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

Hodson EM, Wong SC, Willis NS, Craig JC

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[Intervention Review]

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

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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. This is an update of a review first published in 2004 and updated in 2006 and 2010.

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.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register (up to 2 March 2016) through contact with the Information Specialist using search terms relevant to this review.

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 risk of bias 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

Nineteen RCTs (820 children enrolled; 773 evaluated) were included. Most studies were small. Eleven studies were at low risk of bias for allocation concealment and only four studies were at low risk of performance bias. Fifteen, eight and 10 studies were at low risk of detection bias, attrition bias and reporting bias respectively. Cyclosporin when compared with placebo or no treatment significantly increased the number of children who achieved complete remission. However this was based on only eight children who achieved remission with cyclosporin compared with no children who achieved remission with placebo/no treatment in three small studies (49 children: RR 7.66, 95% CI 1.06 to 55.34). Calcineurin inhibitors significantly increased the number with complete or partial remission compared with IV cyclophosphamide (2 studies, 156 children: RR 1.98, 95% CI 1.25 to 3.13; I^2 = 20%). There was no significant differences in the number who

achieved complete remission between tacrolimus versus cyclosporin (1 study, 41 children: RR 0.86, 95% CI 0.44 to 1.66), cyclosporin versus mycophenolate mofetil plus dexamethasone (1 study, 138 children: RR 2.14, 95% CI 0.87 to 5.24), oral cyclophosphamide with prednisone versus prednisone alone (2 studies, 91 children: RR 1.06, 95% CI 0.61 to 1.87), IV versus oral cyclophosphamide (1 study, 11 children: RR 3.13, 95% CI 0.81 to 12.06), IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone (1 study, 49 children: RR 1.13, 95% CI 0.65 to 1.96), and azathioprine with prednisone versus prednisone alone (1 study, 31 children: RR 0.94, 95% CI 0.15 to 5.84). One study found no significant differences between three agents (cyclophosphamide, mycophenolate mofetil, leflunomide) used in combination with tacrolimus and prednisone. One study found no significant difference in the percentage reduction in proteinuria (31 children: -12; 95% CI -73 to 110) between rituximab with cyclosporin/prednisolone and cyclosporin/prednisolone alone. Two studies reported ACEi significantly reduced proteinuria.

Authors' conclusions

To date RCTs have demonstrated that calcineurin inhibitors increase the likelihood of complete or partial remission compared with placebo/no treatment or cyclophosphamide. For other regimens assessed, it remains uncertain whether the interventions alter outcomes because the certainty of the evidence is low. Further adequately powered, well designed RCTs are needed to evaluate other regimens for children with idiopathic SRNS. Since SRNS represents a spectrum of diseases, future studies should enrol children from better defined groups of patients with SRNS.

PLAIN LANGUAGE SUMMARY

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

What is the issue?

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 (steroid-resistant nephrotic syndrome) and other agents such as cyclophosphamide, calcineurin inhibitors (cyclosporin, tacrolimus) or angiotensin-converting enzyme inhibitors may be used.

What did we do?

We searched Cochrane Kidney and Transplant's Specialised Register (up to 2 March 2016) through contact with the Information Specialist using search terms relevant to this review. Randomised controlled trials 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 steroid-resistant nephrotic syndrome.

What did we find?

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. Calcineurin inhibitors 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. Angiotensin-converting enzyme inhibitors significantly reduced the degree of proteinuria. However the number of studies was small with small numbers of children per study.

Summary of findings for the main comparison. Cyclosporin versus placebo/no treatment

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology clinics
Intervention: cyclosporin
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with Cyclosporin				
Complete remission: all renal pathologies	Study population		RR 7.66 (1.06 to 55.34)	49 (3)	⊕⊕⊝⊝ LOW [1,2]	
	0 per 1000	0 per 1000 (0 to 0)				
Complete remission: FSGS	Study population		RR 5.83 (0.75 to 45.09)	33 (2)	⊕⊕⊝⊝ LOW [1]	
	0 per 1000	0 per 1000 (0 to 0)				
Complete or partial remission: all renal pathologies	Study population		RR 5.48 (1.95 to 15.44)	49 (3)	⊕⊕⊝⊝ LOW [1,2]	
	87 per 1000	477 per 1000 (170 to 1000)				
Complete or partial remission: FSGS	Study population		RR 5.00 (1.63 to 15.31)	24 (1)	⊕⊕⊝⊝ LOW [1]	
	167 per 1000	833 per 1000 (272 to 1000)				
	Moderate					
	167 per 1000	834 per 1000 (272 to 1000)				

Adverse events: worsening of hypertension	Study population		not estimable	24 (1)	⊕⊕⊖⊖ LOW [1]
	167 per 1000	**Not estimable**			
	Moderate				
	167 per 1000	**Not estimable**			
Adverse events: infection	Study population		not estimable	17 (1)	⊕⊖⊖⊖ VERY LOW [1 3]
	429 per 1000	**Not estimable**			
	Moderate				
	429 per 1000	**Not estimable**			

*__The risk in the intervention group__ (and its 95% CI) 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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Few enrolled patients with few events
[2] Risk of selection bias in 1 of 3 studies; 2 of 3 studies at risk of performance bias
[3] Risk of performance bias

Summary of findings 2. Calcineurin inhibitors versus IV cyclophosphamide

Interventions for idiopathic nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology clinics
Intervention: calcineurin inhibitor (CNI)

Comparison: IV cyclophosphamide (CPA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IV CPA	Risk with CNI				
Remission at 3 to 6 months: complete or partial remission	Study population		RR 1.98 (1.25 to 3.13)	156 (2)	⊕⊕⊝⊝ LOW [1 2]	
	397 per 1000	787 per 1000 (497 to 1000)				
	Moderate					
	318 per 1000	629 per 1000 (397 to 994)				
Remission at 3 to 6 months: complete remission	Study population		RR 3.43 (1.84 to 6.41)	156 (2)	⊕⊕⊝⊝ LOW [1 2]	
	128 per 1000	440 per 1000 (236 to 822)				
	Moderate					
	103 per 1000	354 per 1000 (190 to 662)				
Remission at 3 to 6 months: partial remission	Study population		RR 1.68 (0.43 to 6.56)	156 (2)	⊕⊝⊝⊝ VERY LOW [1 2 3]	
	269 per 1000	452 per 1000 (116 to 1000)				
	Moderate					
	215 per 1000	361 per 1000 (92 to 1000)				
Adverse events: treatment failure (non response, serious infection, persistently elevated creatinine) at 6 months	Study population		RR 0.32 (0.18 to 0.58)	124 (1)	⊕⊕⊕⊝ MODERATE [4]	
	541 per 1000	173 per 1000 (97 to 314)				
	Moderate					

	541 per 1000	173 per 1000 (97 to 314)			
Adverse events: medications ceased due to adverse events	Study population		RR 0.20 (0.04 to 0.86)	131 (1)	⊕⊕⊕⊖ MODERATE [4]
	154 per 1000	31 per 1000 (6 to 132)			
	Moderate				
	154 per 1000	31 per 1000 (6 to 132)			
Adverse events: serious infections	Study population		RR 0.49 (0.16 to 1.56)	131 (1)	⊕⊕⊕⊖ MODERATE [4]
	123 per 1000	60 per 1000 (20 to 192)			
	Moderate				
	123 per 1000	60 per 1000 (20 to 192)			
Adverse events: death	Study population		RR 0.33 (0.01 to 7.92)	131 (1)	⊕⊕⊖⊖ LOW [4]
	15 per 1000	5 per 1000 (0 to 122)			
	Moderate				
	15 per 1000	5 per 1000 (0 to 122)			

*__The risk in the intervention group__ (and its 95% CI) 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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Small patient numbers and events
[2] High risk of attrition bias in one study
[3] Heterogeneity between studies
[4] Single study; small patient numbers and events

Summary of findings 3. Cyclosporin versus mycophenolate mofetil with dexamethasone

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: Paediatric and adult nephrology clinics
Intervention: cyclosporin
Comparison: mycophenolate mofetil with pulse dexamethasone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with mycophenolate mofetil with pulse dexamethasone	Risk with Cyclosporin				
Remission at 52 weeks: complete remission (primary outcome 1,2)	Study population		RR 2.14 (0.87 to 5.24)	138 (1)	⊕⊕⊕⊖ MODERATE [1]	
	91 per 1000	195 per 1000 (79 to 476)				
	Moderate					
	91 per 1000	195 per 1000 (79 to 476)				
Remission at 52 weeks: complete or partial remission (primary outcome 1,2,3)	Study population		RR 1.38 (0.90 to 2.10)	138 (1)	⊕⊕⊕⊖ MODERATE [1]	
	333 per 1000	460 per 1000 (300 to 700)				
	Moderate					
	333 per 1000	460 per 1000 (300 to 700)				

CKD or death: death by 52 weeks	Study population		RR 0.18 (0.01 to 3.75)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
	30 per 1000	5 per 1000 (0 to 114)			
	Moderate				
	30 per 1000	5 per 1000 (0 to 114)			
CKD or death: 50% decline in GFR by 78 weeks	Study population		RR 2.29 (0.46 to 11.41)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
	30 per 1000	69 per 1000 (14 to 346)			
	Moderate				
	30 per 1000	69 per 1000 (14 to 346)			
Adverse effects (weeks 0 to 26): serious infection requiring hospitalisation	Study population		RR 0.65 (0.22 to 1.96)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
	106 per 1000	69 per 1000 (23 to 208)			
	Moderate				
	106 per 1000	69 per 1000 (23 to 208)			
Adverse effects (weeks 0 to 26): neuropsychiatric conditions	Study population		RR 1.26 (0.73 to 2.19)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
	242 per 1000	305 per 1000 (177 to 531)			
	Moderate				
	242 per 1000	305 per 1000 (177 to 531)			
Adverse effects (weeks 0 to 26): hypertension	Study population		RR 1.68 (0.66 to 4.29)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
	91 per 1000	153 per 1000			

		(60 to 390)
Moderate		
91 per 1000	153 per 1000 (60 to 390)	

*__The risk in the intervention group__ (and its 95% CI) 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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Insufficient recruitment to exclude difference between treatments

Summary of findings 4. Oral cyclophosphamide versus prednisone/placebo

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology clinics
Intervention: oral cyclophosphamide
Comparison: prednisone/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with prednisone/placebo	Risk with Oral cyclophosphamide				
Complete remission: all renal pathologies	Study population		RR 1.06 (0.61 to 1.87)	84 (2)	⊕⊕⊝⊝ LOW [1 2]	
	353 per 1000	374 per 1000 (215 to 660)				
	Moderate					

	374 per 1000	396 per 1000 (228 to 699)				
Complete remission: FSGS	Study population		RR 1.01 (0.43 to 2.37)	63 (2)	⊕⊕⊝⊝ LOW [1 2]	
	250 per 1000	253 per 1000 (108 to 593)				
	Moderate					
	143 per 1000	144 per 1000 (61 to 339)				
Complete or partial remission	Study population		RR 0.88 (0.53 to 1.45)	53 (1)	⊕⊕⊝⊝ LOW [2 3]	
	571 per 1000	503 per 1000 (303 to 829)				
	Moderate					
	571 per 1000	503 per 1000 (303 to 829)				
Treatment failure	Study population		RR 1.59 (0.87 to 2.88)	60 (1)	⊕⊕⊝⊝ LOW [2 3]	
	360 per 1000	572 per 1000 (313 to 1000)				
	Moderate					
	360 per 1000	572 per 1000 (313 to 1000)				
Adverse events: all-cause mortality	Study population		not estimable	60 (1)	⊕⊕⊝⊝ LOW [2 3]	Three events in cyclophosphamide group and two in prednisone group
	80 per 1000	**85 per 1000**				
	Moderate					
	80 per 1000	**85 per 1000**				
Adverse events: hypertension with seizures	Study population		not estimable	60 (1)	⊕⊝⊝⊝ VERY LOW [2 3]	One event in each group

	40 per 1000	**28 per 1000**				
	Moderate					
	40 per 1000	**28 per 1000**				
Adverse events: bone marrow suppression	Study population		not estimable	60 (1)	⊕⊝⊝⊝ VERY LOW [2 3]	No events in either group
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% CI) 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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Unclear risk of selection bias; risk of attrition bias in 1 study and selection bias in 1 study; no blinding
[2] Small patient numbers and few events
[3] Unclear risk of selection bias; high risk of attrition bias

BACKGROUND

Description of the condition

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. Children with untreated nephrotic syndrome are at increased risk of bacterial infection, characteristically resulting in peritonitis, cellulitis or septicaemia, of thromboembolic phenomena, protein calorie malnutrition. Prospective studies of children with newly diagnosed idiopathic nephrotic syndrome identified through Pediatric Surveillance Units in the Netherlands, Australia and New Zealand reported incidences of idiopathic nephrotic syndrome of 1.12 to 1.9 per 100,000 children aged below 16 years (El Bakkali 2011; Sureshkumar 2014; Wong 2007).

In clinical studies childhood nephrotic syndrome is classified into steroid-sensitive nephrotic syndrome (SSNS), steroid-resistant nephrotic syndrome (SRNS), congenital and infantile nephrotic syndrome (0 to 12 months) and nephrotic syndrome secondary to other diseases including Henoch Schönlein nephritis, systemic lupus erythematosus and hepatitis B nephropathy. Most children respond to corticosteroid therapy. In those children who fail to respond to corticosteroids, kidney biopsy is performed to determine pathology. The majority of children with SRNS have minimal change disease (MCD), mesangioproliferative glomerulonephritis (MesPGN) or focal segmental glomerulosclerosis (FSGS). FSGS is a leading cause of end-stage kidney disease (ESKD) in children. FSGS is a heterogeneous disease with some children having FSGS secondary to immunological factors, some children having FSGS secondary to mutations in the genes coding for podocyte proteins including podocin and nephrin and a few older children having FSGS secondary to hyperfiltration (reduced kidney mass, obesity, diabetes mellitus) (Deegens 2011). A study of 1783 unrelated families found that single gene mutations responsible for SRNS were identified in 29.5% families overall with mutations in 25.3% children aged 1 to 6 years old, 17.8% in children aged 7 to 12 years and 10.8% in adolescents aged 13 to 18 years (Sadowski 2015). Few children with FSGS secondary to genetic mutations respond to immunosuppressive agents and in these children, nephrotic syndrome rarely recurs following kidney transplantation (Ding 2014). Children with SRNS may have corticosteroid resistant disease from initial presentation (Initial resistance) or may develop steroid resistance after one or more responses to corticosteroids (delayed steroid resistance). About one third of children suffer recurrence of nephrotic syndrome following kidney transplantation. Recent data suggest that recurrence of disease post transplant is much more common in children with SRNS and delayed steroid resistance (Ding 2014). These data are consistent with an immunological cause of SRNS in these children.

Description of the intervention

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 who fail to respond to corticosteroids are treated with immunosuppressive agents such as calcineurin inhibitors (CNI) (cyclosporin, tacrolimus), cyclophosphamide, chlorambucil, mycophenolate mofetil, and the anti CD 20 monoclonal antibody, rituximab. Rates of complete and partial remission with CNI based on observational studies and individual groups in randomised controlled trials (RCTs) vary between 30% and 80% (Choudhry 2009; FSGS Study 2011; Niaudet 1994). Remission rates of up to 60% with combinations of intravenous (IV) methylprednisolone and cyclophosphamide are reported in observational studies (Tune 1996) and of around 50% in individual treatment groups in RCTs (Gulati 2012; ISKDC 1974; ISKDC 1996). Failure to achieve complete or partial remission is associated with progression to ESKD (Gipson 2006). Other non-immunosuppressive agents including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and fish oil have also been used in SRNS.

How the intervention might work

Corticosteroids, immunosuppressive agents and monoclonal antibodies may act by suppressing production of plasma factors by T and B cells since immunological mechanisms are believed to be responsible for some cases of SRNS. Some immunosuppressive medications including dexamethasone, the CNI, and rituximab may be effective in nonimmune causes of SRNS by directly targeting podocytes. ACEi and ARB reduce proteinuria and are aimed at reducing progressive glomerulosclerosis (Deegens 2011).

Why it is important to do this review

There is 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. Despite the use of newer immunosuppressive agents, the response rate to therapy remains relatively low. The aims of the update of this systematic review initially published in 2002 were to identify new RCTs assessing the benefits and harms of interventions used to treat idiopathic SRNS in children and to incorporate them where appropriate in meta-analyses.

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 RCTs and quasi-RCTs, in which different agents were 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 (UP/C) > 0.2 g/mmol (> 2mg/g) or > 40 mg/m^2/h after four weeks or more of daily corticosteroid agent). Where a kidney biopsy was per-

formed, only children with biopsy diagnoses of MCD, MesPGN, IgM nephropathy or FSGS were included. Children with initial steroid resistance and children with delayed steroid resistance were included.

Exclusion criteria

Children with SSNS, children with congenital nephrotic syndrome and children with other kidney or systemic forms of nephrotic syndrome defined on kidney biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schönlein nephritis, systemic lupus erythematosus, membranous glomerulopathy or mesangiocapillary glomerulonephritis) were excluded. Children with FSGS secondary to hyperfiltration (obesity, diabetes mellitus, reduced kidney mass) were excluded.

Types of interventions

All interventions were potentially eligible. Interventions considered were as follows.

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 urine protein was < 1+ on dipstick, urinary UP/C < 0.02 g/mmol (< 2 mg/g) 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 UP/C < 0.2 g/mmol or < 40 mg/m^2/h) and an increase in serum albumin levels
- Number reaching ESKD.

Secondary outcomes

- Changes in kidney function: serum creatinine (SCr); creatinine clearance (CrCl); estimated glomerular filtration rate (eGFR)
- Adverse effects of therapy
- Duration of remission or partial remission
- Reduction in proteinuria.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (up to 2 March 2016) through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

No other resources were searched for this update because the scope of Cochrane Kidney and Transplant's Specialised Register covers the most likely sources of studies.

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 the publication with the most complete data was used in the analyses. Disagreements were resolved in consultation with a third author.

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 2011) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?

- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- 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 reported in the text if they could not be included in meta-analyses.

Unit of analysis issues

Data from cross-over studies were included in the meta-analyses if separate data for the first part of the study were available. Otherwise results of cross-over studies were reported in the text only.

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. We aimed to analyse available data in meta-analyses using ITT data. However, where ITT data were not provided, or additional information could not be obtained from authors, available published data were used in the analyses.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 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). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

The search strategy used aimed to reduce publication bias caused by lack of publication of studies with negative results. Where there were several publications on the same study, all reports were reviewed to ensure that all details of methods and results were included to reduce the risk of selective outcome reporting bias.

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. However there were insufficient studies of each intervention to allow subgroup analyses.

Sensitivity analysis

Sensitivity analysis was planned to determine the effect of removal of a single study on the results of a meta-analysis when results of one study differed from other studies in the meta-analysis. However there were insufficient studies of each intervention to allow sensitivity analysis.

'Summary of findings' tables

For this update we have presented the main results of the review in a 'Summary of findings' table/s. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' table also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We have presented the following outcomes.

- Complete remission
- Partial remission
- Complete or partial remission
- Adverse events

RESULTS

Description of studies

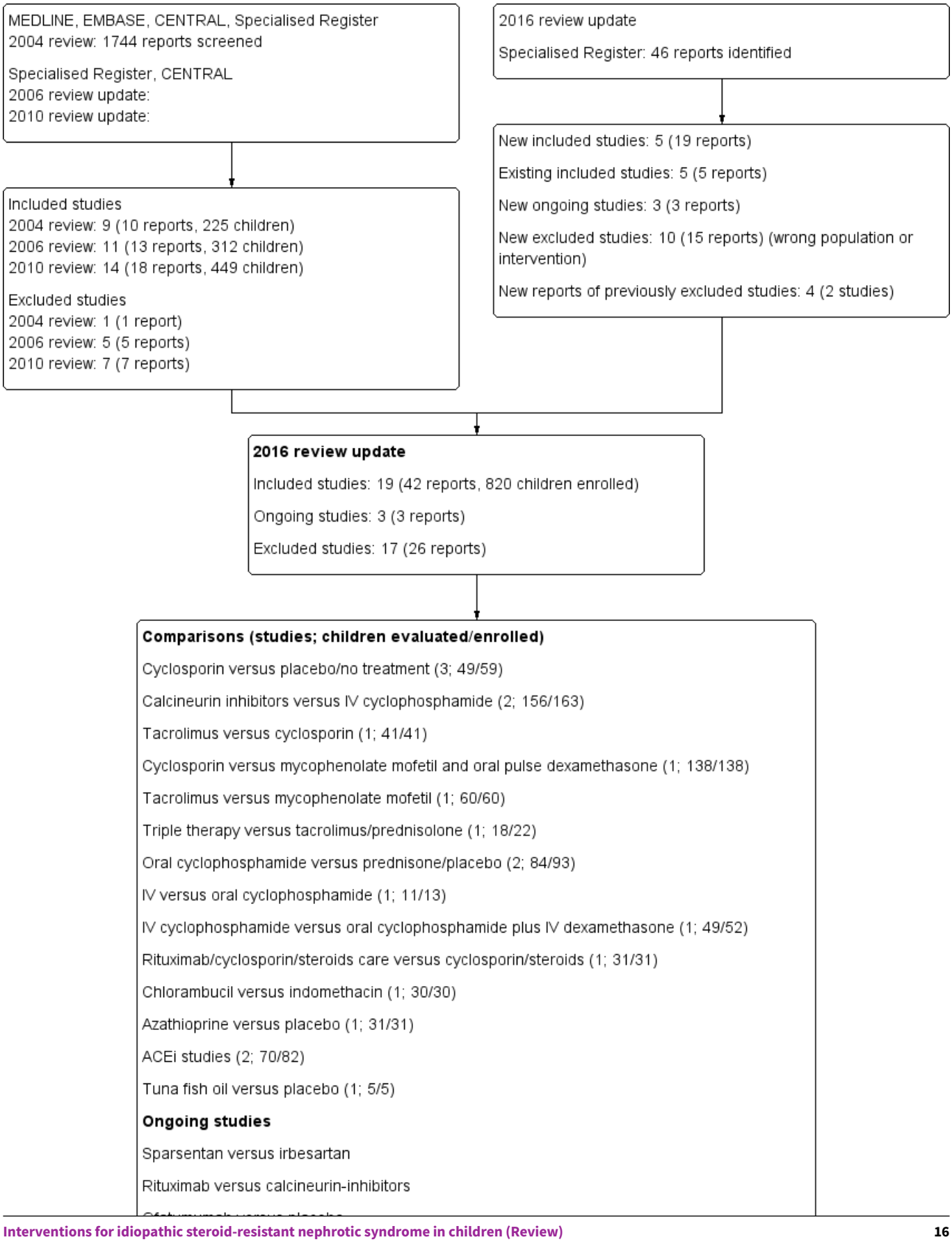
Results of the search

For the initial 2004 version of the review, of the 1744 titles and abstracts screened, 10 studies were identified; one study was excluded so nine studies (10 reports) were included in the review (Bagga 2004; Chongviriyaphan 1999; Elhence 1994; Garin 1988; ISKDC 1970; ISKDC 1974; ISKDC 1996; Lieberman 1996; Ponticelli 1993a). An update in 2006 identified four additional studies of which two were included (Kleinknecht 1980; Yi 2006) so the 2006 update included 11 studies (13 reports). A second update in 2010 identified three additional studies and the full publication of one study previously available as an abstract (Yi 2006). Therefore 14 studies (18 reports) were included in the 2010 update; 494 children entered the studies and 449 were evaluated.

A further search to March 2, 2016 identified 21 new studies, of which five were included (FSGS Study 2011; Gulati 2012; Magnasco 2012; Sinha 2015; Wu 2015). The 2016 update includes 19 studies (42 reports) comprising 820 children of whom 773 were evaluated (Figure 1). Although we were not able to obtain separate paediatric data from the authors, we chose to include FSGS Study 2011 because it was one of the largest studies looking at interventions for SRNS,

93 (67%) of participants were below 18 years of age and subgroup analyses by study authors showed no differences in outcomes between paediatric and adult participants. We also identified three ongoing studies. The first study is evaluating the safety and efficacy of sparsentan (a dual endothelin receptor) in a phase 2 study compared with irbesartan (an ARB) (NCT01613118). The second study is evaluating the 12 month relapse free survival in children with SRNS treated with rituximab or tacrolimus (NCT02382575). The third study is evaluating ofatumumab compared with placebo in children with steroid- and calcineurin-inhibitor-resistant nephrotic syndrome (NCT02394106).

Figure 1. Flowchart of included and excluded studies



Included studies

Study characteristics are shown in Characteristics of included studies

- Three studies compared cyclosporin with placebo or no treatment (49 children evaluated) (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. Lieberman 1996; Ponticelli 1993a included only children with initial steroid resistance.
- Two studies compared oral CNI with IV cyclophosphamide. APN 2008 (32 children) compared oral cyclosporin with IV cyclophosphamide in children with initial steroid resistance. Gulati 2012 (131 children) compared oral tacrolimus with IV cyclophosphamide in children with initial and delayed steroid resistance. Both studies included children with MCD, FSGS and MesPGN.
- Choudhry 2009 (41 children) compared oral cyclosporin with oral tacrolimus in children with initial or delayed steroid resistance. The study included children with MCD, FSGS and MesPGN.
- FSGS Study 2011 (138 participants) compared cyclosporin with mycophenolate mofetil (MMF) and oral dexamethasone in children (93) and adults (45) with biopsy confirmed primary FSGS and initial steroid resistance. Separate paediatric data could not be obtained from the authors.
- Wu 2015 (18/22 children evaluated) compared MMF, IV cyclophosphamide or leflunomide in three groups already receiving prednisone and tacrolimus. The study included children with MCD, FSGS, MesPGN and IgM nephropathy. The authors did not state whether the children had initial or delayed steroid resistance.
- Sinha 2015 (60 children) compared tacrolimus with MMF to maintain remission in children with initial or delayed steroid resistance, who had achieved remission with tacrolimus. The study included children with MCD and FSGS.
- Two studies (91/93 children evaluated) compared oral cyclophosphamide and prednisone with prednisone alone in children with initial steroid resistance (ISKDC 1974; ISKDC 1996). ISKDC 1974 included children with MCD, FSGS and MesPGN. ISKDC 1996 only included children with FSGS.
- Two studies compared IV with oral cyclophosphamide in children with initial or delayed steroid resistance (Elhence 1994; Mantan 2008). In Mantan 2008 (49/51 children evaluated), IV dexamethasone was given to children in the oral cyclophosphamide group. Elhence 1994 (13 children) only included children with MCD while Mantan 2008 included children with MCD, FSGS and MesPGN.
- Magnasco 2012 (31 children) compared rituximab and standard care (prednisolone and cyclosporin) with standard care alone in children with MCD, FSGS and unknown histology and with initial or delayed steroid resistance.
- Kleinknecht 1980 (30 children) compared chlorambucil with indomethacin. This study did not report whether patients had initial or delayed steroid resistance. The study included children with MCD, FSGS and MesPGN.
- ISKDC 1970 (31 children) compared azathioprine (AZA) and prednisone with placebo and prednisone in children with MCD, FSGS or MesPGN, who had initial steroid resistance.
- Two studies evaluated ACEi. Bagga 2004 (25 children) compared different doses of the ACEi, enalapril in children with MCD, FSGS or MesPGN in a cross over study. Yi 2006 (45/55 children evaluated) compared the ACEi, fosinopril, and prednisone with prednisone alone. Both studies included children with initial and delayed steroid resistance.
- Chongviriyaphan 1999 (5 children) compared fish oil with placebo in children with FSGS or MesPGN in a cross over study; the authors did not state whether the children had initial or delayed resistance.

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

Excluded studies

Seventeen studies (26 reports) were excluded.

- Adeniyi 1979 was excluded because 31/36 included children had nephrotic syndrome considered secondary to *Plasmodium malariae*
- Three studies were excluded because paediatric data could not be separated from adult data (Bhaumik 2002; Jung 1990; Shibasaki 2004)
- Eight studies did not include children (Arora 2002; Koshikawa 1993; Kumar 2004a; Li 2006g; Ren 2011; Ren 2013; Saito 2014; Walker 1990a)
- Two studies did not include children with nephrotic syndrome (Kano 2003) or included children with an ineligible renal pathology (Buyukcelik 2002)
- Two studies evaluated interventions in children with SSNS (Hiraoka 2000; Iyengar 2006)
- One study evaluated interventions in both children with steroid-resistant and steroid-dependent disease and the results could not be separated (Zhao 2013a).

Risk of bias in included studies

Figure 2; Figure 3

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

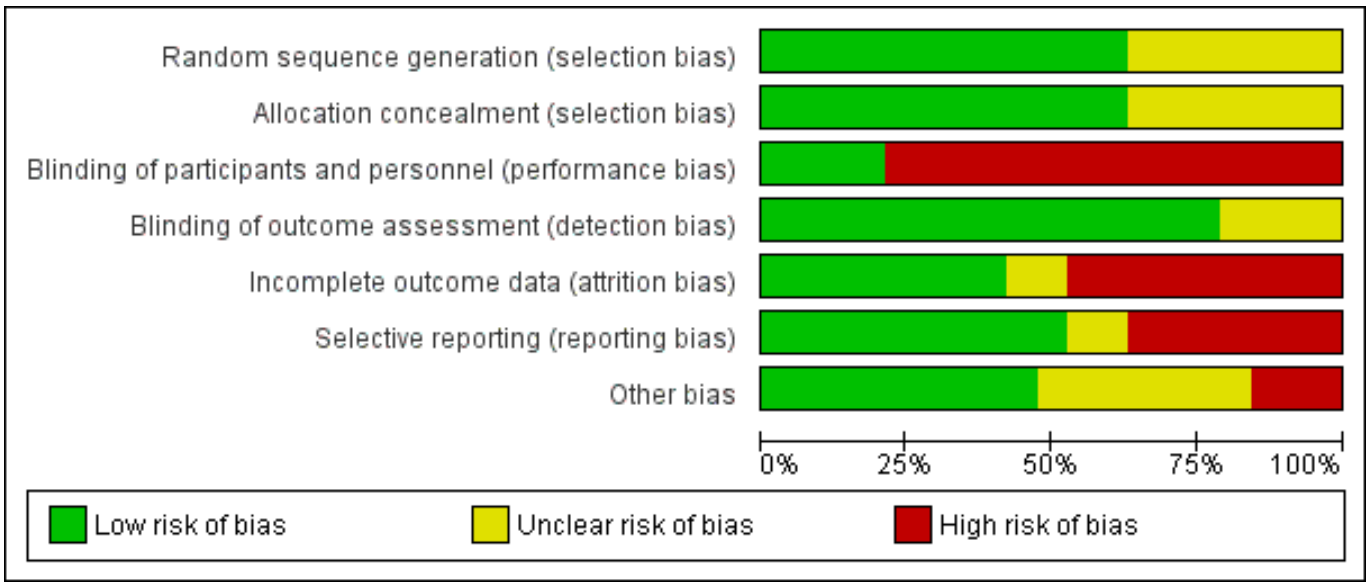


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

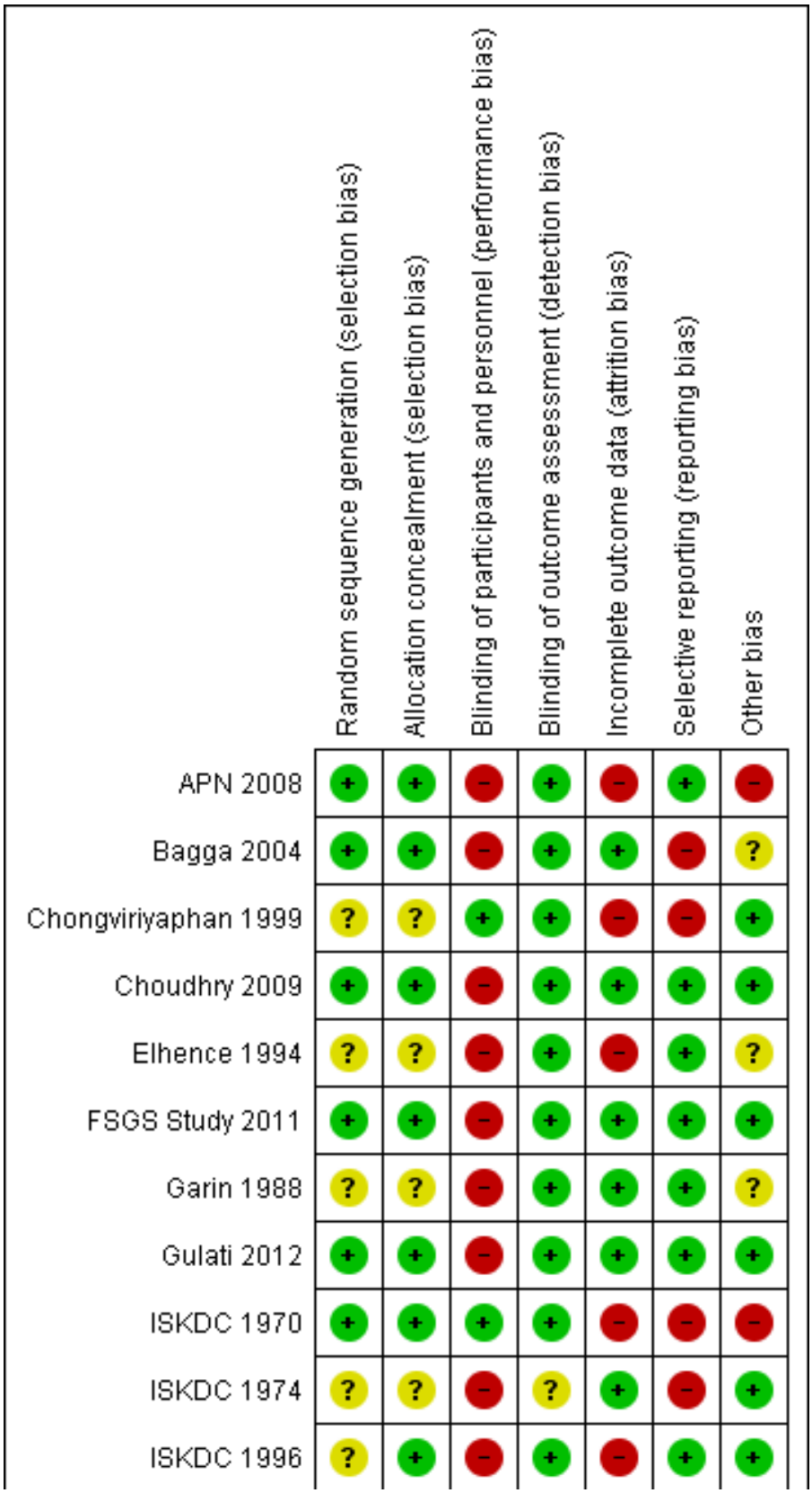
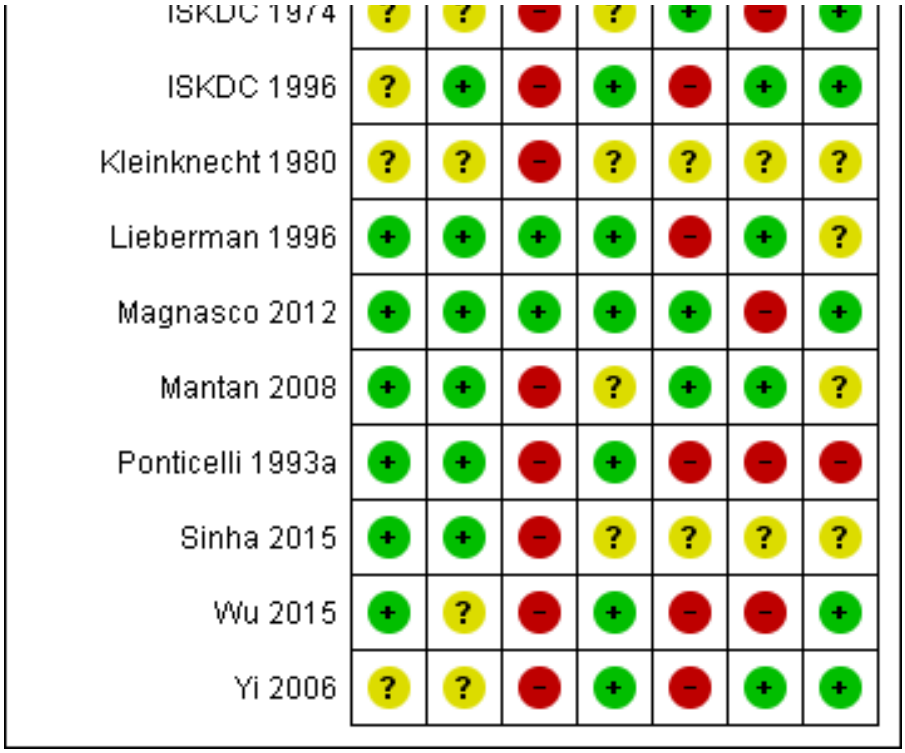


Figure 3. (Continued)



Allocation

Sequence generation was satisfactory in 12 studies (APN 2008; Bagga 2004; Choudhry 2009; FSGS Study 2011; Gulati 2012; ISKDC 1970; Lieberman 1996; Magnasco 2012; Mantan 2008; Ponticelli 1993a; Sinha 2015; Wu 2015) and unclear in the remaining seven studies.

Allocation concealment was adequate in 12 studies (APN 2008; Bagga 2004; Choudhry 2009; FSGS Study 2011; Gulati 2012; ISKDC 1970; ISKDC 1996; Lieberman 1996; Magnasco 2012; Mantan 2008; Ponticelli 1993a; Sinha 2015) and unclear in the remaining seven studies.

Blinding

Four studies reported that care givers (families, research staff) were blinded to treatment groups (Chongviriyaphan 1999; ISKDC 1970; Lieberman 1996; Magnasco 2012). In the remaining fifteen studies care givers were not blinded to treatment groups.

Fifteen studies were considered at low risk of detection bias as the outcome was laboratory-based and unlikely to be influenced by blinding. In two studies (ISKDC 1974; Mantan 2008), outcome of proteinuria was measured on dipstick or in a laboratory and it was unclear in how many children the outcome was laboratory-based. In two studies (Kleinknecht 1980; Sinha 2015), no information was provided on how the outcome was assessed.

Incomplete outcome data

Attrition bias was considered to be present if more than 10% of participants were excluded from analysis. Eight studies were considered to have provided complete outcome data (Bagga 2004; Choudhry 2009; FSGS Study 2011; Garin 1988; Gulati 2012; ISKDC 1974; Magnasco 2012; Mantan 2008). Nine studies did not provide complete outcome data. In the remaining two studies, available only as abstracts (Kleinknecht 1980; Sinha 2015), it was unclear whether complete outcome data was provided.

Selective reporting

Reporting bias was considered to be present if studies did not report on the number of patients with remission (complete or partial) and on adverse effects and if results of the primary outcome were not reported in a way that allowed inclusion of the data in meta-analyses. Ten studies were considered to be free of selective reporting (APN 2008; Choudhry 2009; Elhence 1994; FSGS Study 2011; Garin 1988; Gulati 2012; ISKDC 1996; Lieberman 1996; Mantan 2008; Yi 2006). Seven studies were considered to have reported outcomes selectively or no results could be included in meta-analyses (Bagga 2004; Chongviriyaphan 1999; ISKDC 1970; ISKDC 1974; Magnasco 2012; Ponticelli 1993a; Wu 2015) as results for adverse events were either not reported or incompletely reported. In the remaining two studies (Kleinknecht 1980; Sinha 2015) available only as abstracts, it was unclear whether there was selective reporting of outcomes.

Other potential sources of bias

Nine studies reported funding by university or government agencies and were considered free of other potential sources of bias (Chongviriyaphan 1999; Choudhry 2009; FSGS Study 2011; Gulati 2012; ISKDC 1974; ISKDC 1996; Magnasco 2012; Yi 2006; Wu 2015). 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.

The definition of steroid resistance varied between studies.

- Eight studies defined steroid resistance as persistent proteinuria of > 4 mg/m^2/h or UP/C > 1g/g after four weeks (FSGS Study 2011; Lieberman 1996; Wu 2015), five weeks (Kleinknecht 1980), six weeks (APN 2008) or eight weeks of prednisone (Bagga 2004; ISKDC 1970; ISKDC 1974).
- Eight studies defined steroid resistance as persistent proteinuria > 40 mg/m^2/h, > 2g/g or above 1 g/m^2/d after four weeks (Choudhry 2009; Gulati 2012; Mantan 2008; Sinha 2015), five weeks (Ponticelli 1993a), eight weeks (Garin 1988; ISKDC 1996) or six months (Magnasco 2012) of 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).

Effects of interventions

See: **Summary of findings for the main comparison** Cyclosporin versus placebo/no treatment; **Summary of findings 2** Calcineurin inhibitors versus IV cyclophosphamide; **Summary of findings 3** Cyclosporin versus mycophenolate mofetil with dexamethasone; **Summary of findings 4** Oral cyclophosphamide versus prednisone/placebo

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 children): RR 7.66, 95% CI 1.06 to 55.34; I^2 = 0%). The number who achieved complete or partial remission also was significantly increased with cyclosporin (Analysis 1.2.1 (3 studies, 49 children): RR 5.48, 95% CI 1.95 to 15.44; I^2 = 0%).

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 children): RR 5.83, 95% CI 0.75 to 45.09; I^2 = 0%) 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 children): RR 5.00, 95% CI 1.63 to 15.31) significantly more frequently than children treated with placebo or no treatment. 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

Lieberman 1996 reported no statistically significant difference in the number of children with worsening hypertension (Analysis 1.3.1 (1 study, 24 children): RR 1.00, 95% CI 0.17 to 5.98), and Ponticelli 1993a reported no statistically significant difference in the number of children with bacterial infections (Analysis 1.3.2 (1 study, 17 children): RR 0.70, 95% CI 0.20 to 2.51). However small numbers of events resulted in imprecision in the results so that it remains

uncertain whether whether cyclosporin therapy is associated with any differences in adverse effects compared with placebo/no treatment. The Ponticelli 1993a study did not report adverse events (except bacterial infections) separately in children and adults. In the cross-over study by Garin 1988, no child was reported to develop hypertension in either the cyclosporin or control group while one child developed kidney dysfunction while receiving cyclosporin and two developed kidney dysfunction while in the control group.

Calcineurin inhibitors versus intravenous cyclophosphamide

Remission by three to six months

CNI significantly increased the number of children who achieved complete or partial remission (Analysis 2.1.1(2 studies, 156 children): RR 1.98, 95% CI 1.25 to 3.13; I^2 = 20%) or complete remission (Analysis 2.1.2 (2 studies, 156 children): RR 3.43, 95% CI 1.84 to 6.41; I^2 = 0%) compared with intravenous cyclophosphamide. While there was no statistically significant difference between treatment groups in the numbers achieving partial remission (Analysis 2.1.3 (2 studies, 156 children): RR 1.68, 95% CI 0.43 to 6.56; I^2 = 71%), there was significant heterogeneity between the two studies leading to imprecision in the results so it is uncertain whether the intervention had any effect on the number of participants achieving partial remission.

Gulati 2012 reported the mean time to remission was significantly shorter with tacrolimus compared with cyclophosphamide (Analysis 2.2 (1 study, 124 children): MD -1.00 months, 95% CI -1.60 to -0.40). The likelihood of complete or partial remission was significantly higher with tacrolimus within subgroups of initial steroid resistance (HR 2.78, 95% CI 1.54 to 5.03), delayed steroid resistance (HR 2.35; 95% CI 1.11 to 4.97), MCD (HR 2.37, 95% CI 1.32 to 4.23) and FSGS (HR 2.54, 95% CI 1.09 to 4.23). Within the tacrolimus treated subgroups, Gulati 2012 found no difference in efficacy based on pathology or whether children had initial or delayed steroid resistance.

Outcomes at 12 months in children who achieved complete or partial remission

In Gulati 2012, 42 children achieved complete remission by six months and all maintained remission or developed SSNS with no significant difference between the treatment groups (Analysis 2.3.1 (1 study, 42 children): RR 1.00, 95% CI 0.86 to 1.16). Among 38 children who achieved partial remission by six months there was no statistically significant difference between the treatment groups in the numbers who subsequently achieved complete remission (Analysis 2.3.2 (1 study, 38 children): RR 1.67, 95% CI 0.46 to 6.01), non-nephrotic proteinuria (Analysis 2.4.1 (1 study, 38 children): RR 1.00, 95% CI 0.58 to 1.72) or recurrence of steroid resistance (Analysis 2.4.2 (1 study, 38 children): RR 0.14, 95% CI 0.01 to 2.59). However because of small patient numbers and imprecision of results with wide CI, it remains uncertain whether tacrolimus or cyclophosphamide could have differential effects on these outcomes.

Adverse effects

Gulati 2012 reported treatment failure (non-response at 6 months, > 1 episode of serious infection requiring hospitalisation or declining GFR) (Analysis 2.5.1 (1 study, 124 children): RR 0.32, 95% CI 0.18 to 0.58), any serious adverse event (Analysis 2.5.2 (1 study, 131 children): RR 0.47, 95% CI 0.23 to 0.95) and the need to cease medications (Analysis 2.5.3 (1 study, 131 children): RR 0.20, 95% CI 0.04 to 0.86) were significantly more common in children treated with cyclophosphamide compared with tacrolimus. There were no significant differences between treatment groups in serious infections (Analysis 2.5.4 (1 study, 131 children): RR 0.49, 95% CI 0.16 to 1.56), persistent nephrotoxicity (Analysis 2.5.5 (131 children): RR 4.93, 95% CI 0.24 to 100.65) or deaths (Analysis 2.5.6 (1 study, 131 children): RR 0.33, 95% CI 0.01 to 7.92). Although there was no statistically significant difference between the groups for the outcomes of persistent nephrotoxicity and death, the CI were wide with the limits indicating imprecision of results so it remains uncertain whether there are differences in adverse effects between the interventions.

Tacrolimus versus cyclosporin

Remission

At six months Choudhry 2009 found no significant differences between tacrolimus and cyclosporin treatment in the numbers of children who achieved complete remission (Analysis 3.1.1 (1 study, 41 children): RR 0.86, 95% CI 0.44 to 1.66), achieved partial remission (Analysis 3.1.2 (1 study, 41 children): RR 1.43, 95% CI 0.62 to 3.28), or achieved complete or partial remission (Analysis 3.1.3 (1 study, 41 children): RR 1.07, 95% CI 0.81 to 1.42) in children with initial or delayed steroid resistance. There were no significant differences in these outcomes at 12 months (Analysis 3.2). However

Significantly fewer children relapsed following treatment with tacrolimus compared with cyclosporin (Analysis 3.3 (1 study, 34 children): 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 (Analysis 3.4) or complete or partial remission (Analysis 3.5).

Adverse events

Choudhry 2009 found no significant difference between medications in change in GFR (Analysis 3.6 (1 study, 41 children): MD -0.70 mL/min, 95% CI -16.71 to 15.31). Hypertrichosis (Analysis 3.7.6 (1 study, 41 children): RR 0.02, 95% CI 0.00 to 0.38) and gingival hypertrophy (Analysis 3.7.7 (1 study, 41 children): RR 0.08, 95% CI 0.01 to 0.56) were significantly less common with tacrolimus compared with cyclosporin. Diarrhoea was more common with tacrolimus (Analysis 3.7.9 (1 study, 41 children): RR 5.71, 95% CI 0.75 to 43.36) however this result was not statistically significant. Other reported adverse events including persistent and reversible nephrotoxicity and worsening of hypertension did not differ significantly between treatments (Analysis 3.7). However the wide CI indicate imprecision of results so it remains unclear whether there are differences in adverse effects between interventions. No children with new-onset hypertension were reported.

Cyclosporin versus mycophenolate mofetil plus pulse oral dexamethasone

Remission

FSGS Study 2011 found no statistically significant differences between therapies in complete remission (Analysis 4.1.1 (1 study, 138 children): RR 2.14, 95% CI 0.87 to 5.24), partial remission (Analysis 4.1.2 (1 study, 138 children): RR 1.09, 95% CI 0.61 to 1.93), or complete or partial remission (Analysis 4.1.3 (1 study, 138 children): RR 1.38, 95% CI 0.90 to 2.10).

FSGS Study 2011 found no statistically significant differences between therapies for sustainable remission of proteinuria between 52 and 78 weeks in numbers with complete remission (Analysis 4.2.1 (1 study, 138 children): RR 1.38, 95% CI 0.41 to 4.66), partial remission (Analysis 4.2.2 (1 study, 138 children): RR 1.05, 95% CI 0.56 to 1.98), or no sustainable remission (Analysis 4.2.3 (1 study, 138 children): RR 0.95, 95% CI 0.77 to 1.18).

Adverse events

FSGS Study 2011 found no significant differences between therapies for death, 50% decline in GFR, or development of ESKD (Analysis 4.3). Adverse effects were reported for 0 to 26 weeks as all children were included up to that time. No significant differences between therapies were detected for serious infection requiring hospitalisation, total infections, total hospitalisations, gastrointestinal adverse effects, neuropsychiatric conditions, or hypertension (Analysis 4.4).

While no significant differences were identified for the outcomes of remission and adverse events, the CI was wide, with the limits indicating the possibility of benefit or harm from cyclosporin compared with MMF with dexamethasone. The results are therefore imprecise, and results of future trials could change these estimates.

Triple therapy using different agents combined with tacrolimus and prednisone

Wu 2015 found no statistically significant differences in short term (complete remission) and long term responses (complete remission at 12 months) to cyclophosphamide, MMF or leflunomide combined with tacrolimus and prednisone between medications (Analysis 5.1; Analysis 5.2). However because of small numbers of patients and events, it remains uncertain whether any differences in efficacy exist between the interventions.

Adverse effects were poorly reported but did not differ between groups.

Tacrolimus versus mycophenolate mofetil to maintain remission

Remission

Sinha 2015 found no significant differences in the number with complete or partial remission (Analysis 6.1.1: (60 children): RR 1.33, 95% CI 0.77 to 2.27) or frequent relapses (Analysis 6.1.3 (60 children): RR 0.35, 95% CI 0.10 to 1.20). Infrequent relapses (Analysis 6.1.2 (60 children): RR 10.29, 95% CI 1.42 to 74.79) and steroid resistance (Analysis 6.1.4 (60 children): RR 0.06, 95% CI 0.00 to 0.91) were significantly fewer with tacrolimus. The authors concluded that 28/31 (90%) children treated with tacrolimus maintained remission satisfactorily (complete/partial remission or infrequent relapses) while 13/29 (48%) children treated with MMF maintained remission satisfactorily.

The mean relapse rate/year did not differ significantly between therapies (Analysis 6.2 (60 children): MD -0.50 N/y, 95% CI -1.09 to 0.09).

Adverse events

Sinha 2015 reported the mean prednisone dose was significantly lower in the tacrolimus group compared to MMF (Analysis 6.3 (60 children): MD -0.20 mg/d, 95% CI -0.36 to -0.04). There was no significant difference in change in GFR (Analysis 6.4 (60 children): MD 13.00 mL/min, 95% CI -3.71 to 29.71) between the tacrolimus and MMF treated children though the wide CI indicate that it remains uncertain whether change in GFR differs between treatment groups.

Cyclophosphamide versus prednisone/placebo

Remission

There was no significant difference in the overall number of children (Analysis 7.1.1 (2 studies, 84 children): RR 1.06, 95% CI 0.61 to 1.87) or in those with FSGS (Analysis 7.1.2 (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.

ISKDC 1996 reported the number of children who achieved complete or partial remission did not differ significantly between treatment groups (Analysis 7.2 (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.

ISKDC 1996 reported treatment failure (increase in SCr by ≥ 30%, SCr > 4 mg/dL, dialysis, or transplant) occurred in 36% (9/25) of the control group and 57% (20/35) of the treatment group (Analysis 7.3 (1 study, 60 children); 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 7.4).Three children treated with cyclophosphamide and two with prednisone died (ISKDC 1996) (Analysis 7.4.1 (1 study, 60 children): RR 1.07, 95% CI 0.19 to 5.95). Deaths were related to sepsis, cardiorespiratory arrest and unknown factors. Adverse events in ISKDC 1974 were not reported separately for steroid-sensitive and steroid-resistant children.

Intravenous versus oral cyclophosphamide

Remission

Elhence 1994 found no significant difference in the numbers of children achieving remission (Analysis 8.1.1 (1 study, 11 children): RR 3.13, 95% CI 0.81 to 12.06); small patient numbers resulted in wide CI so it remains uncertain whether any difference in efficacy exists. Two children treated with IV cyclophosphamide subsequently relapsed at 12 months.

Adverse events

Elhence 1994 reported vomiting was significantly more common in children treated with IV cyclophosphamide (Analysis 8.2.1 (1 study, 11 children): RR 5.63, 95% CI 0.38 to 83.67) but the numbers with bacterial infections (Analysis 8.2.2 (1 study, 11 children): RD -0.25, 95% CI -0.69 to 0.19) did not differ between treatment groups.

IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone

Remission

Mantan 2008 found no significant differences in the number of children with initial or delayed steroid resistance who achieved complete remission (Analysis 9.1.1 (1 study, 49 children): RR 1.13, 95% CI 0.65 to 1.96), partial remission (Analysis 9.1.2 (1 study, 49 children): RR 0.88, 95% CI 0.14 to 5.79), or complete or partial remission

(Analysis 9.1.3 (1 study, 49 children): RR 1.09, 95% CI 0.68 to 1.74) after six months of treatment.

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 children): RR 1.13, 95% CI 0.65 to 1.96). Chronic kidney disease developed in one patient in each treatment group during 18 months of follow-up (Analysis 9.2.2 (1 study, 49 children): RR 0.88, 95% CI 0.06 to 13.35).

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 children): RR 0.96, 95% CI 0.46 to 2.01) or late SRNS (Analysis 9.3.2 (1 study, 31 children): RR 1.17, 95% CI 0.64 to 2.15) though CI were wide due to small patient numbers indicating uncertainty as to whether differences exist between interventions. 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 children): RR 1.09, 95% CI 0.61 to 1.93) or among children with FSGS or MesPGN (Analysis 9.3.4 (1 study, 25 children): RR 1.08, 95% CI 0.51 to 2.30).

Adverse events

Mantan 2008 reported hypertension (Analysis 9.4.1 (1 study, 49 children): RR 0.04, 95% CI 0.00, 0.68) and hypokalaemia (Analysis 9.4.7 (1 study, 49 children): RR 0.06, 95% CI 0.00, 0.98) were significantly less common in children treated with IV cyclophosphamide. The other reported adverse events (cataracts/glaucoma, leucopenia, cushingoid features, cystitis, bacterial infections, steroid encephalopathy, hair loss) were not significantly different between treatment groups (Analysis 9.4).

Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone

Magnasco 2012 reported no significant differences in the percentage reduction in proteinuria at three months (-12; 95% CI -73 to 110) between treatment groups overall or among children with initial SRNS (-3, 95% CI -6.7 to 179) or among children with delayed steroid resistance (-48. 95% CI -79 to 93). There were no significant differences between treatment groups in the number of children, who achieved remission; remission was only seen in children with delayed steroid resistance (Analysis 10.1.2 (1 study, 15 children): RR 1.14, 95% CI 0.33 to 3.94), though event numbers were small indicating imprecision so it remains uncertain rituximab influences remission in children with delayed steroid resistance.

There were no significant differences between end of study creatinine (Analysis 10.2 (1 study, 31 participants): MD 0.00 mg/dL, 95% CI -0.23 to 0.23) and albumin levels (Analysis 10.3 (1 study, 31 participants): MD 0.25 g/L, 95% CI -0.22 to 0.72).

Only adverse reactions related to rituximab were reported (abdominal pain; bronchospasm resulting in discontinuation of treatment; hypotension; skin rash; mild dyspnoea). There were no significant differences between the two treatment groups (Analysis 10.4).

Chlorambucil versus indomethacin

Remission

Kleinknecht 1980 reported no significant difference between chlorambucil and indomethacin in the number who achieved complete remission (Analysis 11.1 (1 study; 30 children): RR 1.00, 95% CI 0.42 to 2.40) and in the number reaching ESKD (Analysis 11.2 (1 study, 30 children): RR 0.20, 95% CI 0.01 to 3.85).

Adverse events

Adverse events of chlorambucil or indomethacin were not reported.

Azathioprine versus placebo

Remission

ISKDC 1970 reported no significant difference in the number of children who achieved complete remission (Analysis 12.1.1 (1 study, 31 children): RR 0.94, 95% CI 0.15 to 5.84) or complete or partial remission (Analysis 12.2.1 (1 study, 31 children): RR 0.94, 95% CI 0.28 to 3.09) after treatment with azathioprine and prednisone compared with placebo and prednisone.

Adverse events

Adverse events of azathioprine were not reported.

High versus low dose enalapril

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 plus prednisone versus prednisone alone

Yi 2006 reported that fosinopril plus prednisone significantly reduced the 24 hour urinary protein excretion after four (Analysis 13.1.1 (1 study, 45 children): MD -1.27 g/d, 95% CI -1.62 to -0.92), eight (Analysis 13.1.2 (1 study, 45 children): MD -1.26 g/d, 95% CI -1.47 to -1.05) and 12 weeks of treatment (Analysis 13.1.3 (1 study, 45 children): 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 13.2.1 (1 study, 45 children): MD -0.21 mg/L, 95% CI -0.33 to -0.09) and beta-2 microglobulin (Analysis 13.2.2 (1 study, 45 children): MD -0.17 mg/L, 95% CI -0.27 to -0.07). Serum albumin at the end of the study did not differ significantly between the groups (Analysis 13.3 (1 study, 45 children): MD 1.20 g/L, 95% CI -6.58 to 8.98).

No changes were reported in systolic blood pressure (Analysis 13.4 (1 study, 45 children): MD -0.87 mm Hg, 95% CI -3.33 to 1.59), CrCl (Analysis 13.5 (1 study, 45 children): MD -5.28 mL/min, 95% CI -9.66 to -0.90) or serum potassium (Analysis 13.6 (1 study, 45 children): MD 0.20 mmol/L, 95% CI -0.34 to 0.74).

Tuna fish oil versus placebo

In one small cross-over 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 cross-over study were combined so that the RR and 95% CI could not be calculated.

Adverse events were not reported.

DISCUSSION

Summary of main results

In this update we have now included 19 studies, enrolling 820 children of which 773 were evaluated.

Three studies examined the efficacy of CNI compared with placebo or supportive treatment. 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 or partial remission. However this result was based on only 8/26 children, who achieved remission with cyclosporin compared with 0/23 children who achieved remission with placebo/no treatment. Nevertheless 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 kidney function.

Two studies found no statistically significant differences in remission rates or prevention of kidney function deterioration with oral cyclophosphamide compared with prednisone alone (ISKDC 1974; ISKDC 1996). In addition children treated with oral CNI were significantly more likely to achieve complete or partial remission compared with IV cyclophosphamide (APN 2008; Gulati 2012). Choudhry 2009 found no significant differences in efficacy between tacrolimus and cyclosporin though the important cosmetic adverse effects of hirsutism and gum hypertrophy were limited to cyclosporin therapy. FSGS Study 2011 found no significant differences in efficacy between cyclosporin and mycophenolate mofetil with dexamethasone in children and young adults with primary FSGS. Among children, who achieved remission with tacrolimus, Sinha 2015 found that satisfactory remission (complete or partial remission and infrequent relapses) occurred more commonly with tacrolimus than mycophenolate mofetil.

These data suggest that CNI should be used in preference to cyclophosphamide in children with SRNS. Further studies are required to determine the relative efficacies of CNI and mycophenolate mofetil.

In the remaining studies of immunosuppressive agents, two studies (Elhence 1994; Mantan 2008) compared IV with oral cyclophosphamide and found no significant differences in efficacy between treatment groups. Single studies of azathioprine (ISKDC 1970) or tuna fish oil (Chongviriyaphan 1999) showed no evidence of benefit. Kleinknecht 1980 found no significant differences between chlorambucil and indomethacin in the number who achieved remission or developed ESKD. Wu 2015 found no significant differences in efficacy between mycophenolate mofetil, cyclophosphamide or leflunomide in children already treated with tacrolimus and prednisone. Magnasco 2012 found no significant benefit of rituximab over CNI with prednisone in children with SRNS, who were resistant to corticosteroids and CNI.

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 kidney function.

Overall completeness and applicability of evidence

Currently CNI, cyclophosphamide and mycophenolate mofetil are used to treat SRNS. There are limited data from RCTs to demonstrate the efficacy of CNI compared with placebo and from RCTs to show no significant benefit of cyclophosphamide. However two studies have demonstrated that CNI are more effective than cyclophosphamide with less toxicity. These data support the use of CNI in children with SRNS and suggest that cyclophosphamide should not be used. Although a single study (FSGS Study 2011) found no significant difference in efficacy between cyclosporin and mycophenolate mofetil with dexamethasone, it was underpowered so it could not completely exclude a significant difference between the interventions. Further studies are required to assess the efficacy of mycophenolate mofetil in SRNS though Sinha 2015 found that tacrolimus was more effective in maintaining satisfactory remission than mycophenolate mofetil. Magnasco 2012 found no benefit of rituximab in children with SRNS. However this was a small study with only three months of follow up in children with SRNS, who were also resistant to CNI. Therefore a role for rituximab in children with SRNS has not been excluded particularly in children who show some response to CNI.

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). While no differences in efficacy in children with MCD or FSGS could be demonstrated for comparisons between cyclosporin and cyclophosphamide or tacrolimus and mycophenolate mofetil, the studies were too small to exclude a difference in treatment responses between pathologies. Observational studies (Ehrich 2007) had suggested that the relative efficacies of treatment regimens differed between children with initial compared with delayed steroid resistance. Subgroup analyses in studies which enrolled children with initial and delayed steroid resistance found no differences in efficacy between such patient groups (Gulati 2012; Mantan 2008; Sinha 2015). However the subgroups involved small numbers of patients so a difference in efficacy of CNI between children with initial or delayed steroid resistance cannot be completely excluded.

Data from the PodoNet Registry cohort (Trautmann 2015) found that 22% of 1234 children with SRNS had received oral or pulse cyclophosphamide while 44% had received steroid pulses although no RCTs were identified, which examined the benefits or harms of high dose steroids with alkylating agents compared with placebo, prednisone or no specific therapy. 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. No RCTs comparing a CNI and low or high dose prednisone with placebo, prednisone or no specific treatment were identified. 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). In the PodoNet Registry cohort, a CNI with oral corticosteroids was the most commonly used intervention with 65% of children with SRNS receiving one or more periods of treatment with these medications (Trautmann 2015).

No study to date has taken into account the information that a proportion of patients with FSGS have mutations in genes coding for podocin, nephrin and other proteins and are unlikely to respond to therapy (Ehrich 2007). Two studies included information about genetic studies (APN 2008; Choudhry 2009) but the data were not used to exclude children from studies. Response to therapy with any medication varies between studies with the number of children achieving complete or partial remission varying between 0% to 100% (Lombel 2013). For example, FSGS Study 2011 found that in the USA 46% of patients responded to cyclosporin while studies from India (Choudhry 2009; Gulati 2012) found that over 80% responded to CNI. The differences in response to CNI between studies could be related to differences in the incidence of genetic mutations between different racial groups, to differences in the proportions of children with FSGS and MCD and to the inclusion of children with initial and delayed steroid resistance. FSGS Study 2011 only enrolled subjects with FSGS and initial steroid resistance whereas the Indian studies (Choudhry 2009; Gulati 2012) included children with FSGS and MCD and children with initial or delayed steroid resistance. If SRNS with delayed steroid resistance is more likely than initial steroid-resistant disease to have an immunological cause as suggested by the higher incidence of recurrence post transplant in children with delayed steroid resistance (Ding 2014), then children with delayed steroid resistance may have increased response rates to immunosuppressive agents.

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. Episodes of Infection were more common with alkylating agents than with cyclosporin.

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. 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). Eleven studies were at low risk for selection bias. Four studies were at low risk of performance bias although, since the majority of studies (15 studies) used a laboratory measurement of proteinuria for the primary outcome of remission, there was less risk of detection bias. Eight and 10 studies respectively were considered to be free of attrition or selective outcome bias. It is possible that attrition bias influenced the outcomes in the studies comparing cyclosporin with placebo/no treatment. In three studies 10/59 (17%) randomised patients, included in the meta-analysis comparing cyclosporin with placebo/no treatment, were excluded from analyses after randomisation. Studies with attrition bias and thus no intention-to-treat analysis can exaggerate the efficacy of the experimental treatment (Hollis 1999).

In many analyses there were no statistically significant differences between the groups. However the CI were often very wide, with the limits indicating the possibility of substantial benefit or substantial harm from the intervention(s) compared with the comparator(s). The results in many studies for some outcomes were therefore imprecise indicating that if these interventions were analysed in new studies, the results could change the estimates of benefits and harms considerably. This is reflected in the Summary of Findings Tables. The overall quality of the evidence (GRADE) was considered low for the comparison of cyclosporin with placebo/no treatment (Summary of findings for the main comparison) because of small numbers of patients and events and because of increased risk of selection and performance bias. In the comparison of CNI with IV cyclophosphamide, the overall quality of the evidence for complete or partial remission was considered low or very low but considered to be moderate or low for adverse effects (Summary of findings 2). The quality of the evidence was downgraded because of small numbers of patients and events resulting in imprecision and the high risk of attrition bias in one study. In the comparison of cyclosporin with MMF and IV dexamethasone, the overall quality of the evidence was considered moderate (Summary of findings 3). It was downgraded because the number of recruited patients was insufficient to exclude a difference between medications. For the comparison of cyclophosphamide with prednisone/placebo, the quality of the evidence was considered low or very low because of imprecision and risk of bias (Summary of findings 4).

Potential biases in the review process

This review identified 19 studies of which two were 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 including studies only available as abstracts. Since 40% of study reports in the Cochrane Kidney and Transplant's Specialised Register have been identified by handsearching of conference proceedings, 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 six 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 alky-

lating 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. Based on these studies, the KDIGO guidelines (Lombel 2013) recommend that the initial treatment of children with SRNS should be with a CNI for a minimum of six months.

AUTHORS' CONCLUSIONS

Implications for practice

The update of this systematic review continues to highlight how few studies have addressed the efficacy of interventions for SRNS in children. The studies were generally small and of variable quality. Many studies did not provide data on the duration of remission, on kidney dysfunction including the number progressing to ESKD or on mortality although these are important patient centred outcomes. However based on the included studies, CNI appear to be of benefit for children with SRNS while cyclophosphamide is less effective and more toxic suggesting that the initial treatment of SRNS should be with CNI. ACEi significantly reduce proteinuria in children with SRNS so they should be used in children with SRNS (Lombel 2013).

Implications for research

Further studies are required to assess therapies in SRNS. In particular further studies of mycophenolate mofetil or rituximab compared with CNI are warranted. These studies should be of sufficient duration to assess complete remission rates, relapse rates, kidney function and adverse events and to assess any differences in response between children with MCD or FSGS and children with initial steroid resistance and those with delayed steroid resistance. In addition studies should attempt to investigate the optimal dosing or blood concentrations of CNI or mycophenolate mofetil required to achieve remission in children with SRNS. Children with genetic mutations resulting in SRNS rarely respond to therapy. Children entering RCTs should be screened for mutations before study entry and those with mutations should be excluded from studies of immunosuppressive agents because of the risks of toxic therapies in such children.

The responses of children with SRNS to current immunosuppressive agents are variable but in many studies fewer than 50% respond to any therapies. Therefore different strategies are needed to treat SRNS. Medications that stabilise the podocyte skeleton (dexamethasone, CNI, rituximab) and antifibrotic drugs (pioglitazone) are being evaluated as treatments for SRNS (Deegens 2011).

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* 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: January 2001 to November 2004 • Follow-up period: 48 weeks for whole study

Participants	• Setting: tertiary, multicentre study
	• Countries: 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 (21), MCD (10) or MesPGN (1) on biopsy; normal C3; CrCl > 70 mL/min/1.73 m^2
	• Number
	  * CSA group: 15 (MCD (6), FSGS (8), MesPGN (1))
	  * CPA group: 17 (MCD (4), FSGS (13), MesPGN (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

APN 2008 *(Continued)*

	• Oral CSA 150 mg/m^2/d in 2 divided doses aiming for trough levels of 120 to 180 ng/mL for 24 weeks and then CSA to achieve trough level of 80 to 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 to 40 mg/m^2/h at 24 weeks) at 12 weeks • Adverse events
Notes	• Exclusions post randomisation but pre-intervention: none • 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; 6 patients in CPA 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
Random sequence generation (selection bias)	Low risk	Computer generated random lists, stratified by centre
Allocation concealment (selection bias)	Low risk	Central allocation by study coordinator
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory measure of primary outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Complete follow-up to 12 weeks, then non-responders could be withdrawn to enter non-responder protocol 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)
Selective reporting (reporting bias)	Low risk	Complete or partial remission, adverse effects reported at 12 weeks

APN 2008 *(Continued)*

Other bias	High risk	Funded in part by a grant from Novartis Pharma

Bagga 2004

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 20 weeks; first part of cross-over included so outcome at 8 weeks used

Participants	• Setting: tertiary centre
	• Country: India
	• SRNS (no remission after 8 weeks of prednisone); patients with initial SRNS (15) or late SRNS (10) following response to prednisone
	• Number (high dose/low dose): 14/11
	• Age (range)
	  * High dose: 78 months (60 to 104.7)
	  * Low dose: 96 months (80.5 to 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: severe hypertension (SBP or DBP > 99th percentile); GFR < 70 mL/min/1.73 m^2; secondary nephrotic syndrome (SLE, HSP, Hepatitis B, amyloidosis); single functioning kidney; treatment with daily prednisone, IV steroids, alkylating agents, levamisole, CSA, 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/Cr ratios (median, 95% CI) after 8 weeks • Urine albumin/Cr reduction (median, 95% CI) after 8 weeks • Levels of Cr, albumin, cholesterol, potassium, BP • Adverse events: cough
Notes	• Exclusions post randomisation but pre-intervention: 4 (high dose group (1), low dose group (3)) excluded after randomisation and before treatment • Stop or end points/s: not reported • 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

Bagga 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes opened by investigator, who did not manage the patients (information from author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory assessment of outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were included and completed the study (information from authors)
Selective reporting (reporting bias)	High risk	Outcomes reported (urinary albumin excretion, kidney function, adverse events) but no results could be included in meta-analyses
Other bias	Unclear risk	Funding source not stated

Chongviriyaphan 1999

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 32 weeks but outcome data provided at 8 weeks
Participants	• Setting: tertiary centre • Country: Thailand • SRNS, no response to CPA, normotension, Cr < 3 mg/dL, GFR > 15 mL/min/1.73 m^2 • Number: 5 • Age range: 7 to 17 years • Sex (M/F): all male • Histology (4 patients): FSGS (3); MesPGN (1) • Not stated whether children had initial or delayed steroid resistance • 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: not reported
Outcomes	• Urine protein excretion at 8 weeks • CrCl at 8 weeks • SCr and lipids at 8 weeks
Notes	• Exclusions post randomisation but pre-intervention: not reported

Chongviriyaphan 1999 *(Continued)*

- Stop or end points/s: not reported
- Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomised double-blind placebo controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomised double-blind placebo controlled study
Incomplete outcome data (attrition bias) All outcomes	High risk	Cross-over study of 6 patients; I patient (17%) did not complete the study with no reason provided
Selective reporting (reporting bias)	High risk	Outcomes (urine protein excretion, CrCl) reported; no report of adverse effects
Other bias	Low risk	Study supported by Ramathibodi Research Grant No.25/1996, Mahidol University, Bangkok

Choudhry 2009

Methods

- Study design: parallel RCT
- Time frame: August 2005 to July 2007
- Follow-up period: 12 months

Participants

- Setting: tertiary centre
- Country: India
- SRNS (UP/C > 2 g/g, albumin < 2.5 mg/dL, oedema) despite prednisone for 4 weeks at 2 mg/kg/d, initial (23) and late steroid resistance (18) with MCD (17), FSGS (17), MesPGN (7)
- Number (TAC/CSA): 21/20
- 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

Choudhry 2009 *(Continued)*

	• Exclusion criteria: immunosuppression other than prednisone in previous 12 weeks; secondary SRNS; Cr >1.5 mg/dL; eGFR < 60 mL/min/1.73m^2; history of DM or liver disease; time between onset of SRNS and study > 24 months
Interventions	TAC group • 0.1 to 0.2 mg/kg/d in 2 divided doses for 12 months • Trough levels 5 to 8 ng/mL CSA group • 5 to 6 mg/kg/d in 2 divided doses for 12 months • Trough levels 100 to 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 to 10 mg/d for cholesterol > 200 mg/dL; calcium and vitamin D supplements
Outcomes	• Complete (UP/C < 0.2 g/g, albumin > 2.5 g/dL) or partial remission (UP/C 0.2 to 2 g/g, albumin > 2.5 g/dL) at 6 and 12 months • Treatment failure: non-response (UP/C > 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: not reported • Stop or end points/s: not reported • Additional data requested from authors: numbers with response related to early/late resistance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation list were generated off site by colleague not involved in the study
Allocation concealment (selection bias)	Low risk	Sealed opaque serially numbered envelopes opened at randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding; blinding of outcome assessors, who assessed gum hypertrophy and hirsutism
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up
Selective reporting (reporting bias)	Low risk	Outcomes (complete remission, partial remission, relapse, adverse events) reported

Choudhry 2009 *(Continued)*

Other bias	Low risk	Study medications only provided by Pancea Biotec, India

Elhence 1994

Methods	• Study design: parallel RCT • Time frame: 1990 to 1991 • Follow-up period: 12 months

Participants	• Setting: tertiary centre
	• Country: India
	• SRNS, initial (5) and delayed (8) steroid resistance with MCD
	• Number (IV/oral): 7/6
	• Age (range)
	  * IV group: 3 to 16 years
	  * Oral group: 9 to 14.5 years
	• Sex (M/F)
	  * IV CPA: 6/1
	  * Oral CPA: 5/1
	• Exclusion criteria: not reported

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: not reported
Outcomes	• Remission: proteinuria < 4 mg/m^2/h and albumin > 35 g/L at 6 months • Adverse events
Notes	• Exclusions post randomisation but pre-intervention: none reported • Stop or end points/s: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management

Elhence 1994 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 15%; 2 from control group lost to follow-up and excluded from analysis
Selective reporting (reporting bias)	Low risk	Outcome (complete remission, non-remission, adverse effects) reported
Other bias	Unclear risk	Funding source not reported

FSGS Study 2011

Methods	• Study design: parallel RCT • Time frame: November 2004 to November 2009 • Follow-up period: 78 weeks

Participants	• Setting: multicentre (66 sites)
	• Country: USA
	• Adults and children with SRNS; with biopsy-confirmed primary FSGS and initial steroid resistance; steroid resistance (UP/C > 1.0 after 4 weeks of steroid therapy), persistent proteinuria (UP/C > 1.0) and eGFR > 40 mL/min/1.73 m^2
	• Number: 138 participants aged 2 to 40 years (but no difference in results of subgroup analysis by age)
	  * DEXA/MMF group: 66
	  * CSA group: 72
	• Age (< 18 years/≥ 18 years): 93/45
	• Sex (M/F): 73/65
	• Exclusion criteria: secondary FSGS; previous therapy with sirolimus, CSA, tacrolimus, MMF or AZA; treatment with CPA, chlorambucil, levamisole, methotrexate, or nitrogen mustard within 30 days of enrolment; received > 3 pulses of methylprednisolone; allergic to the study medications; obesity; ANC < 2000/mm^3; HCT < 28%; uncontrolled hypertension; DM; active or serious infection; cirrhosis or chronic active liver disease; history of significant GI disorder; organ transplantation; history of malignancy; participation in another therapeutic trial within 30 days before randomisation; lactation, pregnancy, child-bearing age and refused birth control

Interventions	DEXA/MMF group • Oral pulse DEXA: 0.9 mg/kg/d (max 40 mg) daily on 2 consecutive days at start of weeks 1 to 8, then daily on 2 consecutive days at the start of every second week in weeks 10 to 26, then every 4 weeks from week 30 to 50, for a total of 46 doses (over 12 months) • Oral MMF 25 to 36 mg/kg/d (max 2 g/d) divided into 2 divided doses for 12 months CSA group • Oral CSA 5 to 6 mg/kg/d (max initial dose 250 mg/d) in 2 divided doses for 12 months. CSA dose adjusted to achieve a 12 h trough concentration of 100 to 250 ng/ml Co-interventions • Prednisone (or prednisolone for children taking liquid preparation) 0.3 mg/kg/dose (max 15 mg) every other day for the first 6 months of treatment period • Lisinopril (0.36 ± 0.12 (range 0.04 to 0.56) mg/kg/d) for 18 months • Losartan (1.10 ± 0.50 (range 0.55 to 2.69) mg/kg/d) for patients intolerant of ACEi

FSGS Study 2011 *(Continued)*

	• Additional antihypertensive therapies were not restricted by study protocol
Outcomes	Primary outcomes • Complete remission (UP/C < 0.2) at 52 weeks (outcomes 1 and 2 on ordinal classification of proteinuria primary outcome) • Partial remission UP/C < 50% of baseline at 52 weeks (outcome 3) • No remission at 52 weeks (outcome 4 to 6) • Treatment failure with no remission at 26 weeks (outcomes 5,6) or no remission at 52 weeks (outcome 4) or reached protocol defined stop point Secondary outcomes • Persistence of complete or partial remission between weeks 52 to 78 following cessation of treatment (outcomes 1 to 3 on ordinal classification of proteinuria secondary outcome) • Adverse events
Notes	• Stop points: 50% decline in baseline GFR to ≤ 75 mL/min/1.73 m^2, dialysis, pregnancy, pre-specified medication related toxicity • Exclusions post randomisation but pre-intervention: none • Additional data requested from authors: breakdown of data to paediatric and adult data; no data received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedules using randomly permuted blocks of random sizes were prepared by the Data Coordinating centre stratified by eGFR, race
Allocation concealment (selection bias)	Low risk	Study investigators were blinded to randomised schedules
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study; lack of blinding could influence patient management differently between treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study investigators were blinded to results of interim analyses done for the Data and Safety Monitoring Board Laboratory values for primary outcomes and some secondary outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal participants were lost to follow up/did not attend assessments (< 1%); all patients included in outcome measurement
Selective reporting (reporting bias)	Low risk	All expected outcomes (remission, relapse, adverse effects) were reported
Other bias	Low risk	NIH funded

Garin 1988

Methods	• Study design: cross-over RCT

Garin 1988 *(Continued)*

- Time frame: not reported
- Follow-up period: 3 months

Participants	• 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); not reported whether children had initial or delayed steroid resistance • Number: 8 • Age: 3 to 18 years • Sex (M/F): 6/2 • Histology: MCD (4); FSGS (4) • Exclusion criteria: not reported
Interventions	CSA group • 5 mg/kg/d for 8 weeks adjusted to level ≤ 200 ng/mL No treatment group • No treatment for 8 weeks Co-interventions • Not reported; 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: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants/investigators not blinded; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory outcome based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up and accounted for
Selective reporting (reporting bias)	Low risk	Complete/partial remission/adverse effects reported

Garin 1988 *(Continued)*

Other bias	Unclear risk	Funding source not reported

Gulati 2012

Methods	• Study design: parallel RCT • Time frame: March 2008 to September 2010 • Follow-up period: 12 months
Participants	• Setting: multicentre (5 paediatric nephrology units) • Country: India • SRNS newly diagnosed initial or late SRNS; initial resistance was the absence of remission despite therapy with prednisolone at 2 mg/kg/d (max 60 mg) for 4 weeks; patients with remission at onset but steroid resistance in a subsequent relapse were defined as late resistance • Number: TAC group (66); CPA group (65) • Age range: 2 to 16 years • Sex (M/F): 86/45 • Histology: MCD (78), FSGS (43), MesPGN (10) • Initial steroid resistance (81); late steroid resistance (50) • Exclusion criteria: impaired kidney function GFR < 60 mL/min/1.73 m^2; Intake of immunosuppressive medications other than prednisolone in the preceding 6 months in patients with late resistance; prior therapy with CPA or CNI; infection with hep B or C or HIV; IgA nephropathy or collapsing glomerulopathy; inability to swallow TAC capsules
Interventions	TAC group • 0.1 to 0.15 mg/kg/d for 12 months, adjusted to a level of 5 to 7 ng/mL or lower levels if patient in remission CPA group • IV CPA 500 mg/m^2 once a month for 6 months Co-interventions • Prednisolone: 1.5 mg/kg on alternate days for 2 weeks then tapered by 0.25 mg/kg every 2 weeks to 0.5 mg/kg • Enalapril • Calcium supplements
Outcomes	Primary outcomes • Complete or partial remission at 6 months (based on spot UP/C) Secondary outcomes • Sustained remission or steroid-sensitive nephrotic syndrome at 12 months • Non-nephrotic proteinuria with serum albumin > 2.5 g/dL • Recurrence of steroid resistance • Adverse effects • eGFR
Notes	• Stop points: non-response at 6 months; > 1 episode of severe infection; persistent elevation of Cr ≥ 30% despite dose reduction; eGFR < 50 mL/min/1.73 m^2

Risk of bias

Gulati 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation with stratification, by initial or late resistance, was performed centrally by individuals not involved in trial implementation
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque sealed envelopes The investigators were blinded to the randomisation schedules
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel delivering therapy were not blinded (one arm received tablets, one arm received injections)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment is at low risk of bias as it was a laboratory measure and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients were lost to follow-up (TAC (3), CPA (4)); this makes up 5% (7/131) and this number is unlikely to alter results; all included in safety analysis
Selective reporting (reporting bias)	Low risk	All outcomes of interest (complete or partial remission, remission, adverse effects) have been reported
Other bias	Low risk	Study medications (tacrolimus and cyclophosphamide) were provided by Panacea Biotec Study was supported by funding from the Indian Council of Medical Research

ISKDC 1970

Methods	• Study design: parallel RCT • Time frame: January 1967 to December 1969 • Follow-up period: 3 months; non-responders at 90 days randomised to 2nd course of 90 days of AZA
Participants	• Setting: tertiary, multicentre • Countries: 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; all had initial steroid resistance • Number (AZA/placebo): 16/15 • Age: not reported • Sex (M/F): not reported • Histology: MCD (5); FSGS (10); MesPGN (15); unknown (3) • Exclusion criteria: secondary nephrotic syndrome (SLE, diabetes, amyloidosis, syphilis, HSP, malaria)
Interventions	AZA group • 60 mg/m^2/d • Intermittent prednisone for 90 days Placebo group • Placebo

ISKDC 1970 *(Continued)*

	• Intermittent prednisone for 90 days Co-interventions: not reported
Outcomes	• Complete remission at 90 days: proteinuria ≤ 4 mg/m^2/h for 3 consecutive days • Partial remission at 90 days
Notes	• Exclusions post randomisation but pre-intervention: none reported • Stop or end points/s: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally derived table of random numbers
Allocation concealment (selection bias)	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 of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants/investigators
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants/investigators
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients followed up; 18% (7/38) excluded from analysis
Selective reporting (reporting bias)	High risk	Definition of partial remission not stated; no report of adverse effects
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: April 1970 to June 1972 • Follow-up period: 24 months

Participants	• Setting: tertiary, multicentre
	• Countries: Europe, USA, Mexico, Hong Kong, Japan
	• SRNS: failure to achieve remission (proteinuria ≤ 4 mL/m^2/h) after 8 weeks of prednisone (60 mg/m^2/d for 4 weeks then 40 mg/m^2/d for 3 consecutive days out of 7); aged 12 weeks to 16 years at onset of nephrotic syndrome; all had initial steroid resistance
	• Number
	  * CPA-prednisone group: 18
	  * Prednisone group: 13 (2 patients with MNS excluded)
	• Age: not reported

ISKDC 1974 *(Continued)*

- Sex (M/F): not reported
- 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: not reported

Interventions	CPA-prednisone group • Oral CPA 5 mg/kg/d till WCC < 5000 then 1 to 3 mg/kg/d • Intermittent prednisone for 90 days Prednisone group • Intermittent prednisone for 90 days Co-interventions: not reported
Outcomes	• Complete remission: proteinuria ≤ 4 mg/m^2/h for 3 consecutive days at about 3 to 4 months but unclear • Partial remission
Notes	• Exclusions post randomisation but pre-intervention: none reported • Stop or end points/s: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessment by quantitative measurement of protein on overnight urine collection or semi-quantitative based on urinalysis Unclear how many patients had laboratory assessment of outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up
Selective reporting (reporting bias)	High risk	Complete and partial remission reported but no definition for partial remission provided; adverse effects not reported specifically for steroid-resistant patients
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: September 1974 to June 1980 • Follow-up period: 3 to 102 months

Participants	• Setting: tertiary, multicentre
	• Countries: Europe, USA, Canada
	• SRNS: Proteinuria 40 mg/m^2/h after prednisone (60 mg/m^2/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/m^2/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; all had initially steroid-resistant disease
	• Number (analysed/randomised)
	  * CPA-prednisone group: 32/35
	  * Prednisone group: 21/25
	• Mean age (± SEM)
	  * CPA-prednisone group: 8.6 ± 0.85 years
	  * Prednisone group: 7.4 ± 0.75 years
	• Sex (M/F): not reported
	• 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/m^2 for 12 months Prednisone group • Alternate day prednisone for 12 months Co-interventions: not reported
Outcomes	• Complete remission during study: proteinuria < 4 mg/m^2/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: not reported • 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
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Central randomisation

ISKDC 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	32/35 in treatment group and 21/25 in control group analysed for complete/partial remission and unclear why other patients not included. 11% excluded
Selective reporting (reporting bias)	Low risk	Outcomes of complete and partial remission, adverse events, kidney function included
Other bias	Low risk	Supported by NIH Grant 1 RO1 AM18234 and multiple other not for profit agencies in USA, UK, Netherlands

Kleinknecht 1980

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: greater than 6 months

Participants	• Setting: tertiary centre
	• Country: France
	• Children with SRNS (persistent nephrotic syndrome after 5 weeks or more of prednisone at 2 mg/kg/d); not stated whether children had initial or delayed steroid resistance
	• Number (chlorambucil/indomethacin): 15/15
	• Age: not reported
	• Sex (M/F): not reported
	• 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 not reported

Interventions	Chlorambucil group • 0.2 mg/kg/d for 6 months Indomethacin group • 3 mg/kg/d for 6 months Co-interventions: not reported
Outcomes	• Remission of nephrotic syndrome: definition not reported after at least 6 months • ESKD
Notes	• Exclusions post randomisation but pre-intervention: not reported • Stop or end points/s: not reported • Additional data requested from authors: none

Kleinknecht 1980 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of investigators/participants; lack of blinding could influence management.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about how primary outcome was measured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data only available from conference proceedings
Selective reporting (reporting bias)	Unclear risk	Complete remission (no definition provided), ESKD
Other bias	Unclear risk	Funding source not stated Data from conference proceedings

Lieberman 1996

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 6 months

Participants	• Setting: tertiary, multicentre
	• Country: USA
	• Age 6 months to 12 years; FSGS on biopsy; proteinuria > 4 mg/m^2/h or UP/C 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; all had initial steroid resistance
	• Number
	  * CSA group: 12/16 analysed; excluded for noncompliance (2); rising Cr (1); unknown reason (1)
	  * Placebo group: 12/15 analysed; excluded for noncompliance (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

Lieberman 1996 *(Continued)*

Interventions	CSA group • 6 mg/kg/d for 6 months, adjusted to 300 to 500 ng/mL Placebo group • Placebo for 6 months Co-interventions • Calcium channel blockers for hypertension
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, BP; 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
Random sequence generation (selection bias)	Low risk	Central computer generated list
Allocation concealment (selection bias)	Low risk	Central co-ordinator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants/investigators; placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory measurement of primary outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	4/16 excluded from cyclosporin group and 3/15 excluded from control group for noncompliance (2 each group, 1 unknown CSA group, 1 each group for rising Cr). In view of small numbers, results likely to influence results (23% excluded)
Selective reporting (reporting bias)	Low risk	Outcomes of complete or partial remission, adverse events, kidney function
Other bias	Unclear risk	Funding source not stated

Magnasco 2012

Methods	• Study design: parallel RCT • Time frame: 2007 to 2010

Magnasco 2012 *(Continued)*

	• Follow-up period: Whole study 18 months

Participants	• Setting: paediatric nephrology centres (4)
	• Country: Italy
	• 31 children aged 16 years or younger; eGFR > 60 mL/min/1.73 m^2; history of INS unresponsive to the combination of prednisone and CNI for at least 6 months
	• FSGS (19); MCD (7); biopsy not performed (4); inadequate material (1)
	• Initial steroid resistance (16); late steroid resistance (15)
	• Number
	  * RTX group: 15
	  * Control group: 16
	• Mean age ± SD
	  * RTX group: 8.5 ± 4.4 years
	  * Control group: 7.3 ± 3.7 years
	• Sex (M/F)
	  * RTX group: 10/6
	  * Control group: 9/6
	• Exclusion criteria: infantile onset (< 1 year); previous episodes of macrohaematuria; hepatitis B virus, hepatitis C virus or HIV infection; positivity for any marker of autoimmunity; low C3 levels; positive results on genetic testing for NPHS2 and WT1

Interventions	RTX group • 2 doses IV RTX 375 mg/m^2; first dose at randomisation and second dose 2 weeks later Control group • No additional intervention other than standard therapy Co-interventions • Prednisolone, tapered off by 0.3 mg/kg/wk if proteinuria < 1 g/d/m^2 • CNI (at pre-enrolment doses): TAC (16), cyclosporin (15) for RTX group, after 2 weeks from prednisone withdrawal, CNI was decreased by 50% and ceased after 2 additional weeks • ARB or ACEi in 25 participants
Outcomes	• Proteinuria at baseline and 3 months (performed at a central lab) • Numbers with complete remission • Kidney function, plasma proteins, cell blood counts, and cholesterol obtained monthly • Primary efficacy measure was the percentage change in daily proteinuria at 3 months
Notes	Trial registration number EUDRA CT 2007-007796-16

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated block randomisation with blocks of variable size
Allocation concealment (selection bias)	Low risk	Allocation was concealed by contacting the holder of the allocation schedule at central administration
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinical investigators, study nurses enrolling patients, and the statistician were not blinded to group assignment

Magnasco 2012 *(Continued)*

		Study staff responsible for follow up were blinded so their management of patients would not be influenced by treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study staff responsible for facilitating follow-up data measurements by contacting patient families by phone were kept blinded Also, as the outcome measured was a laboratory value, lack of blinding is unlikely to affect outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up All patients analysed; 1 patient from each group did not complete treatment due to adverse side effects
Selective reporting (reporting bias)	High risk	Data on partial remission not included Primary outcome (end study proteinuria) not provided in a form that can be included in meta-analysis Adverse effects related to RTX were only reported
Other bias	Low risk	Supported by Italian Ministry of Health, the Renal Child Foundation, two other non-Pharma related foundations

Mantan 2008

Methods	• Study design: parallel RCT • Time frame: April 2001 to December 2003 • Follow-up period: 18 months

Participants	• 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 (24), FSGS (14), MesPGN (11); aged 1 to 18 years
	• Number
	  * IV CPA group: 26/27 evaluated
	  * Oral CPA + IV DEXA group: 23/25 evaluated
	• Median age (range)
	  * IV CPA group: 51 (16 to 156) months
	  * Oral CPA + IV DEXA group: 92 (15 to 198) months
	• 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

Mantan 2008 *(Continued)*

	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/C < 0.2 g/g, albumin > 2.5 g/dL) or partial remission (UP/C 0.2 to 2 g/g, albumin > 2.5 g/dL) at 6 months • Treatment failure: non-response (UP/C > 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; ophthalmological; steroid related; leucopenia; cystitis; hair loss; vomiting
Notes	• Exclusions post randomisation but pre-intervention: none reported • Stop or end points/s: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	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 (selection bias)	Low risk	"Allocation was concealed in sealed opaque envelopes, which were opened by an associate not involved in the study"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome was serum albumin + urinary protein; urine protein measured either by urinalysis or UP/C. Unclear how many patients had laboratory measure of proteinuria
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/52 (6%) patients excluded after randomisation (IV CPA group (1); oral CPA + IV DEXA group (2)) for non-compliance; unlikely to have influenced results
Selective reporting (reporting bias)	Low risk	Primary outcomes: number in complete or partial remission and adverse effects reported
Other bias	Unclear risk	Funding source not reported

Ponticelli 1993a

Methods	• Study design: parallel RCT • Time frame: not reported

Ponticelli 1993a *(Continued)*

	• Follow-up period: 1 year

Participants	• 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 (9) or MCD (8) on biopsy; all had initial steroid resistance
	• Number
	  * CSA group: 10/10 analysed
	  * No treatment group: 7/10 analysed (3 excluded for noncompliance)
	• 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 • 6 mg/kg/d for 6 months adjusted to 250 to 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, NSAIDs, 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: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed opaque envelopes numbered in sequence according to a random number table; stratified for adults/children
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory measure of primary outcome unlikely to be influenced by lack of blinding.

Ponticelli 1993a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	3/20 (15%) children (all from no treatment group) lost to follow-up and not included in results
Selective reporting (reporting bias)	High risk	No separate data available for adverse events in children
Other bias	High risk	Funded in part by Sandoz P.F, Milano, Italy

Sinha 2015

Methods	• Study design: parallel RCT • Time frame: enrolment commenced April 2012 • Follow-up period: 12 months from randomisation of responders to 6 months of treatment with TAC

Participants	• Setting: tertiary, multicentre study
	• Country: India
	• SRNS 60 of 84 patients who entered study and achieved complete remission with 6 months treatment with TAC; included initial (28) or late (32) non-responders; FSGS (26), MCD (34) on biopsy. CrCl > 60 mL/min/1.73m^2; SRNS defined as no response to treatment with oral prednisolone at 2 mg/kg/d for 4 weeks, in absence of significant infection with UP/C > 2 mg/mg; biopsy showing MCD or FSGS; aged 1 to 18 years at onset of disease
	• Number
	  * TAC group: 31
	  * MMF group: 29
	• Age (mean ± SD)
	  * TAC group: 76 ± 46 months
	  * MMF group: 77 ± 46 months
	• Sex (M/F)
	  * TAC group: no information provided
	  * MMF group: no information provided
	• Exclusion criteria: failure to achieve remission with TAC; patients with initial steroid resistance who have received treatment with non-corticosteroid immunosuppressive medications; patients with late steroid resistance who have ever received MMF or tacrolimus exceeding 14 days; or other immunosuppressive medications in the preceding 3 months; infection with hepatitis B,C, parvovirus, HIV, TB; nephrotic syndrome secondary to infections, IgA nephropathy, systemic disease; GFR < 60 mL/min/1.73 m^2; allergy to study medications; history of malignancy, DM, organ or bone marrow transplant

Interventions	TAC group • 0.15 mg/kg/d aiming for trough levels of 4 to 8 ng/ml MMF group • 0.75 to 1 g/m^2/d • TAC tapered and discontinued within two weeks of randomisation Co-interventions • Prednisolone on alternate days (dose tapered) • Enalapril
Outcomes	• Number with complete or partial remission • Number with infrequent relapses

Sinha 2015 *(Continued)*

	• Number with frequent relapses • Number with recurrence of steroid resistance • Relapse per year • Change in GFR
Notes	• Abstract only • Enrolment was closed after interim ITT analysis of outcome in 1/3 sample

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified block randomisation; stratified for histology and type of response
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could result in differences in management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on how outcome was measured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only; complete follow-up to 12 months
Selective reporting (reporting bias)	Unclear risk	Abstract only
Other bias	Unclear risk	No information provided

Wu 2015

Methods	• Study design: parallel RCT • Time frame: January 2008 to December 2012 • Follow-up period: 6 to 12 months

Participants	• Setting: tertiary, single centre
	• Country: China
	• SRNS non responsive after > 4 weeks of prednisone (1.5 to 2 mg/kg/d); age > 2 years; FSGS (5), MCD (10), MesPGN (1) and IgM nephropathy (2) on biopsy; divided into TAC sensitive but frequently relapsing (10) and TAC resistant (12); aged 1 to 17 years; not reported whether participants had initial or delayed steroid resistance
	• Number
	  * MMF group: 6/7 analysed
	  * CPA group: 5/8 analysed
	  * LEF group: 7/7 analysed
	• Mean age (± SD) of participants included in analysis

Wu 2015 *(Continued)*

- * MMF group: 81.67 ± 16.74 months
  * CPA group: 78.56 ± 20.19 months
  * LEF group: 74.57 ± 11.66 months
- Sex (M/F) of participants included in analysis
  * MMF group: 2/4
  * CPA group: 5/0
  * LEF group: 4/3
- Exclusion criteria: secondary nephrotic syndrome; nephrotic syndrome due to other primary glomerulonephritis: concomitant infection

Interventions	MMF group • 20 to 30 mg/kg/d, divided into 2 doses daily for 12 months CPA group • 8 to 12 mg/kg daily for 2 days and then repeated at 2 to 4 week intervals for 3 to 6 months to maximum dose of less than 150 mg/kg LEF group • 0.5 to 0.6 mg/kg (maximum dose 30 mg) for 2 days and then 0.2 mg/kg/d (maximum dose 15 mg) for 12 months Co-interventions • TAC and prednisone
Outcomes	• Relapse free period (primary outcome); remission defined as proteinuria < 4 mg/h/m^2 BSA • Time to treatment failure • Relapse rate • Time to 3 relapses in 12 months or 2 relapses in 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Simple randomization using a randomised digital table"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Four (18%) excluded from analysis for loss to follow up or other

Wu 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Incomplete reporting of adverse events
Other bias	Low risk	Supported by National Natural Science Foundation of China and others

Yi 2006

Methods	• Study design: parallel RCT • Time frame: February 2000 to January 2001 • Follow-up period: 12 weeks

Participants	• 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; Hb ≥ 90 g/L
	• 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: previous treatment with ACEi; hypertension; secondary nephrotic syndrome; ESKD; Hb < 90 g/L

Interventions	Fosinopril-prednisone group • Fosinopril for 12 weeks (5 mg/d for < 5 years of age; 5 to 7.5 mg/d for 5 to 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 1 mg/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, BP • Urinary retinol binding protein and beta-2 microglobulin
Notes	• Exclusions post randomisation but pre-intervention: none reported • Stop or end points/s: not reported • 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

Yi 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Computer generated random numbers were used to randomly allocate patients ..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/investigators; lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory measurement of primary outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	12/57 (21%) (fosinopril group (5); prednisone group (7)) lost to follow-up and excluded from analysis
Selective reporting (reporting bias)	Low risk	Primary outcomes of study were reduction in proteinuria, CrCl; adverse effects reported
Other bias	Low risk	Ministry of Health Science Foundation of China (98-1-117)

ACEi - angiotensin converting enzyme inhibitors; ANC - absolute neutrophil count; APN - Arbeitgemeinschaft fur Padiatrische Nephrologie; ARB - angiotensin receptor blocker; AZA - azathioprine; BP - blood pressure; CNI - calcineurin inhibitor; CPA - cyclophosphamide; CSA - cyclosporin; Cr - creatinine; CrCl - creatinine clearance; DBP - diastolic blood pressure; DEXA - dexamethasone; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; FSGS - focal segmental glomerulosclerosis; GFR - glomerular filtration rate; GI - gastrointestinal; GN - glomerulonephritis; HCT - haematocrit; HIV - human immunodeficiency virus; HSP - Henoch-Schonlein purpura; INS - idiopathic nephrotic syndrome; intermittent - prednisone given on 3 consecutive days out of 7; ISKDC - International Study of Kidney Disease in Children; LEF - leflunomide; LFT - liver function test; M/F - male/female; MCD - minimal change disease; MCGN - mesangiocapillary glomerulonephritis; MesPGN - mesangioproliferative glomerulonephritis; MMF - mycophenolate mofetil; MNS - membranous nephrotic syndrome; NSAIDs - nonsteroidal anti-inflammatory drugs; RCT - randomised controlled trial; RTX - rituximab; SBP - systolic blood pressure; SCr - serum creatinine; SD - standard deviation; SLE - systemic lupus erythematosus; SRNS - steroid-resistant nephrotic syndrome; TAC - tacrolimus; UP/C - 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)
Arora 2002	Adult patients
Bhaumik 2002	Mixed population of adults and children; unable to separate data
Buyukcelik 2002	Study of gemfibrozil on lipid profiles in children with nephrotic syndrome; ineligible renal pathology as all except one had MPGN
Hiraoka 2000	SSNS patients
Iyengar 2006	SSNS patients

Study	Reason for exclusion
Jung 1990	Mixed population; unable to separate data
Kano 2003	Included patients did not have nephrotic syndrome but moderate proteinuria with normal serum albumin levels
Koshikawa 1993	Adult patients
Kumar 2004a	Adults patients
Li 2006g	Adult patients
Ren 2011	Adult patients
Ren 2013	Adult patients
Saito 2014	Adult 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
Walker 1990a	Adult patients
Zhao 2013a	Includes both steroid-resistant and steroid dependent patients and results cannot be separated

MCD - minimal change disease; FSGS - focal segmental glomerulosclerosis; MPGN - membranoproliferative glomerulonephritis; RCT - randomised controlled trial; SSNS - steroid-sensitive nephrotic syndrome

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

NCT01613118

Trial name or title	Efficacy and safety of RE-021, a dual endothelin receptor and angiotensin receptor blocker, in patients with focal segmental glomerulosclerosis (FSGS): a randomised, double-blind, active-control, dose-escalation study
Methods	Double blind RCT
Participants	Children and adults aged 8 to 75 years with primary FSGS
Interventions	Sparsentan (a dual endothelin receptor) versus irbesartan (ARB)
Outcomes	Change in UP/C in FSGS patients receiving Sparsentan over a range of doses (200 mg, 400 mg, 800 mg daily) for 8 weeks to determine safety and efficacy compared to treatment with irbesartan (300 mg daily) as active control
Starting date	2013
Contact information	Dr Howard Trachtman
Notes	Estimated primary completion date is December 2015; only US sites are enrolling children

NCT02382575

Trial name or title	Efficacy and safety of rituximab to that of calcineurin inhibitors in children with steroid resistant nephrotic syndrome
Methods	Open label RCT
Participants	Children aged 3 to 16 years with SRNS (MCD, MesPGN or FSGS)
Interventions	Rituximab infusions weekly for 2 to 4 doses over up to 4 weeks compared with oral tacrolimus given until the child has achieved 6 months of relapse free survival
Outcomes	12-month relapse-free survival in the ITT population; adverse effects
Starting date	March 2015; estimated enrolment 120 children
Contact information	Dr. Biswanath Basu, Nilratan Sircar Medical College, India (basuv3000@gmail.com)
Notes	Estimated study completion date March 2017 Other study numbers: PednephroRCT/PM/NRSMCH-33, CTRI/2015/01/005364

NCT02394106

Trial name or title	Ofatumumab in children with steroid- and calcineurin-inhibitor-resistant nephrotic syndrome: a double-blind randomised, controlled, superiority trial
Methods	RCT
Participants	Children aged 2 to 18 years with SRNS (MCD, MesPGN or FSGS) and resistance to CNI and MMF
Interventions	Single dose of IV Ofatumumab in normal saline versus placebo (normal saline alone); other immunosuppressive therapies will be withdrawn; all children with receive an ACEi
Outcomes	Complete or partial disease remission; adverse events
Starting date	March 2015; estimated enrolment 50 children
Contact information	Dr Gian Marco Ghiggeri, Istituto Giannina Gaslini, Italy (gmarcoghiggeri@ospedale-gaslini.ge.it)
Notes	Estimated study completion date March 2018

ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blocker; CNI - calcineurin inhibitor; FSGS - focal segmental glomerulosclerosis; MCD - minimal change disease; MesPGN - mesangioproliferative glomerulonephritis; MMF - mycophenolate mofetil

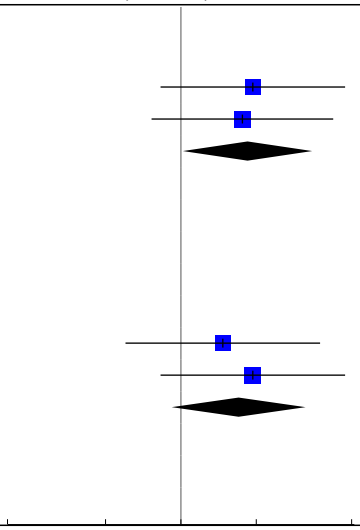
DATA AND ANALYSES

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 Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Worsening of hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

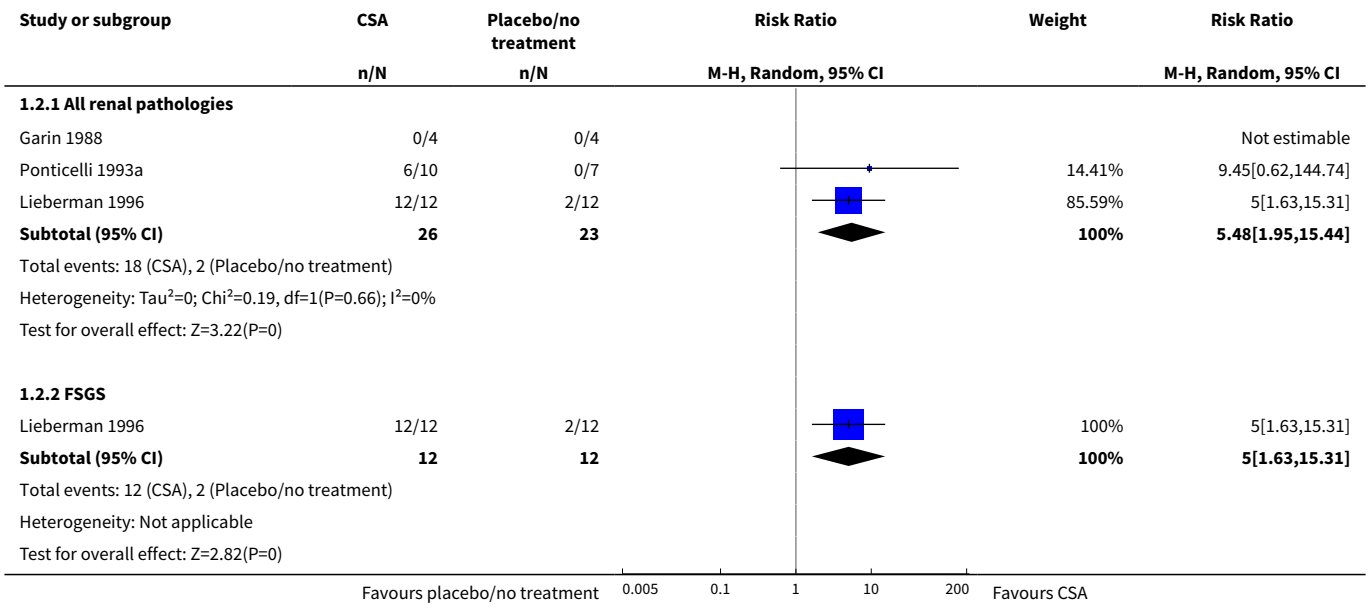
Analysis 1.1. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 1 Complete remission.

Study or subgroup	CSA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All renal pathologies					
Garin 1988	0/4	0/4			Not estimable
Lieberman 1996	4/12	0/12		49.24%	9[0.54,150.81]
Ponticelli 1993a	4/10	0/7		50.76%	6.55[0.41,105.1]
Subtotal (95% CI)	**26**	**23**		**100%**	**7.66[1.06,55.34]**
Total events: 8 (CSA), 0 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					
1.1.2 FSGS					
Ponticelli 1993a	1/4	0/5		47.35%	3.6[0.18,70.34]
Lieberman 1996	4/12	0/12		52.65%	9[0.54,150.81]
Subtotal (95% CI)	**16**	**17**		**100%**	**5.83[0.75,45.09]**
Total events: 5 (CSA), 0 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=1.69(P=0.09)					

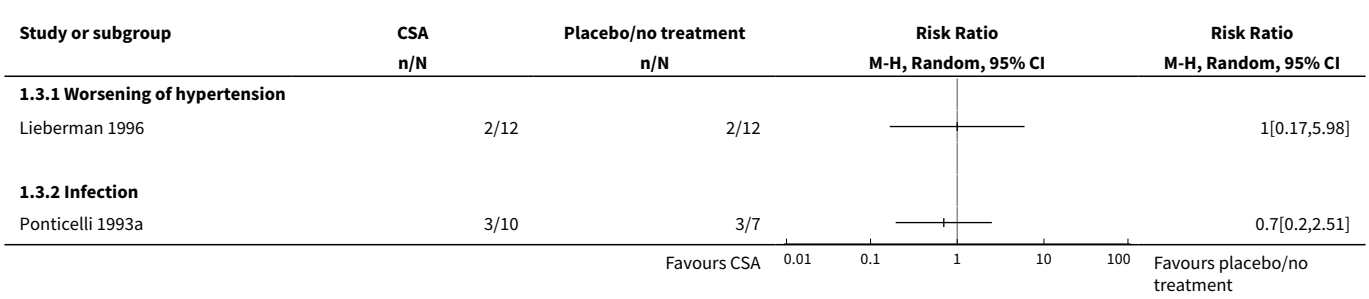


Favours placebo/no treatment — Favours CSA

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.



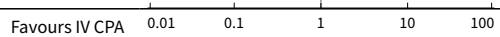
Comparison 2. Calcineurin inhibitor versus IV cyclophosphamide

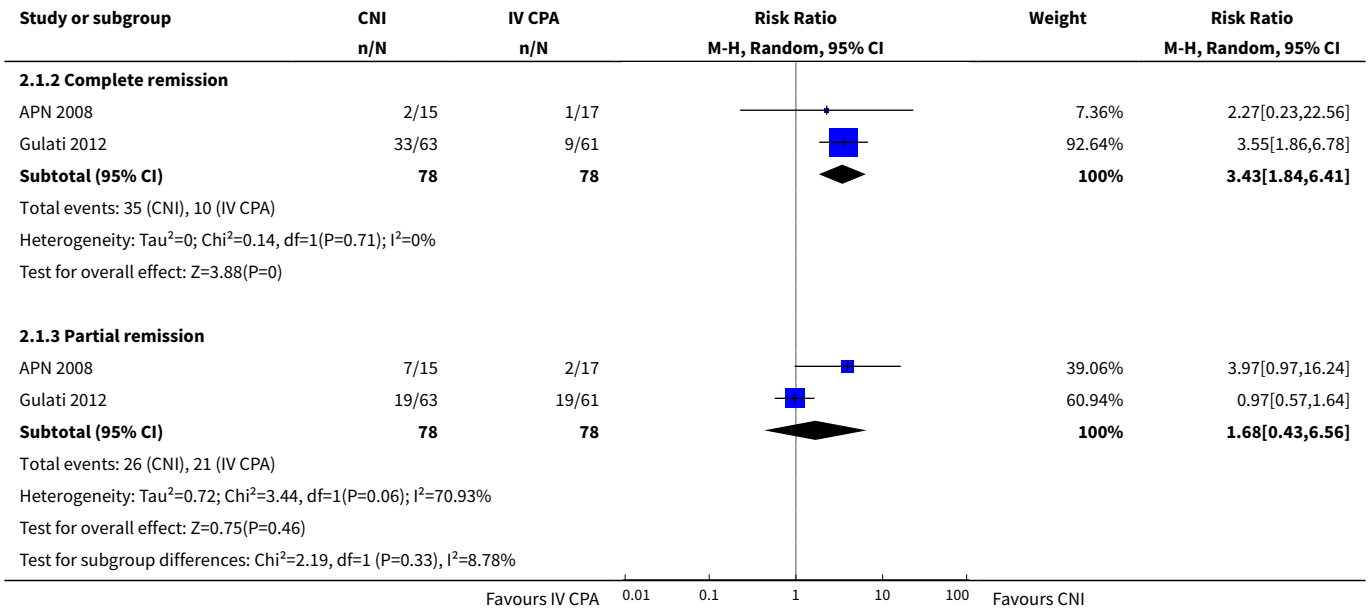
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response at 3 to 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Complete or partial remission	2	156	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.25, 3.13]
1.2 Complete remission	2	156	Risk Ratio (M-H, Random, 95% CI)	3.43 [1.84, 6.41]
1.3 Partial remission	2	156	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.43, 6.56]
2 Mean time to remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Complete remission/SSNS at 12 months in 80 patients with com-	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
plete or partial remission at 6 months				
3.1 Complete remission in patients with complete remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Complete remission in patients with partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Other outcomes at 12 months in 38 patients with partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Number with non-nephrotic proteinuria	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Number developing steroid resistance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Treatment failure (non response, serious infection, persistently elevated creatinine) at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Any serious adverse effect	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Medications ceased due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Serious infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.5 Persistent nephrotoxicity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.6 Death	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

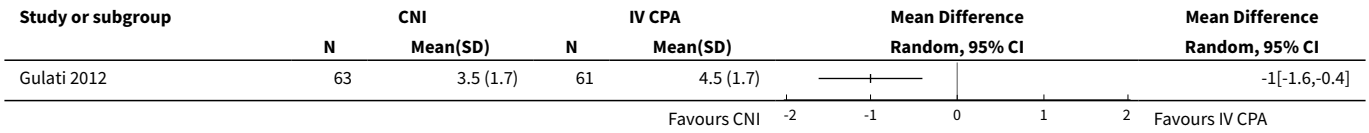
Analysis 2.1. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 1 Treatment response at 3 to 6 months.

Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Complete or partial remission					
APN 2008	9/15	3/17		15.17%	3.4[1.12,10.28]
Gulati 2012	52/63	28/61		84.83%	1.8[1.34,2.42]
Subtotal (95% CI)	**78**	**78**		**100%**	**1.98[1.25,3.13]**
Total events: 61 (CNI), 31 (IV CPA)					
Heterogeneity: Tau^2=0.04; Chi^2=1.24, df=1(P=0.26); I^2=19.67%					
Test for overall effect: Z=2.92(P=0)					

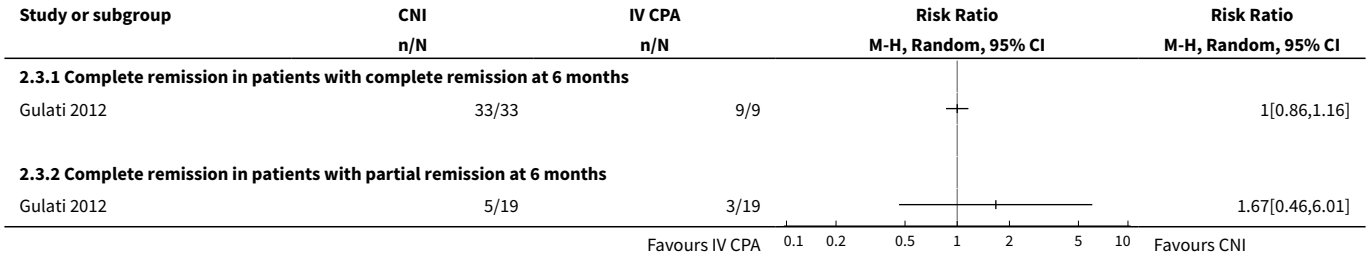




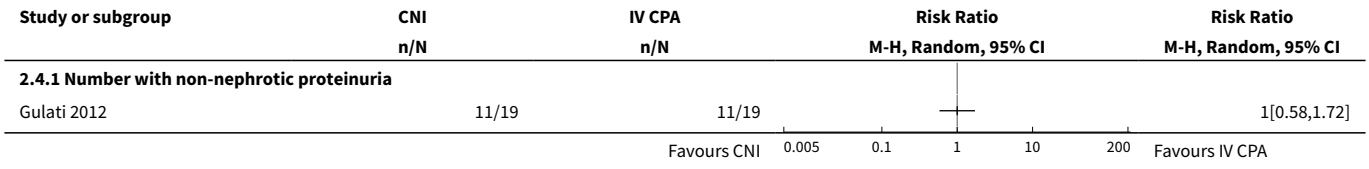
Analysis 2.2. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 2 Mean time to remission.

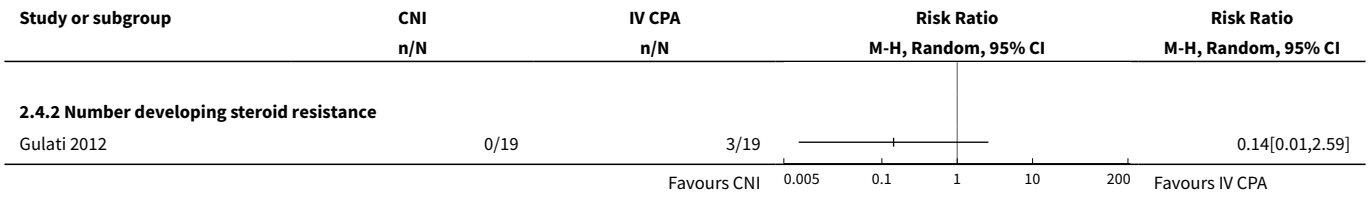


Analysis 2.3. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 3 Complete remission/SSNS at 12 months in 80 patients with complete or partial remission at 6 months.

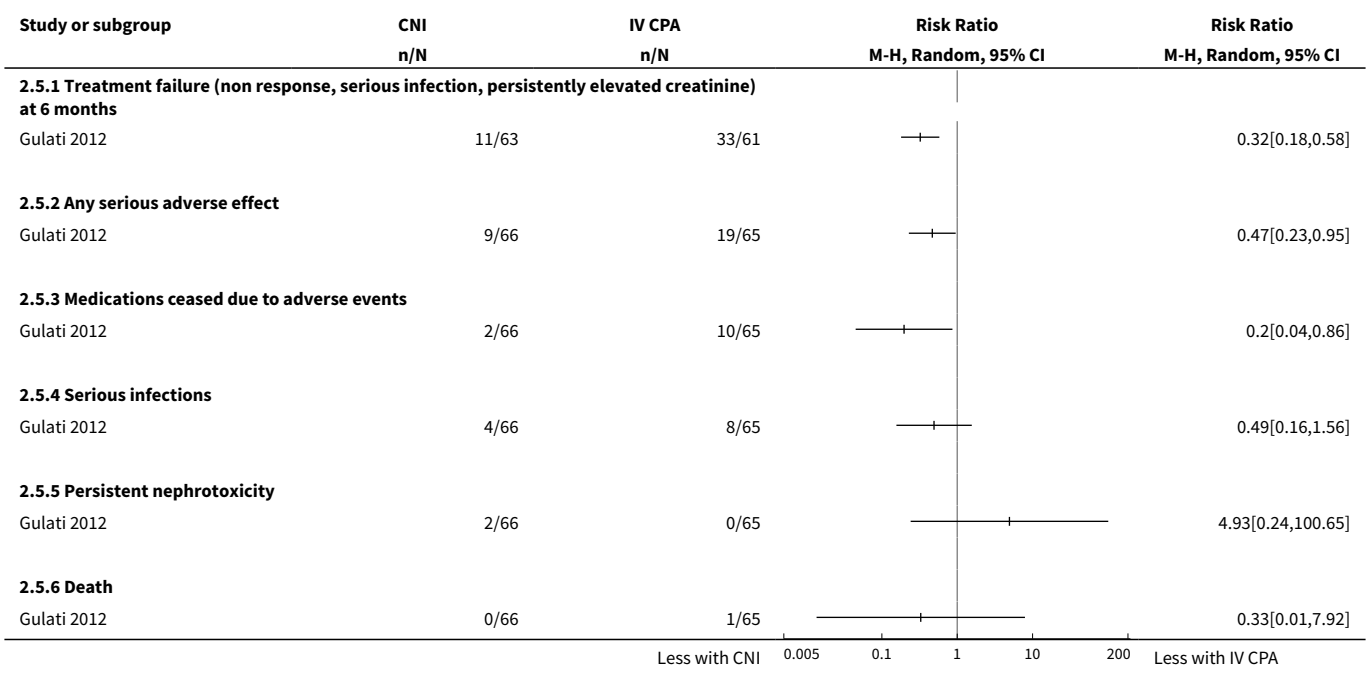


Analysis 2.4. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 4 Other outcomes at 12 months in 38 patients with partial remission at 6 months.





Analysis 2.5. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 5 Adverse events.



Comparison 3. Tacrolimus versus cyclosporin

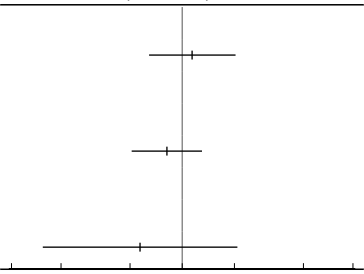
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment response at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial remission	1		Risk Ratio (M-H, Random,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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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 eGFR over 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Persistent nephrotoxicity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Reversible nephrotoxicity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Worsening of hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.5 Paraesthesia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.6 Hypertrichosis	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
7.7 Gingival hyperplasia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.8 Acne or skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.9 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.10 Sepsis/pneumonia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

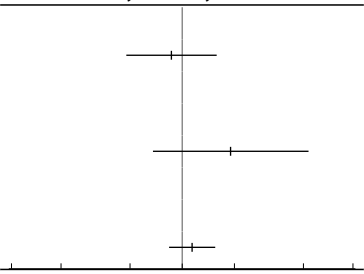
Analysis 3.1. Comparison 3 Tacrolimus versus cyclosporin, Outcome 1 Treatment response at 6 months.

Study or subgroup	TAC n/N	CSA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 Complete remission				
Choudhry 2009	9/21	10/20		1.14[0.64,2.03]
3.1.2 Partial remission				
Choudhry 2009	9/21	6/20		0.82[0.51,1.3]
3.1.3 Complete and partial remission				
Choudhry 2009	18/21	15/20		0.57[0.16,2.08]



Analysis 3.2. Comparison 3 Tacrolimus versus cyclosporin, Outcome 2 Treatment response at 12 months.

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

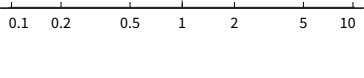


Analysis 3.3. Comparison 3 Tacrolimus versus cyclosporin, Outcome 3 Relapse following complete or partial remission.

Study or subgroup	TAC n/N	CSA 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 3.4. Comparison 3 Tacrolimus versus cyclosporin, Outcome 4 Post hoc analysis: complete remission in initial and late onset SRNS.

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

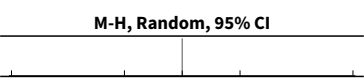


Analysis 3.5. Comparison 3 Tacrolimus versus cyclosporin, Outcome 5 Post hoc analysis: complete or partial remission in initial and late onset SRNS.

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

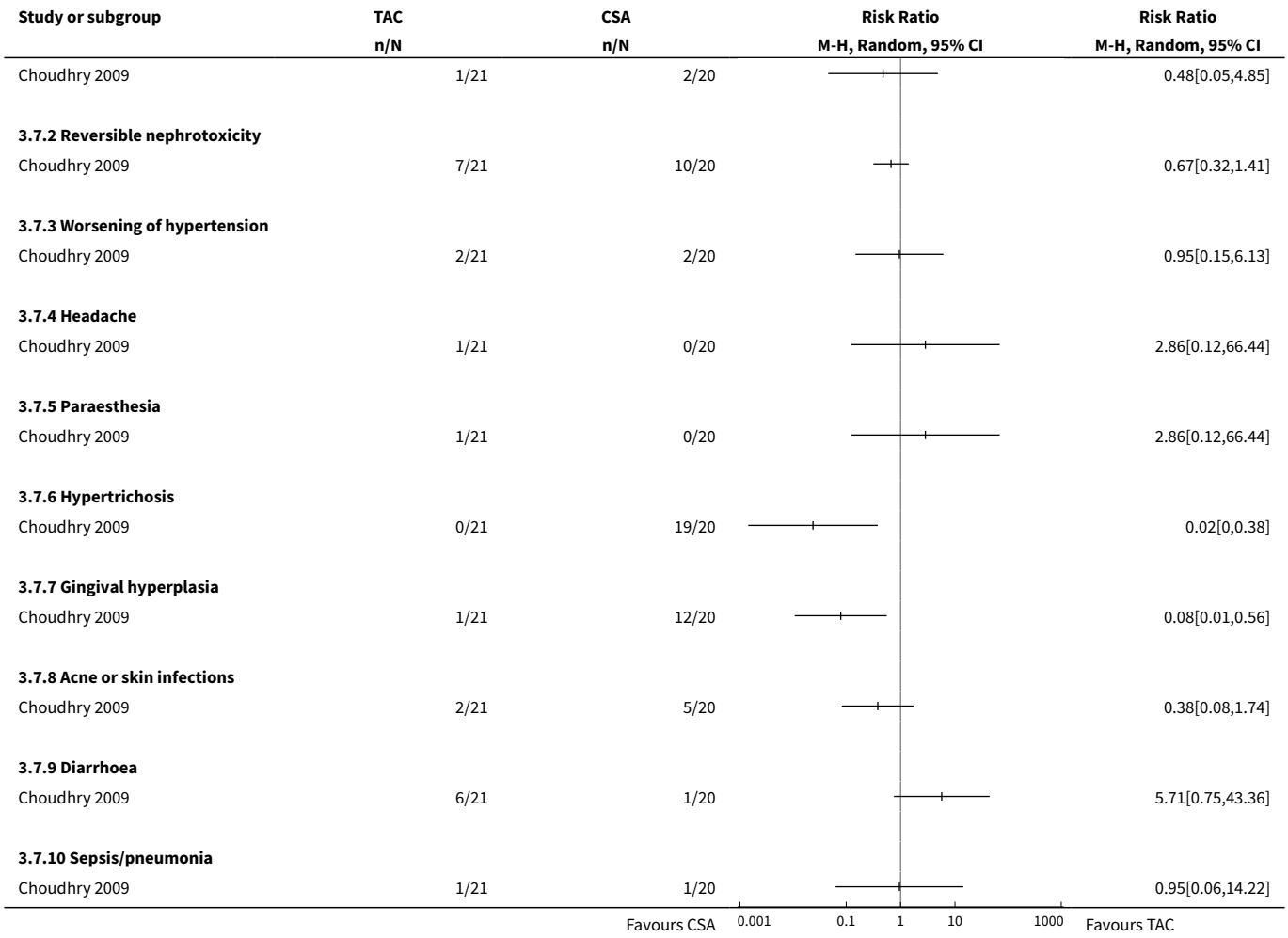
Analysis 3.6. Comparison 3 Tacrolimus versus cyclosporin, Outcome 6 Change in eGFR over 12 months.

Study or subgroup	TAC N	TAC Mean(SD)	CSA N	CSA 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 3.7. Comparison 3 Tacrolimus versus cyclosporin, Outcome 7 Adverse events.

Study or subgroup	TAC n/N	CSA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.7.1 Persistent nephrotoxicity				



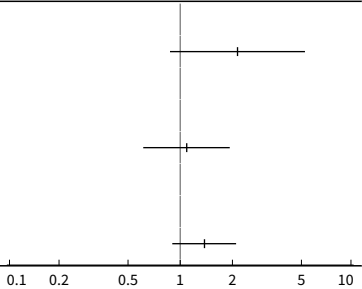
Comparison 4. Cyclosporin versus mycophenolate mofetil with pulse dexamethasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response at 52 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete remission (primary outcome 1,2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial remission (primary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Complete or partial remission (primary outcome 1,2,3)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Sustainable remission between 52 and 78 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete remission (secondary outcome 1,2)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Partial remission (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 No sustainable remission (secondary outcome 4,5)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 CKD or death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Death by 52 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 50% decline in GFR by 78 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 ESKD by 78 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events (weeks 0 to 26)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Serious infection requiring hospitalisation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Total Infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Total hospitalisations	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Gastrointestinal adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Neuropsychiatric conditions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Cyclosporin versus mycophenolate mofetil with pulse dexamethasone, Outcome 1 Treatment response at 52 weeks.

Study or subgroup	CSA n/N	MMF+DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.1.1 Complete remission (primary outcome 1,2)				
FSGS Study 2011	14/72	6/66		2.14[0.87,5.24]
4.1.2 Partial remission (primary outcome 3)				
FSGS Study 2011	19/72	16/66		1.09[0.61,1.93]
4.1.3 Complete or partial remission (primary outcome 1,2,3)				
FSGS Study 2011	33/72	22/66		1.38[0.9,2.1]

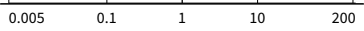


Analysis 4.2. Comparison 4 Cyclosporin versus mycophenolate mofetil with pulse dexamethasone, Outcome 2 Sustainable remission between 52 and 78 weeks.

Study or subgroup	CSA n/N	MMF+DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 Complete remission (secondary outcome 1,2)				
FSGS Study 2011	6/72	4/66		1.38[0.41,4.66]
4.2.2 Partial remission (secondary outcome 3)				
FSGS Study 2011	16/72	14/66		1.05[0.56,1.98]
4.2.3 No sustainable remission (secondary outcome 4,5)				
FSGS Study 2011	50/72	48/66		0.95[0.77,1.18]

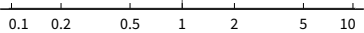
Analysis 4.3. Comparison 4 Cyclosporin versus mycophenolate mofetil with pulse dexamethasone, Outcome 3 CKD or death.

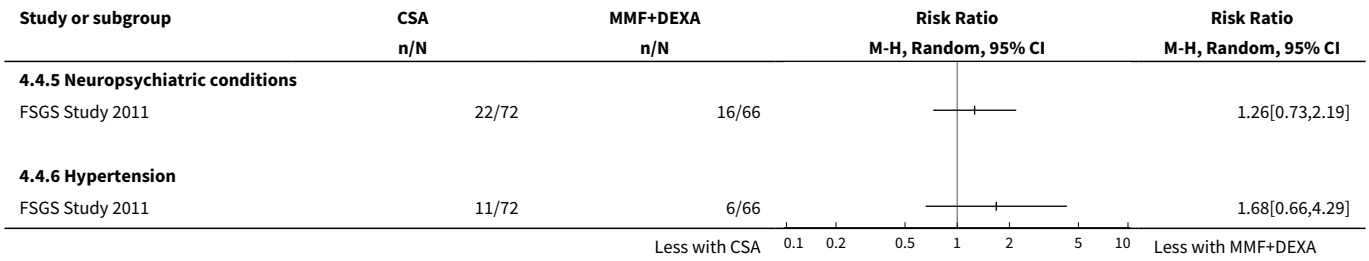
Study or subgroup	CSA n/N	MMF+DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.3.1 Death by 52 weeks				
FSGS Study 2011	0/72	2/66		0.18[0.01,3.75]
4.3.2 50% decline in GFR by 78 weeks				
FSGS Study 2011	5/72	2/66		2.29[0.46,11.41]
4.3.3 ESKD by 78 weeks				
FSGS Study 2011	5/72	1/66		4.58[0.55,38.22]



Analysis 4.4. Comparison 4 Cyclosporin versus mycophenolate mofetil with pulse dexamethasone, Outcome 4 Adverse events (weeks 0 to 26).

Study or subgroup	CSA n/N	MMF+DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.4.1 Serious infection requiring hospitalisation				
FSGS Study 2011	5/72	7/66		0.65[0.22,1.96]
4.4.2 Total Infections				
FSGS Study 2011	23/72	27/66		0.78[0.5,1.22]
4.4.3 Total hospitalisations				
FSGS Study 2011	12/72	14/66		0.79[0.39,1.57]
4.4.4 Gastrointestinal adverse effects				
FSGS Study 2011	47/72	47/66		0.92[0.73,1.15]

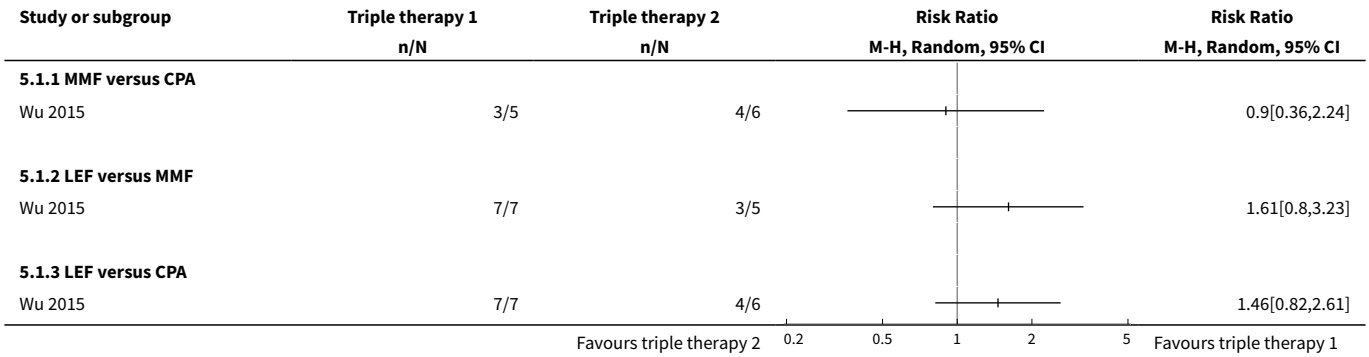




Comparison 5. Triple therapy with cyclophosphamide, mycophenolate mofetil or leflunomide

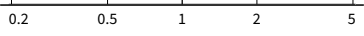
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 MMF versus CPA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 LEF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 LEF versus CPA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Long-term response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 MMF versus CPA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 LEF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 LEF versus CPA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Triple therapy with cyclophosphamide, mycophenolate mofetil or leflunomide, Outcome 1 Short-term response.



Analysis 5.2. Comparison 5 Triple therapy with cyclophosphamide, mycophenolate mofetil or leflunomide, Outcome 2 Long-term response.

Study or subgroup	Triple therapy 1 n/N	Triple therapy 2 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.2.1 MMF versus CPA				
Wu 2015	3/5	3/6		1.2[0.41,3.51]
5.2.2 LEF versus MMF				
Wu 2015	5/7	3/5		1.19[0.51,2.8]
5.2.3 LEF versus CPA				
Wu 2015	5/7	3/6		1.43[0.57,3.61]



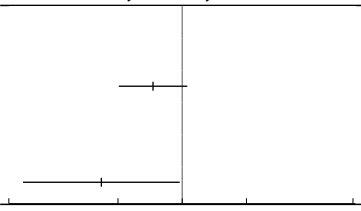
Comparison 6. Tacrolimus versus mycophenolate mofetil to maintain remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Infrequent relapses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Frequent relapses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Steroid resistance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Relapses per year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Prednisone dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Change in GFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Tacrolimus versus mycophenolate mofetil to maintain remission, Outcome 1 Treatment response.

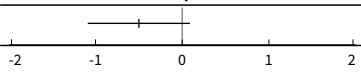
Study or subgroup	TAC n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 Complete or partial remission				
Sinha 2015	17/31	12/29		1.33[0.77,2.27]
6.1.2 Infrequent relapses				
Sinha 2015	11/31	1/29		10.29[1.42,74.79]

Study or subgroup	TAC n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.3 Frequent relapses				
Sinha 2015	3/31	8/29		0.35[0.1,1.2]
6.1.4 Steroid resistance				
Sinha 2015	0/31	8/29		0.06[0,0.91]



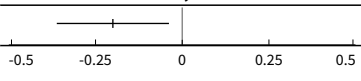
Analysis 6.2. Comparison 6 Tacrolimus versus mycophenolate mofetil to maintain remission, Outcome 2 Relapses per year.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2015	31	0.8 (1)	29	1.3 (1.3)		-0.5[-1.09,0.09]



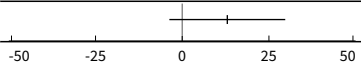
Analysis 6.3. Comparison 6 Tacrolimus versus mycophenolate mofetil to maintain remission, Outcome 3 Prednisone dose.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2015	31	0.3 (0.2)	29	0.5 (0.4)		-0.2[-0.36,-0.04]



Analysis 6.4. Comparison 6 Tacrolimus versus mycophenolate mofetil to maintain remission, Outcome 4 Change in GFR.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2015	31	-6 (35)	29	-19 (31)		13[-3.71,29.71]



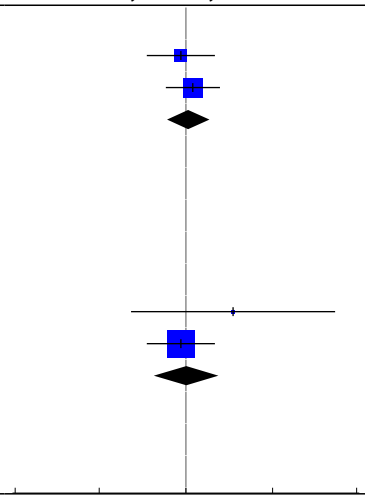
Comparison 7. Oral cyclophosphamide versus prednisone/placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Hypertension with seizures	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Cystitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Bone marrow suppression	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Oral cyclophosphamide versus prednisone/placebo, Outcome 1 Complete remission.

Study or subgroup	Oral CPA n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 All renal pathologies					
ISKDC 1996	8/32	6/21		38.67%	0.88[0.35,2.16]
ISKDC 1974	10/18	6/13		61.33%	1.2[0.59,2.47]
Subtotal (95% CI)	**50**	**34**		**100%**	**1.06[0.61,1.87]**
Total events: 18 (Oral CPA), 12 (Prednisone/placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
7.1.2 FSGS					
ISKDC 1974	3/7	0/3		10.02%	3.5[0.23,52.56]
ISKDC 1996	8/32	6/21		89.98%	0.88[0.35,2.16]
Subtotal (95% CI)	**39**	**24**		**100%**	**1.01[0.43,2.37]**
Total events: 11 (Oral CPA), 6 (Prednisone/placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					

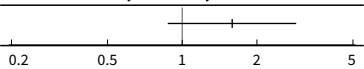


Analysis 7.2. Comparison 7 Oral cyclophosphamide versus prednisone/placebo, Outcome 2 Complete or partial remission.

Study or subgroup	Oral CPA n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 FSGS				
ISKDC 1996	16/32	12/21		0.88[0.53,1.45]

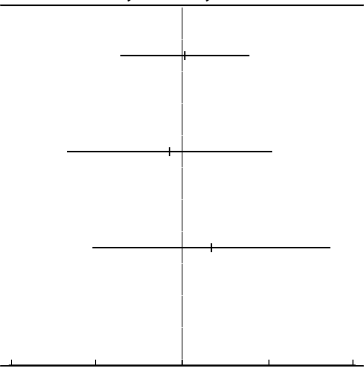
Analysis 7.3. Comparison 7 Oral cyclophosphamide versus prednisone/placebo, Outcome 3 Treatment failure.

Study or subgroup	Oral CPA n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ISKDC 1996	20/35	9/25		1.59[0.87,2.88]



Analysis 7.4. Comparison 7 Oral cyclophosphamide versus prednisone/placebo, Outcome 4 Adverse events.

Study or subgroup	Oral CPA n/N	Prednisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.4.1 All-cause mortality				
ISKDC 1996	3/35	2/25		1.07[0.19,5.95]
7.4.2 Hypertension with seizures				
ISKDC 1996	1/35	1/25		0.71[0.05,10.89]
7.4.3 Cystitis				
ISKDC 1996	1/35	0/25		2.17[0.09,51.1]
7.4.4 Bone marrow suppression				
ISKDC 1996	0/35	0/25		Not estimable

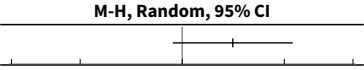


Comparison 8. IV versus oral cyclophosphamide

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

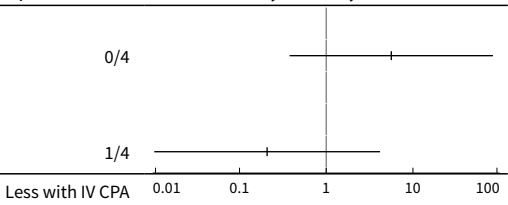
Analysis 8.1. Comparison 8 IV versus oral cyclophosphamide, Outcome 1 Complete remission.

Study or subgroup	IV CPA n/N	Oral CPA 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 8.2. Comparison 8 IV versus oral cyclophosphamide, Outcome 2 Adverse events.

Study or subgroup	IV CPA n/N	Oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.2.1 Vomiting				
Elhence 1994	4/7	0/4		5.63[0.38,83.67]
8.2.2 Bacterial infection				
Elhence 1994	0/7	1/4		0.21[0.01,4.18]



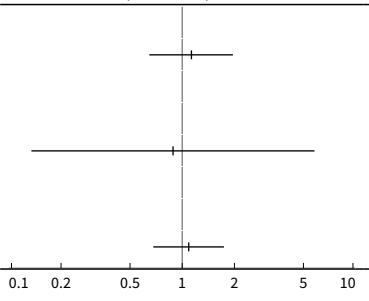
Comparison 9. IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone

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]
3.4 FSGS or MesPGN	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 cataract/glaucoma	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Cushingoid features	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Leucopenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Cystitis	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
4.6 Bacterial infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.7 Hypokalaemia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.8 Steroid encephalopathy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.9 Hair loss	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

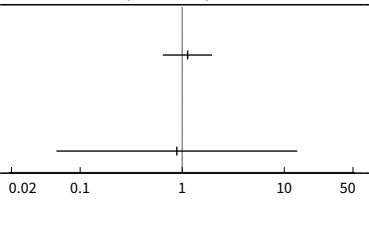
Analysis 9.1. Comparison 9 IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone, Outcome 1 Treatment response at 6 months.

Study or subgroup	IV CPA n/N	oral CPA/IV DEXA 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]



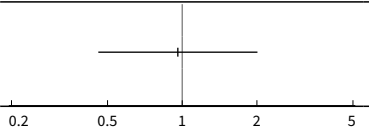
Analysis 9.2. Comparison 9 IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone, Outcome 2 Treatment response at 18 months.

Study or subgroup	IV CPA n/N	oral CPA/IV DEXA 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 oral cyclophosphamide plus IV dexamethasone, Outcome 3 Complete or partial resistance in subgroups.

Study or subgroup	IV CPA n/N	oral CPA/IV DEXA 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]

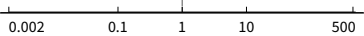


Study or subgroup	IV CPA n/N	oral CPA/IV DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.3.2 Late SRNS				
Mantan 2008	10/16	8/15		1.17[0.64,2.15]
9.3.3 Minimal change disease				
Mantan 2008	9/13	7/11		1.09[0.61,1.93]
9.3.4 FSGS or MesPGN				
Mantan 2008	7/13	6/12		1.08[0.51,2.3]

IV dexamethasone/oral CPA IV CPA

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

Study or subgroup	IV CPA n/N	oral CPA/IV DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.4.1 Hypertension				
Mantan 2008	0/26	10/23		0.04[0,0.68]
9.4.2 cataract/glaucoma				
Mantan 2008	2/26	1/23		1.77[0.17,18.26]
9.4.3 Cushingoid features				
Mantan 2008	15/26	17/23		0.78[0.52,1.17]
9.4.4 Leucopenia				
Mantan 2008	2/26	0/23		4.44[0.22,88.04]
9.4.5 Cystitis				
Mantan 2008	2/26	0/23		4.44[0.22,88.04]
9.4.6 Bacterial infections				
Mantan 2008	6/26	8/23		0.66[0.27,1.63]
9.4.7 Hypokalaemia				
Mantan 2008	0/26	7/23		0.06[0,0.98]
9.4.8 Steroid encephalopathy				
Mantan 2008	0/26	1/23		0.3[0.01,6.94]
9.4.9 Hair loss				
Mantan 2008	7/26	2/23		3.1[0.71,13.44]

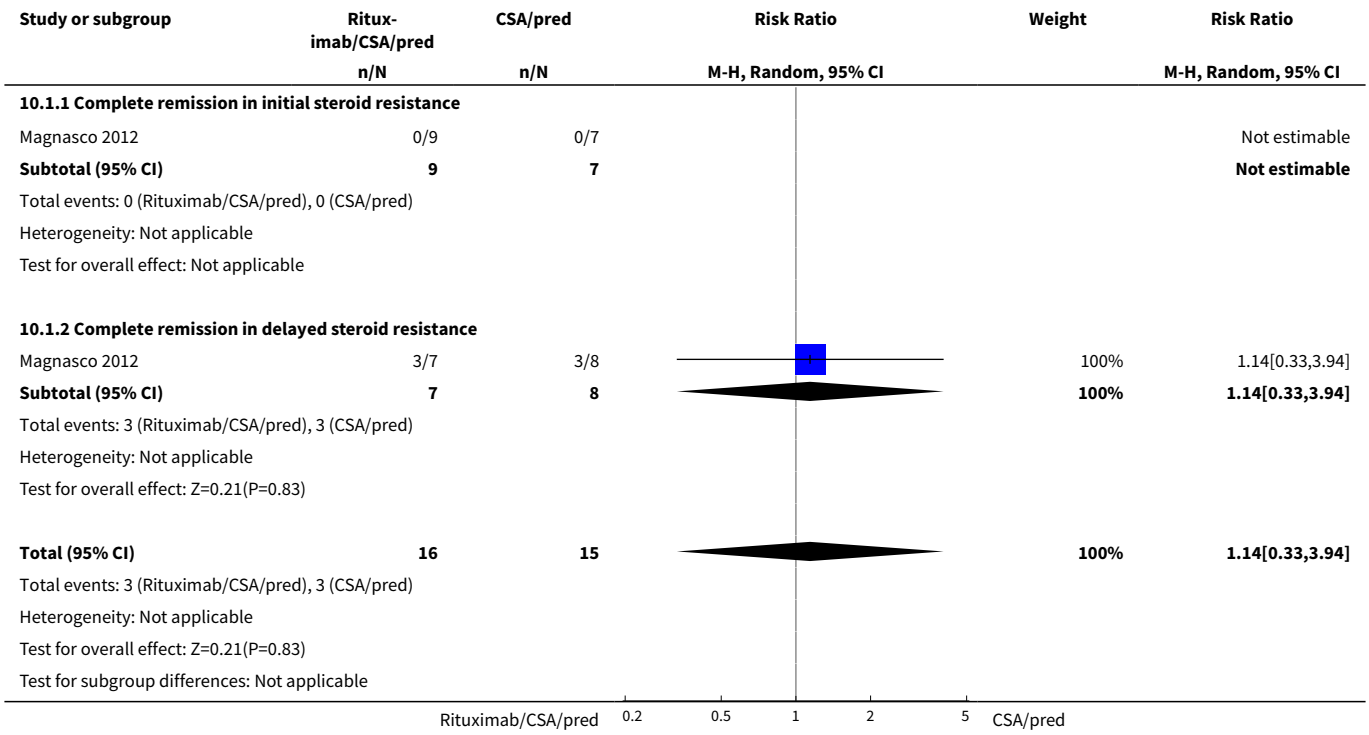


Less with IV CPA Less with oral CPA/IV DEXA

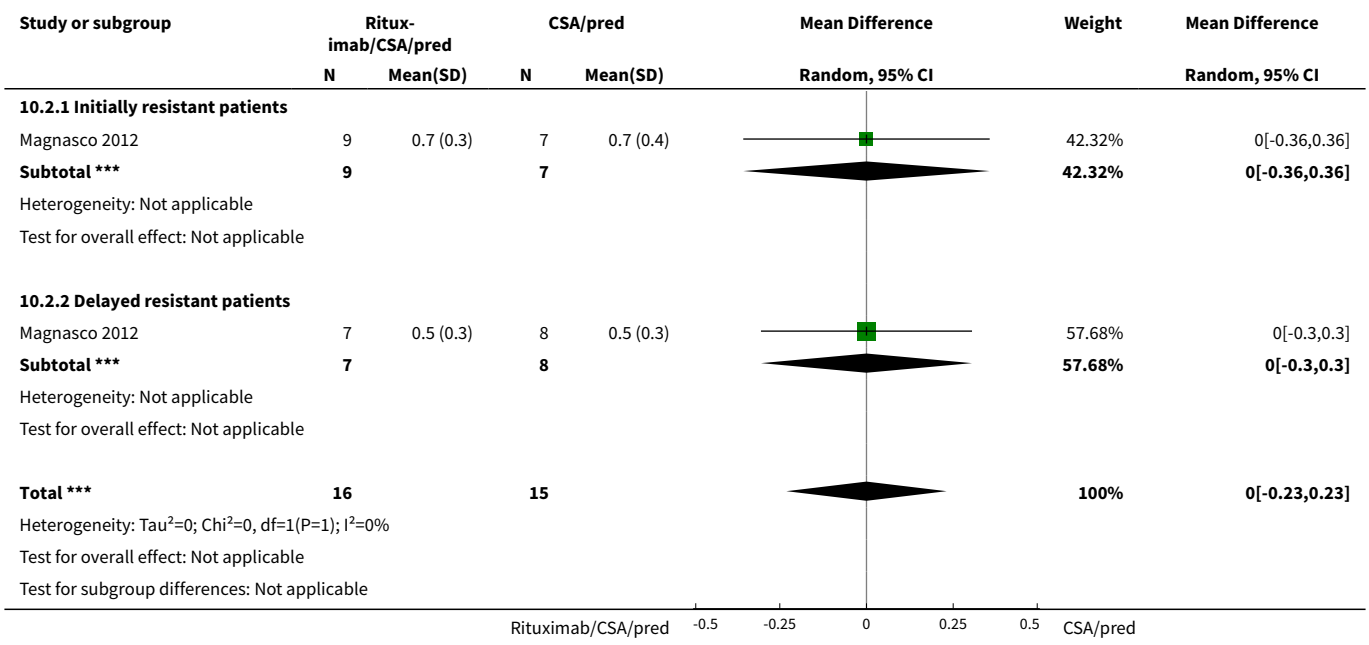
Comparison 10. Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	1	31	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.33, 3.94]
1.1 Complete remission in initial steroid resistance	1	16	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Complete remission in delayed steroid resistance	1	15	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.33, 3.94]
2 End of study creatinine	1	31	Mean Difference (IV, Random, 95% CI)	0.0 [-0.23, 0.23]
2.1 Initially resistant patients	1	16	Mean Difference (IV, Random, 95% CI)	0.0 [-0.36, 0.36]
2.2 Delayed resistant patients	1	15	Mean Difference (IV, Random, 95% CI)	0.0 [-0.30, 0.30]
3 End of study serum albumin	1	31	Mean Difference (IV, Random, 95% CI)	0.25 [-0.22, 0.72]
3.1 Initially resistant patients	1	16	Mean Difference (IV, Random, 95% CI)	0.0 [-0.77, 0.77]
3.2 Delayed resistant patients	1	15	Mean Difference (IV, Random, 95% CI)	0.40 [-0.20, 1.00]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Bronchospasm/treatment discontinued	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Skin rash	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Mild dyspnoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone, Outcome 1 Complete remission.

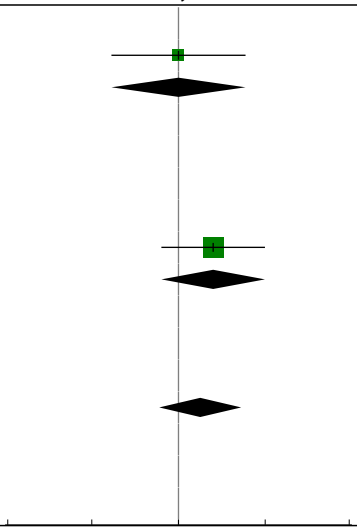


Analysis 10.2. Comparison 10 Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone, Outcome 2 End of study creatinine.



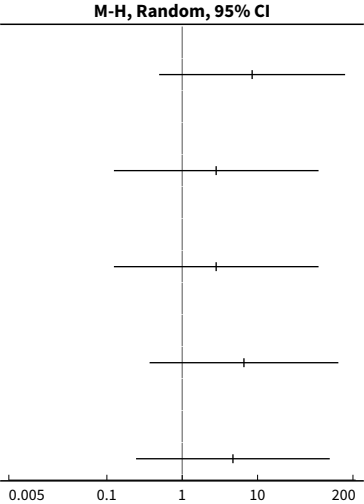
Analysis 10.3. Comparison 10 Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone, Outcome 3 End of study serum albumin.

Study or subgroup	Rituximab/CSA/pred N	Rituximab/CSA/pred Mean(SD)	CSA/pred N	CSA/pred Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
10.3.1 Initially resistant patients							
Magnasco 2012	9	2.1 (0.6)	7	2.1 (0.9)		37.36%	0[-0.77,0.77]
Subtotal ***	**9**		**7**			**37.36%**	**0[-0.77,0.77]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
10.3.2 Delayed resistant patients							
Magnasco 2012	7	3.3 (0.3)	8	2.9 (0.8)		62.64%	0.4[-0.2,1]
Subtotal ***	**7**		**8**			**62.64%**	**0.4[-0.2,1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.31(P=0.19)							
Total ***	**16**		**15**			**100%**	**0.25[-0.22,0.72]**
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%							
Test for overall effect: Z=1.04(P=0.3)							
Test for subgroup differences: Chi^2=0.64, df=1 (P=0.42), I^2=0%							



Analysis 10.4. Comparison 10 Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone, Outcome 4 Adverse events.

Study or subgroup	RTX/CSA/pred n/N	CSA/pred n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.4.1 Abdominal pain				
Magnasco 2012	4/16	0/15		8.47[0.49,145.11]
10.4.2 Bronchospasm/treatment discontinued				
Magnasco 2012	1/16	0/15		2.82[0.12,64.39]
10.4.3 Hypotension				
Magnasco 2012	1/16	0/15		2.82[0.12,64.39]
10.4.4 Skin rash				
Magnasco 2012	3/16	0/15		6.59[0.37,117.77]
10.4.5 Mild dyspnoea				
Magnasco 2012	2/16	0/15		4.71[0.24,90.69]

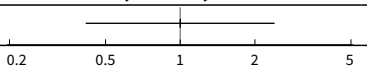


Comparison 11. Chlorambucil versus indomethacin

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

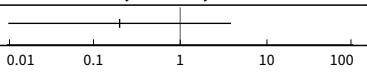
Analysis 11.1. Comparison 11 Chlorambucil versus indomethacin, Outcome 1 Complete remission.

Study or subgroup	Chlorambucil n/N	Indomethacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kleinknecht 1980	6/15	6/15		1[0.42,2.4]



Analysis 11.2. Comparison 11 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 1980	0/15	2/15		0.2[0.01,3.85]

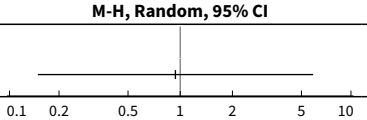


Comparison 12. Azathioprine versus placebo

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 12.1. Comparison 12 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
12.1.1 All renal pathologies				
ISKDC 1970	2/16	2/15		0.94[0.15,5.84]



Analysis 12.2. Comparison 12 Azathioprine versus placebo, Outcome 2 Complete or partial remission.

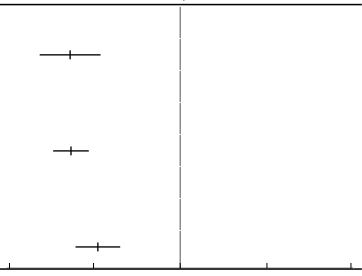
Study or subgroup	Azathioprine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.2.1 All renal pathologies				
ISKDC 1970	4/16	4/15		0.94[0.28,3.09]

Comparison 13. Fosinopril plus 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

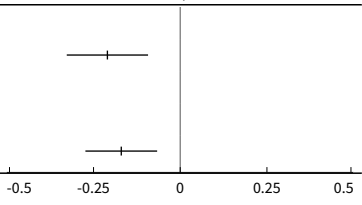
Analysis 13.1. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 1 Proteinuria.

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



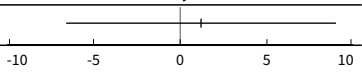
Analysis 13.2. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 2 Tubular proteinuria.

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



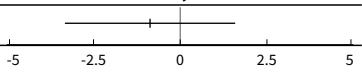
Analysis 13.3. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 3 Serum albumin.

Study or subgroup	Fosinopril+pred N	Fosinopril+pred Mean(SD)	Prednisone N	Prednisone 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]



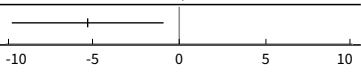
Analysis 13.4. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 4 Systolic blood pressure.

Study or subgroup	Fosinopril+pred N	Fosinopril+pred Mean(SD)	Prednisone N	Prednisone 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]



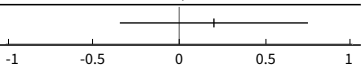
Analysis 13.5. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 5 Creatinine clearance.

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



Analysis 13.6. Comparison 13 Fosinopril plus prednisone versus prednisone alone, Outcome 6 Serum potassium.

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



APPENDICES

Appendix 1. Electronic search strategies

(Continued)

Database	Search terms
CENTRAL	1. MeSH descriptor: [Nephrotic Syndrome] explode all trees 2. MeSH descriptor: [Nephrosis, Lipoid] explode all trees 3. nephrotic syndrome:ti,ab,kw (Word variations have been searched) 4. lipoid nephrosis:ti,ab,kw (Word variations have been searched) 5. minimal change glomerulonephritis:ti,ab,kw (Word variations have been searched) 6. minimal change nephr*:ti,ab,kw (Word variations have been searched) 7. idiopathic steroid resistant nephrotic syndrome:ti,ab,kw (Word variations have been searched) 8. SRNS:ti,ab,kw (Word variations have been searched) 9. {or #1-#8}
MEDLINE	1. Nephrotic Syndrome/ 2. Nephrosis Lipoid/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. minimal change glomerulonephritis.tw. 6. minimal change nephr$.tw. 7. idiopathic steroid resistant nephrotic syndrome.tw. 8. or/1-7
EMBASE	1. Nephrotic Syndrome/ 2. Lipoid Nephrosis/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. minimal change glomerulonephritis.tw. 6. minimal change nephropathy.tw. 7. idiopathic steroid resistant nephrotic syndrome.tw. 8. or/1-7

Appendix 2. Risk of bias assessment tool

(Continued)

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).
	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

(Continued)

	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.
	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
6 October 2016	New citation required and conclusions have changed	Five new studies included, new interventions included
6 October 2016	New search has been performed	New search, summary of findings tables incorporated

HISTORY

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

Date	Event	Description
16 September 2014	New search has been performed	Search strategies updated
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.
9 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Designing the review; EH, DH, JC
- Undertaking review update: EH, DH, SW (2016), NW, JC
- Coordinating the review; EH
- Study selection, quality assessment, data collection; EH, DH, SW, NW
- Entering data into RevMan; DH, EH, SW, NW
- Analysis of data; DH, EH, SW, NW
- Interpretation of data; DH, SW, EH, NW, JC
- Writing the review; DH, EH, NW, JC
- Providing general advice on the review; EH, NW, JC

DECLARATIONS OF INTEREST

- Elisabeth Hodson: none known
- Sophia Wong: none known
- Narelle Willis: none known
- Jonathan Craig: none known

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Internal sources

- No sources of support supplied

External sources

- NHMRC, Australia.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Summary of findings tables have been incorporated into the 2016 update

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]; Leflunomide; 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