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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 to corticosteroids in the first episode of nephrotic syndrome (initial resistance) or develop resistance after one or more responses to corticosteroids (delayed resistance) may be treated with immunosuppressive agents including calcineurin inhibitors (CNI) (cyclosporin or tacrolimus) and with non-immunosuppressive agents such as angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). However, response to these agents is limited so newer agents are being assessed for efficacy. This is an update of a review first published in 2004 and updated in 2006, 2010 and 2016.

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 the Cochrane Kidney and Transplant Register of Studies to 17 September 2019 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (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 steroid-resistant nephrotic syndrome (SRNS). Studies, which enrolled children and adults but in which paediatric data could not be separated from adult data, were also included.

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). For continuous outcomes, results were expressed as mean difference (MD) and 95% CI. Data were pooled using the random effects model. The certainty of the evidence was assessed using the GRADE approach.

Main results

Twenty-five studies (1063 participants) were included. Fourteen studies were at low risk of bias for sequence generation and allocation concealment. Five and 19 studies were at low risk of performance and detection bias. Fourteen, 14 and 13 studies were at low risk of attrition bias, reporting bias and other bias respectively.

Cyclosporin compared with placebo or no treatment may increase the number of participants who achieve complete remission (4 studies, 74 participants: RR 3.50, 95% CI 1.09 to 11.20) or complete or partial remission (4 studies, 74 children: RR 3.15, 95% CI 1.04 to 9.57) by 6 months (low certainty evidence). It is uncertain whether cyclosporin increases the likelihood of worsening hypertension or reduces the likelihood of end-stage kidney disease (very low certainty evidence).

CNI compared with IV cyclophosphamide (CPA) may increase the number of participants with complete or partial remission at 3 to 6 months (2 studies, 156 children: RR 1.98, 95% CI 1.25 to 3.13) (low certainty evidence) and probably reduces the number with treatment failure (non response, serious infection, persistently elevated creatinine (1 study, 124 participants: RR 0.32, 95% CI 0.18 to 0.58) (moderate certainty evidence) with little or no increase in serious infections (1 study, 131 participants: RR 0.49, 95% CI 0.16 to 1.56) (moderate certainty evidence).

Tacrolimus compared with cyclosporin may make little or no difference to the number who achieve complete or partial remission (2 studies, 58 participants: RR 1.05, 95% CI 0.87 to 1.25) (low certainty evidence) or in the number with worsening hypertension (2 studies, 58 participants: RR 0.41, 95% CI 0.08 to 2.15) (low certainty evidence).

Cyclosporin compared with mycophenolate mofetil (MMF) and dexamethasone probably makes little or no difference to the number who achieve complete or partial remission (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24) (moderate certainty evidence) and makes little or no difference to the number dying (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24) or with 50% reduction in glomerular filtration rate (GFR) (1 study, 138 participants: RR 2.29, 95% CI 0.46 to 11.41) (low certainty evidence).

Among children, who have achieved complete remission, tacrolimus compared with MMF may increase the number of children who maintain complete or partial response for 12 months (1 study, 60 children: RR 2.01, 95% CI 1.32 to 3.07) (low certainty evidence).

Oral CPA with prednisone compared with prednisone alone may make little or no difference to the number who achieve complete remission (2 studies, 84 children: RR 1.06, 95% CI 0.61 to 1.87) (low certainty evidence).

IV CPA compared with oral CPA (2 studies, 61 children: RR 1.58, 95% CI 0.65 to 3.85) and IV compared with oral CPA plus IV dexamethasone (1 study, 49 children: RR 1.13, 95% CI 0.65 to 1.96) may make little or no difference to the number who achieve complete remission (low certainty evidence).

It is uncertain whether rituximab and cyclosporin compared with cyclosporin increases the likelihood of remission because the certainty of the evidence is very low.

It is uncertain whether adalimumab or galactose compared with conservative therapy increases the likelihood of remission because the certainty of the evidence is very low.

Two studies reported that ACEi may reduce proteinuria in children with SRNS. One study reported that the dual angiotensin II and endothelin Type A receptor antagonist, sparsentan, may reduce proteinuria more effectively than the angiotensin receptor blocker, irbesartan.

Authors' conclusions

To date RCTs have demonstrated that CNIs may increase the likelihood of complete or partial remission compared with placebo/no treatment or CPA. 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. Other agents such as calcineurin inhibitors (cyclosporin, tacrolimus) or angiotensin-converting enzyme inhibitors are required for those children do not respond to corticosteroids in their first episode of nephrotic syndrome (initial resistance) or who develop steroid resistance after one or more responses to corticosteroids (delayed resistance).

What did we do?

We searched Cochrane Kidney and Transplant's Specialised Register (up to 17 September 2019). Randomised controlled trials were included if they compared different immunosuppressive agents or non-immunosuppressive agents with placebo, prednisone or other agent in children with steroid resistant nephrotic syndrome. Studies of new treatments were included as these included children as well as adults.

What did we find?

This review found that cyclosporin compared with placebo, no treatment or prednisone may increase the number of participants, in whom urine protein disappears (complete remission) or is markedly reduced (partial remission). Calcineurin inhibitors (cyclosporin, tacrolimus) also may increase the number of children, who achieve complete or partial remission compared with intravenous cyclophosphamide. There may be little or no benefit of other immunosuppressive agents studied so far. Angiotensin-converting enzyme inhibitors may reduce the amount of protein in the urine.

Conclusions

Calcineurin inhibitors may increase the likelihood of complete or partial remission compared with placebo/no treatment or cyclophosphamide. However, the certainty of the evidence is low because the studies were small. It remains uncertain whether other interventions may alter outcomes due to few small studies. Larger and well-designed randomised controlled trials are needed to evaluate other treatment combinations for children with steroid resistant nephrotic syndrome.

SUMMARY OF FINDINGS

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

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo/no treatment	Risk with cyclosporin			
Complete remission: all renal pathologies	57 per 1,000	200 per 1,000 (62 to 640)	RR 3.50 (1.09 to 11.20)	74 (4)	⊕⊕⊖⊖ LOW [1,2]
Complete remission: FSGS	69 per 1,000	217 per 1,000 (67 to 702)	RR 3.14 (0.97 to 10.18)	58 (3)	⊕⊕⊖⊖ LOW [1,2]
Complete or partial remission: all renal pathologies	229 per 1,000	720 per 1,000 (238 to 1,000)	RR 3.15 (1.04 to 9.57)	74 (4)	⊕⊕⊖⊖ LOW [1,2]
Complete or partial remission: FSGS	333 per 1,000	887 per 1,000 (283 to 1,000)	RR 2.66 (0.85 to 8.31)	49 (2)	⊕⊕⊖⊖ LOW [1,2]
Adverse events: worsening of hypertension	167 per 1,000	167 per 1,000 (28 to 997)	RR 1.00 (0.17 to 5.98)	24 (1)	⊕⊖⊖⊖ VERY LOW [1,2]
Adverse events: infection	429 per 1,000	300 per 1,000 (86 to 1,000)	RR 0.70 (0.20 to 2.51)	17 (1)	⊕⊖⊖⊖ VERY LOW [1,2]
Adverse events: ESKD	333 per 1,000	77 per 1,000 (10 to 597)	RR 0.23 (0.03 to 1.79)	25 (1)	⊕⊖⊖⊖ VERY LOW [1,2]

*__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; **FSGS:** focal segmental glomerulosclerosis; **ESKD:** end-stage kidney disease

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Inadequate or unclear allocation concealment and sequence generation in two studies.
[2] Small numbers of events and included patients in RCTs

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

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

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: calcineurin inhibitor (CNI)
Comparison: IV cyclophosphamide (CPA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IV CPA	Risk with CNI			
Treatment response at 3 to 6 months: complete or partial remission	397 per 1,000	787 per 1,000 (497 to 1,000)	RR 1.98 (1.25 to 3.13)	156 (2)	⊕⊕⊖⊖ LOW [1 2]
Treatment response at 3 to 6 months: complete remission	128 per 1,000	440 per 1,000 (236 to 822)	RR 3.43 (1.84 to 6.41)	156 (2)	⊕⊕⊖⊖ LOW [1 2]
Treatment response at 3 to 6 months: partial remission	269 per 1,000	452 per 1,000 (116 to 1,000)	RR 1.68 (0.43 to 6.56)	156 (2)	⊕⊖⊖⊖ VERY LOW [1 2 3]
Adverse events: treatment failure at 6 months (non response, serious infection, persistently elevated creatinine)	541 per 1,000	173 per 1,000 (97 to 314)	RR 0.32 (0.18 to 0.58)	124 (1)	⊕⊕⊕⊖ MODERATE [2]
Adverse events: medications ceased due to adverse events	154 per 1,000	31 per 1,000 (6 to 132)	RR 0.20 (0.04 to 0.86)	131 (1)	⊕⊕⊕⊖ MODERATE [2]
Adverse events: serious infections	123 per 1,000	60 per 1,000 (20 to 192)	RR 0.49 (0.16 to 1.56)	131 (1)	⊕⊕⊕⊖ MODERATE [2]
Adverse events: death	15 per 1,000	5 per 1,000	RR 0.33	131 (1)	⊕⊕⊖⊖

	(0 to 122)	(0.01 to 7.92)		LOW [4]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One study at high risk of attrition bias
[2] Small numbers of patients included in studies
[3] Significant heterogeneity between studies
[4] Few events in singles study

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

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

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: Paediatric nephrology services
Intervention: tacrolimus
Comparison: cyclosporin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with cyclosporin	Risk with tacrolimus			
Treatment response at 6 months: complete remission	500 per 1,000	570 per 1,000 (320 to 1,000)	RR 1.14 (0.64 to 2.03)	41 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 6 months: complete and partial remission	750 per 1,000	428 per 1,000 (120 to 1,000)	RR 0.57 (0.16 to 2.08)	41 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 12 months: complete remission	500 per 1,000	400 per 1,000 (225 to 710)	RR 0.80 (0.45 to 1.42)	58 (2)	⊕⊕⊖⊖ LOW [2]
Treatment response at 12 months: complete and partial remission	833 per 1,000	875 per 1,000 (725 to 1,000)	RR 1.05 (0.87 to 1.25)	58 (2)	⊕⊕⊖⊖

					LOW [2]
Adverse events: persistent nephrotoxicity	100 per 1,000	48 per 1,000 (5 to 485)	RR 0.48 (0.05 to 4.85)	41 (1)	⊕⊕⊖⊖ LOW [1]
Adverse events: worsening of hypertension	No events	No events	-	58 (2)	⊕⊕⊖⊖ LOW [2 3]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Single small study
[2] Two small studies with few events
[3] Serious risk of bias issues in one included study

Summary of findings 4. Cyclosporin versus mycophenolate mofetil with pulse dexamethasone for idiopathic steroid-resistant nephrotic syndrome in children

Cyclosporin versus mycophenolate mofetil with pulse dexamethasone for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: cyclosporin
Comparison: mycophenolate mofetil with pulse dexamethasone (MMF + IV DEXA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with MMF + IV DEXA	Risk with cyclosporin			
Treatment response at 52 weeks: complete remission (primary outcome 1, 2)	91 per 1,000	195 per 1,000 (79 to 476)	RR 2.14 (0.87 to 5.24)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
Treatment response at 52 weeks: partial remission (primary outcome 3)	242 per 1,000	264 per 1,000 (148 to 468)	RR 1.09 (0.61 to 1.93)	138 (1)	⊕⊕⊕⊖

					MODERATE [1]
Sustainable remission between 52 and 78 weeks: complete or partial remission (primary outcome 1, 2, 3)	333 per 1,000	460 per 1,000 (300 to 700)	RR 1.38 (0.90 to 2.10)	138 (1)	⊕⊕⊕⊖ MODERATE [1]
CKD or death: death by 52 weeks	30 per 1,000	5 per 1,000 (0 to 114)	RR 0.18 (0.01 to 3.75)	138 (1)	⊕⊕⊖⊖ LOW [1 2]
CKD or death: 50% decline in GFR by 78 weeks	30 per 1,000	69 per 1,000 (14 to 346)	RR 2.29 (0.46 to 11.41)	138 (1)	⊕⊕⊖⊖ LOW [1 2]
Adverse events (weeks 0 to 26): serious infection requiring hospitalisation	106 per 1,000	69 per 1,000 (23 to 208)	RR 0.65 (0.22 to 1.96)	138 (1)	⊕⊕⊖⊖ LOW [1 2]
Adverse events (weeks 0 to 26): hypertension	91 per 1,000	153 per 1,000 (60 to 390)	RR 1.68 (0.66 to 4.29)	138 (1)	⊕⊕⊖⊖ LOW [1 2]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Inadequate enrolment lead to uncertainty in results
[2] Few events in study groups

Summary of findings 5. Tacrolimus versus mycophenolate mofetil to maintain remission for idiopathic steroid-resistant nephrotic syndrome in children

Tacrolimus versus mycophenolate mofetil to maintain remission for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: tacrolimus to maintain remission
Comparison: mycophenolate mofetil (MMF) to maintain remission

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants	Certainty of the evidence

	Risk with MMF to maintain remission	Risk with tacrolimus		(studies)	(GRADE)
Number with complete or partial response at one year	448 per 1,000	901 per 1,000 (592 to 1,000)	RR 2.01 (1.32 to 3.07)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Number with complete response at one year	414 per 1,000	741 per 1,000 (459 to 1,000)	RR 1.79 (1.11 to 2.90)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Number with partial response at one year	34 per 1,000	161 per 1,000 (20 to 1,000)	RR 4.68 (0.58 to 37.68)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Number with treatment failure by one year	552 per 1,000	99 per 1,000 (33 to 298)	RR 0.18 (0.06 to 0.54)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Number with frequent relapses by one year	345 per 1,000	97 per 1,000 (31 to 317)	RR 0.28 (0.09 to 0.92)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Number with steroid resistance by one year	207 per 1,000	14 per 1,000 (0 to 254)	RR 0.07 (0.00 to 1.23)	60 (1)	⊕⊕⊖⊖ LOW [1,2]
Change in GFR	Change in GFR was 13 mL/min higher with tacrolimus (3.71 lower to 29.71 higher) compared to MMF		-	60 (1)	⊕⊕⊖⊖ LOW [1,2]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: 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 how primary outcome of continuing remission was measured and whether it was blinded
[2] Small study with few events

Summary of findings 6. Oral cyclophosphamide versus prednisone or placebo for idiopathic steroid-resistant nephrotic syndrome in children

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with prednisone/placebo	Risk with oral CPA			
Complete remission: all renal pathologies	353 per 1,000	374 per 1,000 (215 to 660)	RR 1.06 (0.61 to 1.87)	84 (2)	⊕⊕⊖⊖ LOW [1 2]
Complete remission: FSGS	250 per 1,000	253 per 1,000 (108 to 593)	RR 1.01 (0.43 to 2.37)	63 (2)	⊕⊕⊖⊖ LOW [1 2]
Complete or partial remission	571 per 1,000	503 per 1,000 (303 to 829)	RR 0.88 (0.53 to 1.45)	53 (1)	⊕⊕⊖⊖ LOW [1 2]
Complete or partial remission: FSGS	571 per 1,000	503 per 1,000 (303 to 829)	RR 0.88 (0.53 to 1.45)	53 (1)	⊕⊕⊖⊖ LOW [1 2]
Treatment failure	360 per 1,000	572 per 1,000 (313 to 1,000)	RR 1.59 (0.87 to 2.88)	60 (1)	⊕⊕⊖⊖ LOW [1 2]
Adverse events: death (all causes)	80 per 1,000	86 per 1,000 (15 to 476)	RR 1.07 (0.19 to 5.95)	60 (1)	⊕⊕⊖⊖ LOW [1 2]
Adverse events: hypertension with seizures	40 per 1,000	28 per 1,000 (2 to 436)	RR 0.71 (0.05 to 10.89)	60 (1)	⊕⊖⊖⊖ VERY LOW [1 2]

*__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; **FSGS:** focal segmental glomerulosclerosis

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Serious risk of bias issues. Unclear sequence generation and allocation concealment. Attrition bias

[2] Small number of included participants

Summary of findings 7. IV versus oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children

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

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: IV cyclophosphamide (CPA)
Comparison: oral CPA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral CPA	Risk with IV CPA			
Complete remission	414 per 1,000	654 per 1,000 (269 to 1,000)	RR 1.58 (0.65 to 3.85)	61 (2)	⊕⊕⊖⊖ LOW [1 2]
Partial remission	80 per 1,000	80 per 1,000 (12 to 524)	RR 1.00 (0.15 to 6.55)	50 (1)	⊕⊕⊖⊖ LOW [3]
Continuing remission at one year	160 per 1,000	120 per 1,000 (30 to 482)	RR 0.75 (0.19 to 3.01)	50 (1)	⊕⊕⊖⊖ LOW [2 3]
Adverse events: renal insufficiency	120 per 1,000	40 per 1,000 (5 to 359)	RR 0.33 (0.04 to 2.99)	50 (1)	⊕⊕⊖⊖ LOW [2 3]
Adverse events: bacterial infection	103 per 1,000	106 per 1,000 (10 to 1,000)	RR 1.02 (0.10 to 10.62)	61 (2)	⊕⊖⊖⊖ VERY LOW [1 2 3]
Adverse events: vomiting	34 per 1,000	82 per 1,000 (12 to 558)	RR 2.38 (0.35 to 16.17)	61 (2)	⊕⊖⊖⊖ VERY LOW [1 2 3]
Adverse events: alopecia	80 per 1,000	120 per 1,000 (22 to 658)	RR 1.50 (0.27 to 8.22)	50 (1)	⊕⊕⊖⊖ LOW [2 3]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One study had unclear sequence generation and allocation concealment and significant attrition
[2] Small numbers of enrolled patients
[3] Small numbers of events

Summary of findings 8. IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone for idiopathic steroid-resistant nephrotic syndrome in children

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

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: IV cyclophosphamide (CPA)
Comparison: oral CPA plus IV dexamethasone (DEXA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral CPA plus IV DEXA	Risk with IV CPA			
Treatment response at 6 months: complete remission	478 per 1,000	540 per 1,000 (311 to 937)	RR 1.13 (0.65 to 1.96)	49 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 6 months: partial remission	87 per 1,000	77 per 1,000 (12 to 503)	RR 0.88 (0.14 to 5.79)	49 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 6 months: complete or partial remission	565 per 1,000	616 per 1,000 (384 to 983)	RR 1.09 (0.68 to 1.74)	49 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 18 months: sustained remission/steroid-sensitive relapses	478 per 1,000	540 per 1,000 (311 to 937)	RR 1.13 (0.65 to 1.96)	49 (1)	⊕⊕⊖⊖ LOW [1]
Treatment response at 18 months: CKD	43 per 1,000	38 per 1,000 (3 to 580)	RR 0.88 (0.06 to 13.35)	49 (1)	⊕⊕⊖⊖ LOW [1]
Adverse events: hypertension	435 per 1,000	17 per 1,000 (0 to 296)	RR 0.04 (0.00 to 0.68)	49 (1)	⊕⊕⊖⊖ LOW [1]

Adverse events: bacterial infections	348 per 1,000	230 per 1,000 (94 to 567)	RR 0.66 (0.27 to 1.63)	49 (1)	⊕⊕⊖⊖ LOW [1]

*__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; **CKD:** chronic kidney disease

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Single study with small number of enrolled participants

Summary of findings 9. Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone for idiopathic steroid-resistant nephrotic syndrome in children

Rituximab/cyclosporin/prednisolone compared to cyclosporin/prednisolone for idiopathic steroid-resistant nephrotic syndrome in children

Patient or population: idiopathic steroid-resistant nephrotic syndrome in children
Setting: paediatric nephrology services
Intervention: rituximab/cyclosporin/prednisolone (RTX/CSA/PRED)
Comparison: CSA/PRED

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with CSA/PRED	Risk with RTX/CSA/PRED			
Number with complete remission: complete remission in initial steroid resistance	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	16 (1)	⊕⊖⊖⊖ VERY LOW [1 2]
Number with complete remission: complete remission in delayed steroid resistance	375 per 1,000	428 per 1,000 (124 to 1,000)	RR 1.14 (0.33 to 3.94)	15 (1)	⊕⊖⊖⊖ VERY LOW [1 2]
Number with complete remission: complete remission in all patients	200 per 1,000	188 per 1,000 (44 to 788)	RR 0.94 (0.22 to 3.94)	31 (1)	⊕⊖⊖⊖ VERY LOW [1 2]
Adverse events: bronchospasm/treatment discontinued	0 per 1,000	0 per 1,000 (0 to 0)	RR 2.82 (0.12 to 64.39)	31 (1)	⊕⊖⊖⊖ VERY LOW [1 2]

Adverse events: hypotension	0 per 1,000	0 per 1,000 (0 to 0)	RR 2.82 (0.12 to 64.39)	31 (1)	⊕⊖⊖⊖ VERY LOW [1] [2]
Adverse events: skin rash	0 per 1,000	0 per 1,000 (0 to 0)	RR 6.59 (0.37 to 117.77)	31 (1)	⊕⊖⊖⊖ VERY LOW [1] [2]
Adverse events: mild dyspnoea	0 per 1,000	0 per 1,000 (0 to 0)	RR 4.71 (0.24 to 90.69)	31 (1)	⊕⊖⊖⊖ VERY LOW [1] [2]

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of attrition bias
[2] Very small number of patients with few events

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 and of protein calorie malnutrition with significant reductions in quality of life. Prospective studies of children with newly diagnosed idiopathic nephrotic syndrome identified through Paediatric 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). A literature review of studies from 1946 to 2014 found the average incidence of nephrotic syndrome from retrospective and prospective studies to be 4.7 (range 1.15 to 16.9) per 100,000 children (Chanchlani 2016). The proportion of children with steroid resistance disease varied between 2.1 to 27.3% (average 12.4%).

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 with primary nephrotic syndrome respond to corticosteroid therapy within four weeks. In those children who fail to respond to corticosteroids, kidney biopsy is performed to determine pathology. The majority of children with SRNS have focal segmental glomerulosclerosis (FSGS), mesangioproliferative glomerulonephritis (MesPGN) or minimal change disease (MCD). 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, 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 resistance); children with delayed steroid resistance do not have disease causing gene mutations (Bierzynska 2017). 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 (CPA), chlorambucil, mycophenolate mofetil (MMF), 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-CT 2011; Niaudet 1994). Remission rates of up to 60% with combinations of intravenous (IV) methylprednisolone and CPA 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, 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 low. The aims of the update of this systematic review initially published in 2004 and updated in 2006, 2010 and 2016 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 to increase the evidence base available on the efficacy of treatment of SRNS in children.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs, in which different agents were used in the treatment of participants including 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 (> 2 g/g) or > 40 mg/m^2/h after four weeks or more of daily corticosteroid agent). Where a kidney biopsy was performed, 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. Children with disease-causing genetic mutations associated with FSGS where kidney biopsy was not performed could also be included.

Where studies included adults and children were included and where paediatric data could not be separated, data of all participants in these studies were included in this review.

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.

- IV corticosteroid agent versus oral corticosteroid agent, placebo or no intervention
- Different doses and/or durations of IV corticosteroid agent
- Non-corticosteroid immunosuppressive agent (with or without concomitant use of corticosteroid agent) versus corticosteroid agent alone, placebo or no treatment
- Two different non-corticosteroid agents (with or without concomitant use of corticosteroid agent)
- Different doses, durations and routes of administration of the same non-corticosteroid agent (with or without concomitant use of corticosteroid agent)
- 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 (< 0.2 g/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 Register of Studies up to 17 September 2019 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following 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 and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

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

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 the Cochrane Kidney and Transplant Register of Studies 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 intention-to-treat (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

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a CI for I^2) (Higgins 2011).

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

We presented the main results of the review in 'Summary of findings' tables. 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' tables 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; GRADE 2011). 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

presented the following outcomes in the 'Summary of findings' tables.

- Complete remission
- Partial remission
- Complete or partial remission
- Chronic kidney disease
- 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 2 March 2016 identified 21 new studies, of which five were included (FSGS-CT 2011; Gulati 2012; Magnasco 2012; Sinha 2017; Wu 2015). The 2016 update included 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-CT 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 evaluated the safety and efficacy of sparsentan (a dual endothelin receptor) in a phase 2 study compared with irbesartan (DUET 2017). 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 CNI-resistant nephrotic syndrome (NCT02394106).

Figure 1. Flowchart of included and excluded studies

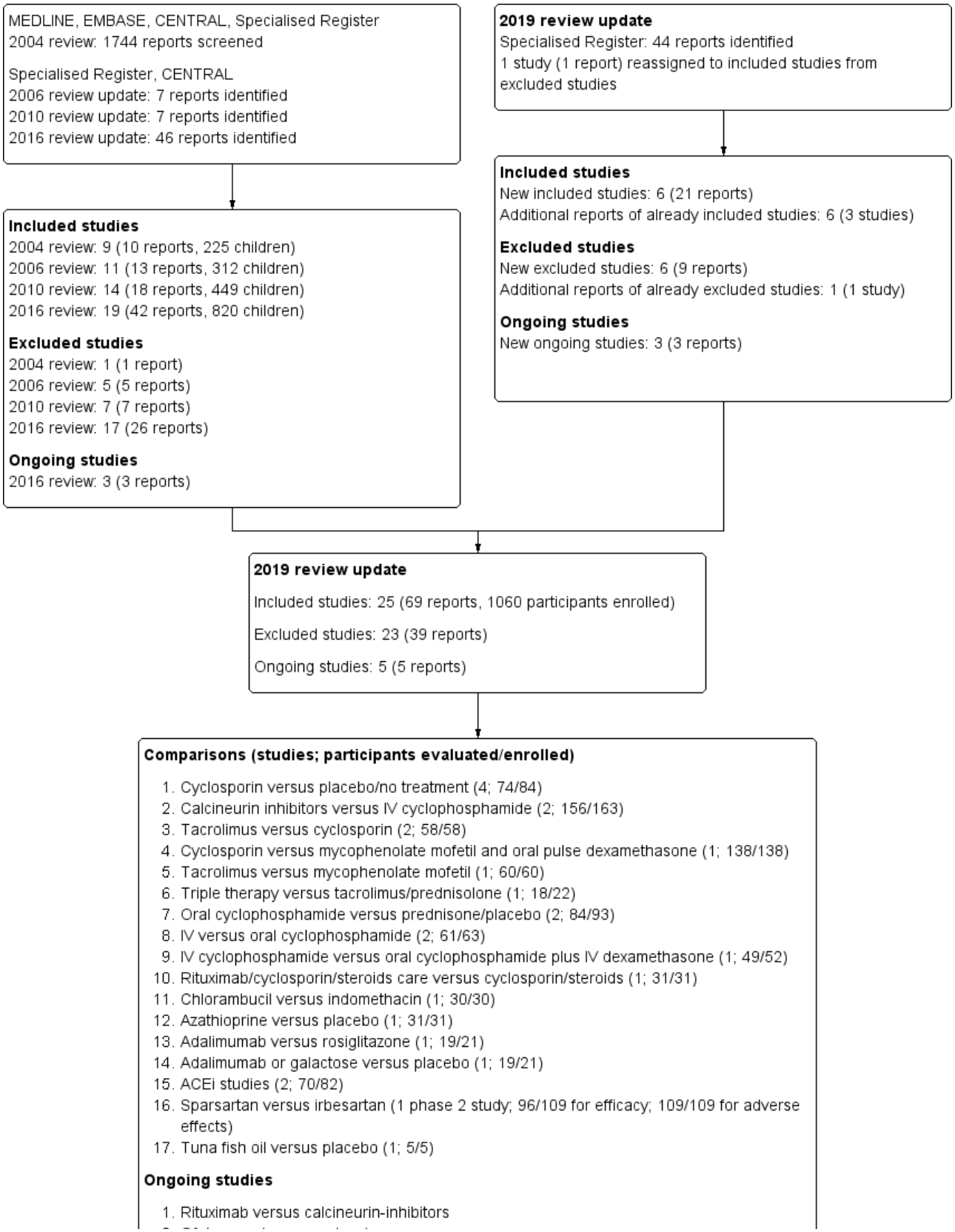


Figure 1. (Continued)

1. Rituximab versus calcineurin-inhibitors
2. Ofatumumab versus placebo
3. Abatacept versus placebo
4. ACTH versus routine treatment
5. Sparsentan versus irbesartan (phase 3 study)

In 2019 we identified four new included studies (FONT I 2009; FONT II 2011; Shah 2017; Valverde 2010), In addition, results from the DUET 2017 study, which had been identified as an ongoing study in the 2016 update, were available. A review of previously excluded studies revealed an eligible study for inclusion (Bhaumik 2002). Four studies included both adult and paediatric participants and separate paediatric data were not available (Bhaumik 2002; DUET 2017; FONT I 2009; FONT II 2011). There were six additional reports of three already included studies (FSGS-CT 2011; Gulati 2012; Sinha 2017), and one new report of an already excluded study. Two studies (NCT02382575; NCT02394106) listed as ongoing in the 2016 update are continuing. Of three additional ongoing studies, one is evaluating abatacept (Trachtman 2018), one is evaluating ACTH (NCT02972346), and one is evaluating sparsentan in a phase 3 study (DUPLEX 2018) in treatment resistant nephrotic syndrome. The 2019 update included 25 studies (69 reports) with five ongoing studies (Figure 1).

Included studies

The 25 included studies enrolled 1063 participants of which 1012 were evaluated. Study characteristics are shown in Characteristics of included studies.

- Four studies compared cyclosporin with placebo, no treatment or methylprednisolone (84 enrolled/74 children and adults evaluated) (Bhaumik 2002; Garin 1988; Lieberman 1996; Ponticelli 1993a). Two studies (Garin 1988; Ponticelli 1993a) included children with MCD and FSGS, while two studies (Bhaumik 2002; Lieberman 1996) included only participants with FSGS. Three studies (Bhaumik 2002; Lieberman 1996; Ponticelli 1993a) included only participants with initial steroid resistance.
- Two studies compared oral CNI with IV CPA. APN 2008 (32 children) compared oral cyclosporin with IV CPA in children with initial steroid resistance. Gulati 2012 (124/131 children evaluated) compared oral tacrolimus with IV CPA in children with initial and delayed steroid resistance. Both studies included children with MCD, FSGS and MesPGN.
- Two studies (Choudhry 2009 (41 children); Valverde 2010 (17 children)) compared oral cyclosporin with oral tacrolimus. Choudhry 2009 included children with initial or delayed steroid resistance and children with MCD, FSGS and MesPGN. Valverde 2010 did not report whether patients had initial or delayed steroid resistance, and did not state histological types.
- FSGS-CT 2011 (138 participants) compared cyclosporin with 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 CPA 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 2017 (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 (84/93 children evaluated) compared oral CPA 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.
- Three studies compared IV with oral CPA in children with initial or delayed steroid resistance (Elhence 1994; Mantan 2008; Shah 2017). In Mantan 2008 (49/52 children evaluated), IV dexamethasone was given to children in the oral CPA group. Elhence 1994 (11/13 children evaluated) only included children with MCD while Mantan 2008 and Shah 2017 (50 children) 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 (45/57 children evaluated) compared the ACEi, fosinopril, and prednisone with prednisone alone. Both studies included children with initial and delayed steroid resistance.
- DUET 2017 (96/109 adults and children evaluated for efficacy; all evaluated for adverse effects) compared the dual angiotensin II and endothelin type A receptor antagonist, sparsentan with the ARB, irbesartan in patients with primary FSGS.
- 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.
- FONT I 2009 (19/21 adults and children evaluated) compared adalimumab with rosiglitazone in participants with FSGS and initial steroid resistance.
- FONT II 2011 (19/21 adults and children evaluated) compared adalimumab, galactose and conservative therapy in participants with therapy resistant primary FSGS.

Excluded studies

23 studies (39 reports) were excluded.

- Adeniyi 1979 was excluded because 31/36 included children had nephrotic syndrome considered secondary to *Plasmodium malariae.*
- Nine studies did not include children (Arora 2002; Koshikawa 1993; Kumar 2004a; Li 2006g; Ren 2011; Ren 2013; Saito 2014; Shibasaki 2004; Walker 1990).
- Four studies did not include children with nephrotic syndrome (Kano 2003) or included children with an ineligible renal pathology (Buyukcelik 2002; Hari 2018; Saito 2017).
- Two studies evaluated interventions in children with SSNS (Hiraoka 2000; Iyengar 2006).
- Five studies evaluated interventions in both children with steroid-resistant and steroid-dependent disease and the results could not be separated (Jung 1990; Khemani 2016; Tejani 1988; Yi 2008; Zhao 2013a).
- In one study, only children with SSNS were randomised; children with SRNS were not randomised (Ahn 2018).
- One study was excluded because it was a single arm study (JPRN-C000000007).

Risk of bias in included studies

See Figure 2; Figure 3.

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

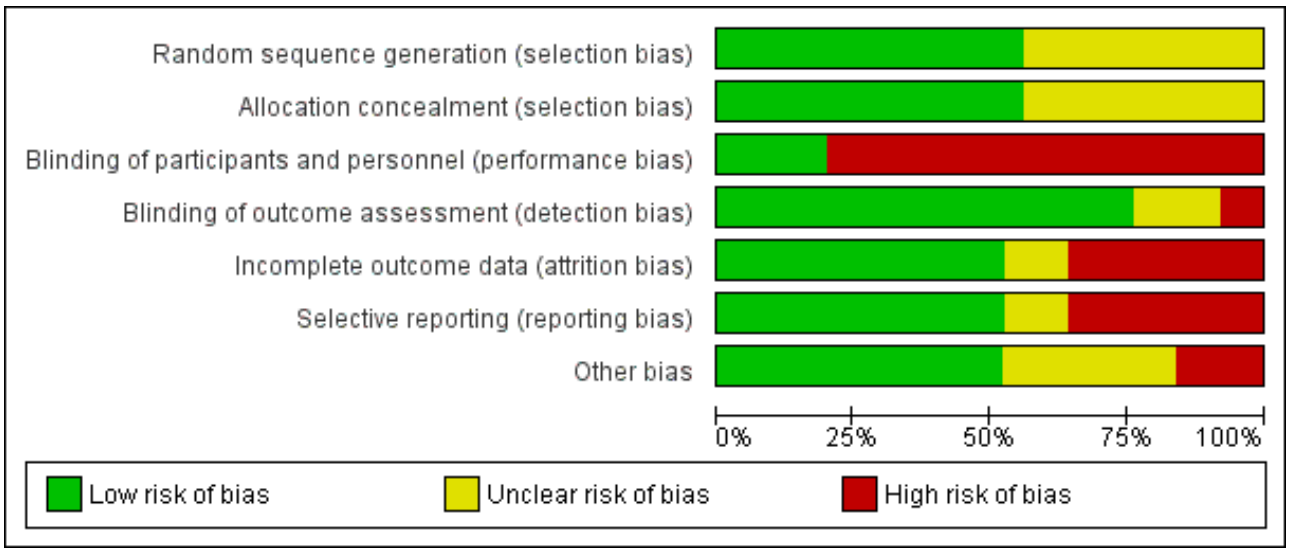


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

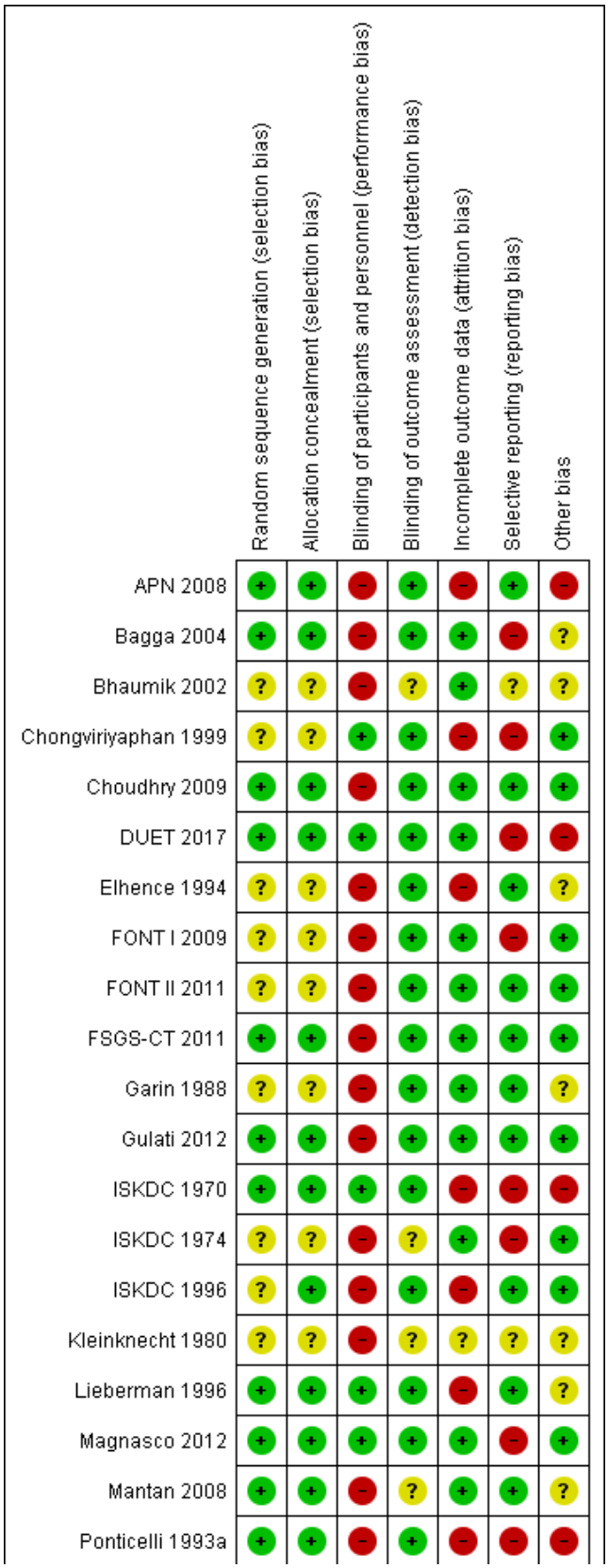
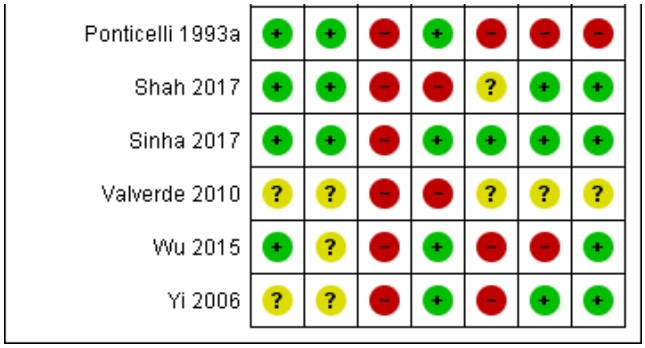


Figure 3. (Continued)



Allocation

Sequence generation was satisfactory in 14 studies (APN 2008; Bagga 2004; Choudhry 2009; DUET 2017; FSGS-CT 2011; Gulati 2012; ISKDC 1970; Lieberman 1996; Magnasco 2012; Mantan 2008; Ponticelli 1993a; Shah 2017; Sinha 2017; Wu 2015) and unclear in the remaining studies.

Allocation concealment was adequate in 14 studies (APN 2008; Bagga 2004; Choudhry 2009; DUET 2017; FSGS-CT 2011; Gulati 2012; ISKDC 1970; ISKDC 1996; Lieberman 1996; Magnasco 2012; Mantan 2008; Ponticelli 1993a; Shah 2017; Sinha 2017) and unclear in the remaining studies.

Blinding

Five studies reported that care givers (families, research staff) were blinded to treatment groups (Chongviriyaphan 1999; DUET 2017; ISKDC 1970; Lieberman 1996; Magnasco 2012). In the remaining 20 studies, care givers were not blinded to treatment groups.

Nineteen studies were considered at low risk of detection bias as the outcome was laboratory-based and unlikely to be influenced by blinding (APN 2008; Bagga 2004; Choudhry 2009; Elhence 1994; FONT I 2009; FONT II 2011; FSGS-CT 2011; Garin 1988; ISKDC 1970; ISKDC 1996; Lieberman 1996; Ponticelli 1993a; Sinha 2017; Wu 2015; Yi 2006) or the outcome assessors were blinded to treatment groups (Chongviriyaphan 1999; DUET 2017; Gulati 2012; Magnasco 2012). 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 (Bhaumik 2002; Kleinknecht 1980), no information was provided on how the outcome was assessed. In two studies (Shah 2017; Valverde 2010) there was no blinding and outcome assessment could be influenced by lack of blinding.

Incomplete outcome data

Attrition bias was considered to be present if more than 10% of participants were excluded from analysis. Fourteen studies were considered to have provided complete outcome data (Bagga 2004; Bhaumik 2002; Choudhry 2009; DUET 2017; FONT I 2009; FONT II 2011; FSGS-CT 2011; Garin 1988; Gulati 2012; ISKDC 1974; Magnasco 2012; Mantan 2008; Shah 2017; Sinha 2017). Nine studies did not provide complete outcome data. In the remaining two studies, available only as abstracts (Kleinknecht 1980; Valverde 2010), 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. Thirteen studies were considered to be free of selective reporting (APN 2008; Choudhry 2009; DUET 2017; Elhence 1994; FONT II 2011; FSGS-CT 2011; Garin 1988; Gulati 2012; ISKDC 1996; Lieberman 1996; Mantan 2008; Shah 2017; Yi 2006). Nine studies were considered to have reported outcomes selectively or results for the primary outcome could not be included in meta-analyses (Bagga 2004; Chongviriyaphan 1999; DUET 2017; FONT I 2009; ISKDC 1970; ISKDC 1974; Magnasco 2012; Ponticelli 1993a; Wu 2015). In the remaining three studies (Bhaumik 2002; Kleinknecht 1980; Valverde 2010), available only as abstracts, it was unclear whether there was selective reporting of outcomes.

Other potential sources of bias

Thirteen studies reported funding by university or government agencies or stated that they did not receive monetary support and were considered free of other potential sources of bias (Chongviriyaphan 1999; Choudhry 2009; FONT I 2009; FONT II 2011; FSGS-CT 2011; Gulati 2012; ISKDC 1974; ISKDC 1996; Magnasco 2012; Shah 2017; Sinha 2017; Yi 2006; Wu 2015). Four studies reported funding from pharmaceutical companies and were considered at risk of potential bias (APN 2008; DUET 2017; ISKDC 1970; Ponticelli 1993a). Other potential sources of bias were unclear in the remaining eight studies as none reported on support.

The definition of steroid resistance varied between studies.

- Nine studies defined steroid resistance as persistent proteinuria of > 4 mg/m^2/h or UP/C > 1g/g after four weeks (FONT I 2009; FSGS-CT 2011; Lieberman 1996; Wu 2015), five weeks (Kleinknecht 1980), six weeks (APN 2008) or eight weeks of daily prednisone (Bagga 2004; ISKDC 1970; ISKDC 1974). One study (FONT II 2011) defined steroid resistance as persistent proteinuria of > 4 mg/m^2/h or UP/C > 1g/g "following a standard course of prednisone/prednisolone/methylprednisolone prescribed for FSGS therapy".
- Nine studies defined steroid resistance as persistent proteinuria > 40 mg/m^2/h, > 2 g/g or above 1 g/m^2/d after four weeks (Choudhry 2009; Gulati 2012; Mantan 2008; Shah 2017; Sinha 2017), five weeks (Ponticelli 1993a), eight weeks (Garin 1988; ISKDC 1996) or six months (Magnasco 2012) of prednisone.

- Two studies defined steroid resistance as no response after eight weeks of prednisone (Bhaumik 2002; Yi 2006) but did not define the degree of proteinuria.
- Four studies did not define steroid resistance (Chongviriyaphan 1999; DUET 2017; Elhence 1994; Valverde 2010).

Effects of interventions

See: **Summary of findings for the main comparison** Cyclosporin versus placebo or no treatment for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 2** Calcineurin inhibitor versus IV cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 3** Tacrolimus versus cyclosporin for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 4** Cyclosporin versus mycophenolate mofetil with pulse dexamethasone for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 5** Tacrolimus versus mycophenolate mofetil to maintain remission for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 6** Oral cyclophosphamide versus prednisone or placebo for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 7** IV versus oral cyclophosphamide for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 8** IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone for idiopathic steroid-resistant nephrotic syndrome in children; **Summary of findings 9** Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone for idiopathic steroid-resistant nephrotic syndrome in children

Cyclosporin versus placebo/prednisone

Remission by six months

- Cyclosporin may increase the number of participants with SRNS who achieve complete remission compared with placebo or no treatment, irrespective of renal pathology (Analysis 1.1.1 (4 studies, 74 participants): RR 3.50, 95% CI 1.09 to 11.20; I^2 = 0%) and in participants with FSGS (Analysis 1.1.2 (3 studies, 58 participants): RR 3.14, 95% CI 0.97 to 10.18; I^2 = 0%) (low certainty evidence).
- Cyclosporin may increase the number of participants achieving complete or partial remission irrespective of renal pathology (Analysis 1.2.1 (4 studies, 74 participants): RR 3.15, 95% CI 1.04 to 9.57; I^2 = 60%) and in patients with FSGS (Analysis 1.2.2 (2 studies, 49 participants): RR 2.66, 95% CI 0.85 to 8.31; I^2 = 70%) (low certainty evidence).

Subgroup analysis, other than for renal pathology, was not possible because of small patient numbers.

Adverse events

- It is uncertain whether cyclosporin increases the likelihood of worsening hypertension (Analysis 1.3.1), bacterial infections (Analysis 1.3.2), or reduces the likelihood of ESKD (Analysis 1.3.3) because the certainty of the evidence is very low.

The evidence was downgraded because of increased risk of bias and imprecision resulting from small study numbers with few events (Summary of findings for the main comparison),

Calcineurin inhibitors versus intravenous cyclophosphamide

Remission by three to six months

- CNI compared with IV CPA may increase the number of children who achieve 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 2.1.3 (2 studies, 156 children): RR 3.43, 95% CI 1.84 to 6.41; I^2 = 0%) (low certainty evidence).
- It is uncertain whether CNI compared with IV CPA increases the number of children with partial remission (Analysis 2.1.2 (2 studies, 156 children): RR 1.68, 95% CI 0.43 to 6.56; I^2 = 71%) because the certainty of this evidence is very low.
- Gulati 2012 reported the mean time to remission may be shorter with tacrolimus compared with IV CPA (Analysis 2.2 (1 study, 124 children): MD -1.00 months, 95% CI -1.60 to -0.40).

Adverse effects

- Gulati 2012 reported CNI compared with IV CPA probably reduces the number of children with treatment failure (non-response at 6 months, > 1 episode of serious infection requiring hospitalisation or declining GFR) (Analysis 2.3.1 (1 study, 124 children): RR 0.32, 95% CI 0.18 to 0.58), the number with any serious adverse event (Analysis 2.3.2 (1 study, 131 children): RR 0.47, 95% CI 0.23 to 0.95), and the number who need to cease medications (Analysis 2.3.3 (1 study, 131 children): RR 0.20, 95% CI 0.04 to 0.86) (Moderate certainty evidence).
- CNI compared with IV CPA may make little or no difference in the number with serious infections (Analysis 2.3.4 (1 study, 131 children): RR 0.49, 95% CI 0.16 to 1.56), the number of deaths (Analysis 2.3.5 (1 study, 131 children): RR 0.33, 95% CI 0.01 to 7.92) (low certainty evidence), or the number with persistent nephrotoxicity (Analysis 2.3.6 (1 study, 131 children): RR 4.93, 95% CI 0.24 to 100.65).

The certainty of the evidence was downgraded because of imprecision, heterogeneity between studies and risk of bias attributes (Summary of findings 2)

Tacrolimus versus cyclosporin

Remission by six and 12 months

- At 6 months, Choudhry 2009 reported tacrolimus compared to cyclosporin may make little or no difference to the number of children who achieve complete remission (Analysis 3.1.1 (1 study, 41 children): RR 0.86, 95% CI 0.44 to 1.66), partial remission (Analysis 3.1.2 (1 study, 41 children): RR 1.43, 95% CI 0.62 to 3.28), or 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 (low certainty evidence).
- At 12 months, tacrolimus compared to cyclosporin may make little or no difference to the number of children who achieve complete remission (Analysis 3.2.1 (2 studies, 58 children): RR 0.80, 95% CI 0.45 to 1.42; I^2 = 0%), achieve partial remission (Analysis 3.2.2 (2 studies, 58 children): RR 1.53, 95% CI 0.92 to 2.56; I^2 = 0%), or achieve complete or partial remission (Analysis 3.2.3 (2 studies, 58 children): RR 1.05, 95% CI 0.87 to 1.25; I^2 = 0%) (low certainty evidence).
- Choudhry 2009 reported tacrolimus compared with cyclosporin may reduce the number of children who relapse during

treatment (Analysis 3.3 (1 study, 34 children): RR 0.22, 95% CI 0.06 to 0.90).

Adverse events

- Choudhry 2009 reported tacrolimus compared with cyclosporin may make little or no difference to change in GFR (Analysis 3.4 (1 study, 41 children): MD -0.70 mL/min, 95% CI -16.71 to 15.31).
- Tacrolimus compared with cyclosporin may make little or no difference to the number with nephrotoxicity (Analysis 3.5.1; Analysis 3.5.2) or with worsening hypertension (Analysis 3.5.3) (low certainty evidence).
- It is uncertain whether other reported adverse events differ between treatment groups (Analysis 3.5).

The certainty of the evidence was downgraded because of imprecision resulting from small studies with few events (Summary of findings 4)

Cyclosporin versus mycophenolate mofetil plus pulse oral dexamethasone

Remission by 12 months

- FSGS-CT 2011 reported cyclosporin compared with MMF with oral dexamethasone probably makes little or no difference to the number achieving complete remission (Analysis 4.1.1 (1 study, 138 participants): RR 2.14, 95% CI 0.87 to 5.24), partial remission (Analysis 4.1.2 (1 study, 138 participants): RR 1.09, 95% CI 0.61 to 1.93), or complete or partial remission (Analysis 4.1.3 (1 study, 138 participants): RR 1.38, 95% CI 0.90 to 2.10) (moderate certainty evidence) at 12 months.
- Cyclosporin compared with MMF with dexamethasone probably makes little or no difference to the numbers with complete (Analysis 4.2.1 (1 study, 138 participants): RR 1.38, 95% CI 0.41 to 4.66), partial (Analysis 4.2.2 (1 study, 138 participants): RR 1.05, 95% CI 0.56 to 1.98), or no sustainable remission of proteinuria between 52 and 78 weeks (Analysis 4.2.3 (1 study, 138 participants): RR 0.95, 95% CI 0.77 to 1.18) (moderate certainty evidence).

Adverse events

- FSGS-CT 2011 reported cyclosporin compared with MMF with dexamethasone may make little or no difference to the number dying (Analysis 4.3.1 (1 study, 138 participants): RR 2.14, 95% CI 0.87 to 5.24), developing a 50% decline in GFR (Analysis 4.3.2 (1 study, 138 participants): RR 2.29, 95% CI 0.46 to 11.41), or developing ESKD (Analysis 4.3.3 (one study, 138 participants): RR 4.58, 95% CI 0.55 to 38.22) (low certainty evidence). In this study, adverse effects were reported for 0 to 26 weeks as all participants were included up to that time.
- Cyclosporin may make little or no difference to the number with serious infections requiring hospitalisation (Analysis 4.4.1 (1 study, 138 participants): RR 0.65, 95% CI 0.22 to 1.96), hypertension (Analysis 4.4.6 (1 study, 138 participants): RR 1.68, 95% CI 0.66 to 4.29) (low certainty evidence) or other adverse effects (Analysis 4.4).

The evidence was downgraded because of imprecision as the study did not recruit sufficient patients to exclude a difference between treatments and because of small numbers of adverse events.(Summary of findings 4).

Tacrolimus versus mycophenolate mofetil to maintain remission

Remission maintenance at 12 months

- Sinha 2017 reported among children, who have achieved complete remission, tacrolimus compared with MMF may increase the number of children who maintain complete or partial response for 12 months (Analysis 5.1.1 (1 study, 60 participants): RR 2.01, 95% CI 1.32 to 3.07), complete response (Analysis 5.1.2 (1 study, 60 children): RR 1.79, 95% CI 1.11 to 2.90), or partial remission Analysis 5.1.3 (1 study, 60 participants): RR 4.68, 95% CI 0.58 to 37.68) (low certainty evidence).
- Tacrolimus compared with MMF may reduce the number of children with treatment failure (Analysis 5.2.1 (1 study, 60 children): RR 0.18, 95% CI 0.06 to 0.54) and frequent relapses (Analysis 5.2.2 (1 study, 60 children): RR 0.28, 95% CI 0.09 to 0.92) but may make little or no difference to the number of children developing further steroid resistance (Analysis 5.2.3) (low certainty evidence).
- Tacrolimus compared with MMF may make little or no difference to the relapse rate/year (Analysis 5.3 (1 study, 60 children): MD -0.12 number/year, 95% CI -0.56 to 0.32).
- Tacrolimus compared with MMF may allow a lower mean prednisone dose to be used to maintain remission (Analysis 5.4 (1 study, 60 children): MD -0.20 mg/d, 95% CI -0.36 to -0.04).

Adverse events

- Sinha 2017 reported tacrolimus compared with MMF may make little or no change to GFR (Analysis 5.5 (1 study, 60 children): MD 13.00 mL/min, 95% CI -3.71 to 29.71) (low certainty evidence)
- There may be little or no difference in serious adverse events (Analysis 5.6.1) and serious infections (Analysis 5.6.2) between tacrolimus versus MMF.

The evidence was downgraded due to small numbers of included participants, with small number of events, and for unclear risk of detection bias.

Cyclophosphamide versus prednisone/placebo

Remission

- CPA compared with prednisone/placebo may make little or no difference to the overall number of children (Analysis 6.1.1 (2 studies, 84 children): RR 1.06, 95% CI 0.61 to 1.87) or in those with FSGS (Analysis 6.1.2 (2 studies, 63 children): RR 1.01, 95% CI 0.43 to 2.37) who achieve complete remission (low certainty evidence).
- ISKDC 1996 reported CPA compared with prednisone/placebo may make little or no difference to the number of children who achieved complete or partial remission between treatment groups (Analysis 6.2 (1 study, 53 children): RR 0.88, 95% CI 0.53 to 1.45) or to the number of children with treatment failure (increase in SCr by ≥ 30%, SCr > 4 mg/dL, dialysis, or transplant) (Analysis 6.3 (1 study, 60 children); RR 1.59, 95% CI 0.87 to 2.88) (low certainty evidence).

Adverse events

- ISKDC 1996 reported CPA compared with prednisone/placebo may make little or no difference to the number of children who

die (Analysis 6.4.1 (1 study, 60 children): RR 1.07, 95% CI 0.19 to 5.95) (low certainty evidence).
- CPA compared with prednisone/placebo may make little or no difference to the number of children with hypertension with seizures (Analysis 6.4.1, (1 study, 60 children) RR 0.71, 95% CI 0.05, 10.89) (low certainty evidence).
- There may be little or no difference in other adverse events between treatment groups (Analysis 6.4).
- Adverse events in ISKDC 1974 were not reported separately for steroid-sensitive and steroid-resistant children so could not be included in the analyses.

The evidence was downgraded because of small studies with small event rates and risk of bias issues (Summary of findings 7).

Intravenous versus oral cyclophosphamide

Remission

- IV CPA compared with oral CPA may make little or no difference to the number of children with SRNS who achieved complete remission (Analysis 7.1. (2 studies, 61 participants): RR 1.58, 95% CI 0.65 to 3.85), partial remission (Analysis 7.2 (1 study, 50 participants): RR 0.40, 95% CI 0.09 to 1.87), or continuing remission at one year (Analysis 7.3) (low certainty evidence).
- It is uncertain whether IV CPA compared with oral CPA increases the time to remission (Analysis 7.4) or changes the duration of remission (Analysis 7.5).

Adverse events

- Shah 2017 reported IV CPA compared with oral CPA may make little or no difference to the likelihood of renal insufficiency (Analysis 7.6.1 (1 studies, 50 children): RR 0.33, 95% CI 0.04 to 2.99)
- It is uncertain whether IV CPA compared with oral CPA makes any difference to the number with bacterial infections (Analysis 7.6.2 (2 studies, 61 children): RR 1.02, 95% CI 0.10 to 10.62) or to the number with vomiting (Analysis 7.6.3 (2 studies, 61 children): RR 2.38, 95% CI 0.35 to 16.17) (very low certainty evidence).
- IV CPA compared with oral CPA may make little or no difference to the numbers with alopecia (Analysis 7.6.4 (1 studies, 50 children): RR 1.50, 95% CI 0.27 to 8.22) (low certainty evidence).

The evidence was downgraded because of few studies with small numbers of participants and events and for risk of bias issues (Summary of findings 7).

IV cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone

Remission

- Mantan 2008 reported IV CPA compared with oral CPA with dexamethasone may make little or no difference to the number of children with initial or delayed steroid resistance who achieve complete remission (Analysis 8.1.1 (1 study, 49 children): RR 1.13, 95% CI 0.65 to 1.96), partial remission (Analysis 8.1.2 (1 study, 49 children): RR 0.88, 95% CI 0.14 to 5.79), or complete or partial remission (Analysis 8.1.3 (1 study, 49 children): RR 1.09, 95% CI 0.68 to 1.74) after six months of treatment (low certainty evidence).
- There may be little or no difference in the number of children with sustained remission or steroid-sensitive relapses after 18 months of follow up (Analysis 8.2 (1 study, 49 children): RR 1.13, 95% CI 0.65 to 1.96) or in the number developing reduced kidney function (Analysis 8.2 (1 study, 49 children): RR 0.88, 95% CI 0.06 to 13.35) (low certainty evidence).
- Among subgroups of initial SRNS (Analysis 8.3.1), late SRNS (Analysis 8.3.2), kidney pathology (Analysis 8.3.3; Analysis 8.3.4), IV CPA compared with oral CPA with dexamethasone may make little or no difference to the numbers achieving complete or partial remission.

Adverse events

- Mantan 2008 reported IV CPA compared with oral CPA may slightly reduce the likelihood of hypertension (Analysis 8.4.1 (1 study, 49 children): RR 0.04, 95% CI 0.00 to 0.68) but may make little or no difference to the number with bacterial infection (Analysis 8.4.7 (1 study, 49 children): RR 0.66, 95% CI 0.27 to 1.63) (low certainty evidence).
- Except for hypokalaemia, which may be reduced with IV CPA compared with oral CPA, the other reported adverse events (cataracts/glaucoma, leucopenia, cushingoid features, cystitis, steroid encephalopathy, hair loss) may not differ between treatment groups (Analysis 8.4).

The evidence was downgraded because of a single study with small numbers of participants and events and for risk of bias (Summary of findings 8).

Rituximab/cyclosporin/prednisolone versus cyclosporin/prednisolone

- It is uncertain whether rituximab compared with cyclosporin makes any difference 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) (Magnasco 2012).
- It is uncertain whether rituximab compared with cyclosporin makes any difference to the number achieving remission at three months in children with initial steroid resistance (Analysis 9.1.1 (1 study, 15 children): RR not estimable), delayed steroid resistance (Analysis 9.1.2) (1 study, 15 children): RR 1.14 95% CI 0.33 to 3.94), or all children (Analysis 9.1.3) (1 study, 30 children): RR 0.94 95% CI 0.22 to 3.94) because the certainty of the evidence is very low. Remission was only seen in children with delayed steroid resistance (Analysis 9.1.2).
- Comparing the two groups, there may be little or no difference between end of study creatinine (Analysis 9.2 (1 study, 31 participants): MD 0.00 mg/dL, 95% CI -0.23 to 0.23) and albumin levels (Analysis 9.3 (1 study, 31 participants): MD 0.25 g/L, 95% CI -0.22 to 0.72).
- It is uncertain whether rituximab compared with cyclosporin makes any difference to the frequency of bronchospasm requiring treatment discontinuation, hypotension, skin rash, breathlessness or abdominal pain (Analysis 9.4).

The evidence was downgraded because of a single small study with few events and a high risk of attrition bias (Summary of findings 9)

Chlorambucil versus indomethacin

Remission

- It is uncertain whether chlorambucil compared with indomethacin increases the number who achieved complete remission (Analysis 10.1 (1 study, 30 children): RR 1.00, 95% CI 0.42 to 2.40) because of small participant numbers and high risk of bias (Kleinknecht 1980).

Adverse events

- It is uncertain whether chlorambucil compared with indomethacin decreases the number developing ESKD (Analysis 10.2 (1 study, 30 children): RR 0.20, 95% CI 0.01 to 3.85) (Kleinknecht 1980).

Triple therapy using different agents combined with tacrolimus and prednisone

Remission

- It is uncertain whether MMF compared with CPA, leflunomide compared with MMF and leflunomide compared with CPA alters the outcome of remission in the short term or at 12 months (Analysis 11.1; Analysis 11.2) because of small participant numbers and high risk of bias for attrition and selection bias (Wu 2015).

Adverse effects

- These were not reported in sufficient detail to be included in meta-analyses. The authors reported that adverse effects did not differ between groups.

Azathioprine versus placebo

Remission

- ISKDC 1970 reported AZA compared with placebo may make little or no difference to 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). The evidence was downgraded because of a small study with a high risk of attrition and reporting bias.

Adverse events

- Adverse events of AZA were not reported.

Adalimumab or galactose compared with conservative therapy

Response

- It is uncertain whether adalimumab compared with conservative therapy (lisinopril, losartan and atorvastatin) makes any difference to the number of participants with therapy resistant FSGS who achieved a 50% reduction in proteinuria with stable GFR (Analysis 13.1.1 (1 study, 21 adults and children): RR 0.20, 95% CI 0.01 to 3.54). The evidence was downgraded because of small patient numbers and events (FONT II 2011).

Adverse events

- Four serious adverse events were reported in the adalimumab group and three in the galactose group. The nature of these events was not reported.

Adalimumab compared with rosiglitazone

Response

- With adalimumab, 4/10 participants with therapy resistant FSGS achieved a 50% reduction in proteinuria.
- With rosiglitazone, 2/10 participants with therapy resistant FSGS achieved a 40% reduction in proteinuria.

Data were not compared in a meta-analysis as the reported outcome measures differed between groups.

Adverse events

- One (injection site reaction) of nine recorded adverse events was probably related to adalimumab.
- Three (hives, penile swelling, dizziness) of 12 recorded adverse events were possibly related to rosiglitazone.

High versus low dose enalapril

Response

- 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).
- High dose enalapril (0.6 mg/kg/d) reduced median urinary albumin/creatinine ratio from 5.2 (5th to 95th percentiles 2.1 to 10.5) to 2.5 (5th to 95th percentiles 0.8 to 3.3).

No meta-analyses of these data could be performed.

Adverse events

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

Fosinopril plus prednisone versus prednisone alone

Response

- Yi 2006 reported fosinopril plus prednisone compared with prednisone alone may reduce the 24-hour urinary protein excretion after four (Analysis 14.1.1 (1 study, 45 children): MD -1.27 g/d, 95% CI -1.62 to -0.92), eight (Analysis 14.1.2 (1 study, 45 children): MD -1.26 g/d, 95% CI -1.47 to -1.05), and 12 weeks of treatment (Analysis 14.1.3 (1 study, 45 children): MD -0.95 g/d, 95% CI -1.21 to -0.69).
- Fosinopril plus prednisone compared with prednisone alone may reduce tubular proteins including retinol binding protein (Analysis 14.2.1 (1 study, 45 children): MD -0.21 mg/L, 95% CI -0.33 to -0.09) and beta-2 microglobulin (Analysis 14.2.2 (1 study, 45 children): MD -0.17 mg/L, 95% CI -0.27 to -0.07).
- Fosinopril plus prednisone compared with prednisone alone may make little or no difference to serum albumin at the end of treatment (Analysis 14.3 (1 study, 45 children): MD 1.20 g/L, 95% CI -6.58 to 8.98).
- Fosinopril plus prednisone compared with prednisone alone may make little or no difference to systolic blood pressure (Analysis 14.4 (1 study, 45 children): MD -0.87 mm Hg, 95% CI -3.33 to 1.59) or serum potassium (Analysis 14.6 (1 study, 45 children): MD 0.20 mmol/L, 95% CI -0.34 to 0.74).

- Fosinopril plus prednisone compared with prednisone alone may reduce creatinine clearance slightly (Analysis 14.5 (1 study, 45 children): MD -5.28 mL/min, 95% CI -9.66 to -0.90).

The evidence was downgraded because of small participant numbers and risk of bias issues.

Adverse events

- Yi 2006 reported no participant developed cough, anaemia or allergic reactions.

Sparsentan versus irbesartan

Response

- DUET 2017 reported sparsentan (all doses combined) compared with irbesartan may make little or no difference to the number of participants with reduction in proteinuria of > 40% and urinary protein creatinine ratio after eight weeks of treatment (Analysis 15.1 (1 study, 96 participants): RR 3.00, 95% CI 0.95 to 9.44).
- There was a greater reduction in proteinuria with sparsentan (-44.8%, 95% CI -52.7% to -35.7%) compared with irbesartan (-18.5%, 95% CI -34.6% to 1.7%).

Adverse events

- DUET 2017 reported sparsentan compared with irbesartan may make little or no difference to the number of participants with any treatment related adverse event (Analysis 15.2.1. (1 study, 109 participants) RR 1.21, 95% CI 0.73 to 2.01) or to the number of participants withdrawing from the study because of adverse effects (Analysis 15.2.2. (1 study, 109 participants) RR 0.99, 95% CI 0.09 to 10.52). Two patients discontinued sparsentan due to adverse effects (AKI, increased liver enzymes). One patient discontinued irbesartan due to hypoalbuminaemia.
- Sparsentan compared with irbesartan may make little or no difference to the number of participants with hypotension (Analysis 15.2.3), peripheral oedema (Analysis 15.2.4) or hyperkalaemia (Analysis 15.2.5).

The evidence was downgraded because of reporting bias and the short duration of treatment.

Tuna fish oil versus placebo

Response

- It is uncertain whether fish oil compared with placebo makes any change to the degree of proteinuria or in creatinine clearance because the certainty of the evidence is very low (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

- Adverse events were not reported.

The evidence was downgraded because of unclear sequence generation and allocation concealment, attrition and reporting bias.

DISCUSSION

Summary of main results

In this update we have included 25 studies, enrolling 1063 participants of which 1012 were evaluated.

CNI (cyclosporin, tacrolimus) compared with placebo, no treatment, methylprednisolone (Analysis 1.1; Analysis 1.2) or IV CPA (Analysis 2.1) may increase the number of participants with SRNS who achieve complete and/or partial remission irrespective of renal pathology. There may be little or no difference in efficacy between cyclosporin and tacrolimus (Analysis 3.1; Analysis 3.2). Cyclosporin compared with MMF with dexamethasone probably makes little or no difference to the number achieving complete or partial remission (Analysis 4.1). In children, who have achieved remission, tacrolimus compared with MMF may increase the number of participants who maintain remission (Analysis 5.1). Limited information was available on adverse effects in all studies though serious adverse effects were more common with IV CPA (Analysis 2.3).

CPA compared with placebo or prednisone may make little or no difference to the number of children with complete or partial remission (Analysis 6.1; Analysis 6.2). In addition, IV CPA compared with oral CPA without (Analysis 7.1; Analysis 7.2) or with dexamethasone (Analysis 8.1) may make little or no difference to the number achieving complete or partial remission. Limited information on adverse effects was available.

Of newer agents, it is uncertain whether rituximab (compared with cyclosporin) (Analysis 9.1) and whether adalimumab and galactose (both compared with placebo) (Analysis 13.1) increase the number of participants who achieve complete or partial remission because of small numbers of included participants and few events.

ACEi (Analysis 14.1) may reduce proteinuria in studies lasting for eight to 12 weeks but studies were too short to determine whether ACE inhibition provides long term reduction in proteinuria and protects against deterioration in kidney function. Also the dual endothelin receptor and angiotensin receptor blocker, sparsentan, compared with irbesartan may increase the number of participants with partial remission of proteinuria (Analysis 15.1), using a novel definition of > 40% proteinuria reduction and proteinuria ≤ 1.5 g/g (Troost 2018).

Overall completeness and applicability of evidence

Currently CNI, CPA and MMF are used to treat SRNS. Two studies have demonstrated that CNI are more effective than CPA with less toxicity. These data support the use of CNI in children with SRNS and suggest that CPA should not be used as first-line treatment where CNI are available. Although there is moderate certainty evidence from a single study (FSGS-CT 2011) that there is probably little or no difference in efficacy between cyclosporin and MMF with dexamethasone, we need further studies to evaluate the role of MMF as first-line treatment. Rituximab is also used to treat children with SRNS, who are resistant to CNI. However, it is uncertain whether rituximab is of value in SRNS since only one small study (30 participants) with three months follow-up has been published to date. Since a role for rituximab cannot be excluded, more RCTs of rituximab compared with CNI are justified. The efficacy of the new agents (adalimumab, galactose) is uncertain based on small

studies (FONT I 2009; FONT II 2011), which were too small to draw any conclusions.

RCTs to date have been too small to determine any differences in response to immunosuppressive therapies in different pathologic subtypes and in initial compared to delayed steroid resistance. Most studies included a mix of histological subtypes; only seven studies (Bhaumik 2002; DUET 2017; FONT I 2009; FONT II 2011; FSGS-CT 2011; ISKDC 1996; Lieberman 1996) recruited patients with FSGS alone. Non-randomised studies (Ehrich 2007; Inaba 2016; Niaudet 1994) have suggested that children with MCD would be more likely to respond to treatment than children with FSGS. In contrast, the large Podonet study (Trautmann 2015) found no significant difference in remission rates after immunosuppressant therapy between MCD and FSGS.

Most studies have included patients with both initial and 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 2017). 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. Observational studies (Ehrich 2007) suggested that the relative efficacies of treatment regimens differed between children with initial compared with delayed steroid resistance. Children with delayed steroid resistance have a higher incidence of recurrence post-transplant (Ding 2014; Pelletier 2018), suggesting the possibility of a circulating factor pathogenesis, which may be more susceptible to immunosuppressive agents.

In this review, only two studies included information about genetic status (APN 2008; Choudhry 2009) but the data were not used to exclude children from studies. Data from the large PodoNet registry indicate that about a quarter of patients with SRNS (Trautmann 2015) may have an underlying genetic mutation. With the rapid increase in the number of genes identified in children with SRNS, it is likely that this proportion will rise. New studies should take into consideration genetic mutation status in the exclusion criteria as observational studies have shown that these are unlikely to respond to immunosuppressant therapy (Buscher 2010; Kemper 2018).

It remains unclear what therapeutic strategies should be used to maintain remission in patients who have achieved initial remission. We have only identified one study (Sinha 2017) which found that tacrolimus may be more effective than MMF in maintaining remission. An uncontrolled retrospective study of combinations of these agents (Gellermann 2012) suggest utility in adding MMF sequentially to CNI, with subsequent conversion to MMF monotherapy. Such observations of MMF in combination with CNI for maintenance immunotherapy need to be evaluated in an RCT.

There is a dearth of studies regarding new targeted treatments for SRNS. Only one small study has evaluated rituximab in childhood SRNS and found no clear benefit. The results of studies of rituximab, ofatumumab, abatacept and ACTH are awaited (NCT02382575; NCT02394106; NCT02972346; Trachtman 2018).

Although IV pulse methylprednisolone is often used in clinical practice in SRNS either alone or in combination, only one study identified for this review compared it with cyclosporin (Bhaumik 2002) and concluded that cyclosporin was superior in efficacy. In RCTs, dexamethasone was used in combination with MMF (FSGS-CT 2011) and oral CPA (Mantan 2008) but it remains unclear whether dexamethasone contributed to the therapeutic response. There are case reports of the successful use of vincristine (Thalgahagoda 2017) in SRNS but this medication has not been evaluated in an RCT.

The current KDIGO guidelines (KDIGO 2012) recommend the use of ACEi or angiotensin receptor blockers to reduce proteinuria in SRNS patients. DUET 2017 found that sparsentan may be more effective in reducing proteinuria in patients with FSGS. A phase 3 study comparing sparsentan with irbesartan is underway (DUPLEX 2018).

We have not identified any RCTs evaluating any form of non-pharmacologic strategies (e.g. plasmapheresis, LDL-pheresis).

Quality of the evidence

Studies included in this systematic review were small, often of poor methodological quality and addressed several different therapeutic regimens, which limited the opportunities for meta-analysis. Poor study quality can lead to overestimation of the efficacy of an intervention (Schulz 1995) and combining poor quality studies in meta-analyses can thus overestimate the benefits of therapy (Moher 1998). Fourteen studies were at low risk for selection bias. Five studies were at low risk of performance bias although, since the majority of studies (19 studies) used a laboratory measurement of proteinuria for the primary outcome of remission, there was less risk of detection bias. Fourteen studies were considered to be free of attrition or of selective outcome bias. It is possible that attrition bias influenced the outcomes in the studies comparing cyclosporin with placebo/no treatment. In three of four studies included in the meta-analysis comparing cyclosporin with placebo/no treatment, 10/59 (17%) randomised patients 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 differences between the groups. However, the 95% CIs 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. Assessment by GRADE shown in the Summary of Findings Tables indicates that the certainty of evidence was generally low to very low for most comparisons due to increased risk of bias and imprecision. The only exception was the FSGS-CT 2011, where the evidence was of moderate certainty for the primary outcomes (Summary of findings 4).

Potential biases in the review process

This review identified 25 studies of which four were available only as an abstract. Additional information was provided by the authors from two studies. The literature search undertaken and updated to 17 September 2019 is likely to have identified all relevant published studies including studies only available as abstracts. Since about 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. Recently abstracts presented at major conferences have become available via search engines particularly through EMBASE OVID SP.

Agreements and disagreements with other studies or reviews

The treatment of SRNS in children has been comprehensively reviewed 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 CPA on time to remission, the strength of the conclusions was limited by the poor quality of included studies. Chua 2009 assessed observational studies, which evaluated complete or partial remission in 494 children treated with cyclosporin or tacrolimus, 192 treated with oral alkylating agents, 71 treated with IV CPA, and 204 treated with IV pulse corticosteroid with CPA or cyclosporin. Overall these observational studies indicated that one third to a half of patients with SRNS achieve complete remission when treated with cyclosporin or with CPA or with one of these agents combined with IV methylprednisolone. Recent analysis of data in the PodoNet registry confirms these outcomes (Trautmann 2017). RCTs indicate that patients treated with cyclosporin are more likely to achieve complete or partial remission when compared with placebo or no specific therapy or with IV CPA. Based on these studies, the KDIGO guidelines (KDIGO 2012) recommend that the initial treatment of children with SRNS should be with a CNI for a minimum of six months. Updated guidelines on glomerulonephritis including SRNS from KDIGO are expected soon.

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 death although these are important patient-centred outcomes. However, based on the included studies, CNI appear to be of benefit for children with SRNS while CPA is less effective and more toxic indicating that the initial treatment of SRNS should be with CNI if available. 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 MMF or rituximab compared with CNI are warranted including studies that assess the efficacy of different durations of CNI. These studies should be of sufficient duration to assess complete remission rates, relapse rates, kidney function and adverse events including episodes of acute kidney injury and to assess any differences in response between children with MCD or FSGS and between 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 MMF 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 in children without disease causing mutations but with steroid and CNI resistant disease. While newer agents (adalimumab, galactose) have been evaluated in small studies, no clear benefits or harms of these medications have been identified to date.

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

Habashy 2006

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

Hodson 2011

Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD003594.pub4]

Hodson 2016

Hodson EM, Wong SC, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children.

Cochrane Database of Systematic Reviews 2016, Issue 10. [DOI: 10.1002/14651858.CD003594.pub5]

* 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)) • Mean age ± SD (years): CSA group (6.99 ± 5.48); CPA group (6.84 ± 3.90) • Sex (M/F): CSA group (11/4); CPA group (8/9) • Exclusion criteria: hereditary, syndromic and secondary nephrotic syndrome; pre-treatment with immunosuppressive therapy other than prednisone; prednisone regimen other than APN or ISKDC
Interventions	CSA group • Oral 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 CPA 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

APN 2008 *(Continued)*

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
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
	• Mean age, range (months): high dose (78, 60 to 104.7); low dose (96, 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

Bagga 2004 *(Continued)*

	• 0.2 mg/kg/d for 8 weeks in 2 doses Co-interventions • Alternate day prednisone • Furosemide
Outcomes	• Urine albumin/Cr ratio (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
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 reported

Bhaumik 2002

Methods	• Study design: parallel group RCT • Time frame: January 1996 to March 2000 • Follow up period: 6 months
Participants	• Setting: Tertiary centre • Country: India • SRNS (biopsy proven primary FSGS); no response to 8 weeks of prednisolone (2 mg/kg/d)

Bhaumik 2002 *(Continued)*

- Number (group A/group B): 13/12
- Age range: 3 to 49 years
- Sex (M/F): not reported but stated similar between groups
- Exclusion criteria: SSNS

Interventions	Group A • Cyclosporin 1 to 4 mg/kg/day with oral prednisolone for at least 6 months Group B • Methylprednisolone 250-750 mg IV daily for 7 days and then weekly for at least 12 weeks Co-interventions • BP control • Dietary protein 0.8 to 1.0 g/kg/d • ACE inhibitors • Lipid lowering agents
Outcomes	• Complete remission • Decline in proteinuria & stable creatinine • Progression to ESKD • Rate of decline in GFR • Hospitalisation for therapy related complications
Notes	• Abstract-only publication • Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
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	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Abstract-only publication
Other bias	Unclear risk	Insufficient information to permit judgement

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 reported 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 • 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	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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)	High risk	Cross-over study of 6 patients; I patient (17%) did not complete the study with no reason provided

Chongviriyaphan 1999 *(Continued)*
All outcomes

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 • Mean age, 95% CI (months): TAC group (75, 53 to 97); CSA group: 62.6, 43.1 to 82.1) • Sex (M/F): TAC group (14/7); CSA group (11/9) • Early/late resistance: TAC group (12/9); CSA group (11/9) • Exclusion criteria: immunosuppression other than prednisone in previous 12 weeks; secondary SRNS; Cr > 1.5 mg/dL; eGFR < 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

Choudhry 2009 *(Continued)*

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

DUET 2017

Methods	• Study design: parallel RCT (Phase 2) • Time frame: April 2014 to April 2016 • Follow-up period: 8 weeks of RCT
Participants	• Setting: tertiary centres (USA, Belgium, Czech Republic, Italy). • Country: 44 study centres in USA, Europe (European sites could enrol people aged 18 to 75 years) • Biopsy proven primary FSGS (idiopathic or identified podocyte mutation), UPC ≤ 1.0 g/g, eGFR > 30 mL/min/1.73 m^2, BP < 145/96 mm Hg in adults; BP > 90/60 mm Hg and < 95th percentile for age, gender, and height in patients < 18 years, stable immunosuppressive regimens for > 1 month; completed RTX or CPA for > 3 months before study • Number: 185 patients screened, 109 patients randomised; 96 evaluated for efficacy/109 evaluated for adverse effects; Sparsentan 62 evaluated for efficacy/73 randomised; irbesartan 32 evaluated for efficacy/36 randomised • Age (range): 8 to 75 years * Sparsentan group: 13/73 aged ≤ 18 years; Irbesartan group: 10/36 aged ≤ 18 years • Sex (M/F): Sparsentan (41/32); irbesartan (19/17) • Exclusion criteria: secondary FSGS; diabetes; significant cardiac/cerebrovascular disease; hepatitis; malignancy; transplantation; anaemia; hyperkalaemia; BMI > 40; pregnancy; lactation; other investigational drug in previous 28 days; previous sparsentan; unwilling to comply.
Interventions	Sparsentan groups (dual endothelin and angiotensin inhibitor)

DUET 2017 *(Continued)*

	• 200 mg, 400 mg or 800 mg daily for 8 weeks; data from these groups pooled; participants < 50 kg received half dose in each group Irbestartan group (angiotensin inhibitor) • 150 mg daily for first week then 300 mg daily for next 7 weeks; participants < 50 kg received half dose in each group Co-interventions • Immunosuppressives except RTC/CPA: Sparsentan 21/73; irbesartan 13/36
Outcomes	• Change in urinary protein/creatinine ratio (UPC) from baseline to 8 weeks (% with 95% CI) • % with UPC ≤ 1.5 g/g with > 40% reduction at 8 weeks (FSGS partial remission end point) • Changes to baseline albumin, 24-hour urinary protein, GFR, BP, creatinine, lipid profiles • Quality of Life (SF36 in adults; PEDsQL version 4.0 in < 18 years)
Notes	• Double-blind study for 8 weeks then all patients continued on/changed to sparsentan & followed to 144 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "At week 0, a computer-generated randomization sequence, via an interactive Web response system, used to randomise patients (3:1) to receive sparsentan or irbesartan within sequential dose-escalating, 20-patient cohorts." Error in computer programme led to 2:1 randomisation
Allocation concealment (selection bias)	Low risk	At week 0, a computer-generated randomization sequence, via an interactive Web response system, used to randomize patients (3:1) to receive sparsentan or irbesartan
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Investigators, participants, caregivers, and the study sponsor were blinded to treatment allocations until database extraction and unblinding at the completion of the 8-week, double-blind treatment period". Both medications were encapsulated in grey gelatin capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Investigators, participants, caregivers, and the study sponsor were blinded to treatment allocations until database extraction and unblinding at the completion of the 8-week, double-blind treatment period"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on 96/109 (88%) for efficacy; adverse effects reported for all 109 patients
Selective reporting (reporting bias)	High risk	Primary outcome was reduction in UP/Cr reported as geometric mean +/- 95% CI and could not be included in meta-analysis. A secondary outcome defined by the authors of "FSGS partial remission end point (FPRE) (UP/C:≤ 1.5 g/g and > 40% reduction in proteinuria" and not pre-specified in the protocol was included in meta-analyses
Other bias	High risk	Trial organised and supported by Retrophin Inc. (San Diego, CA)

Elhence 1994

Methods	• Study design: parallel RCT

Elhence 1994 *(Continued)*

	• 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 (years): IV group (3 to 16); oral group (9 to 14.5) • Sex (M/F): IV group (6/1); oral group (5/1) • Exclusion criteria: not reported
Interventions	IV CPA group • IV CPA: 500 mg/m^2/mo for 6 months • 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
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

Elhence 1994 *(Continued)*

Other bias	Unclear risk	Funding source not reported

FONT I 2009

Methods	• Study design: parallel RCT (phase 1 study) • Time frame: not reported • Follow-up period: 16 weeks
Participants	• Setting: multicentre • Country: USA • Adults and children aged 2 to 41 years with biopsy-confirmed primary FSGS and initial steroid resistance; steroid resistance (UP/C > 1.0 g/g after 4 weeks of steroid therapy), persistent proteinuria (UP/C > 1.0 g/g) and eGFR > 40 mL/min/1.73 m^2; patients were admitted who failed treatment in the FSGS-CT Study 2011 or were ineligible for FSGS-CT Study because of previous use of study interventions; patients off all immunosuppressive agents for at least 4 weeks. Inclusion criteria assumed to be the same as FSGS-CT study. • Number (enrolled/completed): adalimumab group (10/9); rosiglitazone group (11/10) • Mean age ± SD (years): adalimumab group (16.8 ± 9.0); rosiglitazone group (15.4 ± 6.2) • Sex (M/F): adalimumab group (2/8); rosiglitazone group (8/3) • Exclusion criteria (assumed to be the same as FSGS-CT study): secondary FSGS; 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	Adalimumab group • Adalimumab 24 mg/m^2 subcutaneously (maximum 40 mg/dose) on alternate weeks for 16 weeks for a maximum of 40 mg Rosiglitazone group • Rosiglitazone 3 mg/m^2/twice daily orally for 16 weeks Co-interventions • ACEi or ARB with unchanged dosage • Diuretics • Low dose prednisolone • Lipid lowering agents
Outcomes	• % reduction in proteinuria • eGFR and creatinine • serum albumin • Blood glucose • Adverse events
Notes	• 4/9 participants had reduction in proteinuria of 50% with adalimumab. I adverse effect probably related to adalimumab • 2/10 participants had reduction in proteinuria of 40% with rosiglitazone. 3 adverse effects possibly related to rosiglitazone. • Data not added to meta-analysis as outcomes differed between groups. Information on methods/results requested from authors but none received.

FONT I 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% did not complete study; 1/11 did not complete rosiglitazone arm; 1/10 did not complete adalimumab arm
Selective reporting (reporting bias)	High risk	Expected outcomes reported but data could not be incorporated into meta-analyses
Other bias	Low risk	This work was supported by grants from the NIH–NIDDK (5R21-DK070341), and the GCRC program of the Division of Research Resources, NIH RR00046 (UNC) and NIH RR018535 (North Shore Long Island Jewish Health System)

FONT II 2011

Methods	• Study design: parallel RCT (phase 2) • Time frame: July 2009 to February 2013 • Follow-up period: 26 weeks
Participants	• Setting: multicentre • Country: USA • Adults and children aged 1 to 51 years with biopsy-confirmed primary FSGS or documentation of disease causing mutation; initial steroid resistance and resistance to at least one other immunosuppressive agent; persistent proteinuria (UP/C > 1.0 g/g); eGFR > 40 mL/min/1.73 m^2; patients off all immunosuppressive agents (except low dose prednisolone) for at least 4 weeks • Number (enrolled/completed): adalimumab group (7/6); galactose group (7/7); control group (7/6) • Mean age: 14.7 years (IQR 13.0, 20.8 years) • Sex (M/F): 9/12 • Exclusion criteria: secondary FSGS; allergic to the study medications; HCT < 27%; uncontrolled hypertension; DM; CHF or MI; active or serious infection; cirrhosis or chronic active liver disease; history of significant GI disorder; organ transplantation; history of malignancy/abnormal pap smear; participation in another therapeutic trial within 30 days before randomisation; lactation, pregnancy, childbearing age and refused birth control; prior therapy with study interventions; therapy with other immunosuppressive agents within 30 days and RTX within 12 weeks
Interventions	Adalimumab group • 24 mg/m^2 SC (maximum 40 mg/dose) on alternate weeks for 26 weeks

FONT II 2011 *(Continued)*

	Galactose group • 0.2 g/kg per dose orally twice a day, dissolved in 15 to 30 mL of water and ingested 15 to 30 min before breakfast and dinner for 26 weeks. The maximum single dose was 15 g Control group • Conservative therapy as set out below for 26 weeks Co-interventions in all participants • Lisinopril (maximum dose 10 mg for participants < 40 kg; 20 mg for participants ≥ 40 kg) • Losartan (maximum dose 25 mg for participants < 40 kg; 50 mg for participants ≥ 40 kg) • Atorvastatin (maximum dose 10 mg for participants < 40 kg; 20 mg for participants ≥ 40 kg)
Outcomes	• Primary outcome: preservation of GFR and >50% reduction in proteinuria • Number with >50 % reduction in proteinuria • eGFR preservation • Adverse events
Notes	• Data on method of randomisation requested but no response from authors received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes are laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Funding from the National Institutes of Health—National Institute of Diabetes, Digestive, and Kidney Diseases, grant DK70341 (HT).Abbott Laboratories provided adalimumab for use in the project. Supported by NephCure Kidney International

FSGS-CT 2011

Methods	• Study design: parallel RCT • Time frame: November 2004 to November 2009

FSGS-CT 2011 *(Continued)*

	• 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: 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, TAC, 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 • 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

FSGS-CT 2011 *(Continued)*

- 138 participants aged 2 to 40 years were included but no difference in results of subgroup analysis by age

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 • 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

Garin 1988 *(Continued)*

	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	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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
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)

Gulati 2012 *(Continued)*

	• 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 hepatitis 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

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

Gulati 2012 *(Continued)*

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 CPA) 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 • 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	QUOTE: "Reports were sent to a co-ordinator, who assigned treatment and distributed drugs identified by code numbers to pharmacists at each clinic"

ISKDC 1970 *(Continued)*

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 reported; 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
	• 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

ISKDC 1974 *(Continued)*

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	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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 (years): CPA-prednisone group (8.6 ± 0.85); prednisone group (7.4 ± 0.75) • Sex (M/F): not reported • Histology: All FSGS (both groups) • Exclusion criteria: MCD on biopsy

ISKDC 1996 *(Continued)*

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	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Central 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
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 reported 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	• Abstract-only publication • Exclusions post randomisation but pre-intervention: not 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	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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)	Unclear risk	Data only available from conference proceedings

Kleinknecht 1980 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Complete remission (no definition provided), ESKD
Other bias	Unclear risk	Funding source not reported; 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 (analysed/randomised): CSA group (12/16); placebo group (12/15) • Mean age ± SD (years): CSA group (11.2 ± 4.2); placebo group (11.4 ± 3.9) • Sex (M/F): CSA group (11/4); placebo group (10/5) • Exclusion criteria: CSA or other immunosuppressive agent in previous 3 months; primary cause for FSGS; other significant disease; pregnancy; impaired LFTs; concomitant therapy with nephrotoxic agents including ACEi
Interventions	CSA group • 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) • Exclusions from analyses: CSA group (4; noncompliance (2); rising Cr (1); unknown (1)); placebo group (3; noncompliance (2); rising Cr (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

Lieberman 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	Central computer generated list
Allocation concealment (selection bias)	Low risk	Central coordinator
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	Placebo-controlled study.
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 reported

Magnasco 2012

Methods	• Study design: parallel RCT • Time frame: 2007 to 2010 • Follow-up period: whole study 18 months
Participants	• Setting: paediatric nephrology centres (4) • Country: Italy • 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 (years): RTX group (8.5 ± 4.4); control group (7.3 ± 3.7) • 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/week if proteinuria < 1 g/d/m^2

Magnasco 2012 *(Continued)*

	• 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	

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 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

Mantan 2008 *(Continued)*

	• 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 (analysed/randomised): IV CPA group (26/27); oral CPA + IV DEXA group (23/25) • Median age, range (months): IV CPA group (51, 16 to 156); oral CPA + IV DEXA group (92, 15 to 198) • Sex (M/F): IV CPA group (19/8); oral CPA + IV DEXA group (16/9) • Early/late resistance: IV CPA group (10/16); oral CPA + IV DEXA group (8/15) • Exclusion criteria: previous immunosuppression other than prednisone; secondary SRNS; eGFR < 60 mL/min/1.73 m^2
Interventions	IV CPA group • IV CPA 500 mg/m^2 monthly (max 1g) for 6 doses; dose increased to 750 mg/m^2 monthly if no response at 3 months; dose delayed if WCC < 4000 • Maintenance therapy was then started with prednisone: 0.5 mg/kg alternate days to 18 months Oral CPA + IV DEXA group • Oral CPA 2 mg/kg/d from 3rd to 14th weeks and IV DEXA 5 mg/kg alternate days for 6 doses then every 2 weeks (4 pulses) and then monthly (4 pulses) • Maintenance therapy was then started with prednisone: 0.5 mg/kg alternate days to 18 months Co-interventions • Alternate day prednisone (1.5 mg/kg for 1 month; 1.25 mg/kg for 1 month and 1 mg/kg for 4 months) • Enalapril 0.3 mg/kg/d
Outcomes	• Complete (UP/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	QUOTE: "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	QUOTE: "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

Mantan 2008 *(Continued)*

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 • 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 (analysed/randomised): CSA group (10/10); no treatment group (7/10)
	• Mean age ± SD (years)
	  * CSA group: FSGS group (6.5 ± 4.7); MCD group; 6.8 ± 3.5)
	  * No treatment group: FSGS group (6.6 ± 1.8); MCD group (7.5 ± 7.8)
	• Sex (M/F): CSA group (13/9); no treatment group (13/60)
	• 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 • Exclusions post-intervention: CSA group (0); no treatment group (3 for noncompliance) • Stop or end points/s: not reported • Additional data requested from authors: none
Risk of bias	

Ponticelli 1993a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table; stratified for adults/children
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes numbered in sequence
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.
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

Shah 2017

Methods	• Study design: parallel RCT • Time frame: January 2008 to June 2011 • Follow-up period: 6 months

Participants	• Setting: tertiary, single centre
	• Country: India
	• SRNS definition: SRNS defined as no remission at end of 4 weeks of daily prednisone 60 mg/m^2
	• Pathology
	  * IV group: MCD (15); FSGS (5); MesPGN (5)
	  * Oral group: MCD (14); FSGS (8); MesPGN (3)
	• Number: IV CPA group (25); oral CPA group (25)
	• Mean age ± SD (years): IV CPA group (4.33 ± 3.32); oral CPA group (4.68 ± 3.02)
	• Sex (M/F): IV CPA group (17/8); oral CPA group (14/11)
	• Exclusion criteria: patients on immunosuppressive drugs other than steroids in last 6 months; aged < 1 year; GFR < 60 mL/min/1.73m^2

Interventions	IV CPA group • IV CPA 500 mg/m^2 infusion monthly for 6 months Oral CPA group • 2.5 mg/kg/day for 12 weeks Co-interventions • Alternate day prednisone with reducing doses

Shah 2017 *(Continued)*

Outcomes	• Complete remission at end of treatment: UP/C < 0.1 g/g • Partial remission at end of treatment: UP/C 0.1 to 2 g/g, serum albumin > 2.5 g/dL, no oedema • No remission: UP/C > 2 g/g; serum albumin ≤ 2.5 g/dL; oedema • Time to remission • Duration of remission • Adverse effects: infections, leucopenia, hair loss, CKD
Notes	• Full paper published 2017; abstract 2010 • 55 children enrolled, 50 evaluated; 5 excluded prior to randomisation for high creatinine (2), no consent (3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sequentially number sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and outcome assessment could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all patients who failed to achieve remission are accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Authors state that they received no monetary assistance

Sinha 2017

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) • Mean age, range (months): TAC group 66.6, 44.5 to 115.8); MMF group (67.5, 53 to 112.4)

Sinha 2017 *(Continued)*

	• Sex (M/F): TAC group (23/8); MMF group (21/8) • 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, collapsing glomerulopathy, 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 7 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 (primary outcome) • Treatment failure: (i) recurrence of late resistance, (ii) occurrence of frequent relapses and (iii) elevated serum creatinine > 30% and/or eGFR < 50 mL/min/1.73 m^2 persisting for > 2 weeks • Relapse per year • Change in GFR • Adverse events
Notes	• Enrolment was closed after interim ITT analysis of outcome in 1/3 sample • CTRI/2012/03/002479

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated block randomisation; stratified for histology (FSGS or MCD) and type of remission (complete or partial)
Allocation concealment (selection bias)	Low risk	Allocation sequence, in a 1:1 ratio, was generated using Stata version 10.1 (StataCorp version 10, StataCorp College Station, TX) and sealed in opaque envelopes that were opened at randomisation by an investigator blinded to the randomisation schedule
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	Low risk	Complete or partial remission was laboratory based, using UPCR (primary outcome); relapses were defined by dipstick
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up to 12 months of all but 1 patient (last analysis carried forwards) so data on all patients included in analyses

Sinha 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Study medications were provided by Panacea Biotec (India), which had no role in study development, implementation, or analysis. The study was in part supported by personnel from the Pediatric Renal Biology Program, funded by the Department of Biotechnology, Government of India.

Valverde 2010

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Setting: tertiary, single centre • Country: Mexico • SRNS definition not provided; pathology not reported • Number: group 1 (10); group 2 (7) • Mean age ± SD: not reported • Sex M/F: not reported • Exclusion criteria: not reported
Interventions	Group 1 • CSA and prednisone for 12 months; doses not provided Group 2 • TAC and prednisone for 12 months: doses not provided
Outcomes	• Complete remission • Partial remission • Hypertension • Time to achieve remission
Notes	• Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be "a comparative, randomised clinical trial"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessment and lack of blinding could influence outcomes

Valverde 2010 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all treated patients were included
Selective reporting (reporting bias)	Unclear risk	Abstract-only publication. Incomplete reporting of adverse effects
Other bias	Unclear risk	Insufficient information to permit judgement

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 (analysed/randomised): MMF group (6/7); CPA group (5/8); LEF group (7/7) • Mean age ± SD (months) of analysed participants: MMF group (81.67 ± 16.74); CPA group (78.56 ± 20.19); LEF group (74.57 ± 11.66) • Sex (M/F) of analysed participants: 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 • 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	

Wu 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Simple randomization using a randomised digital table"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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
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 (analysed/randomised): Fosinopril-prednisone group (25/30); prednisone group (20/27)
	• Mean age ± SD (years): fosinopril-prednisone group (8.7 ± 3.5); prednisone group (8.7 ± 3.7)
	• 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

Yi 2006 *(Continued)*

	• 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Computer generated random numbers were used to randomly allocate patients ..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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; CHF - chronic heart failure; 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; IQR - interquartile range; ISKDC - International Study of Kidney Disease in Children; IV - intravenous; LEF - leflunomide; LFT - liver function test; M/F - male/female; MCD - minimal change disease; MCGN - mesangiocapillary glomerulonephritis; MesPGN - mesangioproliferative glomerulonephritis; MI - myocardial infarction; MMF - mycophenolate mofetil; MNS - membranous nephrotic syndrome; NSAIDs - nonsteroidal anti-inflammatory drugs; RCT - randomised controlled trial; RTX - rituximab; SBP - systolic blood pressure; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SLE - systemic lupus erythematosus; SRNS - steroid-resistant nephrotic syndrome; TAC - tacrolimus; TB - tuberculosis; 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	Wrong population: children had nephrotic syndrome secondary to *Plasmodium malariae* (31/36)
Ahn 2018	Wrong study design: children with SRNS were not randomised; only children with FRNS/SDNS were randomised
Arora 2002	Wrong population: adult patients
Buyukcelik 2002	Wrong population: study of gemfibrozil on lipid profiles in children with nephrotic syndrome; ineligible renal pathology as all except one had MPGN
Hari 2018	Mixed population of children with nephrotic syndrome including MPGN, Membranous GN, FSGS and MCD
Hiraoka 2000	Wrong population: SSNS patients
Iyengar 2006	Wrong population: SSNS patients
JPRN-C000000007	Wrong study design: this study started on 1-8-2005 states it is a single arm study on the UMIN-CTR Clinical Trial Registry. Number on Registry is UMIN-CTR registry is C000000009
Jung 1990	Mixed population of steroid dependent and steroid resistant patients; unable to separate data
Kano 2003	Wrong population: included patients did not have nephrotic syndrome but moderate proteinuria with normal serum albumin levels
Khemani 2016	Mixed population: includes SDNS and SRNS patients and the data on these cannot be separated. No reply to email to chief investigator
Koshikawa 1993	Wrong population: adult patients
Kumar 2004a	Wrong population: adults patients
Li 2006g	Wrong population: adult patients
Ren 2011	Wrong population: adult patients
Ren 2013	Wrong population: adult patients
Saito 2014	Wrong population: adult patients
Saito 2017	Wrong population: patients with membranous GN
Shibasaki 2004	Wrong population: not clear if paediatric patients were included in study; includes patients with non MCD or FSGS pathology
Tejani 1988	Mixed population: includes SSNS and SRNS patients and the results cannot be separated
Walker 1990	Wrong population: adult patients
Yi 2008	Probably not an RCT: no mention of "random" and group numbers unequal (87 vs 55). Includes largely steroid dependent patients and not steroid resistant patients

Study	Reason for exclusion
Zhao 2013a	Mixed population: includes both steroid-resistant and steroid-dependent patients and results cannot be separated

FRNS - frequently-relapsing nephrotic syndrome; FSGS - focal segmental glomerulosclerosis; GN - glomerulonephritis; MCD - minimal change disease; MPGN - membranoproliferative glomerulonephritis; RCT - randomised controlled trial; SDNS - steroid-dependent nephrotic syndrome; SRNS - steroid-resistant nephrotic syndrome; SSNS - steroid-sensitive nephrotic syndrome

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

DUPLEX 2018

Trial name or title	DUPLEX study
Methods	Open-label RCT
Participants	Participants aged 8 to 75 years (US) or 18 to 75 years (outside US) with biopsy-proven FSGS or MCD or FSGS with documented genetic mutation in podocyte protein Up/C ≥ 1.5 g/g at screening & eGFR > 30 mL/min/1.73 m^2
Interventions	Sparsentan 400 mg/day titrating to 800 mg/day Irbesartan 150 mg/day titrating to 300 mg/day
Outcomes	Slope of eGFR from week 6 to week 108 Proportion of patients achieving a Up/C ≤ 1.5 g/g and a > 40% reduction from baseline in Up/C at Week 36
Starting date	April 3, 2018
Contact information	Radko Komers, MD, PhD; medinfo@retrophin.com
Notes	NCT03493685. Estimated completion date is December 2022. Other name: 021FSGS16010

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

NCT02382575 *(Continued)*

	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

NCT02972346

Trial name or title	Availability study of ACTH to treat children SRNS/SDNS
Methods	Open-label parallel group RCT
Participants	42 children aged 3 to 12 years with SDNS or SRNS & MCD
Interventions	Intervention: ACTH 0.4 U/kg/day (maximum 25 units) for three consecutive days every 4 weeks + routine treatment. Comparator: Routine treatment
Outcomes	24 hr urinary protein excretion. Remission/relapse
Starting date	November 2016. Estimated completion date June 2019
Contact information	Yufeng Li, Ph.D. mieuniversity@hotmail.com. Xinhua Hospital, Shanghai Jiao Tong University School of Medicine
Notes	Availability and Safety Study of ACTH to Treat Children with SRNS/SDNS

Trachtman 2018

Trial name or title	A phase II randomised, placebo-controlled, double-blind, parallel arms with switchover, pilot study to evaluate the efficacy and safety of intravenous abatacept in treatment resistant nephrotic syndrome (focal segmental glomerulosclerosis/ minimal change disease)

Trachtman 2018 *(Continued)*

Methods	Randomised placebo controlled trial (quadruple blind)
Participants	90 patients aged ≥ 6 years with TRNS due to MCD or FSGS (Collapsing FSGS excluded), GFR ≥ 45 mL/min/1.73 m^2. Patients stratified for age (< 18 and ≥ 18) and *APOL1* risk status. Exclusions: Patients with recurrence of disease post transplant, secondary TRNS, DM, CHF, BMI > 40, recent or chronic infections
Interventions	1. 16 week parallel arms comparing IV abatacept and placebo (normal saline) on days 1, 14, 28 and then every 28 days 2. 16 week cross-over with placebo group receiving abatacept and abatacept group receiving placebo 3. 169 day abatacept extension with all receiving abatacept 4. Weight tiered dose of abatacept from 500 to 1000 mg. Children < 18 years weighing < 75 kg: 10 mg/kg/dose 4. Standard immunosuppression (CNI, MMF, prednisone) unchanged in 1 months, ACEi, ARB
Outcomes	1. Difference in % of participants who achieve a renal response by 113 days (end of first 16 week parallel group study). Renal response defined as a ≥ 50% reduction in Up/C from baseline to day 113 with Up/C < 3g/g and eGFR > 90 mL/min/1.73 m^2 (if below normal at baseline, remaining ≥ 75% of baseline. 2. Change in proteinuria, GFR, remission, quality of life (PROMIS), adverse events
Starting date	March 1, 2016. Estimated completion date June 2020
Contact information	Anna Greka: agreka@bwh.harvard.edu
Notes	27 study sites. NCT02592798. Sponsor: Bristol-Myers Squibb

ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blocker; BMI - body mass index; CHF - chronic heart failure; CNI - calcineurin inhibitor; DM - diabetes mellitus; FSGS - focal segmental glomerulosclerosis; (e)GFR - (estimated) glomerular filtration rate; MCD - minimal change disease; MesPGN - mesangioproliferative glomerulonephritis; MMF - mycophenolate mofetil; SDNS - steroid-dependent nephrotic syndrome; SRNS - steroid-resistant nephrotic syndrome; TRNS - treatment-resistant nephrotic syndrome; Up/C - urinary protein creatinine ratio

DATA AND ANALYSES

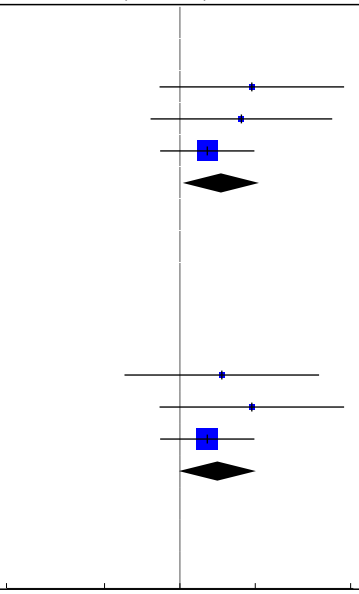
Comparison 1. Cyclosporin (CSA) versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All renal pathologies	4	74	Risk Ratio (M-H, Random, 95% CI)	3.50 [1.09, 11.20]
1.2 FSGS	3	58	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.97, 10.18]
2 Complete or partial remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 All renal pathologies	4	74	Risk Ratio (M-H, Random, 95% CI)	3.15 [1.04, 9.57]
2.2 FSGS	2	49	Risk Ratio (M-H, Random, 95% CI)	2.66 [0.85, 8.31]
3 Adverse events	3		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]
3.3 ESKD	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

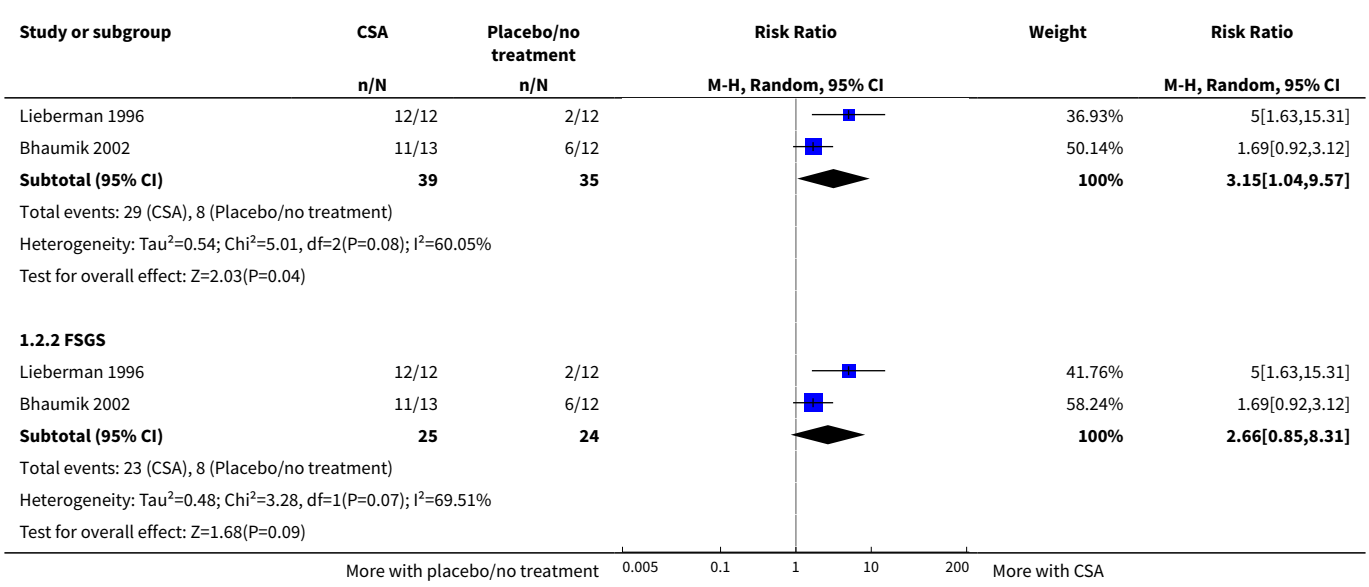
Analysis 1.1. Comparison 1 Cyclosporin (CSA) versus placebo/no treatment, Outcome 1 Complete remission.

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		17.06%	9[0.54,150.81]
Ponticelli 1993a	4/10	0/7		17.58%	6.55[0.41,105.1]
Bhaumik 2002	5/13	2/12		65.36%	2.31[0.55,9.74]
Subtotal (95% CI)	**39**	**35**		**100%**	**3.5[1.09,11.2]**
Total events: 13 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=2(P=0.6); I^2=0%					
Test for overall effect: Z=2.11(P=0.04)					
1.1.2 FSGS					
Ponticelli 1993a	1/4	0/5		15.69%	3.6[0.18,70.34]
Lieberman 1996	4/12	0/12		17.45%	9[0.54,150.81]
Bhaumik 2002	5/13	2/12		66.86%	2.31[0.55,9.74]
Subtotal (95% CI)	**29**	**29**		**100%**	**3.14[0.97,10.18]**
Total events: 10 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.77, df=2(P=0.68); I^2=0%					
Test for overall effect: Z=1.9(P=0.06)					

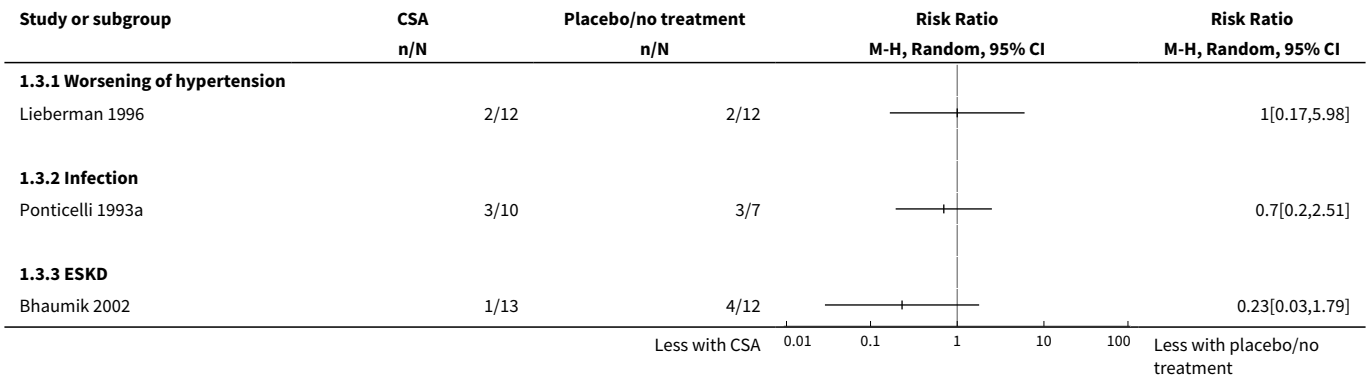


Analysis 1.2. Comparison 1 Cyclosporin (CSA) versus placebo/ no treatment, Outcome 2 Complete or partial remission.

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
1.2.1 All renal pathologies					
Garin 1988	0/4	0/4			Not estimable
Ponticelli 1993a	6/10	0/7		12.93%	9.45[0.62,144.74]



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



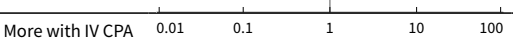
Comparison 2. Calcineurin inhibitor (CNI) versus IV cyclophosphamide (CPA)

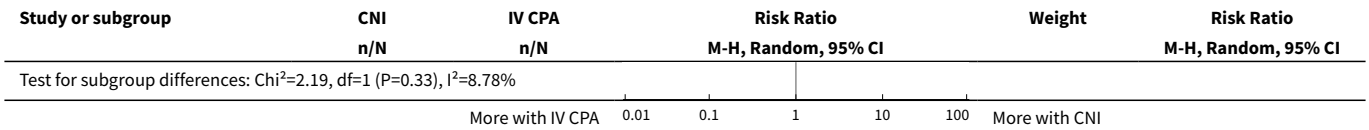
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response at 3 to 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Complete or partial remission	2	156	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.25, 3.13]
1.2 Partial remission	2	156	Risk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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 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]
3.2 Any serious adverse effect	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Medications ceased due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Serious infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Death	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Persistent nephrotoxicity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

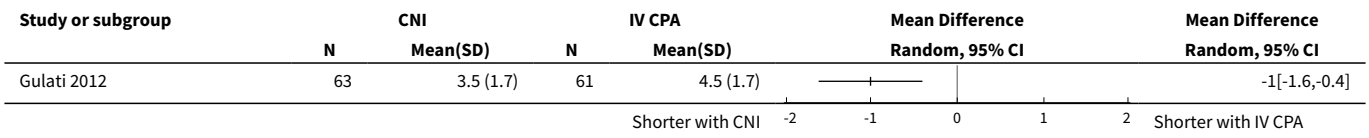
Analysis 2.1. Comparison 2 Calcineurin inhibitor (CNI) versus IV cyclophosphamide (CPA), Outcome 1 Treatment response at 3 to 6 months.

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: Tau²=0.04; Chi²=1.24, df=1(P=0.26); I²=19.67%					
Test for overall effect: Z=2.92(P=0)					
2.1.2 Partial remission					
APN 2008	7/15	2/17		39.06%	3.97[0.97,16.24]
Gulati 2012	19/63	19/61		60.94%	0.97[0.57,1.64]
Subtotal (95% CI)	**78**	**78**		**100%**	**1.68[0.43,6.56]**
Total events: 26 (CNI), 21 (IV CPA)					
Heterogeneity: Tau²=0.72; Chi²=3.44, df=1(P=0.06); I²=70.93%					
Test for overall effect: Z=0.75(P=0.46)					
2.1.3 Complete remission					
APN 2008	2/15	1/17		7.36%	2.27[0.23,22.56]
Gulati 2012	33/63	9/61		92.64%	3.55[1.86,6.78]
Subtotal (95% CI)	**78**	**78**		**100%**	**3.43[1.84,6.41]**
Total events: 35 (CNI), 10 (IV CPA)					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%					
Test for overall effect: Z=3.88(P=0)					

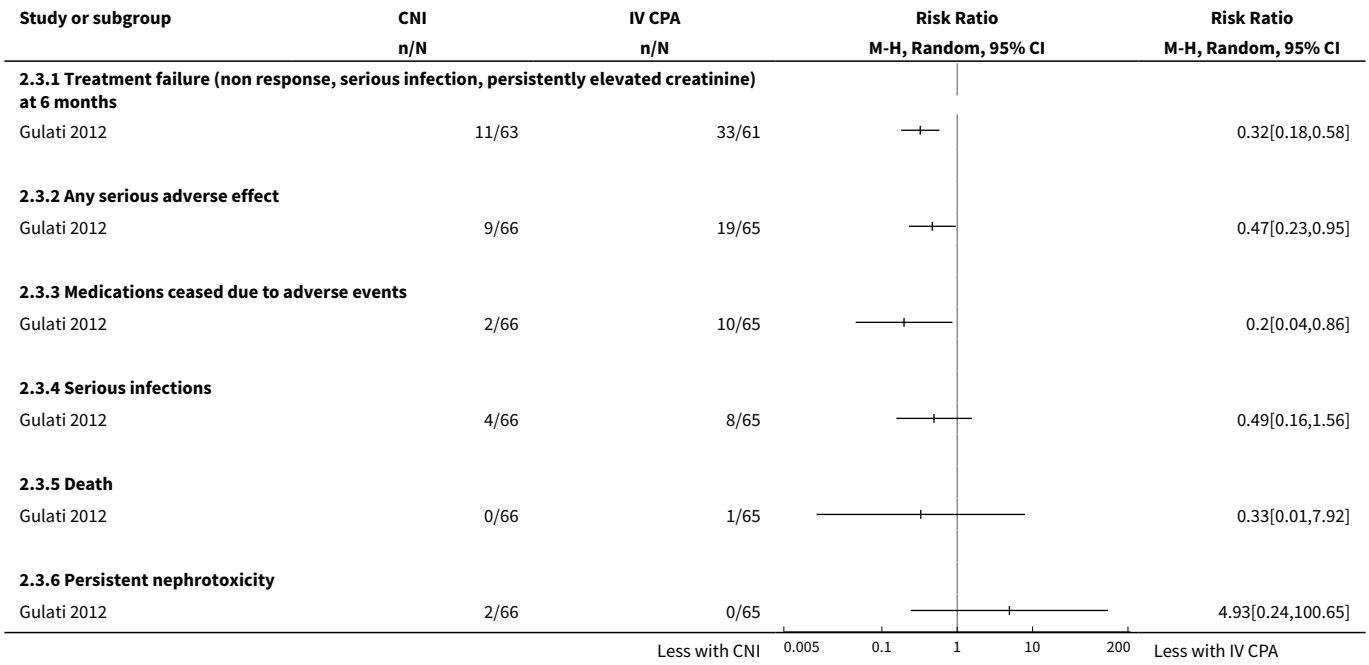




Analysis 2.2. Comparison 2 Calcineurin inhibitor (CNI) versus IV cyclophosphamide (CPA), Outcome 2 Mean time to remission.



Analysis 2.3. Comparison 2 Calcineurin inhibitor (CNI) versus IV cyclophosphamide (CPA), Outcome 3 Adverse events.



Comparison 3. Tacrolimus (TAC) versus cyclosporin (CSA)

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

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
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	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission	2	58	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.42]
2.2 Partial remission	2	58	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.92, 2.56]
2.3 Complete and partial remission	2	58	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.87, 1.25]
3 Relapse following complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Change in eGFR over 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Persistent nephrotoxicity	1	41	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.05, 4.85]
5.2 Reversible nephrotoxicity	1	41	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.41]
5.3 Worsening of hypertension	2	58	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.15]
5.4 Headache	1	41	Risk Ratio (M-H, Random, 95% CI)	2.86 [0.12, 66.44]
5.5 Paraesthesia	1	41	Risk Ratio (M-H, Random, 95% CI)	2.86 [0.12, 66.44]
5.6 Hypertrichosis	1	41	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.38]
5.7 Gingival hyperplasia	1	41	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.56]
5.8 Acne or skin infections	1	41	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.74]

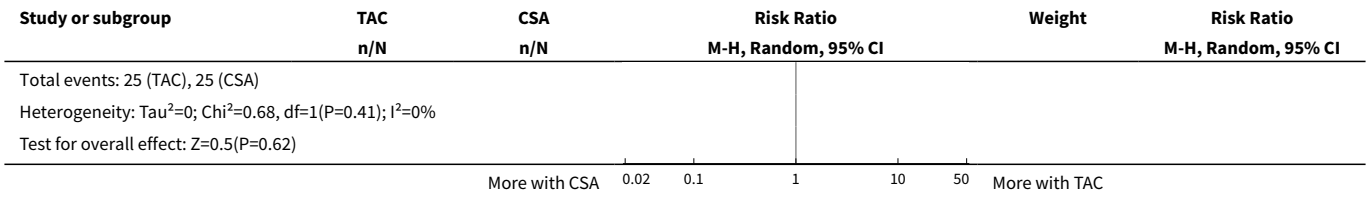
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.9 Diarrhoea	1	41	Risk Ratio (M-H, Random, 95% CI)	5.71 [0.75, 43.36]
5.10 Sepsis/pneumonia	1	41	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.22]

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

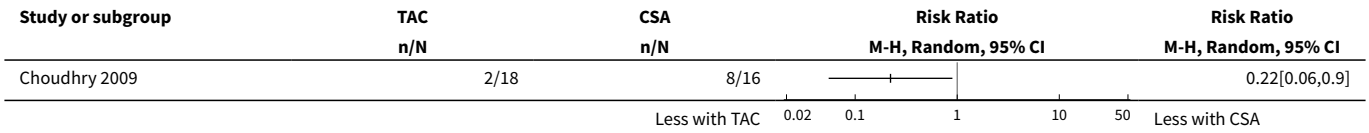
Study or subgroup	TAC n/N	CSA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 Complete remission				
Choudhry 2009	9/21	10/20		0.86[0.44,1.66]
3.1.2 Partial remission				
Choudhry 2009	9/21	6/20		1.43[0.62,3.28]
3.1.3 Complete and partial remission				
Choudhry 2009	18/21	15/20		1.14[0.84,1.55]

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

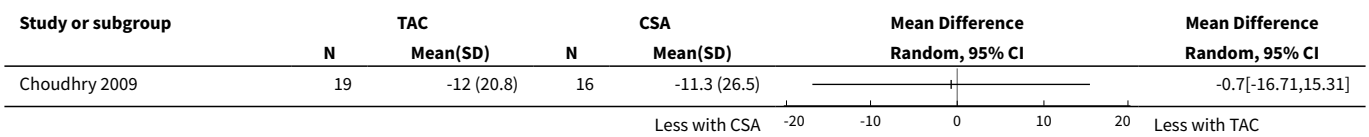
Study or subgroup	TAC n/N	CSA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Complete remission					
Valverde 2010	1/7	4/10		8.48%	0.36[0.05,2.55]
Choudhry 2009	10/21	11/20		91.52%	0.87[0.48,1.58]
Subtotal (95% CI)	**28**	**30**		**100%**	**0.8[0.45,1.42]**
Total events: 11 (TAC), 15 (CSA)					
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=0.75(P=0.45)					
3.2.2 Partial remission					
Choudhry 2009	8/21	4/20		24.6%	1.9[0.68,5.35]
Valverde 2010	6/7	6/10		75.4%	1.43[0.79,2.58]
Subtotal (95% CI)	**28**	**30**		**100%**	**1.53[0.92,2.56]**
Total events: 14 (TAC), 10 (CSA)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					
3.2.3 Complete and partial remission					
Choudhry 2009	18/21	15/20		33.98%	1.14[0.84,1.55]
Valverde 2010	7/7	10/10		66.02%	1[0.8,1.25]
Subtotal (95% CI)	**28**	**30**		**100%**	**1.05[0.87,1.25]**



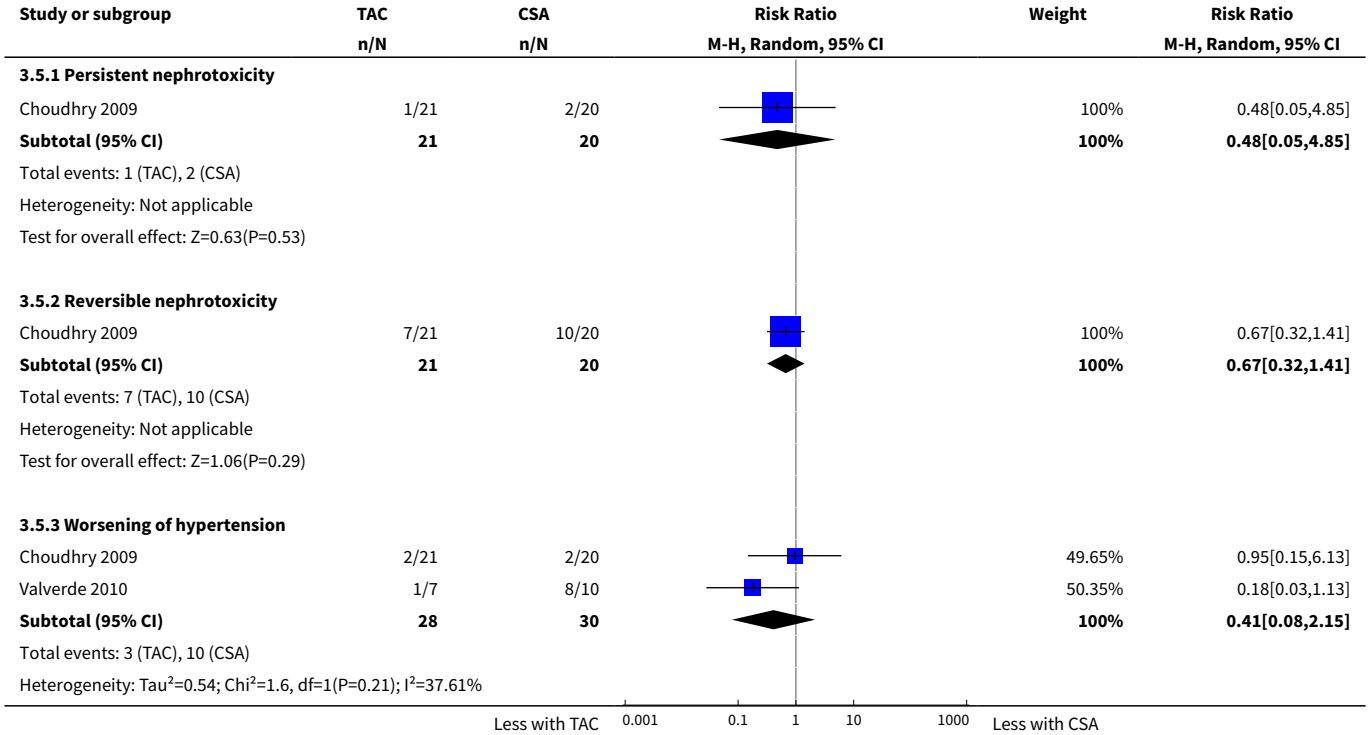
Analysis 3.3. Comparison 3 Tacrolimus (TAC) versus cyclosporin (CSA), Outcome 3 Relapse following complete or partial remission.

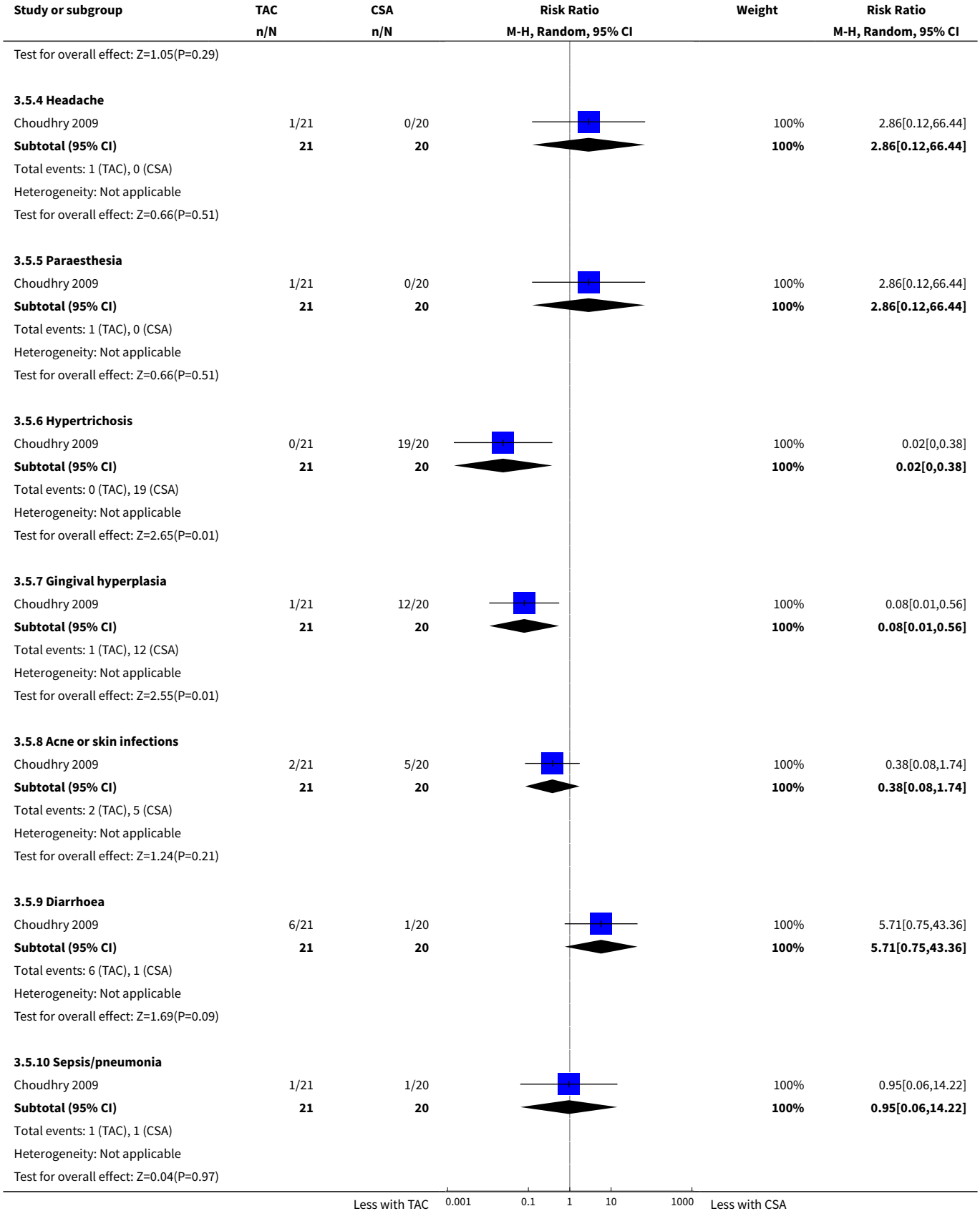


Analysis 3.4. Comparison 3 Tacrolimus (TAC) versus cyclosporin (CSA), Outcome 4 Change in eGFR over 12 months.



Analysis 3.5. Comparison 3 Tacrolimus (TAC) versus cyclosporin (CSA), Outcome 5 Adverse events.





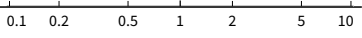
Comparison 4. Cyclosporin (CSA) versus mycophenolate mofetil (MMF) with pulse dexamethasone (DEXA)

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
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Cyclosporin (CSA) versus mycophenolate mofetil (MMF) with pulse dexamethasone (DEXA), 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-CT 2011	14/72	6/66		2.14[0.87,5.24]
4.1.2 Partial remission (primary outcome 3)				
FSGS-CT 2011	19/72	16/66		1.09[0.61,1.93]
4.1.3 Complete or partial remission (primary outcome 1,2,3)				
FSGS-CT 2011	33/72	22/66		1.38[0.9,2.1]

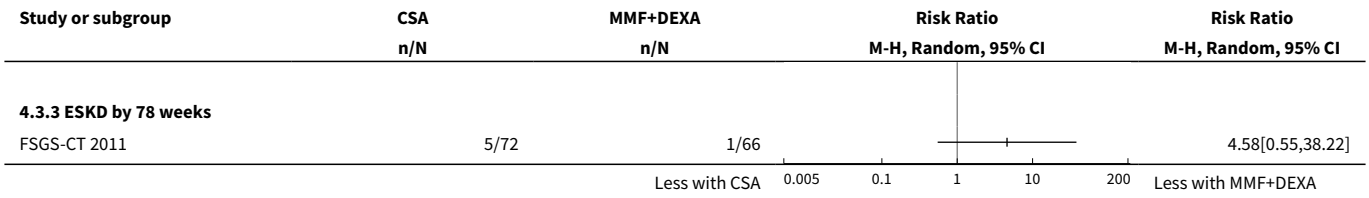


Analysis 4.2. Comparison 4 Cyclosporin (CSA) versus mycophenolate mofetil (MMF) with pulse dexamethasone (DEXA), Outcome 2 Sustainable remission between 52 and 78 weeks.

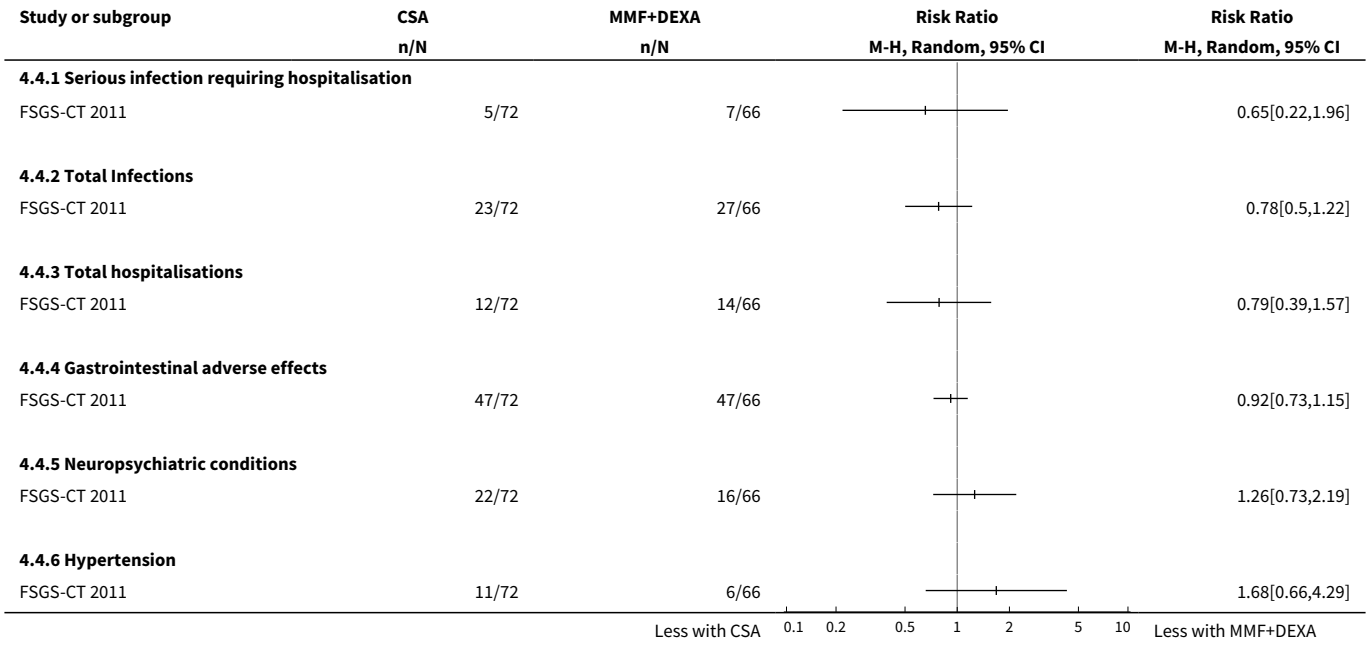
Study or subgroup	CSA n/N	MMF+DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 Complete remission (secondary outcome 1,2)				
FSGS-CT 2011	6/72	4/66		1.38[0.41,4.66]
4.2.2 Partial remission (secondary outcome 3)				
FSGS-CT 2011	16/72	14/66		1.05[0.56,1.98]
4.2.3 No sustainable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

Analysis 4.3. Comparison 4 Cyclosporin (CSA) versus mycophenolate mofetil (MMF) with pulse dexamethasone (DEXA), 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-CT 2011	0/72	2/66		0.18[0.01,3.75]
4.3.2 50% decline in GFR by 78 weeks				
FSGS-CT 2011	5/72	2/66		2.29[0.46,11.41]



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



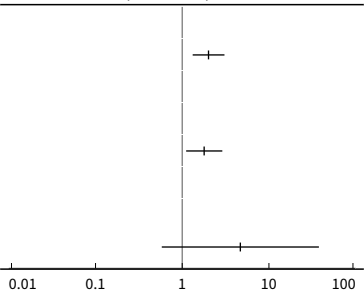
Comparison 5. Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with complete or partial response at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete or partial response	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Complete response	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Partial response	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Number with treatment failure by one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Frequent relapses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Steroid resistance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Relapses per year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Prednisone dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Change in GFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 All serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Serious infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Hypovolaemia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

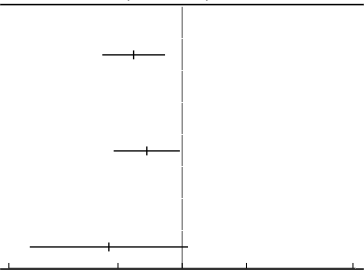
Analysis 5.1. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 1 Number with complete or partial response at one year.

Study or subgroup	TAC n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.1.1 Complete or partial response				
Sinha 2017	28/31	13/29		2.01[1.32,3.07]
5.1.2 Complete response				
Sinha 2017	23/31	12/29		1.79[1.11,2.9]
5.1.3 Partial response				
Sinha 2017	5/31	1/29		4.68[0.58,37.68]



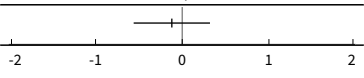
Analysis 5.2. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 2 Number with treatment failure by one year.

Study or subgroup	TAC n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.2.1 Treatment failure				
Sinha 2017	3/31	16/29		0.18[0.06,0.54]
5.2.2 Frequent relapses				
Sinha 2017	3/31	10/29		0.28[0.09,0.92]
5.2.3 Steroid resistance				
Sinha 2017	0/31	6/29		0.07[0,1.23]



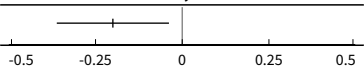
Analysis 5.3. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 3 Relapses per year.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2017	31	0.5 (0.8)	29	0.6 (1)		-0.12[-0.56,0.32]



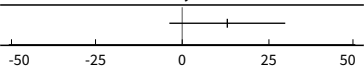
Analysis 5.4. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 4 Prednisone dose.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2017	31	0.3 (0.2)	29	0.5 (0.4)		-0.2[-0.36,-0.04]



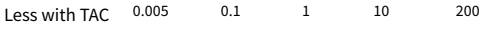
Analysis 5.5. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 5 Change in GFR.

Study or subgroup	TAC N	TAC Mean(SD)	MMF N	MMF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sinha 2017	31	-6 (35)	29	-19 (31)		13[-3.71,29.71]



Analysis 5.6. Comparison 5 Tacrolimus (TAC) versus mycophenolate mofetil (MMF) to maintain remission, Outcome 6 Adverse events.

Study or subgroup	TAC n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.6.1 All serious adverse events				
Sinha 2017	3/31	9/29		0.31[0.09,1.04]
5.6.2 Serious infections				
Sinha 2017	2/31	7/29		0.27[0.06,1.18]
5.6.3 Hypovolaemia				
Sinha 2017	0/31	2/29		0.19[0.01,3.75]

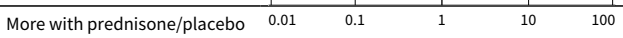


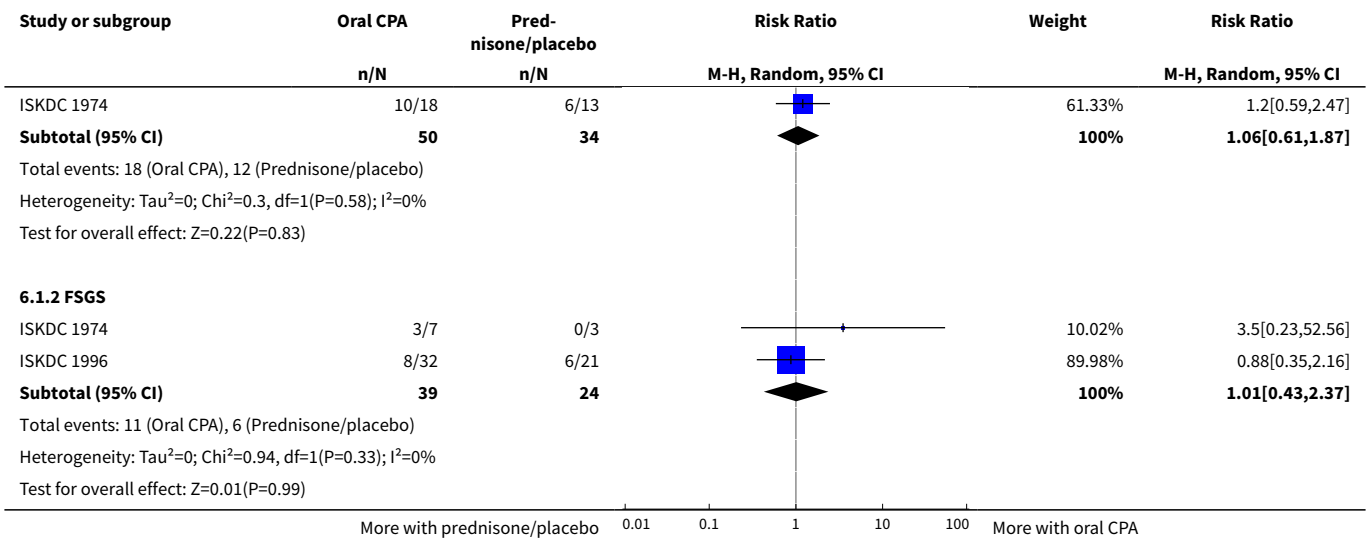
Comparison 6. Oral cyclophosphamide (CPA) versus prednisone/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All renal pathologies	2	84	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.61, 1.87]
1.2 FSGS	2	63	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.43, 2.37]
2 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 FSGS	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Death (all causes)	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]

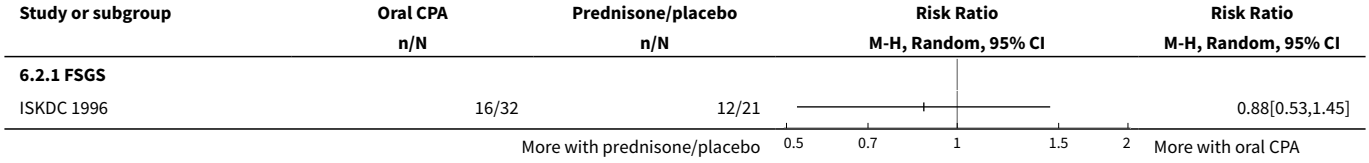
Analysis 6.1. Comparison 6 Oral cyclophosphamide (CPA) versus prednisone/placebo, Outcome 1 Complete remission.

Study or subgroup	Oral CPA n/N	Pred-nisone/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 All renal pathologies					
ISKDC 1996	8/32	6/21		38.67%	0.88[0.35,2.16]

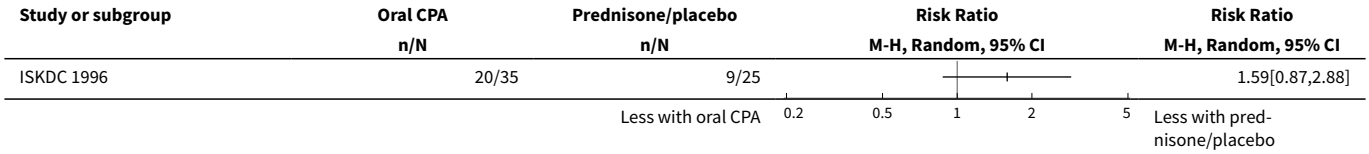




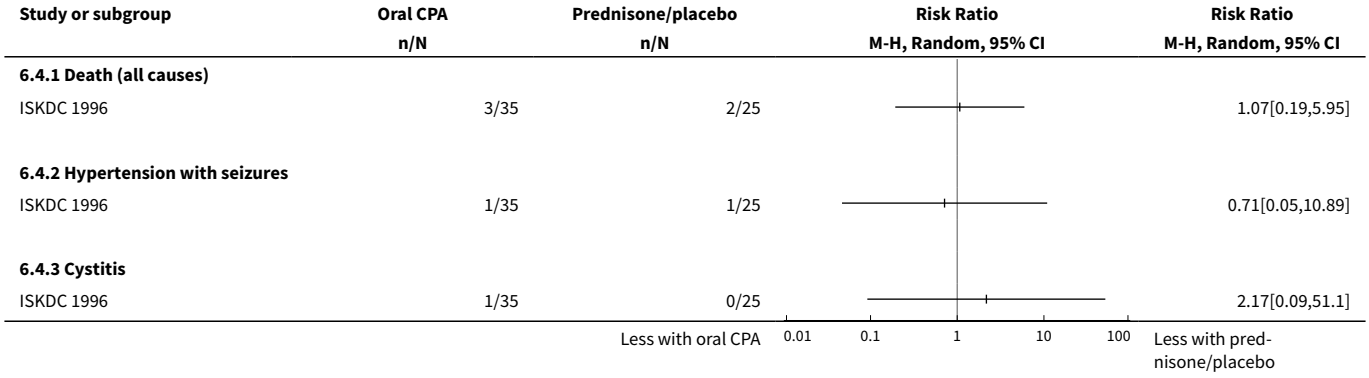
Analysis 6.2. Comparison 6 Oral cyclophosphamide (CPA) versus prednisone/placebo, Outcome 2 Complete or partial remission.

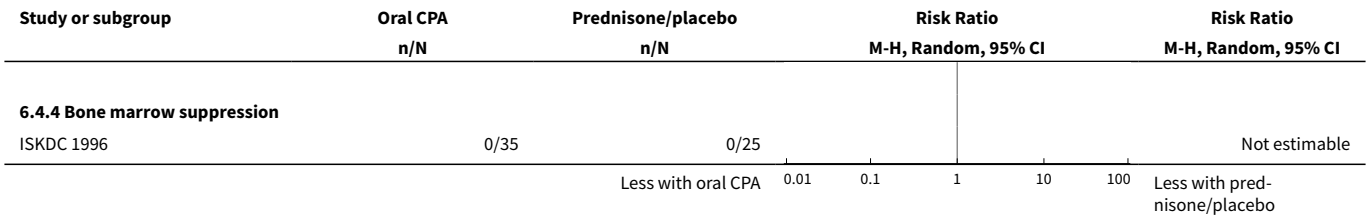


Analysis 6.3. Comparison 6 Oral cyclophosphamide (CPA) versus prednisone/placebo, Outcome 3 Treatment failure.



Analysis 6.4. Comparison 6 Oral cyclophosphamide (CPA) versus prednisone/placebo, Outcome 4 Adverse events.

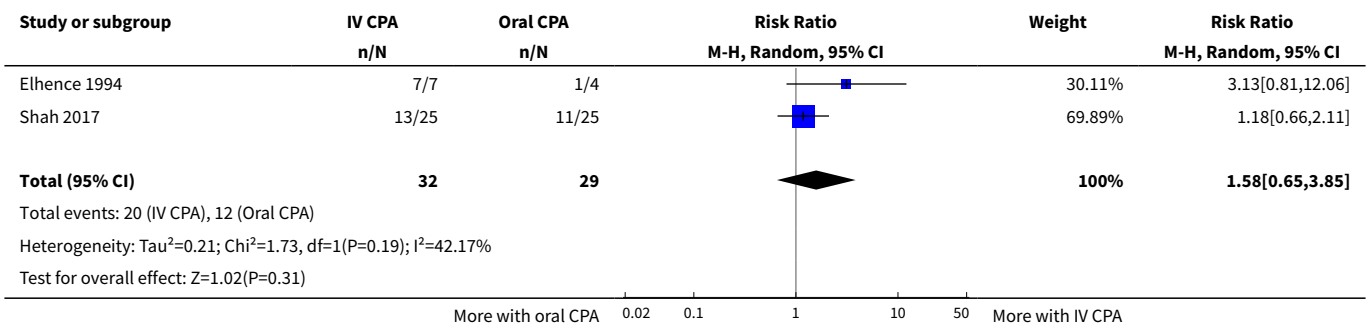




Comparison 7. IV versus oral cyclophosphamide (CPA)

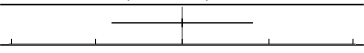
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Complete remission	2	61	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.65, 3.85]
2 Partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Continuing remission at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Time to remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Mean duration of remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Renal insufficiency	1	50	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.99]
6.2 Bacterial infection	2	61	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.10, 10.62]
6.3 Vomiting	2	61	Risk Ratio (M-H, Random, 95% CI)	2.38 [0.35, 16.17]
6.4 Alopecia	1	50	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.27, 8.22]

Analysis 7.1. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 1 Complete remission.



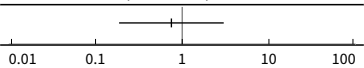
Analysis 7.2. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 2 Partial remission.

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
Shah 2017	2/25	2/25		1[0.15,6.55]



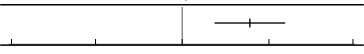
Analysis 7.3. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 3 Continuing remission at one year.

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
Shah 2017	3/25	4/25		0.75[0.19,3.01]



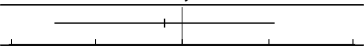
Analysis 7.4. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 4 Time to remission.

Study or subgroup	IV CPA N	IV CPA Mean(SD)	Oral CPA N	Oral CPA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Shah 2017	15	86 (29)	13	47 (26)		39[18.63,59.37]



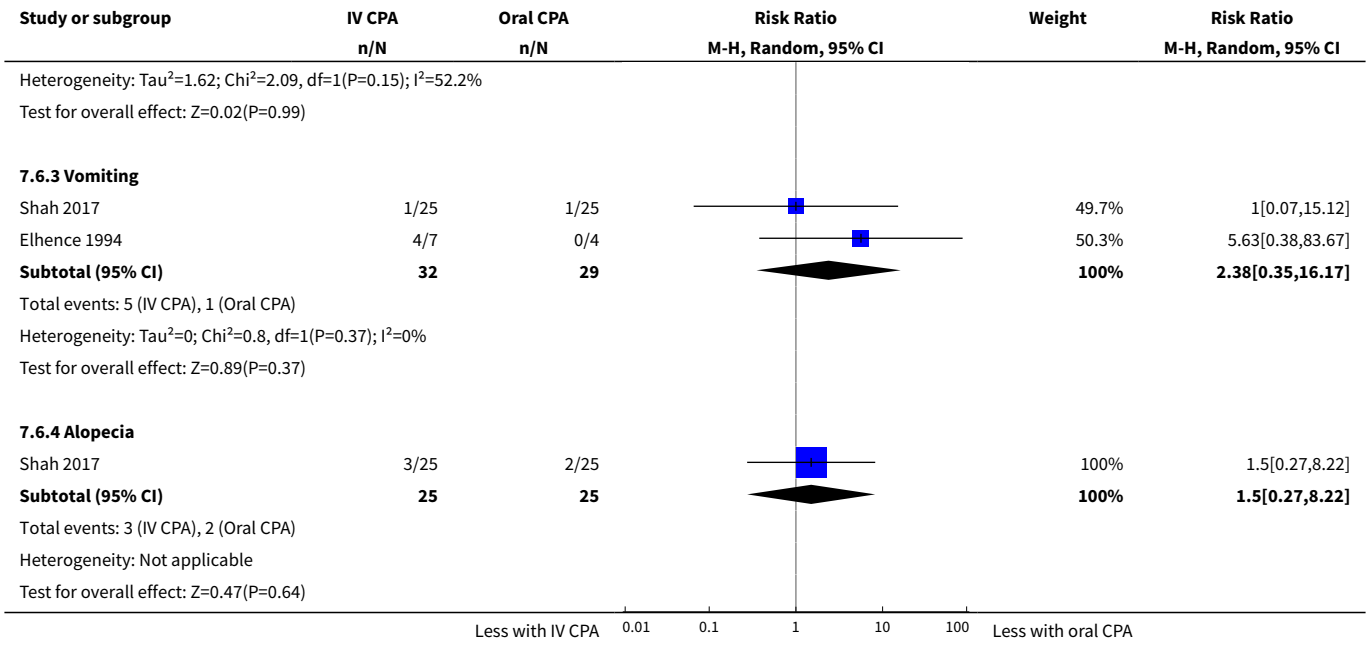
Analysis 7.5. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 5 Mean duration of remission.

Study or subgroup	IV CPA N	IV CPA Mean(SD)	Oral CPA N	Oral CPA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Shah 2017	15	8.1 (8.9)	13	9.2 (8.3)		-1.02[-7.37,5.33]



Analysis 7.6. Comparison 7 IV versus oral cyclophosphamide (CPA), Outcome 6 Adverse events.

Study or subgroup	IV CPA n/N	Oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.6.1 Renal insufficiency					
Shah 2017	1/25	3/25		100%	0.33[0.04,2.99]
Subtotal (95% CI)	**25**	**25**		**100%**	**0.33[0.04,2.99]**
Total events: 1 (IV CPA), 3 (Oral CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					
7.6.2 Bacterial infection					
Elhence 1994	0/7	1/4		36.11%	0.21[0.01,4.18]
Shah 2017	5/25	2/25		63.89%	2.5[0.53,11.7]
Subtotal (95% CI)	**32**	**29**		**100%**	**1.02[0.1,10.62]**
Total events: 5 (IV CPA), 3 (Oral CPA)					



Comparison 8. IV versus oral cyclophosphamide (CPA) plus IV dexamethasone (DEXA)

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

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
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]
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 8.1. Comparison 8 IV versus oral cyclophosphamide (CPA) plus IV dexamethasone (DEXA), Outcome 1 Treatment response at 6 months.

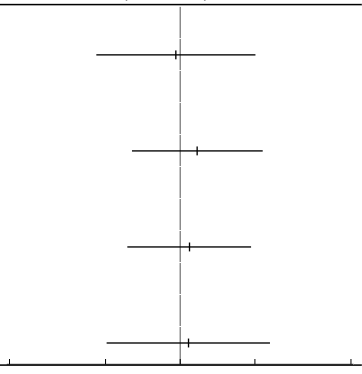
Study or subgroup	IV CPA n/N	Oral CPA/IV DEXA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 Complete remission				
Mantan 2008	14/26	11/23		1.13[0.65,1.96]
8.1.2 Partial remission				
Mantan 2008	2/26	2/23		0.88[0.14,5.79]
8.1.3 Complete or partial remission				
Mantan 2008	16/26	13/23		1.09[0.68,1.74]

Analysis 8.2. Comparison 8 IV versus oral cyclophosphamide (CPA) plus IV dexamethasone (DEXA), 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
8.2.1 Sustained remission/steroid-sensitive relapses				
Mantan 2008	14/26	11/23		1.13[0.65,1.96]
8.2.2 CKD				
Mantan 2008	1/26	1/23		0.88[0.06,13.35]

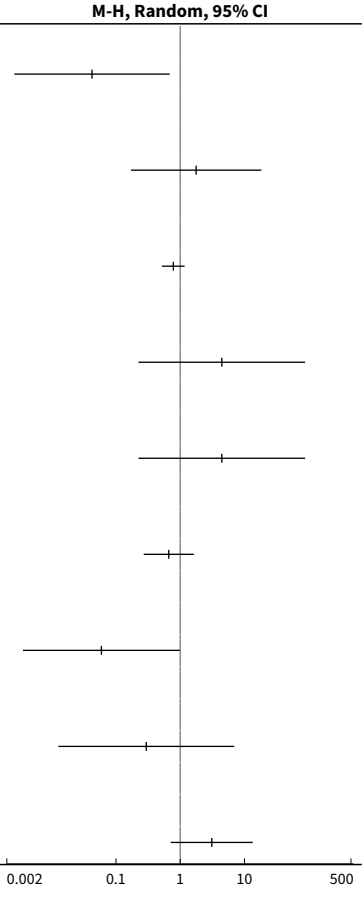
Analysis 8.3. Comparison 8 IV versus oral cyclophosphamide (CPA) plus IV dexamethasone (DEXA), Outcome 3 Complete or partial resistance in subgroups.

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
8.3.1 Initial SRNS				
Mantan 2008	6/10	5/8		0.96[0.46,2.01]
8.3.2 Late SRNS				
Mantan 2008	10/16	8/15		1.17[0.64,2.15]
8.3.3 Minimal change disease				
Mantan 2008	9/13	7/11		1.09[0.61,1.93]
8.3.4 FSGS or MesPGN				
Mantan 2008	7/13	6/12		1.08[0.51,2.3]



Analysis 8.4. Comparison 8 IV versus oral cyclophosphamide (CPA) plus IV dexamethasone (DEXA), 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
8.4.1 Hypertension				
Mantan 2008	0/26	10/23		0.04[0,0.68]
8.4.2 cataract/glaucoma				
Mantan 2008	2/26	1/23		1.77[0.17,18.26]
8.4.3 Cushingoid features				
Mantan 2008	15/26	17/23		0.78[0.52,1.17]
8.4.4 Leucopenia				
Mantan 2008	2/26	0/23		4.44[0.22,88.04]
8.4.5 Cystitis				
Mantan 2008	2/26	0/23		4.44[0.22,88.04]
8.4.6 Bacterial infections				
Mantan 2008	6/26	8/23		0.66[0.27,1.63]
8.4.7 Hypokalaemia				
Mantan 2008	0/26	7/23		0.06[0,0.98]
8.4.8 Steroid encephalopathy				
Mantan 2008	0/26	1/23		0.3[0.01,6.94]
8.4.9 Hair loss				
Mantan 2008	7/26	2/23		3.1[0.71,13.44]

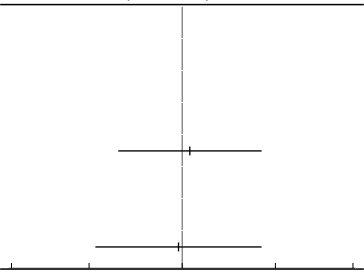


Comparison 9. Rituximab/cyclosporin/prednisolone (RTX/CSA/Pred) versus CSA/Pred

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Complete remission in initial steroid resistance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Complete remission in delayed steroid resistance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Complete remission in all patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 End of study creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Initially resistant patients	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Delayed resistant patients	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 End of study serum albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Initially resistant patients	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Delayed resistant patients	1		Mean Difference (IV, 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 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]

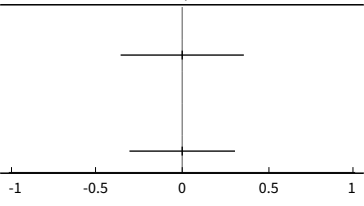
Analysis 9.1. Comparison 9 Rituximab/cyclosporin/prednisolone (RTX/CSA/Pred) versus CSA/Pred, Outcome 1 Number with complete remission.

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
9.1.1 Complete remission in initial steroid resistance				
Magnasco 2012	0/9	0/7		Not estimable
9.1.2 Complete remission in delayed steroid resistance				
Magnasco 2012	3/7	3/8		1.14[0.33,3.94]
9.1.3 Complete remission in all patients				
Magnasco 2012	3/16	3/15		0.94[0.22,3.94]



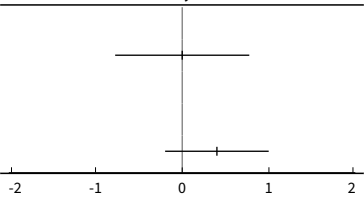
Analysis 9.2. Comparison 9 Rituximab/cyclosporin/prednisolone (RTX/CSA/Pred) versus CSA/Pred, Outcome 2 End of study creatinine.

Study or subgroup	RTX/CSA/Pred N	RTX/CSA/Pred Mean(SD)	CSA/Pred N	CSA/Pred Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
9.2.1 Initially resistant patients						
Magnasco 2012	9	0.7 (0.3)	7	0.7 (0.4)		0[-0.36,0.36]
9.2.2 Delayed resistant patients						
Magnasco 2012	7	0.5 (0.3)	8	0.5 (0.3)		0[-0.3,0.3]



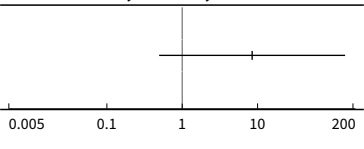
Analysis 9.3. Comparison 9 Rituximab/cyclosporin/prednisolone (RTX/CSA/Pred) versus CSA/Pred, Outcome 3 End of study serum albumin.

Study or subgroup	RTX/CSA/Pred N	RTX/CSA/Pred Mean(SD)	CSA/Pred N	CSA/Pred Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
9.3.1 Initially resistant patients						
Magnasco 2012	9	2.1 (0.6)	7	2.1 (0.9)		0[-0.77,0.77]
9.3.2 Delayed resistant patients						
Magnasco 2012	7	3.3 (0.3)	8	2.9 (0.8)		0.4[-0.2,1]

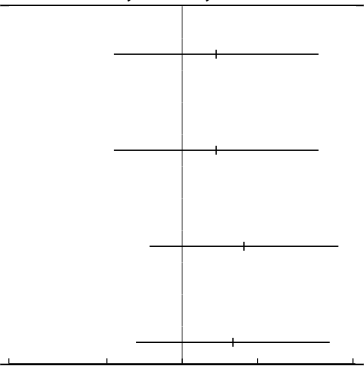


Analysis 9.4. Comparison 9 Rituximab/cyclosporin/prednisolone (RTX/CSA/Pred) versus CSA/Pred, Outcome 4 Adverse events.

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
9.4.1 Abdominal pain				
Magnasco 2012	4/16	0/15		8.47[0.49,145.11]



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
9.4.2 Bronchospasm/treatment discontinued				
Magnasco 2012	1/16	0/15		2.82[0.12,64.39]
9.4.3 Hypotension				
Magnasco 2012	1/16	0/15		2.82[0.12,64.39]
9.4.4 Skin rash				
Magnasco 2012	3/16	0/15		6.59[0.37,117.77]
9.4.5 Mild dyspnoea				
Magnasco 2012	2/16	0/15		4.71[0.24,90.69]

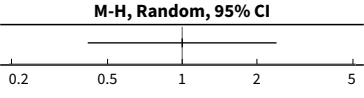


Comparison 10. Chlorambucil versus indomethacin

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 10.1. Comparison 10 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 10.2. Comparison 10 Chlorambucil versus indomethacin, Outcome 2 End-stage kidney disease.

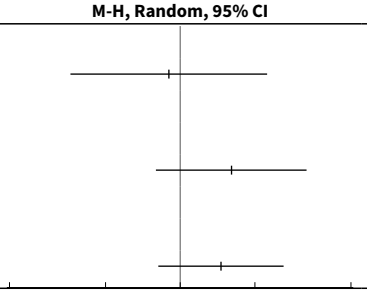
Study or subgroup	Chlorambucil n/N	Indomethacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kleinknecht 1980	0/15	2/15		0.2[0.01,3.85]

Comparison 11. Triple therapy with cyclophosphamide (CPA), mycophenolate mofetil (MMF) or leflunomide (LEF)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Short-term response (remission)	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 (remission at 12 months)	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]

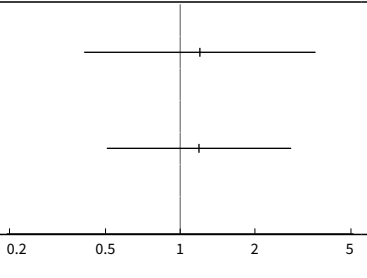
Analysis 11.1. Comparison 11 Triple therapy with cyclophosphamide (CPA), mycophenolate mofetil (MMF) or leflunomide (LEF), Outcome 1 Short-term response (remission).

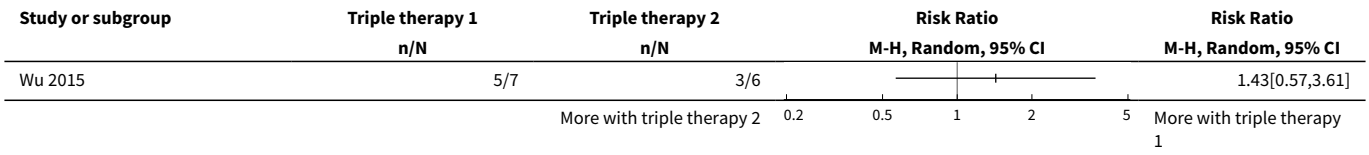
Study or subgroup	Triple therapy 1 n/N	Triple therapy 2 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.1.1 MMF versus CPA				
Wu 2015	3/5	4/6		0.9[0.36,2.24]
11.1.2 LEF versus MMF				
Wu 2015	7/7	3/5		1.61[0.8,3.23]
11.1.3 LEF versus CPA				
Wu 2015	7/7	4/6		1.46[0.82,2.61]



Analysis 11.2. Comparison 11 Triple therapy with cyclophosphamide (CPA), mycophenolate mofetil (MMF) or leflunomide (LEF), Outcome 2 Long-term response (remission at 12 months).

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
11.2.1 MMF versus CPA				
Wu 2015	3/5	3/6		1.2[0.41,3.51]
11.2.2 LEF versus MMF				
Wu 2015	5/7	3/5		1.19[0.51,2.8]
11.2.3 LEF versus CPA				

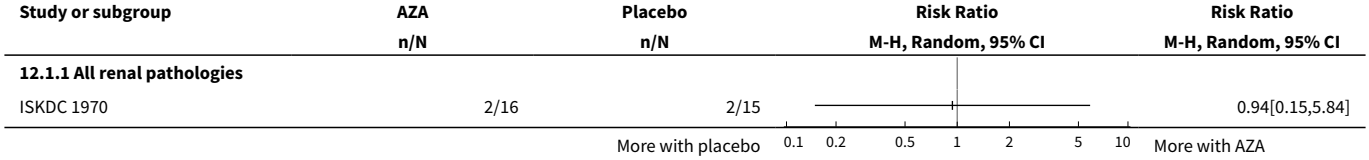




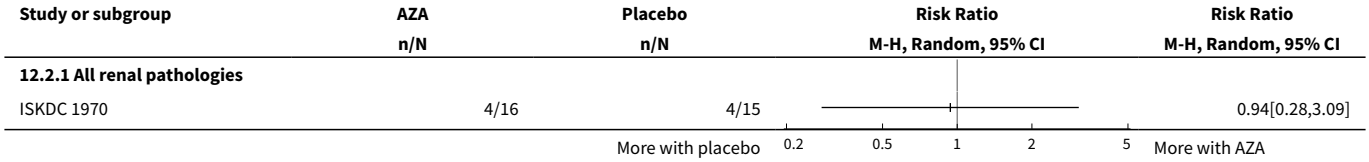
Comparison 12. Azathioprine (AZA) versus placebo

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 (AZA) versus placebo, Outcome 1 Complete remission.



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



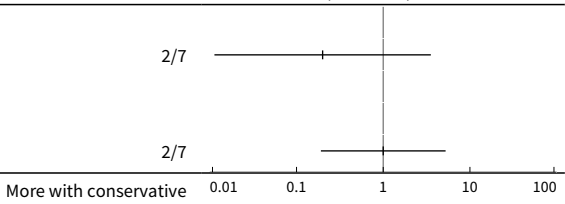
Comparison 13. Adalimumab or galactose (ADA/GAL) versus conservative therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number with reduction in proteinuria & stable GFR	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Adalimumab versus conservative therapy	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
1.2 Galactose versus conservative therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 13.1. Comparison 13 Adalimumab or galactose (ADA/GAL) versus conservative therapy, Outcome 1 Number with reduction in proteinuria & stable GFR.

Study or subgroup	ADA/GAL n/N	Conservative n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
13.1.1 Adalimumab versus conservative therapy				
FONT II 2011	0/7	2/7		0.2[0.01,3.54]
13.1.2 Galactose versus conservative therapy				
FONT II 2011	2/7	2/7		1[0.19,5.24]



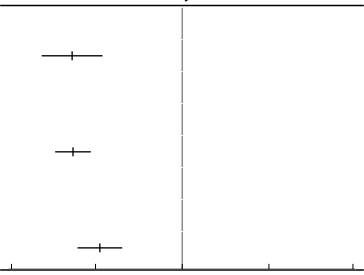
Comparison 14. Fosinopril plus prednisone versus prednisone alone

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

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
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

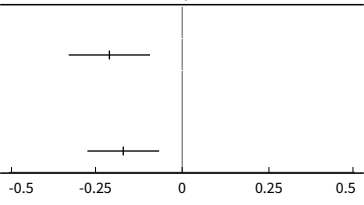
Analysis 14.1. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 1 Proteinuria.

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



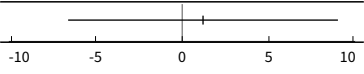
Analysis 14.2. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 2 Tubular proteinuria.

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



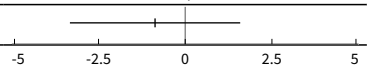
Analysis 14.3. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 3 Serum albumin.

Study or subgroup	Fos+pred N	Fos+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]



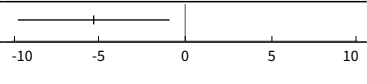
Analysis 14.4. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 4 Systolic blood pressure.

Study or subgroup	Fos+pred N	Fos+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]



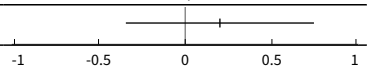
Analysis 14.5. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 5 Creatinine clearance.

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



Analysis 14.6. Comparison 14 Fosinopril plus prednisone versus prednisone alone, Outcome 6 Serum potassium.

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



Comparison 15. Sparsentan versus irbesartan

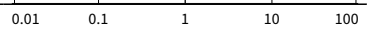
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Partial remission (> 40% reduction in UP/C) at 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Any treatment related adverse effect	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Serious adverse effect requiring study withdrawal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Peripheral oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 15.1. Comparison 15 Sparsentan versus irbesartan, Outcome 1 Partial remission (> 40% reduction in UP/C) at 8 weeks.

Study or subgroup	Sparsentan n/N	Irbesartan n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
DUET 2017	18/64	3/32		3[0.95,9.44]

Analysis 15.2. Comparison 15 Sparsentan versus irbesartan, Outcome 2 Adverse events.

Study or subgroup	Sparsentan n/N	Irbesartan n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
15.2.1 Any treatment related adverse effect				
DUET 2017	32/73	13/36		1.21[0.73,2.01]
15.2.2 Serious adverse effect requiring study withdrawal				
DUET 2017	2/73	1/36		0.99[0.09,10.52]
15.2.3 Hypotension				
DUET 2017	12/73	3/36		1.97[0.59,6.55]
15.2.4 Peripheral oedema				
DUET 2017	9/73	1/36		4.44[0.58,33.69]
15.2.5 Hyperkalaemia				
DUET 2017	1/73	2/36		0.25[0.02,2.63]



APPENDICES

Appendix 1. Electronic search strategies

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.

(Continued)

	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

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	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.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*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).
	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.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is 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.
	High risk of bias: No blinding or incomplete blinding, and the outcome 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, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement

(Continued)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*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 standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	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
Selective reporting Reporting bias due to selective outcome reporting	*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).
	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. sub-scales) 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
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	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 assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
9 October 2019	New citation required but conclusions have not changed	New studies and interventions added
9 October 2019	New search has been performed	New search, new interventions included; types of participants extended to include "Children with disease-causing genetic mutations associated with FSGS in whom a biopsy is not performed"

HISTORY

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

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

DECLARATIONS OF INTEREST

- Isaac Liu: none known
- Narelle Willis: none known
- Jonathan Craig: none known
- Elisabeth Hodson: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHMRC, Australia.

  Cochrane Kidney and Transplant is supported in part by NHMRC grants

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Summary of findings tables have been incorporated into the 2016 update.

NOTES

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

2016: Summary of findings tables have been incorporated

2019: GRADE has been used to assess and report certainty in this 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