.

Interventions	CSA group • CSA 6 mg/kg/d for 6 months, adjusted to 300-500 ng/mL Placebo group • Placebo for 6 months Co-interventions • Calcium channel blockers for hypertension

Lieberman 1996 *(Continued)*

Outcomes	• Complete remission at 6 months: Proteinuria ≤ 4mg/m^2/h • Partial remission at 6 months: reduction in proteinuria, but still remaining in supranormal range • Adverse events
Notes	• Exclusions post randomisation but pre-intervention: CSA group (1) • Stop or end points/s: Potentially serious infection; persistent elevation of Cr, potassium, LFTs, blood pressure; malignancy; development of disease requiring medications not permitted in trial; request of parent; discretion of investigator; poor compliance; pregnancy; other adverse events not resolved by dosage reduction. • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer generated list
Allocation concealment?	Low risk	Central co-ordinator
Blinding? All outcomes	Unclear risk	Blinding of participants/investigators. Not stated for outcome or data assessors
Incomplete outcome data addressed? All outcomes	High risk	4/16 excluded from cyclosporin group and 3/15 excluded from control group for non compliance (2 each group, 1 unknown CSA group, 1 each group for rising Cr). In view of small numbers, results likely to influence results
Free of selective reporting?	Low risk	Outcomes of complete or partial remission, adverse events, renal function
Free of other bias?	Unclear risk	Funding source not stated

Mantan 2008

Methods	• Study design: parallel RCT • Time frame: Apr 2001 to Dec 2003 • Follow-up period: 18 months • Loss to follow-up: 0% but 3 (5.8%) excluded from analysis

Participants	Inclusion criteria
	• Setting: Tertiary, single centre
	• Country: India
	• SRNS (proteinuria > 1g/m^2/d or > 3+ on dipstick, albumin <2.5 mg/dL, oedema) despite prednisone for 4 weeks at 2 mg/kg/d; initial and late non-responders with MCD, FSGS, MesPGN; aged 1 to 18 years
	• IV CYCLOPHOSPHAMIDE GROUP
	• Number
	  * IV CPA group: 26/27 evaluated
	  * Oral CPA + IV DEXA group: 23/25 evaluated
	• Median age (range)
	  * IV CPA group: 51 (16-156) months
	  * Oral CPA + IV DEXA group: 92 (15-198) months

Mantan 2008 *(Continued)*

- Sex (M/F)
  - IV CPA group: 19/8
  - Oral CPA + IV DEXA group: 16/9
- Early/late resistance
  - IV CPA group: 10/16
  - Oral CPA + IV DEXA group: 8/15

Exclusion criteria

- Previous immunosuppression other than prednisone; secondary SRNS; eGFR < 60 mL/min/1.73 m^2

Interventions	IV CPA group • IV CPA 500 mg/m^2 monthly (max 1g) for 6 doses; dose increased to 750 mg/m^2 monthly if no response at 3 months. Dose delayed if WCC < 4000. • Maintenance therapy was then started with prednisone: 0.5 mg/kg alternate days to 18 months Oral CPA + IV DEXA group • Oral CPA 2 mg/kg/d from 3rd to 14th weeks and IV DEXA 5 mg/kg alternate days for 6 doses then every 2 weeks (4 pulses) and then monthly (4 pulses). • Maintenance therapy was then started with prednisone: 0.5 mg/kg alternate days to 18 months Co-interventions • Alternate day prednisone (1.5 mg/kg for 1 month; 1.25 mg/kg for 1 month and 1 mg/kg for 4 months); enalapril 0.3 mg/kg/d
Outcomes	• Complete (UP/UCr < 0.2 g/g, albumin > 2.5 g/dL) or partial remission (UP/UCr 0.2-2 g/g, albumin > 2.5 g/dL) at 6 months • Treatment failure: Non-response (UP/UCr > 2 g/g, albumin < 2.5 g/dL) after 6 months or failure to complete treatment due to serious adverse effect or > 1 serious infection. • Favourable outcome at 18 months: maintenance of complete remission or steroid-sensitive relapses • Adverse events: Hypertension; neurological; severe infection; opthamological; steroid related; leucopenia; cystitis; hair loss; vomiting
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Stratified randomisation, in blocks of four, were done separately with computer-generated numbers to allocate patients with initial and late steroid-resistance randomly..."
Allocation concealment?	Low risk	"Allocation was concealed in sealed opaque envelopes, which were opened by an associate not involved in the study"
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome or data assessors not stated
Incomplete outcome data addressed? All outcomes	Low risk	3/52 patients excluded after randomisation (IV CPA group (1); oral CPA + IV DEXA group (2)) for non-compliance. Unlikely to have influenced results

Mantan 2008 *(Continued)*

Free of selective reporting?	Low risk	Primary outcomes: Number in complete or partial remission reported
Free of other bias?	Unclear risk	Funding source not stated

Ponticelli 1993a

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year • Loss to follow-up: 1 (5%)

Participants	Inclusion criteria
	• Setting: Tertiary, multicentre
	• Country: Italy
	• SRNS proteinuria > 40 mg/m^2/h after 5 weeks of prednisone (60 mg/m^2/d); age > 2 years; FSGS or MCD on biopsy.
	• CYCLOSPORIN GROUP
	• Number
	  * CSA group: 10/10 analysed
	  * No treatment group: 7/10 analysed (3 excluded for non compliance)
	• Mean age (± SD)
	  * CSA group: 6.5 ± 4.7 years in FSGS group (4); 6.8 ± 3.5 years in MCD group (6)
	  * No treatment group: 6.6 ± 1.8 years in FSGS group (5); 7.5 ± 7.8 years in MCD (2)
	• Sex (M/F)
	  * CSA group: 13/9
	  * No treatment group: 13/6
	Exclusion criteria
	• Secondary nephrotic syndrome; malignancy; concomitant infection; severe hypertension; non-compliance; abnormal LFTs; other immunosuppressive therapy in previous 12 months

Interventions	CSA group • CSA 6 mg/kg/d for 6 months adjusted to 250-600 ng/mL; taper by 25% every 2 months No treatment group • No treatment. "rescue" treatment with corticosteroids allowed for progressive kidney failure/severe nephrotic syndrome Co-interventions • Nephrotoxic antibiotics, ACEi, nonsteroidal anti-inflammatory drugs, anti-epileptic drugs not permitted
Outcomes	• Complete remission: proteinuria < 4 mg/m^2/h on 3 non-consecutive days during 12 months • Partial remission: proteinuria < 40 mg/m^2/h on 3 non-consecutive days during 12 months
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None

Ponticelli 1993a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Sealed opaque envelopes numbered in sequence according to a random number table; stratified for adults/children
Allocation concealment?	Low risk	Sealed opaque envelopes
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome or data assessors not stated
Incomplete outcome data addressed? All outcomes	High risk	3/20 children (all from no treatment group) lost to follow-up and not included in results
Free of selective reporting?	High risk	No separate data available for adverse events in children
Free of other bias?	High risk	Funded in part by Sandoz P.F, Milano, Italy

Yi 2006

Methods	• Study design: parallel RCT • Time frame: Feb 2000 to Jan 2001 • Follow-up period: 12 weeks • Loss to follow-up: 21%. 64 eligible for study, 7 did not consent so 57 entered but 12 lost to follow-up and excluded from analysis

Participants	Inclusion criteria
	• Setting: Tertiary centre
	• Country: China
	• Children with SRNS defined as no response to 8 weeks of prednisone at 2 mg/kg/d (max 60 mg); Cr ≤ 1.5 mg/dL; haemoglobin ≥ 90 g/L
	• Fosinopril-prednisone group
	• Number
	  * Fosinopril-prednisone group: 25/30 evaluated
	  * Prednisone group: 20/27 evaluated
	• Mean age (± SD)
	  * Fosinopril-prednisone group: 8.7 ± 3.5 years
	  * Prednisone group: 8.7 ± 3.7 years
	• Sex (M/F)
	  * Fosinopril-prednisone group: 16/9
	  * Prednisone group: 16/6
	• Histology
	  * Fosinopril-prednisone group (17 patients): MCD (1); FSGS (5); MNS (2); MCGN (2); MesPGN (7)
	  * Prednisone group (14 patients): MCD (2); FSGS (5); MNS (1); MCGN (2); MesPGN (4)
	• Initial/late non-responders
	  * Fosinopril-prednisone group: 20/5
	  * Prednisone group: 18/2
	Exclusion criteria

Yi 2006 *(Continued)*

	• Previous treatment with ACEi; hypertension; secondary nephrotic syndrome; chronic kidney failure; haemoglobin < 90 g/L
Interventions	Fosinopril-prednisone group • Fosinopril for 12 weeks (5 mg/d for < 5 years of age; 5-7.5 mg/d for 5-10 years; 10 mg/d for > 10 years) • Prednisone for 12 weeks (2 mg/kg/d then reducing by 5 mg/d every 4 weeks to 1mg/kg/d) Prednisone group • Prednisone for 12 weeks (2 mg/kg/d then reducing by 5 mg/d every 4 weeks to 1mg/kg/d) Co-interventions: None
Outcomes	• Proteinuria (g/d) at 4, 8, 12 weeks • Adverse events: CrCl, potassium level, blood pressure • Urinary retinol binding protein and beta-2 microglobulin
Notes	• Exclusions post randomisation but pre-intervention: None reported • Stop or end points/s: NS • Additional data requested from authors: None • Urine protein at start was 3.94 ± 2.17 g/24 h in treatment group and 4.44 ± 3.06 g/24 h in control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Computer generated random numbers were used to randomly allocate patients ..."
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	High risk	No blinding of participants/investigators. Blinding of outcome or data assessors not stated
Incomplete outcome data addressed? All outcomes	High risk	12/57 (fosinopril group (5); prednisone group (7)) lost to follow-up and excluded from analysis
Free of selective reporting?	Low risk	Primary outcomes of study were reduction in proteinuria, CrCl
Free of other bias?	Low risk	Ministry of Health Science Foundation of China (98-1-117)

ACEi - angiotensin converting enzyme inhibitors; AZA - azathioprine; CPA - cyclophosphamide; CSA - cyclosporin; Cr - creatinine; CrCl - creatinine clearance; DBP - diastolic blood pressure; DEXA - dexamethasone; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; FSGS - focal and segmental glomerulosclerosis; GN - glomerulonephritis; intermittent - prednisone given on 3 consecutive days out of 7; LFT - liver function test; MCD - minimal change disease; MCGN - mesangiocapillary glomerulonephritis; MesPGN - mesangioproliferative glomerulonephritis; MNS - membranous nephrotic syndrome; NS - not stated; SBP - systolic blood pressure; SCr - serum creatinine; SRNS - steroid-resistant nephrotic syndrome; TAC - tacrolimus; UP/UCr - urinary protein/urinary creatinine ratio; WCC - white cell count

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

Study	Reason for exclusion
Adeniyi 1979	children had nephrotic syndrome secondary to *Plasmodium malariae* (31/36)

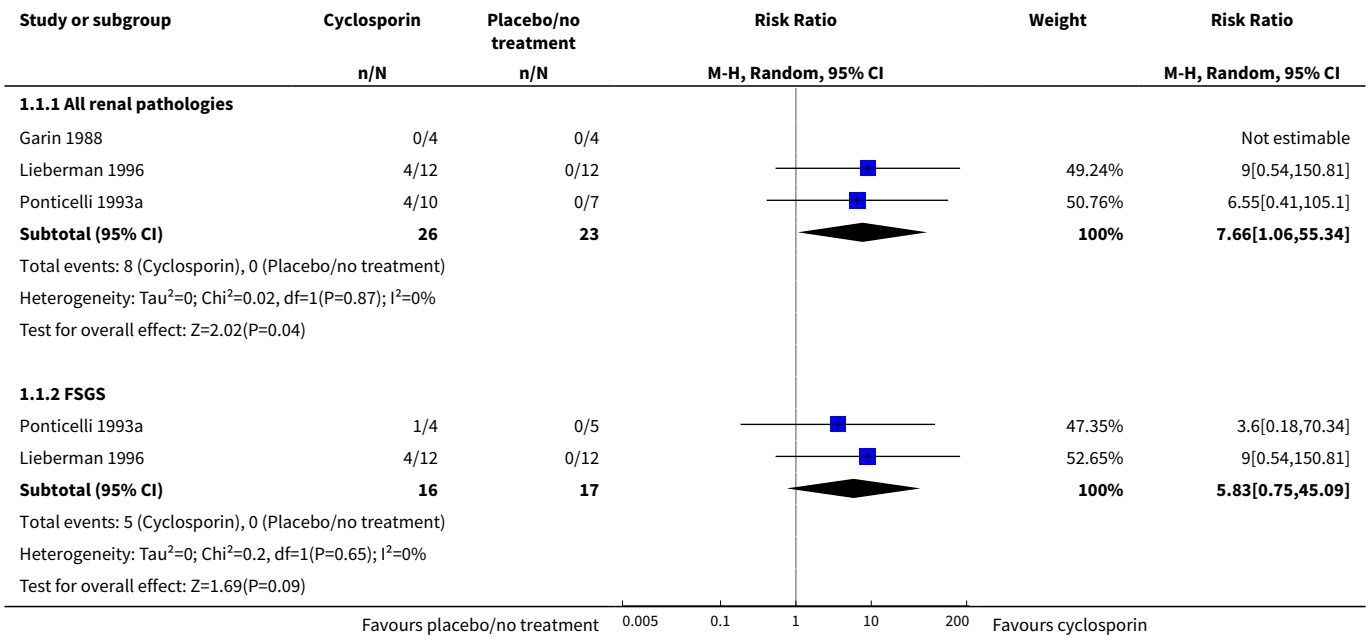
Study	Reason for exclusion
Bhaumik 2002	Mixed population of adults and children. Unable to separate data
Buyukcelik 2002	Study of gemfibrozil on lipid profiles in nephrotic syndrome
Jung 1990	Mixed population. Unable to separate data
Kano 2005	Included patients did not have nephrotic syndrome but moderate proteinuria with normal serum albumin levels
Kumar 2001	Adults patients
Shibasaki 2004	Not clear if paediatric patients were included and these could not be separated from adult patients. Includes patients with non MCD or FSGS pathology

DATA AND ANALYSES

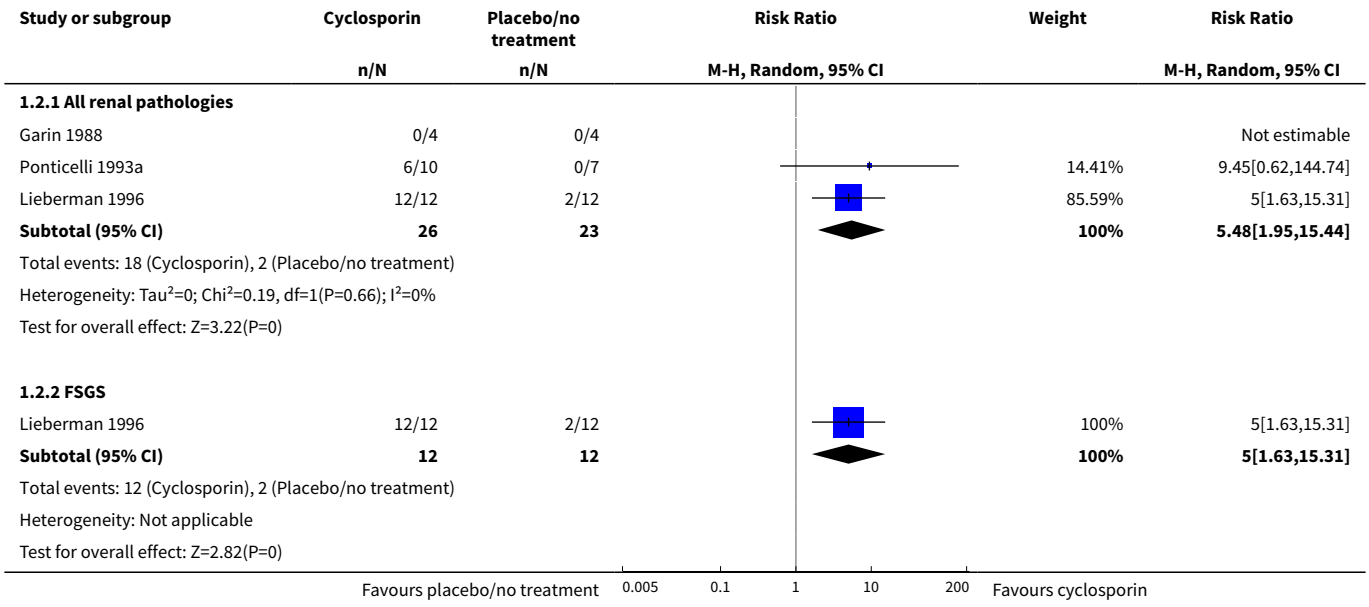
Comparison 1. Cyclosporin versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All renal pathologies	3	49	Risk Ratio (M-H, Random, 95% CI)	7.66 [1.06, 55.34]
1.2 FSGS	2	33	Risk Ratio (M-H, Random, 95% CI)	5.83 [0.75, 45.09]
2 Complete or partial remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All renal pathologies	3	49	Risk Ratio (M-H, Random, 95% CI)	5.48 [1.95, 15.44]
2.2 FSGS	1	24	Risk Ratio (M-H, Random, 95% CI)	5.0 [1.63, 15.31]
3 Adverse events	2		Risk Difference (M-H, Random, 95% CI)	Totals not selected
3.1 Worsening of hypertension	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Infection	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

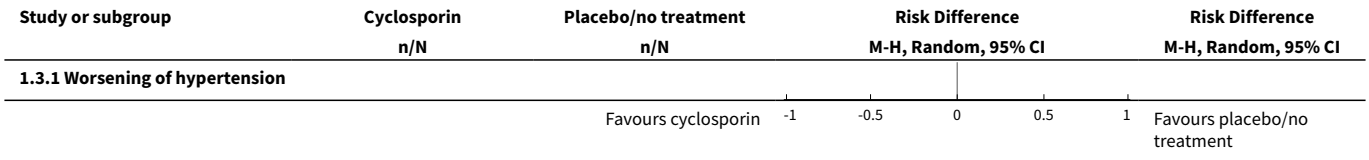
Analysis 1.1. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 1 Complete remission.

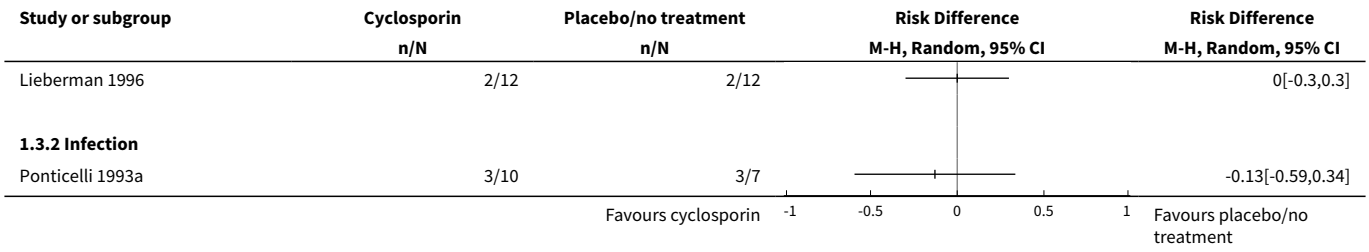


Analysis 1.2. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 2 Complete or partial remission.



Analysis 1.3. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 3 Adverse events.

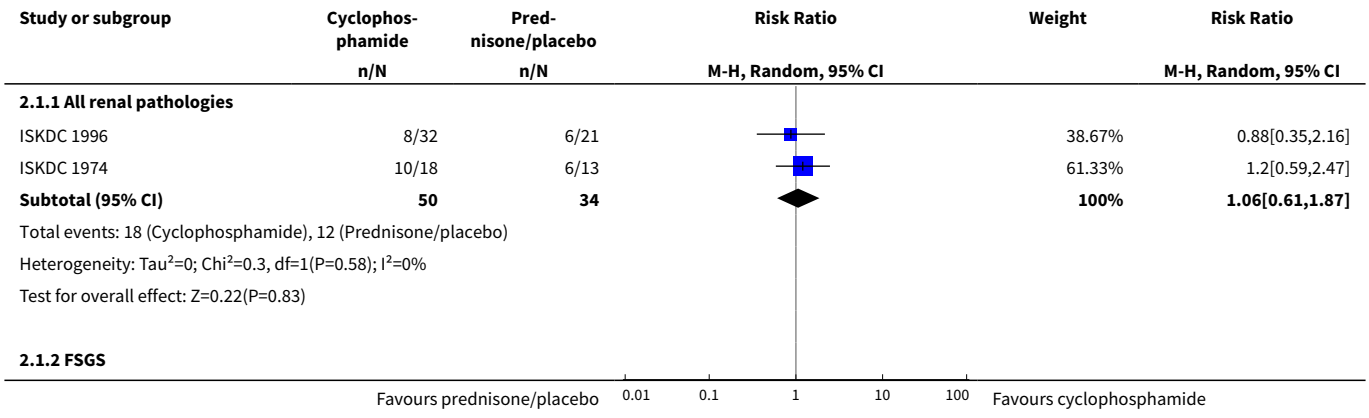


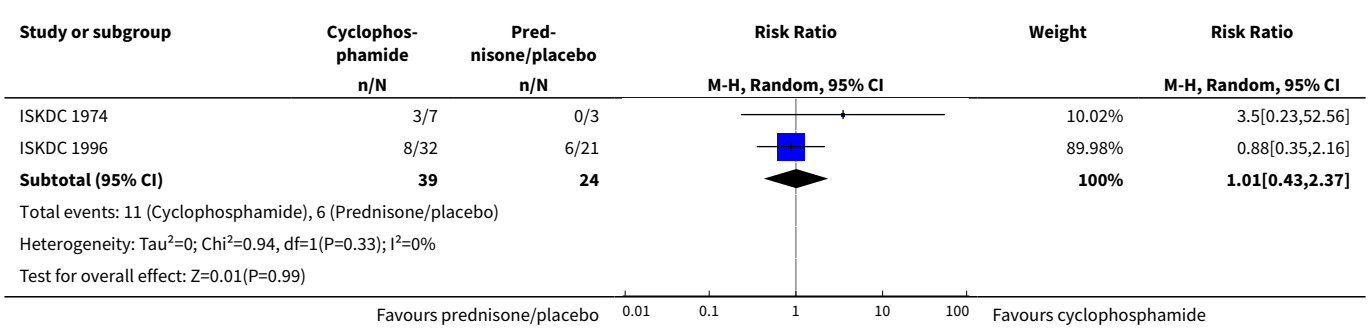


Comparison 2. Oral cyclophosphamide versus prednisone/placebo

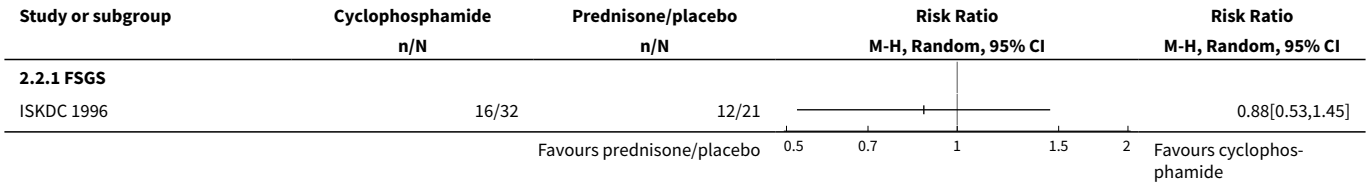
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All renal pathologies	2	84	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.61, 1.87]
1.2 FSGS	2	63	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.43, 2.37]
2 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 FSGS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
4.1 All-cause mortality	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Hypertension with seizures	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Cystitis	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Bone marrow suppression	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Oral cyclophosphamide versus prednisone/placebo, Outcome 1 Complete remission.

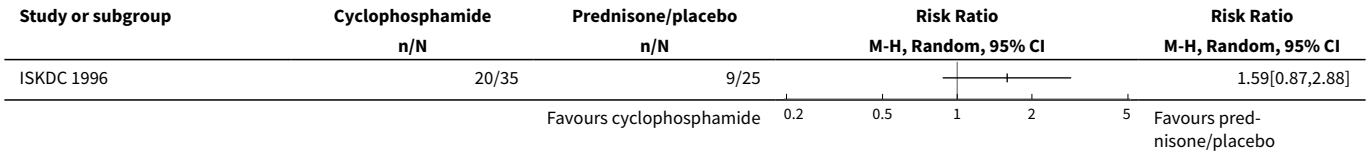




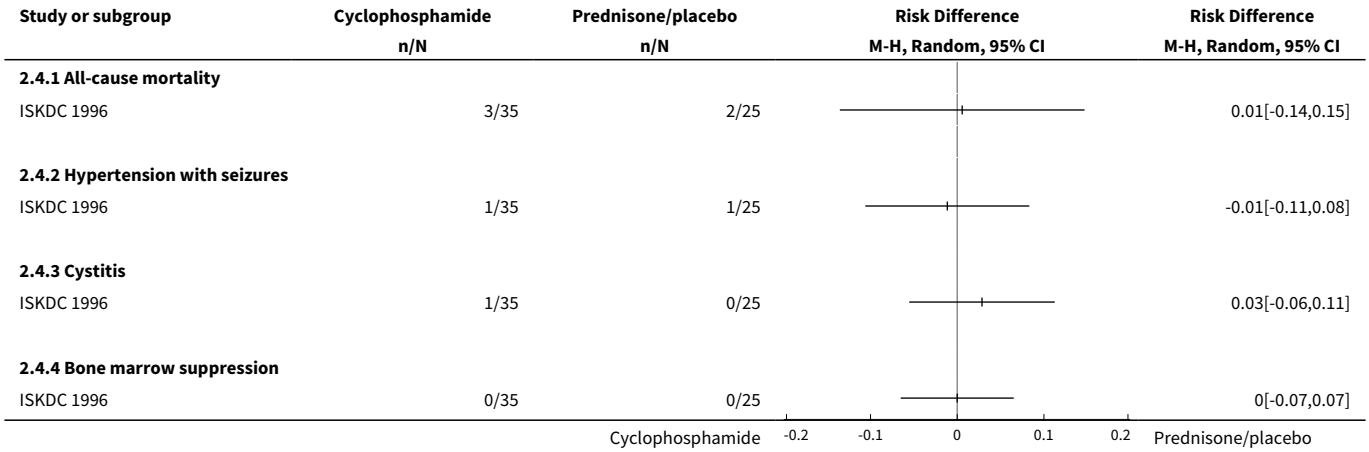
Analysis 2.2. Comparison 2 Oral cyclophosphamide versus prednisone/placebo, Outcome 2 Complete or partial remission.



Analysis 2.3. Comparison 2 Oral cyclophosphamide versus prednisone/placebo, Outcome 3 Treatment failure.



Analysis 2.4. Comparison 2 Oral cyclophosphamide versus prednisone/placebo, Outcome 4 Adverse events.

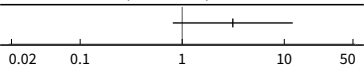


Comparison 3. IV versus oral cyclophosphamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
2.1 Vomiting	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Bacterial infection	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

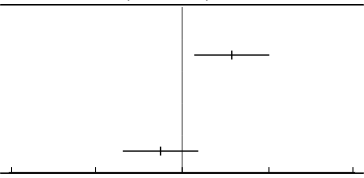
Analysis 3.1. Comparison 3 IV versus oral cyclophosphamide, Outcome 1 Complete remission.

Study or subgroup	IV cyclophosphamide n/N	Oral cyclophosphamide n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Elhence 1994	7/7	1/4		3.13[0.81,12.06]



Analysis 3.2. Comparison 3 IV versus oral cyclophosphamide, Outcome 2 Adverse events.

Study or subgroup	IV cyclophosphamide n/N	Oral cyclophosphamide n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
3.2.1 Vomiting				
Elhence 1994	4/7	0/4		0.57[0.14,1]
3.2.2 Bacterial infection				
Elhence 1994	0/7	1/4		-0.25[-0.69,0.19]



Comparison 4. Azathioprine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 All renal pathologies	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 All renal pathologies	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Azathioprine versus placebo, Outcome 1 Complete remission.

Study or subgroup	Azathioprine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.1.1 All renal pathologies				
ISKDC 1970	2/16	2/15		0.94[0.15,5.84]

Analysis 4.2. Comparison 4 Azathioprine versus placebo, Outcome 2 Complete or partial remission.

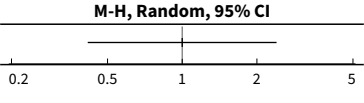
Study or subgroup	Azathioprine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 All renal pathologies				
ISKDC 1970	4/16	4/15		0.94[0.28,3.09]

Comparison 5. Chlorambucil versus indomethacin

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

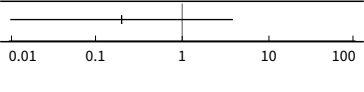
Analysis 5.1. Comparison 5 Chlorambucil versus indomethacin, Outcome 1 Complete remission.

Study or subgroup	Chlorambucil n/N	Indomethacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kleinknecht 1979	6/15	6/15		1[0.42,2.4]



Analysis 5.2. Comparison 5 Chlorambucil versus indomethacin, Outcome 2 End-stage kidney disease.

Study or subgroup	Chlorambucil n/N	Indomethacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kleinknecht 1979	0/15	2/15		0.2[0.01,3.85]

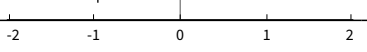


Comparison 6. Fosinopril and prednisone versus prednisone alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 After 4 weeks of treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 8 weeks of treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 After 12 weeks of treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Tubular proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Retinol binding protein (mg/L)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Beta 2 microglobulin (mg/L)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Serum albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum potassium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

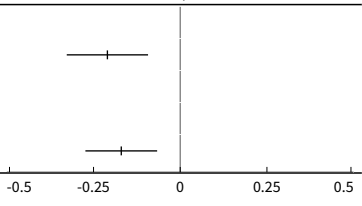
Analysis 6.1. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 1 Proteinuria.

Study or subgroup	Fosinopril + prednisone N	Fosinopril + prednisone Mean(SD)	Prednisone alone N	Prednisone alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
6.1.1 After 4 weeks of treatment						
Yi 2006	25	1.3 (0.6)	20	2.5 (0.6)		-1.27[-1.62,-0.92]
6.1.2 After 8 weeks of treatment						
Yi 2006	25	1.2 (0.5)	20	2.4 (0.2)		-1.26[-1.47,-1.05]
6.1.3 After 12 weeks of treatment						
Yi 2006	25	1.1 (0.4)	20	2.1 (0.5)		-0.95[-1.21,-0.69]



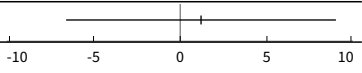
Analysis 6.2. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 2 Tubular proteinuria.

Study or subgroup	Fosinopril + prednisone N	Mean(SD)	Prednisone alone N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
6.2.1 Retinol binding protein (mg/L)						
Yi 2006	25	0.4 (0.2)	20	0.6 (0.2)		-0.21[-0.33,-0.09]
6.2.2 Beta 2 microglobulin (mg/L)						
Yi 2006	25	0.5 (0.1)	20	0.6 (0.2)		-0.17[-0.27,-0.07]



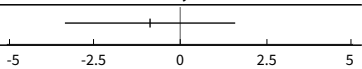
Analysis 6.3. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 3 Serum albumin.

Study or subgroup	Fosinopril + prednisone N	Mean(SD)	Prednisone alone N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Yi 2006	25	30.1 (14.2)	20	28.9 (12.4)		1.2[-6.58,8.98]



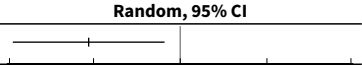
Analysis 6.4. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 4 Systolic blood pressure.

Study or subgroup	Fosinopril + prednisone N	Mean(SD)	Prednisone alone N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Yi 2006	25	90.7 (3.7)	20	91.6 (4.5)		-0.87[-3.33,1.59]



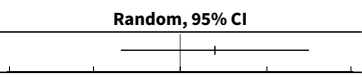
Analysis 6.5. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 5 Creatinine clearance.

Study or subgroup	Fosinopril + prednisone N	Mean(SD)	Prednisone alone N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Yi 2006	25	88.8 (8.3)	20	94.1 (6.7)		-5.28[-9.66,-0.9]



Analysis 6.6. Comparison 6 Fosinopril and prednisone versus prednisone alone, Outcome 6 Serum potassium.

Study or subgroup	Fosinopril + prednisone N	Mean(SD)	Prednisone alone N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Yi 2006	25	4.3 (0.9)	20	4.1 (0.9)		0.2[-0.34,0.74]

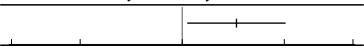


Comparison 7. Cyclosporin versus IV cyclophosphamide

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

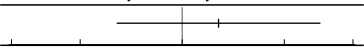
Analysis 7.1. Comparison 7 Cyclosporin versus IV cyclophosphamide, Outcome 1 Complete or partial remission at 12 weeks.

Study or subgroup	Cyclosporin n/N	IV cyclophosphamide n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 2008	9/15	3/17		3.4[1.12,10.28]



Analysis 7.2. Comparison 7 Cyclosporin versus IV cyclophosphamide, Outcome 2 Complete remission at 12 weeks.

Study or subgroup	Cyclosporin n/N	IV cyclophosphamide n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
APN 2008	2/15	1/17		2.27[0.23,22.56]



Comparison 8. Tacrolimus versus cyclosporin

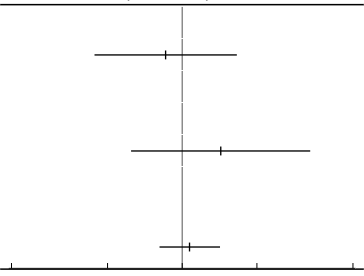
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Complete and partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Treatment response at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Complete and partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Relapse following complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Post hoc analysis: complete remission in initial and late onset SRNS	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Initial SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Late SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Post hoc analysis: complete or partial remission in initial and late onset SRNS	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Initial SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Late SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change in estimated GFR over 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
7.1 Persistent nephrotoxicity	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Reversible nephrotoxicity	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Worsening of hypertension	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Headache	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.5 Paraesthesia	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.6 Hypertrichosis	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.7 Gingival hyperplasia	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.8 Acne or skin infections	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.9 Diarrhoea	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.10 Sepsis/pneumonia	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

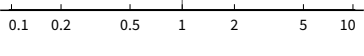
Analysis 8.1. Comparison 8 Tacrolimus versus cyclosporin, Outcome 1 Treatment response at 6 months.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 Complete remission				
Choudhry 2009	9/21	10/20		0.86[0.44,1.66]
8.1.2 Partial remission				
Choudhry 2009	9/21	6/20		1.43[0.62,3.28]
8.1.3 Complete and partial remission				
Choudhry 2009	18/21	16/20		1.07[0.81,1.42]



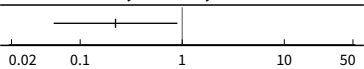
Analysis 8.2. Comparison 8 Tacrolimus versus cyclosporin, Outcome 2 Treatment response at 12 months.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.2.1 Complete remission				
Choudhry 2009	10/21	11/20		0.87[0.48,1.58]
8.2.2 Partial remission				
Choudhry 2009	8/21	4/20		1.9[0.68,5.35]
8.2.3 Complete and partial remission				
Choudhry 2009	18/21	15/20		1.14[0.84,1.55]



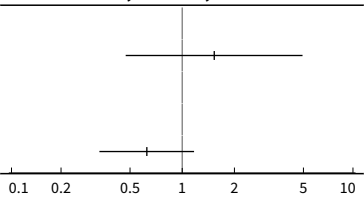
Analysis 8.3. Comparison 8 Tacrolimus versus cyclosporin, Outcome 3 Relapse following complete or partial remission.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Choudhry 2009	2/18	8/16		0.22[0.06,0.9]



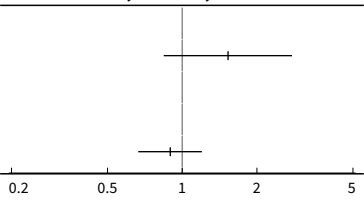
Analysis 8.4. Comparison 8 Tacrolimus versus cyclosporin, Outcome 4 Post hoc analysis: complete remission in initial and late onset SRNS.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.4.1 Initial SRNS				
Choudhry 2009	5/12	3/11		1.53[0.47,4.94]
8.4.2 Late SRNS				
Choudhry 2009	5/9	8/9		0.63[0.33,1.17]



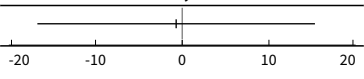
Analysis 8.5. Comparison 8 Tacrolimus versus cyclosporin, Outcome 5 Post hoc analysis: complete or partial remission in initial and late onset SRNS.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.5.1 Initial SRNS				
Choudhry 2009	10/12	6/11		1.53[0.84,2.77]
8.5.2 Late SRNS				
Choudhry 2009	8/9	9/9		0.89[0.67,1.2]



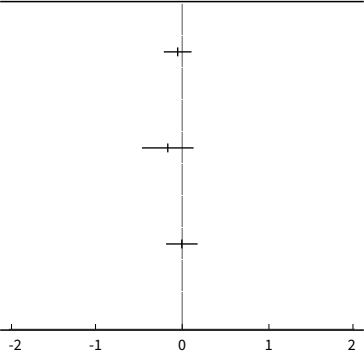
Analysis 8.6. Comparison 8 Tacrolimus versus cyclosporin, Outcome 6 Change in estimated GFR over 12 months.

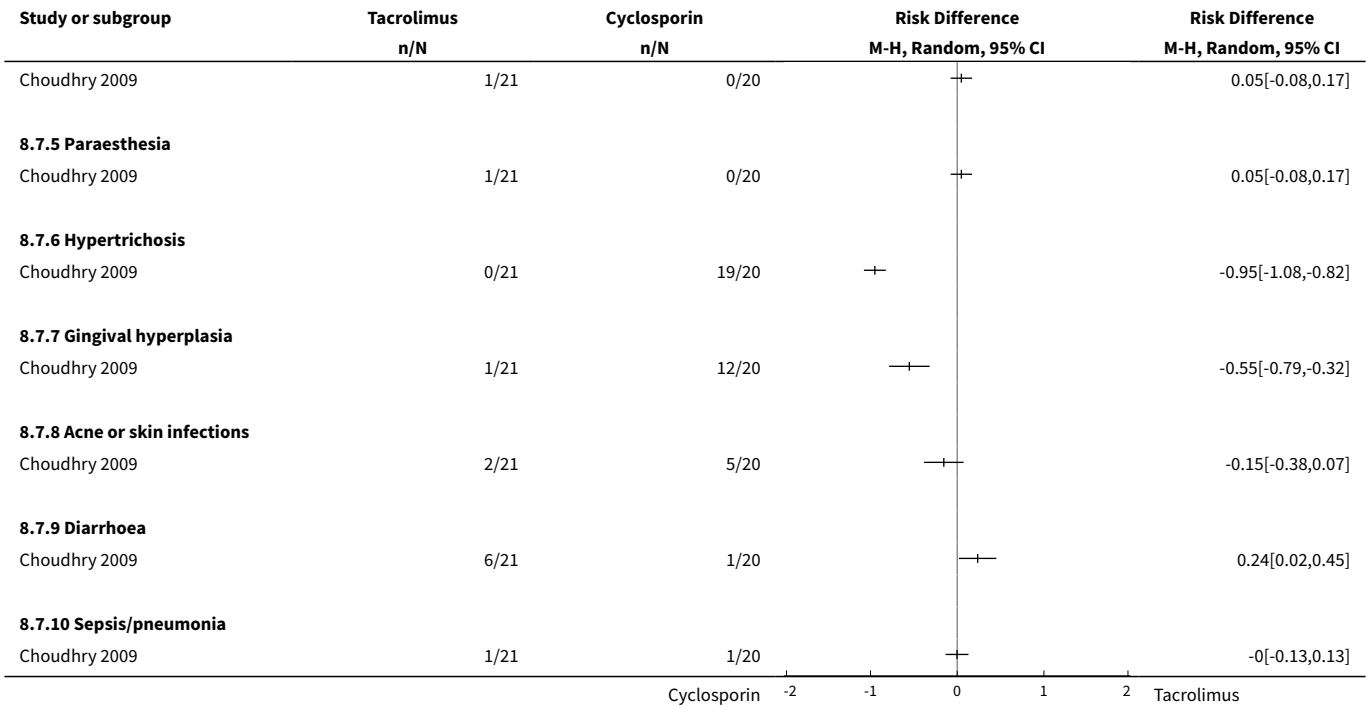
Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Choudhry 2009	19	-12 (20.8)	16	-11.3 (26.5)		-0.7[-16.71,15.31]



Analysis 8.7. Comparison 8 Tacrolimus versus cyclosporin, Outcome 7 Adverse events.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
8.7.1 Persistent nephrotoxicity				
Choudhry 2009	1/21	2/20		-0.05[-0.21,0.11]
8.7.2 Reversible nephrotoxicity				
Choudhry 2009	7/21	10/20		-0.17[-0.46,0.13]
8.7.3 Worsening of hypertension				
Choudhry 2009	2/21	2/20		-0[-0.19,0.18]
8.7.4 Headache				





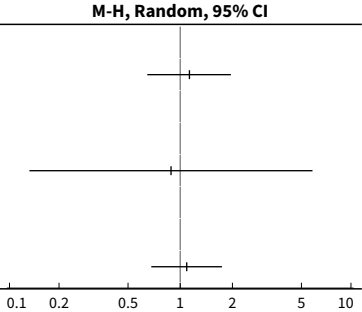
Comparison 9. IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Treatment response at 18 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Sustained remission/steroid sensitive relapses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 CKD	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Complete or partial resistance in subgroups	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Initial SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Late SRNS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Minimal change disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.4 FSGS or MesPGN	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
4.1 Hypertension	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 cataract/glaucoma	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Cushingoid features	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Leucopenia	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Cystitis	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Bacterial infections	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.7 Hypokalaemia	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.8 Steroid encephalopathy	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.9 Hair loss	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

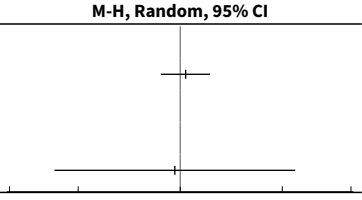
Analysis 9.1. Comparison 9 IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide, Outcome 1 Treatment response at 6 months.

Study or subgroup	IV cyclophosphamide n/N	IV dexametha-sone/oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.1.1 Complete remission				
Mantan 2008	14/26	11/23		1.13[0.65,1.96]
9.1.2 Partial remission				
Mantan 2008	2/26	2/23		0.88[0.14,5.79]
9.1.3 Complete or partial remission				
Mantan 2008	16/26	13/23		1.09[0.68,1.74]



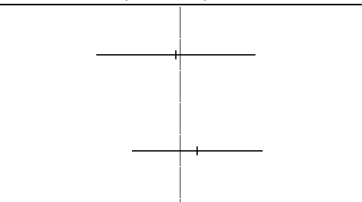
Analysis 9.2. Comparison 9 IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide, Outcome 2 Treatment response at 18 months.

Study or subgroup	IV cyclophosphamide n/N	IV dexamethasone/oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.2.1 Sustained remission/steroid sensitive relapses				
Mantan 2008	14/26	11/23		1.13[0.65,1.96]
9.2.2 CKD				
Mantan 2008	1/26	1/23		0.88[0.06,13.35]



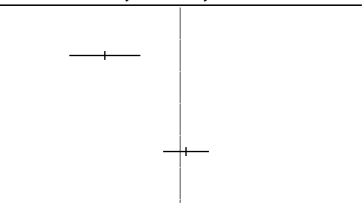
Analysis 9.3. Comparison 9 IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide, Outcome 3 Complete or partial resistance in subgroups.

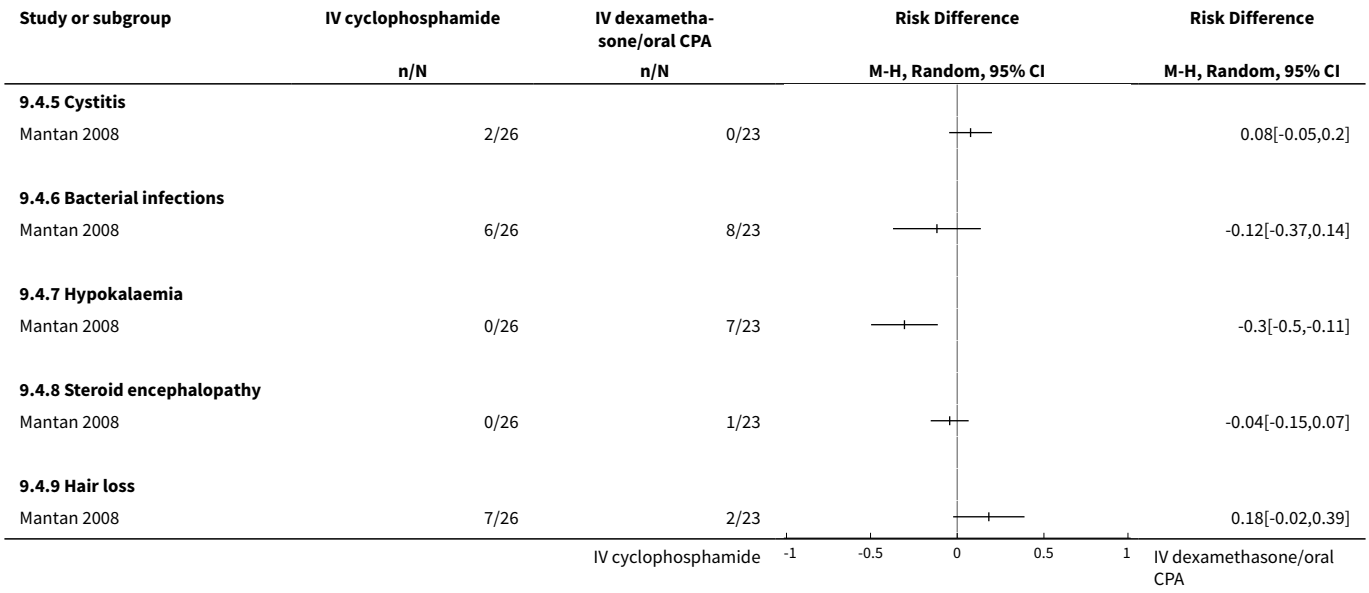
Study or subgroup	IV cyclophosphamide n/N	IV dexamethasone/oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.3.1 Initial SRNS				
Mantan 2008	6/10	5/8		0.96[0.46,2.01]
9.3.2 Late SRNS				
Mantan 2008	10/16	8/15		1.17[0.64,2.15]
9.3.3 Minimal change disease				
Mantan 2008	9/13	7/11		1.09[0.61,1.93]
9.3.4 FSGS or MesPGN				
Mantan 2008	7/13	6/12		1.08[0.51,2.3]



Analysis 9.4. Comparison 9 IV cyclophosphamide versus IV dexamethasone and oral cyclophosphamide, Outcome 4 Adverse events.

Study or subgroup	IV cyclophosphamide n/N	IV dexamethasone/oral CPA n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
9.4.1 Hypertension				
Mantan 2008	0/26	10/23		-0.43[-0.64,-0.23]
9.4.2 cataract/glaucoma				
Mantan 2008	2/26	1/23		0.03[-0.1,0.17]
9.4.3 Cushingoid features				
Mantan 2008	15/26	17/23		-0.16[-0.42,0.1]
9.4.4 Leucopenia				
Mantan 2008	2/26	0/23		0.08[-0.05,0.2]





ADDITIONAL TABLES

Table 1. Quality assessment

Study ID	Allocation concealment	Blinding - investigator	Blinding - patients	Blinding - outcome assessors	ITT	Loss to follow-up
APN 2008	Yes	No	No	Not stated	Yes	0% at 12 weeks
Bagga 2004	Yes	No	No	Not stated	No	0%
Chongviriyaphan 1999	Unclear	Yes	Yes	Not stated	No	17%
Choudhry 2009	Yes	No	No	Yes for side effects	Yes	0%
Elhence 1994	Unclear	No	No	Not stated	No	15%
Garin 1988	Unclear	No	No	Not stated	Unclear	0%
ISKDC 1970	Yes	Yes	Yes	Not stated	No	0%
ISKDC 1974	Unclear	No	No	Not stated	Unclear	0%
ISKDC 1996	Yes	No	No	Not stated	Unclear	Not stated
Kleinknecht 1979	Unclear	No	No	Not stated	Unclear	0%
Lieberman 1996	Yes	Yes	Yes	Not stated	No	0%
Mantan 2008	Yes	No	No	Not stated	No	5.8%
Ponticelli 1993a	Yes	No	No	Not stated	No	5%

Table 1. Quality assessment *(Continued)*

Yi 2006	Unclear	No	No	Not stated	No	21%

ITT - intention-to-treat

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	#1. (Nephrotic and syndrome) #2. Child #3. Nephrosis*.ME #4. Nephrosis-Lipoid*.ME #5. Nephrotic - Syndrome*.ME #6. #1 or #3 or #4 or #5 #7. #2 and #6
MEDLINE	1-22 Cochrane search strategy for MEDLINE as defined in the Cochrane Renal Group Module 23. exp nephrotic syndrome/ or nephrotic syndrome.ti,ab,sh. 24. exp nephrosis, lipoid/ or lipoid nephrosis.ti,ab,sh. 25. 23 or 24 26. exp adult/ 27. 22 and 25 28. 27 not 26
EMBASE	1-12 Cochrane search strategy for EMBASE as defined in the Cochrane Renal Group Module 13. exp nephrotic syndrome/ or nephrotic syndrome.ti,ab,hw,tn,mf. 14. 12 and 13

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*Yes (low risk of bias):* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	No (high risk of bias): Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Was allocation adequately concealed?	*Yes (low risk of bias):* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

(Continued)

	No (high risk of bias): Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Was knowledge of the allocated interventions adequately prevented during the study?	*Yes (low risk of bias):* No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
	No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
Were incomplete outcome data adequately addressed?	*Yes (low risk of bias):* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Are reports of the study free of suggestion of selective outcome reporting?	*Yes (low risk of bias):* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	No (high risk of bias): Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Was the study apparently free of other problems that could put it at a risk of bias?	*Yes (low risk of bias):* The study appears to be free of other sources of bias.

(Continued)

	No (high risk of bias): Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.

WHAT'S NEW

Date	Event	Description
29 September 2010	New citation required and conclusions have changed	Four new studies, new comparisons, risk of bias assessment replaces quality assessment and summary of findings tables included.

HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 2, 2004

Date	Event	Description
9 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Designing the Review; EH, DH, JC
- Coordinating the review; EH
- Study selection, quality assessment, data collection; EH, DH, NW
- Entering data into RevMan; DH, EH, NW
- Analysis of data; DH, EH, NW
- Interpretation of data; DH, EH, NW, JC
- Writing the review; DH, EH, NW, JC
- Providing general advice on the review; EH, NW and JC

DECLARATIONS OF INTEREST

None declared

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHMRC, Australia.

  The Cochrane Renal Group is supported in part by NHMRC grants
- Australian Government Department of Health and Ageing, Australia.

  The Cochrane Renal Group receives funding from the Department of Health and Ageing

NOTES

2010: The risk of bias assessment tool has replaced the quality assessment checklist used in previous versions of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiotensin-Converting Enzyme Inhibitors [therapeutic use]; Azathioprine [therapeutic use]; Cyclophosphamide [therapeutic use]; Cyclosporine [therapeutic use]; Dexamethasone [therapeutic use]; Drug Resistance; Glucocorticoids [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Isoxazoles [therapeutic use]; Mycophenolic Acid [analogs & derivatives] [therapeutic use]; Nephrotic Syndrome [*drug therapy]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant