DATA SUPPLEMENT

Appendix A. Search strategies

Table S1. Search strategies for systematic review topics

Search dates: May 2018; updated search June 2020, updated search April 19, 2023

Guideline chapter	Nephrotic syndrome in children
Clinical question	Glucocorticoid therapy for nephrotic syndrome in children
Search strategy - CENTRAL	1. MeSH descriptor: [Nephrotic Syndrome] this term only 2. MeSH descriptor: [Nephrosis, Lipoid] this term only 3. "nephrotic syndrome":ti,ab,kw 4. "lipoid nephrosis":ti,ab,kw 5. #1 or #2 or #3 or #4 6. child* or infant*:ti,ab,kw 7. boy* or girl*:ti,ab,kw 8. pediatric* or paediatric*:ti,ab,kw 9. #6 or #7 or #8 10. #5 and #9
Search strategy - MEDLINE	1. nephrotic syndrome/ 2. nephrosis, lipoid/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-4 6. exp child/ 7. exp Infant/ 8. child$.tw. 9. infant$.tw. 10. (boy$ or girl$).tw. 11. (pediatric or paediatric).tw. 12. or/7-12 13. and/5,12 14. randomised controlled trial.pt. 15. controlled clinical trial.pt. 16. randomized.ab. 17. placebo.ab. 18. clinical trials as topic/ 19. randomly.ab. 20. (crossover or cross-over).tw. 21. Cross-over Studies/ 22. trial.ti. 23. or/14-22 24. animals/ not (humans/ and animals/) 25. 13 and 23 26. 25 not 24
Search strategy - Embase	1. nephrotic syndrome/ 2. lipoid nephrosis/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-4 6. exp Child/ 7. child$.tw. 8. infant$.tw. 9. (boy$ or girl$).tw. 10. (pediatric or paediatric).tw

	11. or/6-10 12. and/5,11 13. randomised controlled trial/ 14. crossover procedure/ 15. double-blind procedure/ 16. single-blind procedure/ 17. random$.tw. 18. factorial$.tw. 19. crossover$ or cross-over$).tw. 20. placebo$.tw. 21. (double$ adj blind$).tw. 22. (singl$ adj blind$).tw. 23. assign$.tw. 24. allocat$.tw. 25. volunteer$.tw. 26. or/13-25 27. 12 and 26
Systematic review topic	Non-glucocorticoid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children
Search strategy - CENTRAL	1. “nephrotic syndrome”:ti,ab,kw 2. (lipoid next nephrosis):ti,ab,kw 3. #1 or #2
Search strategy - MEDLINE	1. nephrotic syndrome/ 2. nephrosis, lipoid/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-3 6. (exp Adult/ not (exp Aged/ and exp Child/ or exp Infant/ or exp Adolescent/)) 7. 5 not 6 8. (child* or infant* or babies* or boy* or girl* or pediatric* or paediatric* or adolescen*) 9. and/5,8 10. or/7,9 11. randomised controlled trial.pt. 12. controlled clinical trial.pt. 13. randomized.ab. 14. placebo.ab. 15. clinical trials as topic/ 16. randomly.ab. 17. (crossover or cross-over).tw. 18. Cross-over Studies/ 19. trial.ti. 20. or/11-19 21. animals/ not (humans/ and animals/) 22. 9 and 20 23. 22 not 21
Search strategy - Embase	1. Nephrotic Syndrome/ 2. Lipoid Nephrosis/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. or/1-4 6. ((Adult/ or Middle Aged/ or exp Aged/) not ((Adult/ or Middle Aged/ or exp Aged/) and (exp Child or exp/Adolescent))

	7. 5 not 6 8. (child* or infant* or babies* or boy* or girl* or pediatric* or paediatric* or adolescen*) 9. and/5,8 10. or/7,9 11. randomised controlled trial/ 12. crossover procedure/ 13. double-blind procedure/ 14. single-blind procedure/ 15. random$.tw. 16. factorial$.tw. 17. crossover$ or cross-over$).tw. 18. placebo$.tw. 19. (double$ adj blind$).tw. 20. (singl$ adj blind$).tw. 21. assign$.tw. 22. allocat$.tw. 23. volunteer$.tw. 24. or/12-24 25. 10 and 24
Systematic review topic	Interventions for steroid-resistant nephrotic syndrome in children
Search strategy - 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}
Search strategy - MEDLINE	1. Nephrotic Syndrome/ 2. Nephrosis Lipoid/ 3. nephrotic syndrome.tw. 4. lipoid nephrosis.tw. 5. minimal change glomerulonephritis.tw. 6. minimal change nephr$.tw. 7. idiopathic steroid resistant nephrotic syndrome.tw. 8. or/1-7 9. randomised controlled trial.pt. 10. controlled clinical trial.pt. 11. randomized.ab. 12. placebo.ab. 13. clinical trials as topic/ 14. randomly.ab. 15. (crossover or cross-over).tw. 16. Cross-over Studies/ 17. trial.ti. 18. or/9-17 19. animals/ not (humans/ and animals/)

	20. 8 and 18 21. 20 not 19
Search strategy - 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 9. randomised controlled trial/ 10. crossover procedure/ 11. double-blind procedure/ 12. single-blind procedure/ 13. random$.tw. 14. factorial$.tw. 15. crossover$ or cross-over$).tw. 16. placebo$.tw. 17. (double$ adj blind$).tw. 18. (singl$ adj blind$).tw. 19. assign$.tw. 20. allocat$.tw. 21. volunteer$.tw. 22. or/9-21 23. 8 and 22

Appendix B. Concurrence with Institute of Medicine (IOM) standards for guideline development

Table S2. Guideline development checklist - IOM standards for development of trustworthy clinical practice guidelines (1)

IOM Standard	Description	Addressed in 2020 KDIGO BP in CKD guideline
Establishing transparency	Clear description on the process of guideline development.	See *Methods for Guideline Development*
Management of conflicts of interests	Disclosure of a comprehensive conflict of interests of the Work Group against a set-criteria and a clear strategy to manage conflicts of interests	See *Work Group Financial Disclosures*
Guideline group composition and guideline development	Appropriate clinical and methodological expertise in the Work Group The processes of guideline development are transparent and allow for involvement of all Work Group Members	For guideline group composition – see *Work Group Membership* For guideline development process see *Methods for Guideline Development*
Establishing evidence foundations for rating strength of recommendations	Rationale is provided for the rating the strength of the recommendation and the transparency for the rating the quality of the evidence.	See *Methods for Guideline Development*
Articulation of recommendations	Clear and standardized wording of recommendations	All recommendations were written to standards of GRADE and were actionable statements. Please see *Methods for Guideline Development*
External review	An external review of relevant experts and stakeholders was conducted. All comments received from external review are considered for finalization of the guideline.	An external public review was undertaken in January – May 2020.
Updating	An update for the guidelines is planned, with a provisional timeframe provided.	The KDIGO clinical practice guideline will be updated. However, no set timeframe has been provided.

Table S3. Adapted systematic review reporting standards checklist - IOM standards for systematic reviews (2)

Appropriate IOM systematic review standards*	Addressed in 2020 KDIGO diabetes in CKD guideline
Methods	
Include a research protocol with appropriate eligibility criteria (PICO format)	See *Table 4 clinical question and systematic review topics in PICO format*
Include a search strategy	See *Appendix A*
Include a study selection and data extraction process	See guideline development process see *Methods for Guideline Development – Literature searching and article selection, data extraction*
Methods on critical appraisal	See *Methods for Guideline Development – Critical appraisal of studies*
Methods of synthesize of the evidence	See *Methods for Guideline Development – Evidence synthesis and meta-analysis*
Results	
Study selection processes	See *Methods for Guideline Development – Figure MC1 – Search yield and study flow diagram*
Appraisal of individual studies quality	The summary of findings tables in Appendix C & D provide an assessment of risk of bias for all studies in a comparison between intervention and comparator.
Meta-analysis results	See *Appendix C & D* for summary of findings tables for meta-analysis results for all critical and important outcomes
Table and figures	See *Appendix C & D* for summary of findings tables

References

1. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Graham R, Mancher M, editors. National Academies Press Washington, DC; 2011.
2. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness R. In: Eden J, Levit L, Berg A, Morton S, editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved; 2011.

Appendix C. Data supplement - Summary of findings (SoF) tables cited in the guideline text
Steroid-sensitive nephrotic syndrome in children

Table S4.
Population: First episode of nephrotic syndrome in children
Intervention: Glucocorticoid therapy of 12 weeks or more duration
Comparator: Glucocorticoid therapy of 8 weeks duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Glucocorticoid therapy of 8 weeks	Glucocorticoid therapy of ≥12 weeks	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Infection	Relative risk: 0.87 (95% CI: 0.62 - 1.22) Based on data from 265 patients in 3 studies[1] Follow up 18 months (mean)	**342** per 1000	**298** per 1000 Difference: **44 fewer per 1000** (95% CI: 130 fewer - 75 more)	**Low** Due to very serious risk of bias[2]	Compared with 8 weeks, ≥12 weeks of glucocorticoid therapy may have little or no difference on infection
Glucocorticoid-related adverse events - Ophthalmological disorders	Relative risk: 0.53 (95% CI: 0.16 - 1.77) Based on data from 695 patients in 7 studies[3] Follow up 19 months (mean)	**38** per 1000	**20** per 1000 Difference: **18 fewer per 1000** (95% CI: 32 fewer - 29 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[4]	We are uncertain whether ≥12 weeks of glucocorticoid therapy increases or decreases ophthalmological disorders

Glucocorticoid-related adverse events - Retarded growth	Relative risk: 0.54 (95% CI: 0.25 - 1.18) Based on data from 354 patients in 4 studies[5] Follow up 21 months (mean)	**112** per 1000 **60** per 1000 Difference: **52 fewer per 1000** (95% CI: 84 fewer - 20 more)	**Low** Due to very serious risk of bias[6]	Compared with 8 weeks, ≥12 weeks of glucocorticoid therapy may have little or no difference on retarded growth
Glucocorticoid-related adverse events - Cushing's syndrome	Relative risk: 1.17 (95% CI: 0.9 - 1.54) Based on data from 640 patients in 6 studies[7] Follow up 20.5 months (mean)	**276** per 1000 **356** per 1000 Difference: **80 more per 1000** (95% CI: 36 fewer - 248 more)	**Moderate** Due to serious risk of bias[8]	Compared with 8 weeks, ≥12 weeks of glucocorticoid therapy probably makes little or no difference on Cushing's syndrome
Glucocorticoid-related adverse events - Osteoporosis	Relative risk: 0.47 (95% CI: 0.06 - 3.38) Based on data from 233 patients in 3 studies[9] Follow up 20 months (mean)	**45** per 1000 **21** per 1000 Difference: **24 fewer per 1000** (95% CI: 42 fewer - 107 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether ≥12 weeks of glucocorticoid therapy increases or decreases osteoporosis
Relapse 12-24 months	Relative risk: 0.79 (95% CI: 0.65 - 0.95) Based on data from 1108 patients in 11 studies[11] Follow up 18 months (mean)	**701** per 1000 **554** per 1000 Difference: **147 fewer per 1000** (95% CI: 245 fewer - 35 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[12]	Glucocorticoids therapy ≥12 weeks may decrease relapse
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Frequent relapses 12-24 months	Relative risk: 0.79 (95% CI: 0.59 - 1.06) Based on data from 805 patients in 7 studies[13] Follow up 19.7 months (mean)	**396** per 1000 **313** per 1000 Difference: **83 fewer per 1000** (95% CI: 162 fewer - 24 more)	**Moderate** Due to serious risk of bias[14]	Glucocorticoids therapy ≥12 weeks may make little or no difference to frequents relapses
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [352] with included studies: [258], [267], [266] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up.
3. Systematic review [352] with included studies: [249], [246], [255], [331], [258], [267], [275] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Wide confidence intervals.
5. Systematic review [352] with included studies: [258], [246], [249], [255] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Very Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up.
7. Systematic review [352] with included studies: [331], [258], [246], [249], [267], [265] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Selective outcome reporting.
9. Systematic review [352] with included studies: [258], [275], [249] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, due to few events.
11. Systematic review [352] with included studies: [255], [331], [276], [249], [279], [258], [265], [270], [266], [275], [246] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:72%.
13. Systematic review [352] with included studies: [246], [255], [275], [249], [331], [266], [279] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

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Table S5.
Population: Children with nephrotic syndrome and upper respiratory infection
Intervention: Prednisolone 15 mg/m^2 daily (max 40 mg)
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo Prednisolone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies for looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies looked at ≥50% GFR loss
Infection	(95% CI -)	Difference:		No studies looked at infection
Malignancy	(95% CI -)	Difference:		No studies looked at malignancy
Complete remission	(95% CI -)	Difference:		No studies looked at complete remission
Relapse (any cause)	Relative risk: 0.77 (95% CI 0.45 - 1.32) Based on data from 264 patients in 1 study[1] Follow up 12 months	**742** per 1000 **689** per 1000 Difference: **53 fewer per 1000** (95% CI 162 fewer - 56 more)	**Low** Due to very serious imprecision[2]	Prednisolone compared with placebo may have little or no difference on relapse from any cause
Relapse with infection	Relative risk: 0.97 (95% CI 0.73 - 1.27) Based on data from 262 patients in 1 study[3]	**443** per 1000 **427** per 1000 Difference: **15 fewer per 1000**	**Low** Due to very serious imprecision[4]	Prednisolone compared with placebo may have little or no difference

	Follow up 12 months	(95% CI 135 fewer - 105 more)		on relapse with infection
Annual GFR loss 3 years	(95% CI -)	Difference:		No studies looked at complete remission

1. Primary study [Christian 2021 PubMed 33168602] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: No serious. Imprecision: Very serious.** Only data from one study, wide confidence interval;
3. Primary study [Christian 2021 PubMed 33168602] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: No serious. Imprecision: Very serious.** Only data from one study, wide confidence interval;

References

[Christian 2021 PubMed 33168602] Christian, M. T.; Webb, N. J. A.; Mehta, S.; Woolley, R. L.; Afentou, N.; Frew, E.; Brettell, E. A.; Khan, A. R.; Milford, D. V.; Bockenhauer, D.; Saleem, M. A.; Hall, A. S.; Koziell, A.; Maxwell, H.; Hegde, S.; Prajapati, H.; Gilbert, R. D.; Jones, C.; McKeever, K.; Cook, W.; Ives, N.. Evaluation of Daily Low-Dose Prednisolone During Upper Respiratory Tract Infection to Prevent Relapse in Children With Relapsing Steroid-Sensitive Nephrotic Syndrome: The PREDNOS 2 Randomized Clinical Trial. JAMA Pediatrics 2021. [PubMed: 33168602]

Table S6.
Population: Children with nephrotic syndrome and viral infections
Intervention: Daily prednisolone
Comparator: Alternate-day prednisolone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alternate-day prednisolone	Daily prednisolone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies for looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies looked at infection
Malignancy	(95% CI: -)	Difference:			No studies looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies looked at complete remission
Relapse with infection	Relative risk: 0.49 (95% CI: 0.18 - 1.3) Based on data from 40 patients in 1 study[1] Follow up until child had two upper respiratory tract infections	**455** per 1000	**223** per 1000 Difference: **232 fewer per 1000** (95% CI: 373 fewer - 137 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Daily prednisolone compared with placebo may have little or no difference on relapse with infection

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies looked at annual GFR loss
Rate of infection-related relapse[3]	Measured by: relapse/patient/year Scale: - Lower better Based on data from 95 patients in 1 study[4] Follow up 12 months	Mean Mean Difference: **MD 3.3 lower** (95% CI: 4.03 lower - 2.57 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Daily prednisolone compared with alternate day prednisolone may decrease rate of relapse <u>at 1 year</u>
Rate of infection-related relapse[6]	Measured by: relapses/patient/year Scale: - Lower better Based on data from 36 patients in 1 study[7] Follow up 24 months	Mean Mean Difference: **MD 3.3 lower** (95% CI: 4.03 lower - 2.57 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Daily prednisolone compared with alternate day prednisolone may decrease rate of relapse <u>at 2 years</u>

1. Primary study [239] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up (8/48 excluded from study (17%) for need for additional immunosuppression (4), no second viral infection (3), number without further relapses (1)), Selective outcome reporting (Not all the review's pre-specified outcomes were recorded; no mention of adverse events); **Imprecision: Serious.** Low number of patients, Only data from one study, due to few events.
3. (Number of relapses/patients at 1 year)
4. Primary study [251] **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Only data from one study.
6. (Number of relapses/patients at 2 years)
7. Primary study [262] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study.

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Table S7.
Population: Children with frequently relapsing steroid-sensitive nephrotic syndrome
Intervention: Alkylating agents
Comparator: Glucocorticoids, placebo, or both

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Glucocorticoids or placebo or both	 Alkylating agents	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at malignancy
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Relapse - Cyclophosphamide versus prednisone 6-12 months	Relative risk: 0.47 (95% CI: 0.33 - 0.66) Based on data from 157 patients in 4 studies[1] Follow up 17.8 months (mean)	**713** per 1000	**335** per 1000 Difference: **378 fewer per 1000** (95% CI: 478 fewer - 242 fewer)	**Moderate** Due to serious risk of bias[2]	Cyclophosphamide probably decreases relapse at 6-12 months

Relapse - Chlorambucil versus prednisone or placebo 6-12 months	Relative risk: 0.19 (95% CI: 0.03 - 1.09) Based on data from 41 patients in 2 studies[3] Follow up 14.5 months (mean)	**850** per 1000 **161** per 1000 Difference: **689 fewer per 1000** (95% CI: 825 fewer - 77 more)	**Moderate** Due to serious risk of bias[4]	Chlorambucil probably has little or no difference on relapse at 6-12 months
Relapse - Cyclophosphamide versus prednisone 12-24 months	Relative risk: 0.21 (95% CI: 0.07 - 0.65) Based on data from 27 patients in 2 studies[5] Follow up 19 months (mean)	**929** per 1000 **195** per 1000 Difference: **734 fewer per 1000** (95% CI: 864 fewer - 325 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Cyclophosphamide may decrease relapse at 12-24 months
Relapse - Chlorambucil versus prednisone or placebo 12 months	Relative risk: 0.15 (95% CI: 0.02 - 0.95) Based on data from 32 patients in 2 studies[7] Follow up 19 months (mean)	**1000** per 1000 **150** per 1000 Difference: **850 fewer per 1000** (95% CI: 980 fewer - 50 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Chlorambucil may decrease relapse at 12 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [289], [297], [314], [294] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting.
3. Systematic review [333] with included studies: [303], [286] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up.
5. Systematic review [333] with included studies: [294], [297] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients.
7. Systematic review [333] with included studies: [303], [286] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Low number of patients.

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Table S8.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Levamisole
Comparator: Glucocorticoids or placebo or both, or no treatment

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Glucocorticoids or placebo or both, or no treatment	Levamisole	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 4-12 months	Relative risk: 0.52 (95% CI: 0.33 - 0.82) Based on data from 474 patients in 8 studies[1] Follow up 11.3 months (mean)	**764** per 1000	**397** per 1000 Difference: **367 fewer per 1000** (95% CI: 512 fewer - 138 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[2]	Levamisole may decrease relapse at 4-12 months

Relapse 6-12 months	Relative risk: 0.65 (95% CI: 0.48 - 0.88) Based on data from 462 patients in 8 studies[3] Follow up 11.3 months (mean)	**862** per 1000 **560** per 1000 Difference: **302 fewer per 1000** (95% CI: 448 fewer - 103 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[4]	Levamisole may decrease relapse at 6-12 months
Relapse - children with frequently relapsing nephrotic syndrome	Relative risk: 0.57 (95% CI: 0.33 - 0.98) Based on data from 31 patients in 1 study[5] Follow up 12 months	**882** per 1000 **503** per 1000 Difference: **379 fewer per 1000** (95% CI: 591 fewer - 18 fewer)	**Moderate** Due to serious imprecision[6]	Levamisole probably decreases relapse
Relapse - children with steroid-dependent nephrotic syndrome	Relative risk: 0.86 (95% CI: 0.67 - 1.1) Based on data from 68 patients in 1 study[7] Follow up 12 months	**844** per 1000 **726** per 1000 Difference: **118 fewer per 1000** (95% CI: 279 fewer - 84 more)	**Moderate** Due to serious imprecision[8]	Levamisole probably has little or no difference on relapse
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [326] with included studies: [298], [287], [296], [317], [311], [304], [283], [314] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 89%.
3. Primary study [298], [317], [283], [314], [296], [287], [311], [304] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 87%.
5. Systematic review [326] with included studies: [304] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** Only data from one study, Low number of patients.
7. Primary study [304] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Serious.** Only data from one study, Low number of patients.

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Table S9.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Mycophenolate mofetil
Comparator: Levamisole

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Levamisole	Mycophenolate mofetil	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Serious infection	Relative risk: 0.38 (95% CI: 0.08 - 1.92) Based on data from 149 patients in 1 study[1] Follow up 43 months (median)	**343** per 1000	**408** per 1000 Difference: **65 more per 1000** (95% CI: 75 fewer - 278 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil increases or decreases serious infection
Glucocorticoid-related adverse events	Relative risk: 0.48 (95% CI: 0.04 - 5.18) Based on data from 149 patients in 1 study[3] Follow up 43 months (median)	**28** per 1000	**13** per 1000 Difference: **15 fewer per 1000** (95% CI: 27 fewer - 117 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether mycophenolate mofetil improves or worsen glucocorticoid-related adverse events
Frequent relapse	Relative risk: 0.91 (95% CI: 0.64 - 1.28) Based on data from 149 patients in 1 study[5]	**493** per 1000	**449** per 1000 Difference: **44 fewer per 1000** (95% CI: 177 fewer - 138 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Mycophenolate mofetil may have little or no difference on infrequent relapse

	Follow up 43 months (median)			
Infrequent relapse	Relative risk: 0.88 (95% CI: 0.41 - 1.87) Based on data from 149 patients in 1 study[7] Follow up 43 months (median)	**165** per 1000 **145** per 1000 Difference: **20 fewer per 1000** (95% CI: 97 fewer - 144 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Mycophenolate mofetil may have little or no difference on infrequent relapse
Treatment failure	Relative risk: 0.32 (95% CI: 0.01 - 7.74) Based on data from 149 patients in 1 study[11] Follow up 43 months (median)	**14** per 1000 **4** per 1000 Difference: **10 fewer per 1000** (95% CI: 14 fewer - 94 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether mycophenolate mofetil increases or decreases treatment failure
Annual GFR loss	Measured by: Scale: - Lower better	Mean Mean Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
3. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
5. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study.
7. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study.
9. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study.
11. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.

13. Systematic review [326] with included studies: [329] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study.

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Table S10.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Cyclosporine and prednisone
Comparator: Prednisone alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone alone	Cyclosporine and prednisone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 0.33 (95% CI: 0.13 - 0.83) Based on data from 104 patients in 1 study[1] Follow up 24 months	**309** per 1000	**102** per 1000 Difference: **207 fewer per 1000** (95% CI: 269 fewer - 53 fewer)	**Low** Due to serious imprecision, Due to serious indirectness[2]	Cyclosporine and prednisone may decrease relapse
Relapse 12 months	Relative risk: 0.72 (95% CI: 0.46 - 1.13)	**509** per 1000	**366** per 1000	**Low**	Cyclosporine and prednisone may have

	Based on data from 104 patients in 1 study[3] Follow up 24 months	Difference: **143 fewer per 1000** (95% CI: 275 fewer - 66 more) Difference: **MD 2 higher** (95% CI: 2.44 lower - 6.44 higher)	Due to serious imprecision, Due to serious indirectness[4]	little or no difference on relapse at 12 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [306] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: Serious.** Unclear how many participants with FRNS and SDNS; **Imprecision: Serious.** Only data from one study, Low number of patients.
3. Primary study [306] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, unclear blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: Serious.** Unclear how many participants with FRNS and SDNS; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients.
5. Primary study [306] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients.

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Table S11.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Rituximab
Comparator: Placebo or prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or prednisone / Rituximab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.9 (95% CI: 0.26 - 3.15) Based on data from 222 patients in 3 studies[1] Follow up 12 months (mean)	**181** per 1000 / **163** per 1000 Difference: **18 fewer per 1000** (95% CI: 134 fewer - 389 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether rituximab increases or decreases infections
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Relapse 3 months	Relative risk: 0.32 (95% CI: 0.14 - 0.70) Based on data from 132 patients in 3 studies[3] Follow up 3 months (mean)	**530** per 1000 / **170** per 1000 Difference: **360 fewer per 1000** (95% CI: 456 fewer - 159 fewer)	**Moderate** Due to serious risk of bias[4]	Rituximab probably decreases relapse at 3 months

Relapse 6 months	Relative risk: 0.23 (95% CI: 0.12 - 0.43) Based on data from 271 patients in 5 studies[5] Follow up 6 months (mean)	**540** per 1000 **124** per 1000 Difference: **416 fewer per 1000** (95% CI: 475 fewer - 308 fewer)	**Moderate** Due to serious risk of bias[6]	Rituximab probably decreases relapse at 6 months
Relapse 12 months	Relative risk: 0.38 (95% CI: 0.13 - 1.09) Based on data from 108 patients in 3 studies[7] Follow up 12 months (mean)	**974** per 1000 **526** per 1000 Difference: **448 fewer per 1000** (95% CI: 740 fewer – 205 more)	**Low** Due to serious risk of bias; Due to serious imprecision[8]	Rituximab may decrease relapse at 12 months.
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [90], [86] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, due to few events;
3. Systematic review with included studies: [91], [90], [86] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting;
5. Systematic review with included studies: [91], [86], [73], [66] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting
7. Systematic review with included studies: [91], [86], [Ravani 2020a] **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Large effect size, but nonsignificant;

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Table S12.
Population: Children with frequently relapsing (or steroid-dependent) nephrotic syndrome
Intervention: Prednisone 40 mg/m^2 on alternate days x 18 (36 days)
Comparator: Prednisone 40 mg/m^2 tapered over 72 days (same cumulative dose)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisone 72 days	Prednisone 36 days	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked at kidney failure
> 50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at >50% GFR loss
Infection	Relative risk: 2.11 (95% CI 0.41 – 10.83) Based on data from 78 patients in 1 study[1] Follow up 12 months	**50** infections per 1000 patients	**105** infections per 1000 patients Difference: 55 **more** infections per 1000 patients (170 fewer to 60 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether short course prednisone makes a difference in infection
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:			No studies were found that looked at malignancy
Time to remission	Measured by: days Scale: shorter better Based on data from 111 patients in 1 study[3]	**6 days** Mean	**5 days** Mean Difference: **MD 1 day shorter** (95% CI 2.5 fewer – 0.5 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether short course prednisone makes a difference in time to remission

	Follow up 12 months			
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked annual GFR loss
Relapse 6 months	Relative risk: 0.73 (95% CI 0.46 – 1.16) Based on data from 78 patients in 1 study[5] Follow up 12 months	**575** per 1000 **421** per 1000 Difference:**154 fewer per 1000** (95% CI 371 fewer - 63 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Short course prednisone may have little or no effect on relapse

1. Systematic review with included studies: [Gargiulo 2021 PubMed 33152448] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very serious.** Only data from one study, very wide confidence interval.
3. Systematic review with included studies: [Gargiulo 2021 PubMed 33152448] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very serious.** Only data from one study, wide confidence interval.

References

[Gargiulo 2021 PubMed 33152448] Gargiulo, A.; Massella, L.; Ruggiero, B.; et al.. Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children. Kidney Int 2021;99:475-483. [PubMed: 33152448]

Table S13.
Population: Children with relapsing nephrotic syndrome
Intervention: Prednisolone through 2 weeks after remission (40 mg/m^2 on alternate days)
Comparator: Prednisolone through 4 weeks after remission (40 mg/m^2 on alternate days)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone 4 weeks post-remission	Prednisolone 2 weeks post-remission	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked at kidney failure
> 50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at >50% GFR loss
Infection (Respiratory tract)	Relative risk: Not estimable (95% CI -) P = 0.21 Based on data from 114 patients in 1 study[1] Follow up 12 months	**1150** infections per 1000 patients	**741** infections per 1000 patients Difference: 409 **fewer** infections per 1000 patients (CI not estimable)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Prednisolone continuing 2 weeks after remission may have little or no effect on respiratory infections
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:			No studies were found that looked at malignancy
Time to relapse	Measured by: Scale: - Higher better Based on data from 111 patients in 1 study[3] Follow up 12 months	**104 days** Mean	**78 days** Mean Difference: **MD 26 days shorter** (95% CI: 65 lower – 13 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Prednisolone continuing 2 weeks after remission may have little or no effect on relapse
Annual GFR loss 3 years	Measured by: Scale: - Lower better				

		Difference: **lower**		No studies were found that looked annual GFR loss
Relapse, frequent	Relative risk: 0.96 (95% CI: 0.40 – 2.33) Based on data from 111 patients in 1 study[5] Follow up 12 months	**237** per 1000 **231** per 1000 Difference: **6 fewer per 1000** (95% CI: 160 fewer - 150 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether prednisolone continuing 2 weeks after remission makes a difference in rate of frequent relapses

1. Systematic review with included studies: [Kainth 2021 PubMed 33478976] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Only data from one study, 100% in both groups; events, not number of affected patients reported.
3. Systematic review with included studies: [Kainth 2021 PubMed 33478976] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Only data from one study;
5. Systematic review with included studies: [Kainth 2021 PubMed 33478976] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Only data from one study, very wide confidence interval;

References

[Kainth 2021 PubMed 33478976] Kainth, D.; Hari, P.; Sinha, A.; Pandey, S.; Bagga, A.. Short-Duration Prednisolone in Children with Nephrotic Syndrome Relapse: A Noninferiority Randomized Controlled Trial. Clin J Am Soc Nephrol 2021;16:225–232. [PubMed: 33478976]

Table 14.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Ofatumumab
Comparator: Rituximab

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Rituximab Ofatumumab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies were found that looked at ≥50% GFR loss
Serious adverse events	Relative risk: Not estimable (95% CI -) Based on data from 140 patients in 1 study[1] Follow up 6 months	**0** per 1000 **0** per 1000 Difference: **0 more per 1000** (95% CI: 30 fewer - 30 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether ofatumumab compared with rituximab increases or decreases serious adverse events
Malignancy	(95% CI -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:		No studies were found that looked at malignancy
Relapse 12 months	Relative risk: 1.03 (95% CI: 0.75 – 1.41) Based on data from 140 patients in 1 study[3] Follow up 12 months	**514** per 1000 **529** per 1000 Difference: **15 more per 1000** (95% CI: 150 fewer - 180 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Ofatumumab compared with rituximab may have little or no effect on relapse at 12 months
Relapse 24 months	Relative risk: 1.15 (95% CI: 0.93 – 1.43)	**657** per 1000 **757** per 1000	**Low**	Ofatumumab compared with

	Based on data from 140 patients in 1 study [5] Follow up 24 months	Difference: **100 more per 1000** (95% CI: 50 fewer – 250 more)	Due to serious risk of bias, Due to serious imprecision[6]	rituximab may have little or no effect on relapse at 24 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Ravani 2021a PMID 34544820] B**aseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Only one study; no events;
3. Systematic review with included studies: [Ravani 2021a PMID 34544820] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study
5. Systematic review with included studies: [Ravani 2021a PMID 34544820] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study

References

[Ravani 2021a PMID 34544820] Ravani, P.; Colucci, M.; Bruschi, M.; Vivarelli, M.; Cioni, M.; DiDonato, A.; Cravedi, P.; Lugani, F.; Antonini, F.; Prunotto, M.; et al.. Human or Chimeric Monoclonal Anti-CD20 Antibodies for Children with Nephrotic Syndrome: a Superiority Randomized Trial. Journal of the American Society of Nephrology : JASN 2021;32:2652–2663. [PubMed: 34544820]

Table S14.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Mycophenolate mofetil (MMF) x 17 months after rituximab treatment
Comparator: Placebo x 17 months after rituximab treatment

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo MMF	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies were found that looked at ≥50% GFR loss
Serious adverse events	Relative risk: 0.80 (95% CI: 0.54 - 1.18) Based on data from 78 patients in 1 study[1] Follow up 17 months	**641** per 1000 **513** per 1000 Difference: **128 fewer per 1000** (95% CI: 350 fewer - 90 more)	**Low** Due to serious imprecision[2]	MMF may have little or no effect on grade 3 or 4 adverse events
Malignancy	(95% CI -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:		No studies were found that looked at malignancy
Relapse rate	Hazard ratio: 0.26 (95% CI: 0.08 – 0.48) Scale: - Lower better Based on data from 78 patients in 1 study[3] Follow up 17 months	**1.99** per person-year **0.43** per person-year Mean difference: **1.56 less** (95% CI: 2.36 less- 0.76 less)	**Moderate** Due to serious imprecision, upgraded for large effect size[4]	MMF probably reduces the relapse rate
Time to relapse	Hazard ratio: 0.62	**320 days** (median) **654 days** (median)	**Low**	MMF may increase time to relapse

	(95% CI: 0.37 – 1.04) Scale: - Higher better Based on data from 78 patients in 1 study[3] Follow up 17 months	Median difference: **334 days longer** (95% CI -)	Due to serious imprecision[4]	
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Annual GFR loss 3 years		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Iijima 2022 PMID 34880074] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: No serious.** No bias issues; **Imprecision: Serious.** Only one study.
3. Systematic review with included studies: [Iijima 2022 PMID 34880074] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: No serious.** No bias issues; **Imprecision: Serious.** Only one study. **Large magnitude:** Upgraded for large effect size.
5. Systematic review with included studies: [Iijima 2022 PMID 34880074] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: No serious.** No bias issues; **Imprecision: Serious.** Only one study; moderately large effect size, but not statistically significant.

References

[Iijima 2022 PMID 34880074] Iijima, K.; Sako, M.; Oba, M.; Tanaka, S.; Hamada, R.; Sakai, T.; Ohwada, Y.; Ninchoji, T.; Yamamura, T.; Machida, H.; Shima, Y.; Tanaka, R.; Kaito, H.; Araki, Y.; Morohashi, T.; Kumagai, N.; Gotoh, Y.; Ikezumi, Y.; Kubota, T.; Kamei, K.; Fujita, N.; Ohtsuka, Y.; Okamoto, T.; Yamada, T.; Tanaka, E.; Shimizu, M.; Horinouchi, T.; Konishi, A.; Omori, T.; Nakanishi, K.; Ishikura, K.; Ito, S.; Nakamura, H.; Nozu, K.. Mycophenolate Mofetil after Rituximab for Childhood-Onset Complicated Frequently-Relapsing or Steroid-Dependent Nephrotic Syndrome. J Am Soc Nephrol 2022;33:401–419. [PubMed: 34880074]

Steroid-resistant nephrotic syndrome in children

Table S16.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Cyclosporine
Comparator: Placebo or no treatment

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or no treatment	Cyclosporine	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference: **fewer**			No studies were found that looked at kidney failure
Infection	Relative risk: 0.7 (95% CI: 0.2 - 2.51) Based on data from 17 patients in 1 study[1] Follow up 12 months	**429** per 1000	**300** per 1000 Difference: **129 fewer per 1000** (95% CI: 343 fewer - 648 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether cyclosporine increases or decreases infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 7.66 (95% CI: 1.06 - 55.34) Based on data from 49 patients in 3 studies[3] Follow up 7 months (mean)	**0** per 1000	**308** per 1000 Difference: **308 more per 1000** (95% CI: 130 more – 485 more)	**Moderate** Due to serious risk of bias[4]	Cyclosporine probably increases complete remission
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Annual GFR loss	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [351] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients.
3. Systematic review [364] with included studies: [339], [346], [351] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up, Selective outcome reporting.

References

[339] Garin EH, Orak JK, Hiott KL, Sutherland SE. Cyclosporine therapy for steroid-resistant nephrotic syndrome. A controlled study. American Journal of Diseases of Children 1988;142(9):985-988
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[351] Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney International 1993;43(6):1377-1384
[364] Liu ID, Willis NS, Craig JC et al. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews 2019; 11

Table S17.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Calcineurin inhibitors
Comparator: Intravenous cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Intravenous cyclophosphamide	Calcineurin inhibitors	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	Relative risk: 0.33 (95% CI: 0.01 - 7.92) Based on data from 131 patients in 1 study[1] Follow up 12 months	**16** per 1000	**5** per 1000 Difference: **11 fewer per 1000** (95% CI: 16 fewer - 111 more)	**Very Low** Due to very serious imprecision[2]	We are uncertain whether calcineurin inhibitors increases or decreases all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.49 (95% CI: 0.16 - 1.56) Based on data from 131 patients in 1 study[3] Follow up 12 months	**124** per 1000	**61** per 1000 Difference: **63 fewer per 1000** (95% CI: 104 fewer - 69 more)	**Low** Due to very serious imprecision[4]	Calcineurin inhibitors may have little or no difference on infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission 3-6 months	Relative risk: 3.43 (95% CI: 1.84 - 6.41) Based on data from 156 patients in 2 studies[5] Follow up 12 months (mean)	**129** per 1000	**442** per 1000 Difference: **313 more per 1000** (95% CI: 108 more - 698 more)	**Moderate** Due to serious risk of bias[6]	Calcineurin inhibitors probably increases complete remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [251] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Very wide confidence intervals, Only data from one study, Low number of patients.
3. Systematic review [364] with included studies [251] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Only data from one study, Low number of patients, Wide confidence intervals.
5. Systematic review [364] with included studies: [350], [361] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up with high risk of attrition bias.

References

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[361] Gulati A, Sinha A, Gupta A, Kanitkar M, Sreenivas V, Sharma J, Mantan M, Agarwal I, Dinda AK, Hari P, Bagga A. Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. Kidney International 2012;82(10):1130-1135
[364] Liu ID, Willis NS, Craig JC et al. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11)

Table S18.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Cyclosporine
Comparator: Mycophenolate mofetil with dexamethasone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Mycophenolate mofetil with dexamethasone	Cyclosporine	**Certainty of the evidence**	**Plain text summary**
All-cause mortality 12 months	Relative risk: 0.18 (95% CI: 0.01 - 3.75) Based on data from 138 patients in 1 study[1] Follow up 19.5 months	**31** per 1000	**6** per 1000 Difference: **25 fewer per 1000** (95% CI: 31 fewer - 85 more)	**Very Low** Due to serious imprecision[2]	We are uncertain whether cyclosporine increases or decreases all-cause mortality
Kidney failure	Relative risk: 4.58 (95% CI: 0.55 - 38.22) Based on data from 138 patients in 1 study[3] Follow up 19.5 months	**16** per 1000	**73** per 1000 Difference: **57 more per 1000** (95% CI: 7 fewer - 596 more)	**Very Low** Due to serious imprecision[4]	We are uncertain whether cyclosporine increases or decreases kidney failure
≥50% GFR loss	Relative risk: 2.29 (95% CI: 0.46 - 11.41) Based on data from 138 patients in 1 study[5] Follow up 19.5 months	**31** per 1000	**71** per 1000 Difference: **40 more per 1000** (95% CI: 17 fewer - 323 more)	**Very Low** Due to serious imprecision[6]	We are uncertain whether cyclosporine increases or decreases ≥50% GFR loss
Infections	Relative risk: 0.78 (95% CI: 0.5 - 1.22) Based on data from 138 patients in 1 study[7] Follow up 12 months	**410** per 1000	**320** per 1000 Difference: **90 fewer per 1000** (95% CI: 205 fewer - 320 fewer)	**Low** Due to serious imprecision[8]	Cyclosporine may have little or no difference on infections
Serious infection requiring hospitalization	Relative risk: 0.65 (95% CI: 0.22 - 1.96) Based on data from 138 patients in 1 study[9] Follow up 19.5 months	**107** per 1000	**70** per 1000 Difference: **37 fewer per 1000** (95% CI: 83 fewer - 103 more)	**Very Low** Due to serious imprecision[10]	Cyclosporine may have little or no difference serious infection requiring hospitalizations
Malignancy	(95% CI: -)				

		Difference:		No studies were found that looked at malignancy
Complete remission 6 months	Relative risk: 1.14 (95% CI: 0.64 - 2.03) Based on data from 41 patients in 1 study[11] Follow up 12 months	**500** per 1000 **570** per 1000 Difference: **70 more per 1000** (95% CI: 180 fewer - 515 more)	**Low** Due to serious imprecision[12]	Cyclosporine may have little or no difference on complete remission at 6 months
Complete remission 12 months	Relative risk: 0.8 (95% CI: 0.45 - 1.42) Based on data from 58 patients in 2 studies[13] Follow up 12 months (mean)	**500** per 1000 **400** per 1000 Difference: **100 fewer per 1000** (95% CI: 275 fewer - 210 more)	**Low** Due to serious imprecision[14]	Cyclosporine may have little or no difference on complete remission at 12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [340] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Serious.** Only data from one study, Very wide confidence interval.
3. Primary study [340] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Serious.** Only data from one study, Very wide confidence interval.
5. Primary study [340] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Serious.** Only data from one study, Very wide confidence interval.
7. Primary study [340] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Serious.** Only data from one study, Wide confidence interval.
9. Primary study [340] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Only data from one study, Very wide confidence interval.
11. Systematic review [359] with included studies: [337] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Serious.** Only data from one study, Wide confidence interval.
13. Primary study [337], [355] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Serious.** Only data from one study, Wide confidence interval.

References

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[364] Liu ID, Willis NS, Craig JC et al. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews 2019;2019(11)

Table S19.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Tacrolimus to maintain remission
Comparator: Mycophenolate mofetil to maintain remission

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Mycophenolate mofetil	Tacrolimus	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.27 (95% CI: 0.06 - 1.18) Based on data from 60 patients in 1 study[1] Follow up 12 months	**242** per 1000	**65** per 1000 Difference: **177 fewer per 1000** (95% CI: 227 fewer - 44 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Tacrolimus may have little or no difference on infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 1.79 (95% CI: 1.11 - 2.9) Based on data from 60 patients in 1 study[3] Follow up 12 months	**414** per 1000	**741** per 1000 Difference: **327 more per 1000** (95% CI: 46 more - 787 more)	**Low** Due to serious risk of bias, Due to serious imprecison[4]	Tacrolimus may increase complete remission
Frequent relapses	Relative risk: 0.28 (95% CI: 0.09 - 0.92) Based on data from 60 patients in 1 study[5] Follow up 12 months	**345** per 1000	**97** per 1000 Difference: **248 fewer per 1000** (95% CI: 314 fewer - 28 fewer)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded for large effect size[6]	Tacrolimus probably decreases frequent relapses
Annual GFR loss 12 months	Measured by: Scale: - Lower better	ml/min Mean	ml/min Mean	**Low** Due to serious risk of bias, Due to	Tacrolimus may have little or no difference on annual

	Based on data from 60 patients in 1 study[7] Follow up 12 months	Difference: **MD 13 higher** (95% CI: 3.71 lower - 29.71 higher)	serious imprecision[8]	GFR loss after 12 months

1. Systematic review [364] with included studies: [352] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study, Wide confidence interval.
3. Systematic review with included studies: [352] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study.
5. Systematic review [364] with included studies: [352] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study. **Upgraded** for large, statistically significant effect size.
7. Systematic review [364] with included studies: [352] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study, Low number of patients.

References

[352] Sinha A, Gupta A, Kalaivani M, Hari P, Dinda AK, Bagga A. Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome. Kidney International 2017;92(1):248-257

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Appendix D. Data supplement - Additional SoF tables developed as part of the evidence review

Steroid sensitive nephrotic syndrome in children

Table S20.

Population: First episode of nephrotic syndrome in children
Intervention: Glucocorticoid therapy of 1-month duration
Comparator: Glucocorticoid therapy of 2-month duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 2-month duration	1-month duration	**Certainty of the evidence**	**Plain text summary**
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Relapse 6 months	Relative risk: 1.6 (95% CI: 1.01 - 2.54) Based on data from 61 patients in 1 study[1]	**448** per 1000	**717** per 1000 Difference: **269 more per 1000** (95% CI: 4 more - 690 more)	**Low** Due to serious risk of bias, Due to serious imprecision, Due to serious risk of bias[2]	Glucocorticoid therapy for 1 month may increase relapse at 6 months in children with first episode steroid-

	Follow up 24 months			sensitive nephrotic syndrome
Relapse 12-24 months	Relative risk: 1.46 (95% CI: 1.01 - 2.12) Based on data from 60 patients in 1 study[3] Follow up 24 months	**552** per 1000 **806** per 1000 Difference: **254 more per 1000** (95% CI: 6 more - 618 more)	**Low** Due to very serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effect[4]	Glucocorticoid therapy for 1 month may increase relapse at 12 months in children with first episode steroid-sensitive nephrotic syndrome
Frequent relapses	Relative risk: 1.48 (95% CI: 0.85 - 2.59) Based on data from 61 patients in 1 studies[5] Follow up 24 months	**379** per 1000 **561** per 1000 Difference: **182 more per 1000** (95% CI: 57 fewer - 603 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether glucocorticoid therapy for 1 month compared to two months makes little or no difference in the frequent relapses
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [251] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up, Selective outcome reporting, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients;
3. Primary study [251] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients; **Upgrade: Large magnitude of effect.**
5. Primary study [251] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

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Table S21.
Population: First episode of nephrotic syndrome in children
Intervention: Glucocorticoid therapy of 12-month duration
Comparator: Glucocorticoid therapy of 5-month duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 5-month duration	12-month duration	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No study durations were found that looked at complete remission
Relapse	Relative risk: 0.76 (95% CI: 0.51 - 1.13) Based on data from 58 patients in 1 studies[1] Follow up 15 months	**724** per 1000	**550** per 1000 Difference: **174 fewer per 1000** (95% CI: 355 fewer - 94 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Glucocorticoid therapy for 12 months duration may have little or no difference on relapse
Annual GFR loss	Measured by: Scale: - Lower better				

		Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [326] with included studies: [258] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients

References

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Table S22.
Population: First episode of nephrotic syndrome in children
Intervention: Glucocorticoid therapy of 5- or 6-month duration (4 to 6 months in one study)
Comparator: Glucocorticoid therapy of 3-month duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 3-month duration	5- or 6-month duration	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.98 (95% CI: 0.65 - 1.46) Based on data from 702 patients in 5 studies[1] Follow up 19.8 months (mean)	**185** per 1000	**181** per 1000 Difference: **4 fewer per 1000** (95% CI: 65 fewer - 85 more)	**Low** Due to very serious risk of bias[2]	5- or 6-months glucocorticoid therapy duration may have little or no difference on infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Glucocorticoid-related adverse events - Cushingoid appearance	Relative risk: 0.86 (95% CI: 0.6 - 1.23) Based on data from 762 patients in 6 studies[3] Follow up 21 months (mean)	**375** per 1000	**323** per 1000 Difference: **52 fewer per 1000** (95% CI: 150 fewer - 86 more)	**Moderate** Due to serious risk of bias[4]	5- or 6-months glucocorticoid therapy duration probably has little or no difference on cushingoid appearance
Glucocorticoid-related adverse events - Eye complications	Relative risk: 0.46 (95% CI: 0.18 - 1.17)	**36** per 1000	**17** per 1000 Difference: **19 fewer per 1000**	**Moderate** Due to serious risk of bias[6]	5- or 6-months glucocorticoid therapy duration probably has little or

	Based on data from 614 patients in 5 studies[5] Follow up 22 months (mean)	(95% CI: 30 fewer - 6 more)		no difference to eye complications
Relapse 12-24 months	Relative risk: 0.64 (95% CI: 0.50 - 0.82) Based on data from 913 patients in 8 studies[7] Follow up 18.4 months (mean)	**743** per 1000 **476** per 1000 Difference: **267 fewer per 1000** (95% CI: 372 fewer - 134 fewer)	**Moderate** Due to serious risk of bias, [8]	4 to 6 months of glucocorticoid therapy duration probably decreases relapse
Frequent relapses 12-24 months	Relative risk: 0.73 (95% CI: 0.49 - 1.09) Based on data from 707 patients in 6 studies[9] Follow up 18.5 months (mean)	**386** per 1000 **282** per 1000 Difference: **104 fewer per 1000** (95% CI: 197 fewer - 35 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[10]	5- or 6-months glucocorticoid therapy duration may have little or no difference on frequent relapses
Frequent relapses - stratified by low risk of bias for allocation concealment 12-24 months	Relative risk: 1.0 (95% CI: 0.74 - 1.34) Based on data from 377 patients in 3 studies[11] Follow up 25 months (mean)	**438** per 1000 **438** per 1000 Difference: **0 fewer per 1000** (95% CI: 114 fewer - 149 more)	**High**	5- or 6-month glucocorticoid therapy duration makes little or no difference to frequent relapses
Frequent relapses - stratified by high or unclear risk of bias for allocation concealment 12-24 months	Relative risk: 0.48 (95% CI: 0.32 - 0.72) Based on data from 330 patients in 3 studies[12] Follow up 12 months (mean)	**327** per 1000 **157** per 1000 Difference: **170 fewer per 1000** (95% CI: 222 fewer - 92 fewer)	**Moderate** Due to serious risk of bias[13]	In studies of high or unclear risk of bias for allocation concealment, 5- or 6-months glucocorticoid therapy duration probably decreases frequent relapses
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [326] with included studies: [275], [259], [242], [274], [272] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up.
3. Systematic review [326] with included studies: [254], [242], [272], [275], [274], [259] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
5. Systematic review [326] with included studies: [274], [254], [275], [272], [259] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
7. Systematic review [326] with included studies: [264], [254], [272], [259], [275], [269], [274], [Jamshaid 2022 PMID 35576290] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Upgrade: Large magnitude of effect**.
9. Systematic review [326] with included studies: [254], [274], [272], [242], [264], [275] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 68%.
11. Systematic review [326] with included studies: [254], [275], [274] **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [326] with included studies: [264], [272], [242] **Baseline/comparator:** Control arm of reference used for intervention.
13. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias.

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Table S23.
Population: First episode of nephrotic syndrome in children
Intervention: Weight-based prednisolone (1.5 mg/kg [maximum 40 mg])
Comparator: Body-surface area–based dosing of prednisolone (40 mg/m^2)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** BSA-based dosing of prednisone (40 mg/m^2)	**Absolute effect estimates** Weight-based prednisolone (1.5 mg/kg [maximum 40 mg])	**Certainty of the evidence**	**Plain text summary**
Glucocorticoid-related adverse effects - Cushingoid features Follow up 6 months	Relative risk: 1.26 (95% CI: 0.61 - 2.59) Based on data from 84 patients in 1 study[1]	**233** per 1000	**294** per 1000 Difference: **61 more per 1000** (95% CI: 91 fewer - 370 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether weight-based (1.5 mg/kg (maximum 40 mg)) prednisone increases or decreases cushingoid features
Complete remission	(95% CI: -)		Difference:		No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 1.0 (95% CI: 0.66 - 1.53) Based on data from 86 patients in 1 study[3] Follow up 6 months	**500** per 1000	**500** per 1000 Difference: **0 fewer per 1000** (95% CI: 170 fewer - 265 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Weight-based prednisone (1.5 mg/kg (maximum 40 mg)) may have little or no difference on relapse at 6 months
All-cause mortality	(95% CI: -)		Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)		Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)		Difference:		No studies were found that looked at ≥50% GFR loss
Infections	Relative risk: 0.79 (95% CI: 0.19 - 3.3)	**93** per 1000	**73** per 1000	**Very Low**	We are uncertain whether weight-

	Based on data from 84 patients in 1 study[5] Follow up 6 months	Difference: **20 fewer per 1000** (95% CI: 75 fewer - 214 more)	Due to serious risk of bias, Due to very serious imprecision[6]	based (1.5 mg/kg (maximum 40 mg)) increases or decreases infections
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [270] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Primary study [270] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients;
5. Primary study [270] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

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Table S24.
Population: First episode of nephrotic syndrome in children
Intervention: Higher total dose (60 mg/m^2 per day [max 80 mg] for 6 weeks, 40 mg/m^2 on alternate days for 6 weeks) prednisone
Comparator: Lower total dose (40 mg/m^2 per day [max 60 mg] for 6 weeks, 40 mg/m^2 on alternate days for 6 weeks) prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Lower total dose prednisone	Higher total dose prednisone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Glucocorticoid-related adverse effects - Cushing's syndrome	Relative risk: 3.0 (95% CI: 0.9 - 10.01) Based on data from 60 patients in 1 study[1] Follow up 24 months	**100** per 1000	**300** per 1000 Difference: **200 more per 1000** (95% CI: 10 fewer - 901 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether higher total dose prednisone increases or decreases Cushing's syndrome
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission

Relapse 12 months	Relative risk: 0.63 (95% CI: 0.42 - 0.94) Based on data from 59 patients in 1 study[3] Follow up 24 months	**793** per 1000 **500** per 1000 Difference: **293 fewer per 1000** (95% CI: 460 fewer - 48 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Higher total dose of prednisone may decrease relapse at 12 months
Frequently relapsing nephrotic syndrome	Relative risk: 0.69 (95% CI: 0.35 - 1.37) Based on data from 60 patients in 1 study[5] Follow up 24 months	**433** per 1000 **299** per 1000 Difference: **134 fewer per 1000** (95% CI: 281 fewer - 160 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether higher total dose prednisone increases or decreases frequently relapsing nephrotic syndrome
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [253] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Only data from one study, Low number of patients, Wide confidence intervals
3. Primary study [253] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
5. Primary study [253] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

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Table S25.
Population: First episode of nephrotic syndrome in children
Intervention: Deflazacort
Comparator: Prednisolone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone Deflazacort	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:		No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission 6 weeks	Relative risk: 1.17 (95% CI: 0.9 - 1.53) Based on data from 25 patients in 1 study[1] Follow up 6 weeks	**846** per 1000 **990** per 1000 Difference: **144 more per 1000** (95% CI: 85 fewer - 448 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	We are uncertain whether deflazacort increases or decreases remission at 6 weeks
Relapse 9-12 months	Relative risk: 0.47 (95% CI: 0.28 - 0.79) Based on data from 65 patients in 2 studies[3] Follow up 9 months (mean)	**636** per 1000 **299** per 1000 Difference: **337 fewer per 1000** (95% CI: 458 fewer - 134 fewer)	**Moderate** Due to serious risk of bias[4]	Deflazacort probably decreases relapse at 9-12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked annual GFR loss

1. Primary study [273] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients, Only data from one study
3. Systematic review [326] with included studies: [273], [249] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: No serious.** Low number of patients, due to few patients with further relapse by 9-12 Months in one of the studies

References

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Table S26.
Population: First episode of nephrotic syndrome in children
Intervention: High-dose methylprednisolone
Comparator: Prednisolone (2 months of therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone (2-month of therapy)	High-dose methylprednisolone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at annual GFR loss
Time to remission	Measured by: days Scale: - Lower better Based on data from 38 patients in 2 studies	Days Mean Difference: **MD 5.54 days shorter**	Days Mean	**Low** Due to very serious risk of bias, Due to serious imprecision, Upgraded due to	High-dose methylprednisolone may decrease time to remission

	Follow up 23 months (mean)	(95% CI: 8.46 lower - 2.61 lower)	large magnitude of effect[1]	
Time to first relapse	Measured by: Months Scale: - High better Based on data from 15 patients in 1 study[2] Follow up 40 months (mean)	Mean Mean Difference: **MD 8.10 months shorter** (95% CI: 30.51 lower - 14.31 higher)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether high-dose methylprednisolone in the first episode of nephrotic syndrome increases or decreases time to first relapse

1. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up 25%, Selective outcome reporting; **Imprecision: Serious.** Low number of patients, due to few events; **Upgrade: Large magnitude of effect.**
2. Primary study [265] **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up (21%); **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study

References

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[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S27.
Population: First episode of nephrotic syndrome in children
Intervention: Long prednisone duration and Sairei-to
Comparator: Standard prednisone duration and Sairei-to

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard prednisone duration and Sairei-to	Long prednisone duration and Sairei-to	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference: **fewer**			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference: **fewer**			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference: **fewer**			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference: **fewer**			No studies were found that looked at complete remission
Relapse 2 years	Relative risk: 0.92 (95% CI: 0.75 - 1.14) Based on data from 171 patients in 1 study[1] Follow up 24 months	**705** per 1000	**649** per 1000 Difference: **56 fewer per 1000** (95% CI: 176 fewer - 99 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether long duration prednisone and Sairei-to increases or decreases relapse at 2 years

Frequent relapses 2 years	Relative risk: 1.12 (95% CI: 0.64 - 1.94) Based on data from 171 patients in 1 study[3] Follow up 24 months	**216** per 1000 **242** per 1000 Difference: **26 more per 1000** (95% CI: 78 fewer - 203 more)	**Very Low** Due to serious risk of bias, Due to very serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether long duration prednisone and Sairei-to increases or decreases frequent relapse at 2 years
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

1. Primary study [279] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Only data from one study, Low number of patients
3. Primary study [279] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

[279] Yoshikawa N., Ito H., Takehoshi Y., Honda M., Awazu M., Iijima K., et al. Standard versus long-term prednisolone with Sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: a prospective controlled study. Nippon Jinzon Gakkai Shi. Japanese Journal of Nephrology 1998;40(8):587-590
[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S28.
Population: Children with relapsing nephrotic syndrome
Intervention: Intermittent dose prednisone
Comparator: Alternate-day dose prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alternate-day dose	Intermittent dose	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Relapsing during therapy 6-month therapy	Relative risk: 0.6 (95% CI: 0.36 - 1.02) Based on data from 48 patients in 1 study[1] Follow up 6 months	**720** per 1000	**432** per 1000 Difference: **288 fewer per 1000** (95% CI: 461 fewer - 14 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Intermittent dose may decrease relapsing during therapy slightly
Relapse 9-12 months	Relative risk: 1.2 (95% CI: 0.93 - 1.55) Based on data from 48 patients in 1 study[3] Follow up 9-12 months	**760** per 1000	**912** per 1000 Difference: **152 more per 1000** (95% CI: 53 fewer - 418 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	We are uncertain whether intermittent glucocorticoid increases or decreases relapse at 9 to 12 months

Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Annual GFR	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [245] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Only data from one study
3. Primary study [245] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and large loss to follow up; **Imprecision: Serious.** Low number of patients, Only data from one study

References

[245] Anonymous. Alternate-day prednisone is more effective than intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbeitsgemeinschaft fur Padiatrische Nephrologie". European Journal of Pediatrics 1981;135(3):229-237

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S29.
Population: Children with relapsing nephrotic syndrome
Intervention: Daily glucocorticoid therapy
Comparator: Intermittent glucocorticoid therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Intermittent glucocorticoid therapy	Daily glucocorticoid therapy	**Certainty of the evidence**	**Plain text summary**
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse	Relative risk: 0.2 (95% CI: 0.05 - 0.82) Based on data from 50 patients in 1 study[1] Follow up ≥8 months	**400** per 1000	**80** per 1000 Difference: **320 fewer per 1000** (95% CI: 380 fewer - 72 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision,[2]	Daily glucocorticoid therapy may decrease relapse
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [244] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and large loss to follow up ((10/64 (15.6%) not included in analysis because of protocol violation)), Selective outcome reporting (not all of the review's pre-specified primary outcomes have been reported, adverse events not reported); **Imprecision: Serious.** Only data from one study;

References

[244] Anonymous. Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. Journal of Pediatrics 1979;95(2):239-243

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S30.
Population: Children with relapsing nephrotic syndrome
Intervention: Daily prednisone
Comparator: Alternate-day prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alternate-day prednisone	Daily prednisone	**Certainty of the evidence**	**Plain text summary**
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Annual GFR loss	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at annual GFR loss
Relapse rate per year 12 months	Measured by: Scale: - Lower better Based on data from 62 patients in 1 study[1]	Mean	Mean Difference: **MD 0.90 lower** (95% CI: 1.33 lower - 0.47 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Daily prednisone for relapsing nephrotic syndrome may decrease the annual rate of relapse

	Follow up 12 months			

1. Primary study [278] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study

References

[278] Yadav M., Sinha A., Hari P., Bagga A. Efficacy of low-dose daily versus alternate day prednisone in children with frequently relapsing nephrotic syndrome (FRNS): Open-label randomized controlled trial (RCT) [abstract]. Pediatric Nephrology 2016;31(10):1752-1752

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S31.
Population: Children with relapsing nephrotic syndrome
Intervention: Intravenous glucocorticoid therapy
Comparator: Oral glucocorticoid therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral glucocorticoid therapy	Intravenous glucocorticoid therapy	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 9-12 months	Relative risk: 1.06 (95% CI: 0.75 - 1.52) Based on data from 64 patients in 1 study[1] Follow up 18 months (mean)	**636** per 1000	**674** per 1000 Difference: **38 more per 1000** (95% CI: 159 fewer - 331 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Intravenous glucocorticoid therapy may have little or no difference on further relapses by 9-12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [255] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study

References

[255] Imbasciati E., Gusmano R., Edefonti A., Zucchelli P., Pozzi C., Grassi C., et al. Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. British Medical Journal Clinical Research Ed 1985;291(6505):1305-1308

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S32.
Population: Children with relapsing nephrotic syndrome
Intervention: Single glucocorticoid dose
Comparator: Divided-dose glucocorticoid therapy (3 doses/day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Divided dose glucocorticoid therapy	**Absolute effect estimates** Single glucocorticoid dose	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 9-12 months	Relative risk: 1.07 (95% CI: 0.93 - 1.55) Based on data from 94 patients in 1 study[1] Follow up 9 months	**574** per 1000	**614** per 1000 Difference: **40 more per 1000** (95% CI: 40 fewer - 316 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Single glucocorticoid dose may have little or no difference on further relapse by 9-12 months
Serious adverse events	Relative risk: 0.41	**278** per 1000	**114** per 1000	**Low**	Single glucocorticoid dose

	(95% CI: 0.18 - 0.91) Based on data from 138 patients in 2 studies[3] Follow up 7.5 months (mean)	Difference: **164 fewer per 1000** (95% CI: 228 fewer - 25 fewer)	Due to very serious risk of bias[4]	may decrease serious adverse events
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss
Mean time to relapse 2 months therapy	Measured by: Months Scale: - Lower better Based on data from 94 patients in 1 study[5] Follow up 9 months	Mean Mean Difference: **MD 0.30 shorter** (95% CI: 1.64 lower - 1.04 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Glucocorticoid therapy in relapse of nephrotic syndrome may have little or no difference on mean time to relapse

1. Primary study [282] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and large loss to follow up; **Imprecision: Serious.** Wide confidence intervals, Only data from one study;
3. Systematic review [326] with included studies: [261], [282] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting;
5. Primary study [282] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and large loss to follow up; **Imprecision: Serious.** Wide confidence intervals, Only data from one study;

References

[261] Li X., Li Z., Cheng Z. Treatment of children with simple nephrotic syndrome using prednisone once per day. Acta Academiae Medicinae Hubei 1994;15(4):386-388

[282] Ekka BK, Bagga A., Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatric Nephrology 1997;11(5):597-599

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S33.
Population: Children with relapsing nephrotic syndrome
Intervention: Single glucocorticoid dose (60 mg/day)
Comparator: Divided-dose glucocorticoid therapy (40 mg/day AM, 20 mg/day PM)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Divided-dose glucocorticoid therapy	Single glucocorticoid dose	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked all-cause mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked kidney failure
≥50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:			No studies were found that looked at complete remission
Relapse	(95% CI -)	Difference:			No studies were found that looked at relapse (as a dichotomous outcome)
Serious adverse events	Relative risk: Not estimable (95% CI -)	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (95% CI 37 fewer - 37 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether single versus divided-dose glucocorticoid

	Based on data from 104 patients in 2 studies[1] Follow up 12 months			therapy makes a difference in serious adverse events
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss
Time to remission	Measured by: Days Scale: - Shorter better Based on data from 104 patients in 1 study[3] Follow up 12 months	**8.02** Mean **9.74** Mean Difference: **MD 1.72 days longer** (95% CI 0.64 longer – 2.80 longer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Divided-dose glucocorticoid may decrease time to remission

1. Primary study [Weerasooriya 2023 PubMed 36757496] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Vert serious.** Only data from one study, no events in study;
3. Primary study [Weerasooriya 2023 PubMed 36757496] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study

References

[Weerasooriya 2023 PubMed 36757496] Weerasooriya, Walk; Abeyagunawardena, A. S.; Thalgahagoda, R. S.. Single vs split dose of prednisolone in the treatment of relapses of childhood nephrotic syndrome. Eur J Pediatr 2023. [PubMed: 36757496]

Table S34.
Population: Children with relapsing nephrotic syndrome
Intervention: 1 mg/kg glucocorticoid
Comparator: 2 mg/kg glucocorticoid

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 2 mg/kg glucocorticoid	1 mg/kg glucocorticoid	**Certainty of the evidence**	**Plain text summary**
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
>50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at >50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission (4 weeks)	Relative risk: 0.96 (95% CI: 0.84 - 1.10) Based on data from 62 patients in 1 study Follow up 6 months	**943** per 1000	**906** per 1000 Difference: **37 fewer per 1000** (95% CI: 159 fewer - 90 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	1 mg/kg glucocorticoid compared with 2 mg/kg glucocorticoid may have little or no difference on remission at 4 weeks

Time to remission	Measured by: Months Scale: - Lower better Based on data from 79 patients in 2 studies[1] Follow up 3-12 months	Mean Mean Difference: **MD 0.53 months longer** (95% CI: 0.43 shorter – 1.49 longer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	1 mg/kg glucocorticoid may have little or no difference on time to remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss
Relapse	Relative risk: 1.16 (95% CI: 0.88 - 1.52) Based on data from 76 patients in 3 studies[5] Follow up 7 months (mean)	**464** per 1000 **544** per 1000 Difference: 74 more per 1000 (95% CI 55 fewer - 241 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	1 mg/kg glucocorticoid compared with 2 mg/kg glucocorticoid may have little or no difference on relapse

1. Systematic review with included studies: [25] [Sheik 2021 PubMed 33861375] Baseline/comparator: Control arm of reference used for intervention .
2. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,; Imprecision: Serious. Only data from one study;
3. Systematic review with included studies: [25] [Sheik 2021 PubMed 33861375] Baseline/comparator: Control arm of reference used for intervention .
4. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting (no report of adverse events); Imprecision: Serious. Wide confidence interval;
5. Systematic review with included studies: [25] [Sheik 2021 PubMed 33861375] [Tu 2022] Baseline/comparator: Control arm of reference used for intervention .
6. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting (no report of adverse events); Imprecision: Serious. Wide confidence interval;

References

[25] Borovitz Y., Haskin O., Levi S., Kaz S., Alfandary H., Davidovits M., et AL : Lower prednisone dosing for nephrotic syndrome relapse: a prospective randomized study [abstract no:O-07]. Pediatric Nephrology 2017;32(9):1647-1647

[104] Hahn D, Hodson EM, Willis NS, Craig JC : Corticosteroid therapy for nephrotic syndrome in children. The Cochrane database of systematic reviews 2015;(3):CD001533

[Sheik 2021 PubMed 33861375] Sheikh, S.; Mishra, K.; Kumar, M.. Low-dose versus conventional-dose prednisolone for nephrotic syndrome relapses: a randomized controlled non-inferiority trial. Pediatr Nephrol 2021;36:3143–3150. [PubMed: 33861375]

[Tu 2022] Tu, J.; Chen, C. Y.; Geng, H. Y.; Li, H. R.; Xia, H.; Lin, Y.; Lin, T. T.; Sun, J. S.. Clinical assessment of moderate-dose glucocorticoid in the treatment of recurrence of primary nephrotic syndrome in children: a prospective randomized controlled trial. Zhongguo Dang Dai Er Ke Za Zhi 2022.

Table S35.
Population: Children with relapsing nephrotic syndrome
Intervention: 1 mg/kg alternate days prednisolone
Comparator: 1.5 mg/kg alternate days prednisolone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 1.5 mg/kg prednisolone	 1 mg/kg prednisolone	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked at kidney failure
>50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at >50% GFR loss
Infection	(95% CI -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission 3 months	Relative risk: Not estimable (95% CI -) Based on data from 40 patients in 1 study[1] Follow up 3 months	**1000** per 1000	**1000** per 1000 Difference: **0 fewer per 1000** (95% CI; 90 fewer - 90 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	1 compared with 1.5 mg/kg prednisolone on alternate days may have little or no difference on remission at 3 months
Time to remission	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at time to remission
Annual GFR loss	Measured by: Scale: - Lower better				

3 years		Difference:		No studies were found that looked annual GFR loss
Relapse 3 months	Relative risk: 1.24 (95% CI 0.34 – 4.46) Based on data from 40 patients in 1 study[3] Follow up 3 months	**350** per 1000 **400** per 1000 Difference: **50 more per 1000** (95% CI: 250 fewer - 350 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether 1 compared with 1.5 mg/kg prednisolone on alternate days makes a difference in relapse

1. Systematic review with included studies: [Mantan 2022 PubMed 36704589] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study, 100% in both groups;
3. Systematic review with included studies: [Mantan 2022 PubMed 36704589] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Vert serious.** Only data from one study, very wide confidence interval;

References

[Mantan 2022 PubMed 36704589] Mantan, M.; Kansal, A.; Swarnim, S.. Effectiveness of a Low Dose Prednisolone Regimen for Treatment of Relapses in Children with Steroid Sensitive Nephrotic Syndrome. Indian J Nephrol 2022;588-594. [PubMed: 36704589]

Table S36.
Population: Children with relapsing nephrotic syndrome
Intervention: Prednisone: 60 mg/m^2 per day for 4 weeks and tapered daily dose for 4 weeks
Comparator: Prednisone: 60 mg/m^2 per day until remission and 40 mg/m^2 on 3/7 consecutive days

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Intermittent oral glucocorticoid therapy	Prolonged oral glucocorticoids	**Certainty of the evidence**	**Plain text summary**
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked all-cause mortality
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 9-12 months	Relative risk: 1.0 (95% CI: 0.89 - 1.12) Based on data from 50 patients in 1 study[1] Follow up 8 months	**960** per 1000	**960** per 1000 Difference: **0 fewer per 1000** (95% CI: 106 fewer - 115 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether prolonged glucocorticoid therapy decreases further relapses at 9-12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [244] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and large loss to follow up (15.6% not included in analysis because of protocol violation), Selective outcome reporting (adverse events not reported); **Imprecision: Serious.** Only data from one study

References

[244] Anonymous. Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. Journal of Pediatrics 1979;95(2):239-243

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S37.
Population: Children with relapsing nephrotic syndrome
Intervention: Prolonged glucocorticoid therapy (7 months): 60 mg/m^2 per day for 4 weeks, then 60 mg/m^2 on alternate days, reducing alternate-day dose by 10 mg/m^2 every 4 weeks
Comparator: Standard duration (2 months): prednisolone 60 mg/m^2 per day until urine protein-free for 3 days, then 40 mg/m^2 on alternate days for 4 weeks

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard duration (2 months)	Prolonged glucocorticoid therapy (7 months)	**Certainty of the evidence**	**Plain text summary**
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Relapse 6 months	Relative risk: 0.04 (95% CI: 0.01 - 0.25) Based on data from 90 patients in 1 study[1] Follow up 6 months	**630** per 1000	**25** per 1000 Difference: **605 fewer per 1000** (95% CI: 624 fewer - 472 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Prolonged glucocorticoid therapy (7 months) for relapsing nephrotic syndrome may decrease relapse at 6 months
Relapse 1 year	Relative risk: 0.43 (95% CI: 0.29 - 0.65) Based on data from 76 patients in 1 study[3] Follow up 12 months	**882** per 1000	**379** per 1000 Difference: **503 fewer per 1000** (95% CI: 626 fewer - 309 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Prolonged glucocorticoid therapy (7 months) for relapsing nephrotic syndrome may decrease relapse at 1 year
Relapse 2 years	Relative risk: 0.6 (95% CI: 0.45 - 0.8) Based on data from 64 patients in 1 study[5] Follow up 2 years	**964** per 1000	**578** per 1000 Difference: **386 fewer per 1000** (95% CI: 530 fewer - 193 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Prolonged glucocorticoid therapy (7 months) for relapsing nephrotic syndrome may decrease relapse at 2 years
Relapse 3 years	Relative risk: 0.71 (95% CI: 0.56 - 0.9)	**1000** per 1000	**710** per 1000	**Low**	Prolonged glucocorticoid

	Based on data from 53 patients in 1 study[7] Follow up 3 years	Difference: **290 fewer per 1000** (95% CI: 440 fewer - 100 fewer)	Due to serious risk of bias, Due to serious imprecision[8]	therapy (7 months) for relapsing nephrotic syndrome may decrease relapse at 3 years
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Frequently relapsing or steroid-dependent nephrotic syndrome 6 months	Relative risk: 0.43 (95% CI: 0.19 - 0.95) Based on data from 72 patients in 1 study[9] Follow up 6 months	**406** per 1000 **175** per 1000 Difference: **231 fewer per 1000** (95% CI: 329 fewer - 20 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[10]	Prolonged glucocorticoid therapy (7 months) for relapsing nephrotic syndrome may decrease frequently relapsing or steroid-dependent nephrotic syndrome
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [326] with included studies: [257] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Serious.** Only data from one study
3. Systematic review [326] with included studies: [257] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,

Incomplete data and large loss to follow up (25%), Selective outcome reporting; **Imprecision: Serious.** Only data from one study

5. Systematic review [326] with included studies: [257] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision: Serious.** Only data from one study
7. Systematic review [326] with included studies: [257] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, large loss to follow up (25%), Selective outcome reporting; **Imprecision: Serious.** Only data from one study
9. Systematic review [326] with included studies: [257] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, large loss to follow up (25%), Selective outcome reporting; **Imprecision: Serious.** Only data from one study

References

[257] Jayantha UK. Prolong versus standard steroid therapy for children with relapsing course of nephrotic syndrome [abstract no: P026]. Pediatric Nephrology 2004;19(9):C99-C99

[326] Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2015;(3):CD001533

Table S38.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Cyclophosphamide
Comparator: Chlorambucil

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Chlorambucil	Cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 1.15 (95% CI: 0.69 - 1.94) Based on data from 50 patients in 1 study[1] Follow up 24 months	**500** per 1000	**575** per 1000 Difference: **75 more per 1000** (95% CI: 155 fewer - 470 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether cyclophosphamide increases or decreases relapse at 12 months
Relapse 24 months	Relative risk: 1.31 (95% CI: 0.8 - 2.13)	**500** per 1000	**655** per 1000	**Low**	

	Based on data from 50 patients in 1 study Follow up 24 months	Difference: **155 more per 1000** (95% CI: 100 fewer - 565 more)	Due to serious risk of bias, Due to serious imprecision[3]	Cyclophosphamide may have little or no difference on relapse
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [291] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

[291] Anonymous. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. New England Journal of Medicine 1982;306(8):451-454

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S39.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Chlorambucil increasing dose
Comparator: Chlorambucil stable dose

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Chlorambucil stable dose	Chlorambucil increasing dose	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 0.18 (95% CI: 0.01 - 3.41) Based on data from 21 patients in 1 studies[1] Follow up 28 months (mean)	**200** per 1000	**36** per 1000 Difference: **164 fewer per 1000** (95% CI: 198 fewer - 482 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether increasing or stable chlorambucil dose increases or decreases relapse

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [292] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

[292] Baluarte HJ, Hiner L., Gruskin AB. Chlorambucil dosage in frequently relapsing nephrotic syndrome: a controlled clinical trial. Journal of Pediatrics 1978;92(2):295-298

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S40.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Cyclophosphamide longer duration
Comparator: Cyclophosphamide shorter duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide shorter duration	**Absolute effect estimates** Cyclophosphamide longer duration	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies ere found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse - 8 weeks vs. 2 weeks 6 months	Relative risk: 0.27 (95% CI: 0.07 - 1.07) Based on data from 29 patients in 1 study[1] Follow up 5-26 months	**500** per 1000	**135** per 1000 Difference: **365 fewer per 1000** (95% CI: 465 fewer - 35 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether cyclophosphamide for 8 weeks duration increases or decreases relapse at 6 months

Relapse - 12 weeks vs. 8 weeks 12 months	Relative risk: 1.01 (95% CI: 0.73 - 1.39) Based on data from 72 patients in 1 study[3] Follow up 42 months (mean)	**677** per 1000 **684** per 1000 Difference: **7 more per 1000** (95% CI: 183 fewer - 264 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Cyclophosphamide for 12 weeks duration may have little or no difference on relapse at 12 months
Relapse - 12 weeks vs. 8 weeks 24 months	Relative risk: 0.98 (95% CI: 0.74 - 1.28) Based on data from 73 patients in 1 study[5] Follow up 42 months (mean)	**750** per 1000 **735** per 1000 Difference: **15 fewer per 1000** (95% CI: 195 fewer - 210 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Cyclophosphamide for 12 weeks duration may have little or no difference on relapse at 24 months
Relapse - 8 weeks vs. 2 weeks 12 months	Relative risk: 0.25 (95% CI: 0.07 - 0.92) Based on data from 22 patients in 1 study[7] Follow up 5-26 months	**727** per 1000 **182** per 1000 Difference: **545 fewer per 1000** (95% CI: 676 fewer - 58 fewer)	**Low** Due to very serious risk of bias[8]	Cyclophosphamide duration for 8 weeks may decrease relapse at 12 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [294] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [333] with included studies: [317] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients
5. Primary study [317] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients
7. Primary study [294] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: No serious.** Only data from one study, Low number of patients

References

[294] Barratt TM, Cameron JS, Chantler C., Ogg CS, Soothill JF. Comparative trial of 2 weeks and 8 weeks cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Archives of Disease in Childhood 1973;48(4):286-290
[317] Ueda N., Kuno K., Ito S. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. Archives of Disease in Childhood 1990;65(10):1147-1159
[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S41.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Low-dose cyclophosphamide (2.5 mg/kg per day)
Comparator: High-dose cyclophosphamide (5 mg/kg per day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** High-dose cyclophosphamide (5 mg/kg/d)	**Absolute effect estimates** Low-dose cyclophosphamide (2.5 mg/kg/d)	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 2.33 (95% CI: 0.11 - 48.99) Based on data from 14 patients in 1 study[1] Follow up 18 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (95% CI: 0 fewer - 0 fewer)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	There were too few who experienced the relapse, to determine whether low dose cyclophosphamide made a difference

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [321] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

[321] McCrory WW, Shibuya M, Lu WH, Lewy JE. Therapeutic and toxic effects observed with different dosage programs of cyclophosphamide in treatment of steroid-responsive but frequently relapsing nephrotic syndrome. The Journal of pediatrics 1973;82(4):614-8

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S42.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Intravenous cyclophosphamide
Comparator: Oral cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral cyclophosphamide	**Absolute effect estimates** Intravenous cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.14 (95% CI: 0.03 - 0.72) Based on data from 83 patients in 2 studies[1] Follow up 17 months (mean)	**238** per 1000	**33** per 1000 Difference: **205 fewer per 1000** (95% CI: 231 fewer - 67 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Intravenous cyclophosphamide may decrease infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 0.54 (95% CI: 0.34 - 0.88) Based on data from 83 patients in 2 studies[3]	**524** per 1000	**283** per 1000 Difference: **241 fewer per 1000** (95% CI: 346 fewer - 63 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Intravenous cyclophosphamide may decrease relapse

	Follow up 17 months (mean)			
Continuing frequently relapsing or steroid-dependent nephrotic syndrome 6 months	Relative risk: 0.4 (95% CI: 0.18 - 0.89) Based on data from 47 patients in 1 study[5] Follow up 22.5 months (mean)	**571** per 1000 **228** per 1000 Difference: **343 fewer per 1000** (95% CI: 468 fewer - 63 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Intravenous cyclophosphamide may decrease continuing frequently relapsing or steroid-dependent nephrotic syndrome
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [311], [285] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
3. Systematic review with included studies: [285], [311] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients
5. Systematic review [333] with included studies: [311] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients

References

[285] Abeyagunawardena AS, Trompeter RS. Intravenous pulsed vs oral cyclophosphamide therapy in steroid dependent nephrotic syndrome [abstract]. Pediatric Nephrology 2006;21(10):1535-1535

[311] Prasad N., Gulati S., Sharma RK, Singh U., Ahmed M. Pulse cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatric Nephrology 2004;19(5):494-498

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S43.
Population: *Post hoc* analysis: Children with frequently relapsing and steroid-dependent nephrotic syndrome
Intervention: Alkylating agents in frequently relapsing patients
Comparator: Alkylating agents in steroid-dependent patients

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alkylating agents in steroid-dependent patients	Alkylating agents in frequently relapsing patients	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 24 months	Relative risk: 0.35 (95% CI: 0.15 - 0.85) Based on data from 50 patients in 1 study[1]	**706** per 1000	**247** per 1000 Difference: **459 fewer per 1000** (95% CI: 600 fewer - 106 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Alkylating agents use in frequently relapsing steroid-sensitive nephrotic syndrome may decrease relapse

	Follow up 24 months			
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [291] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients

References

[291] Anonymous. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. New England Journal of Medicine 1982;306(8):451-454

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S44.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Alkylating agents
Comparator: Cyclosporine

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporine	Alkylating agents	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse - chlorambucil vs. cyclosporine 6-9 months	Relative risk: 0.82 (95% CI: 0.44 - 1.53) Based on data from 40 patients in 1 study[1] Follow up 2-3 years	**550** per 1000	**451** per 1000 Difference: **99 fewer per 1000** (95% CI: 308 fewer - 291 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether chlorambucil increases or decreases relapse
Relapse- chlorambucil	Relative risk: 0.47	**950** per 1000	**447** per 1000	**Low**	

vs. cyclosporine 12 months	(95% CI: 0.29 - 0.78) Based on data from 40 patients in 1 study[3] Follow up 30 months (mean)	Difference: **503 fewer per 1000** (95% CI: 674 fewer - 209 fewer)	Due to serious risk of bias, Due to serious imprecision[4]	Chlorambucil may decrease relapse at 12 months
Relapse - chlorambucil vs. cyclosporine 12-24 months	Relative risk: 0.58 (95% CI: 0.38 - 0.87) Based on data from 40 patients in 1 study[5] Follow up 30 months (mean)	**950** per 1000 **551** per 1000 Difference: **399 fewer per 1000** (95% CI: 589 fewer - 123 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Chlorambucil may decrease relapse at 12-24 months
Relapse - cyclophosphamide vs. cyclosporine 6-9 months	Relative risk: 1.07 (95% CI: 0.48 - 2.35) Based on data from 55 patients in 1 study[7] Follow up 30 months (mean)	**300** per 1000 **321** per 1000 Difference: **21 more per 1000** (95% CI: 156 fewer - 405 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether cyclophosphamide increases or decreases relapse
Hypertrichosis	Relative risk: 0.05 (95% CI: 0.01 - 0.36) Based on data from 112 patients in 2 studies[9] Follow up 22 months (mean)	**339** per 1000 **17** per 1000 Difference: **322 fewer per 1000** (95% CI: 336 fewer - 217 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[10]	Alkylating agents may decrease hypertrichosis
Serum creatinine increase >30%	Relative risk: 0.18 (95% CI: 0.02 - 1.54) Based on data from 112 patients in 2 studies[11] Follow up 22 months (mean)	**89** per 1000 **16** per 1000 Difference: **73 fewer per 1000** (95% CI: 87 fewer - 48 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether alkylating agents increases or decreases serum creatinine increases >30%
Relapse - Cyclophosphamide versus cyclosporine 12-24 months	Relative risk: 0.4 (95% CI: 0.22 - 0.73) Based on data from 55 patients in 1 studies[13] Follow up 3 months to 2 years	**800** per 1000 **320** per 1000 Difference: **480 fewer per 1000** (95% CI: 624 fewer - 216 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[14]	Cyclophosphamide may decrease relapse

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [322] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [333] with included studies: [322] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
5. Primary study [322] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
7. Systematic review [333] with included studies: [322] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
9. Systematic review [333] with included studies: [322], [302] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients
11. Systematic review [333] with included studies: [302], [322] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients
13. Systematic review [333] with included studies: [302] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients

References

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[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S45.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Cyclophosphamide
Comparator: Vincristine

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Vincristine	Cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 0.54 (95% CI: 0.26 - 1.16) Based on data from 39 patients in 1 study[1] Follow up 24 months	**619** per 1000	**334** per 1000 Difference: **285 fewer per 1000** (95% CI: 458 fewer - 99 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Cyclophosphamide may have little or no difference on relapse at 12 months
Relapse 24 months	Relative risk: 0.73	**762** per 1000	**556** per 1000	**Low**	Cyclophosphamide may have little or no

	(95% CI: 0.45 - 1.18) Based on data from 39 patients in 1 study[3] Follow up 24 months	Difference: **206 fewer per 1000** (95% CI: 419 fewer - 137 more)	Due to serious risk of bias, Due to serious imprecision[4]	difference on relapse at 24 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at complete remission

1. Systematic review [333] with included studies: [284] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [333] with included studies: [284] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

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[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S46.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Levamisole
Comparator: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide	Levamisole	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 1.08 (95% CI: 0.67 - 1.75) Based on data from 40 patients in 1 study[1] Follow up 24 months	**600** per 1000	**648** per 1000 Difference: **48 more per 1000** (95% CI: 198 fewer - 450 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether levamisole increases or decreases infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Relapse 6-9 months after therapy	Relative risk: 1.17 (95% CI: 0.76 - 1.81) Based on data from 97 patients in 2 studies[3] Follow up 18 months (mean)	**532** per 1000	**622** per 1000 Difference: **90 more per 1000** (95% CI: 128 fewer - 431 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	Levamisole may have little or no difference on relapse
Relapse 12 months after therapy	Relative risk: 0.89 (95% CI: 0.68 - 1.16)	**900** per 1000	**801** per 1000 Difference: **99 fewer per 1000**	**Low** Due to serious risk of bias, Due to	Levamisole may have little or no difference on relapse

	Based on data from 40 patients in 1 study[5] Follow up 24 months	(95% CI: 288 fewer - 144 more)	serious imprecision[6]	after 12 months of therapy
Relapse 24 months after therapy	Relative risk: 0.89 (95% CI: 0.73 - 1.1) Based on data from 40 patients in 1 study[7] Follow up 24 months	**950** per 1000 **845** per 1000 Difference: **105 fewer per 1000** (95% CI: 256 fewer - 95 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Levamisole may have little or no difference on relapse after 24 months of therapy
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Relapse End of therapy	Relative risk: 2.14 (95% CI: 0.22 - 20.95) Based on data from 97 patients in 2 studies[9] Follow up 18 months (mean)	**255** per 1000 **546** per 1000 Difference: **291 more per 1000** (95% CI: 199 fewer - 5087 more)	**Very Low** Due to serious risk of bias, Due to very serious inconsistency, Due to very serious imprecision[10]	We are uncertain whether levamisole increases or decreases relapse at the end of therapy
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [300] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [333] with included studies: [315], [300] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients
5. Systematic review [333] with included studies: [300] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
7. Systematic review [333] with included studies: [300] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
9. Primary study [300], [315] **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Very Serious.** The magnitude of statistical heterogeneity was high, with I^2: 79%., Point estimates vary widely; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients

References

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[315] Sural S., Pahari DK, Mitra K., Bhattacharya S., Mondal S., Taraphder A. Efficacy of levamisole compared to cyclophosphamide and steroid in frequently relapsing (FR) minimal change nephrotic syndrome (MCNS) [abstract]. Journal of the American Society of Nephrology 2001;12(Program & Abstracts):126A-126A
[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S47.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Mycophenolate mofetil
Comparator: Cyclosporine

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporine	Mycophenolate mofetil	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection - Pneumonia	Relative risk: 3.0 (95% CI: 0.13 - 67.06) Based on data from 24 patients in 1 study[1] Follow up 12 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (95% CI: 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil increases or decreases relapse at infection - pneumonia
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 1.9 (95% CI: 0.66 - 5.46) Based on data from 82 patients in 2 studies[3] Follow up 12 months (mean)	**238** per 1000	**452** per 1000 Difference: **214 more per 1000** (95% CI: 81 fewer - 1061 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether mycophenolate mofetil increases or decreases relapse at 12 months

Hypertrichosis	Relative risk: 0.23 (95% CI: 0.1 - 0.5) Based on data from 140 patients in 3 studies[5] Follow up 10 months (mean)	**426** per 1000 **98** per 1000 Difference: **328 fewer per 1000** (95% CI: 383 fewer - 213 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Mycophenolate mofetil may decrease hypertrichosis
Annual GFR loss	Measured by: Scale: - Lower better Based on data from 24 patients in 1 study[7] Follow up 12 months	ml/min/1.73 m^2 Mean ml/min/1.73 m^2 Mean Difference: **MD 20 higher** (95% CI: 5.49 higher - 34.51 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Mycophenolate mofetil may improve annual GFR loss

1. Primary study [301] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [333] with included studies: [324], [301] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients
5. Systematic review [333] with included studies: [301], [316], [324] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Low number of patients
7. Primary study [301] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Only data from one study, Low number of patients

References

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[324] Gellermann J, Weber L, Pape L, Tönshoff B, Hoyer P, Querfeld U. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. Journal of the American Society of Nephrology: JASN 2013;24(10):1689-97
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Table S48.
Population: Children with frequently relapsing steroid-sensitive nephrotic syndrome
Intervention: Changing cyclosporine dose
Comparator: Fixed cyclosporine dose

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Fixed cyclosporine dose	Changing cyclosporine dose	**Certainty of the evidence**	**Plain text summary**
Relapse 24 months	Relative risk: 0.65 (95% CI: 0.45 - 0.94) Based on data from 44 patients in 1 study[1] Follow up 24 months	**900** per 1000	**585** per 1000 Difference: **315 fewer per 1000** (95% CI: 495 fewer - 54 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Changing dose cyclosporine may decrease relapse at 24 months
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission

Relapse 6 months	Relative risk: 0.31 (95% CI: 0.1 - 1.02) Based on data from 44 patients in 1 study[3] Follow up 24 months	**400** per 1000 **124** per 1000 Difference: **276 fewer per 1000** (95% CI: 360 fewer - 8 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Changing cyclosporine dose may have little or no difference on relapse
Relapse 12 months	Relative risk: 0.33 (95% CI: 0.16 - 0.7) Based on data from 44 patients in 1 study[5] Follow up 24 months	**750** per 1000 **248** per 1000 Difference: **502 fewer per 1000** (95% CI: 630 fewer - 225 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Changing dose cyclosporine may decrease relapse at 12 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [310] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients; **Upgrade: Large magnitude of effect.**
3. Primary study [310] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients
5. Primary study [310] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients

References

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[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S49.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: High cyclosporine dose
Comparator: Low cyclosporine dose

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low cyclosporine dose	High cyclosporine dose	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 1.13 (95% CI: 0.61 - 2.07) Based on data from 85 patients in 1 study[1] Follow up 24 months	**310** per 1000	**350** per 1000 Difference: **40 more per 1000** (95% CI: 121 fewer - 332 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether higher dose cyclosporine increases or decreases infection
Pneumonia	Relative risk: 2.93 (95% CI: 0.32 - 27.06) Based on data from 85 patients in 1 study[3] Follow up 24 months	**24** per 1000	**70** per 1000 Difference: **46 more per 1000** (95% CI: 16 fewer - 625 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether higher dose cyclosporine increases or decreases pneumonia
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)				

		Difference:		No studies were found that looked at complete remission
Relapse 2 years	Relative risk: 0.74 (95% CI: 0.45 - 1.22) Based on data from 85 patients in 1 study[5] Follow up 24 months	**500** per 1000 **370** per 1000 Difference: **130 fewer per 1000** (95% CI: 275 fewer - 110 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	High dose cyclosporine dose may have little or no difference on relapse at 2 years
Number with frequently relapsing or steroid-dependent nephrotic syndrome 2 years	Relative risk: 0.42 (95% CI: 0.18 - 0.99) Based on data from 85 patients in 1 study[7] Follow up 24 months	**334** per 1000 **140** per 1000 Difference: **194 fewer per 1000** (95% CI: 274 fewer - 3 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	High dose cyclosporine may decrease the number of patients that develop frequently relapsing or steroid-dependent nephrotic syndrome at 2 years
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Primary study [308] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Primary study [308] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
5. Primary study [308] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients
7. Primary study [308] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients

References

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Table S50.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Azathioprine
Comparator: Glucocorticoids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Glucocorticoids	Azathioprine	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:			No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 0.9 (95% CI: 0.59 - 1.38) Based on data from 60 patients in 2 studies[1] Follow up 7 months (mean)	**567** per 1000	**510** per 1000 Difference: **57 fewer per 1000** (95% CI: 232 fewer - 215 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether azathioprine increases or decreases relapse
Annual GFR loss	Measured by: Scale: - Lower better	Mean	Mean		

		Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [293], [286] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Serious.** Wide confidence intervals

References

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[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S51.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Mizoribine
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo Mizoribine	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:		No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Adverse effects	Relative risk: 1.56 (95% CI: 0.97 - 2.49) Based on data from 197 patients in 1 study[1] Follow up 18 months	**214** per 1000 **334** per 1000 Difference: **120 more per 1000** (95% CI: 6 fewer - 319 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Mizoribine may have little or no difference on adverse effects
Annual GFR loss	Measured by: Scale: - Lower better			

		Difference:		No studies were found that looked at annual GFR loss

1. Primary study [319] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients

References

[319] Yoshioka K., Ohashi Y., Sakai T., Ito H., Yoshikawa N., Nakamura H., et al. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. Kidney International 2000;58(1):317-324

[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S52.
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Azithromycin
Comparator: Glucocorticoids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Glucocorticoids	Azithromycin	**Certainty of the evidence**	**Plain text summary**
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Relapse 6 months	Relative risk: 0.59 (95% CI: 0.33 - 1.07) Based on data from 189 patients in 1 study[1] Follow up 6 months	**253** per 1000	**149** per 1000 Difference: **104 fewer per 1000** (95% CI: 170 fewer - 18 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether azithromycin increases or decreases relapse at 6 months
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Annual GFR loss	Measured by: Scale: - Lower better	Difference:			No studies were found that looked at annual GFR loss

1. Systematic review [333] with included studies: [320] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in

potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Serious.** Only data from one study

References

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[333] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

Table S53.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Rituximab, single dose
Comparator: Mycophenolate mofetil (MMF) 350 mg/day twice a day (low dose)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** MMF (low dose) Rituximab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies were found that looked at ≥50% GFR loss
Adverse events	Relative risk: Not estimable (95% CI -) Based on data from 30 patients in 1 study[1] Follow up 12 months	**0** per 1000 **0** per 1000 Difference: **0 more per 1000** (95% CI: 120 fewer - 120 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether single dose rituximab compared with low dose MMF increases or decreases serious adverse events
Malignancy	(95% CI -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:		No studies were found that looked at malignancy
Relapse 12 months	Relative risk: 0.17 (95% CI 0.04 – 0.62) Based on data from 30 patients in 1 study[3] Follow up 12 months	**800** per 1000 **133** per 1000 Difference: **667 fewer per 1000** (95% CI: 930 fewer - 400 fewer)	**Low** Due to very serious risk of bias, Due to serious imprecision[4]	Single dose rituximab compared with low dose MMF r decreases relapse at 12 months

Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Ravani 2021b PMID 33616641] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Study terminated early to to high relapse in control group. Unclear reporting about randomization, allocation concealment, and blinding; Selective outcome reporting; **Imprecision: Very Serious.** Only one study; no events; no events.

References

[Ravani 2021b PMID 33616641] Ravani, P.; Lugani, F.; Drovandi, S.; Caridi, G.; Angeletti, A.; Ghiggeri, G. M.. Rituximab vs Low-Dose Mycophenolate Mofetil in Recurrence of Steroid-Dependent Nephrotic Syndrome in Children and Young Adults: A Randomized Clinical Trial. JAMA Pediatr 2021;175(6):631-632. [PubMed: 33616641]

Table S54.
Population: Children with frequently relapsing or steroid-dependent, but difficult to treat nephrotic syndrome
Intervention: Rituximab
Comparator: Tacrolimus

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Tacrolimus Rituximab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	Measured by: infections/patient Scale: - Lower better Based on data from 34 patients in 1 study[1] Follow up 12 months	**1.6** per patient/year **1.1** per patient/year Difference: **0.5 fewer** infections per patient/year (95% CI: 1.1 fewer – 0.1 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Rituximab may have little or no different effect on infection rate than tacrolimus
Malignancy	(95% CI -)	Difference:		No studies were found that looked at malignancy
Complete remission, sustained	Relative risk: 1.00 (95% CI: 0.57 - 1.75) Based on data from 40 patients in 1 study[3] Follow up 12 months	**550** per 1000 **550** per 1000 Difference: **0 fewer per 1000** (95% CI: 310 fewer - 310 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain about the relative effect on sustained complete remission with rituximab versus tacrolimus
Relapse	Relative risk: 0.85 (95% CI: 0.47 – 1.54) Based on data from 74 patients in 2 studies[5]	**405** per 1000 **324** per 1000 Difference: **61 fewer per 1000** (95% CI: 215 fewer - 219 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Rituximab may have little or no different effect on relapse than tacrolimus

	Follow up 12 months			
Time to relapse	Measured by: Scale – Higher better Based on data from 34 patients in 1 study[7] Follow up 12 months	**4.6 months** **8.3 months** Mean difference: **3.7 months longer** (statistically significant, implied)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Rituximab may have result in a longer time to relapse than tacrolimus
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Annual GFR loss 3 years		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study.
3. Systematic review with included studies: [Matthew 2022 PMID 35286456] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very serious.** Only one study; very wide confidence interval.
5. Systematic review with included studies: [Matthew 2022 PMID 35286456][Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Wide confidence interval.
7. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study.

References

[Matthew 2022 PMID 35286456] Mathew, G.; Sinha, A.; Ahmed, A.; Grewal, N.; Khandelwal, P.; Hari, P.; Bagga, A.. Efficacy of rituximab versus tacrolimus in difficult-to-treat steroid-sensitive nephrotic syndrome: an open-label pilot randomized controlled trial. Pediatr Nephrol 2022;37:3117–3126. [PubMed: 35286456]
[Wang 2022 PMID 35154548] Wang, L.; Zhu, J.; Xia, M.; Hua, R.; Deng, F.. Comparison of rituximab, cyclophosphamide, and tacrolimus as first steroid-sparing agents for complicated relapsing/steroid-dependent nephrotic syndrome in children: an evaluation of the health-related quality of life. Arch Med Sci 2022;1:275-278. [PubMed: 35154548]

Table S55.
Population: Children with frequently relapsing or steroid-dependent, but difficult to treat nephrotic syndrome
Intervention: Rituximab
Comparator: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide Rituximab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	Measured by: infections/patient Scale: - Lower better Based on data from 34 patients in 1 study[1] Follow up 12 months	**2.6** per patient/year **1.1** per patient/year Difference: **1.5 fewer** infections per patient/year (95% CI: 2.2 fewer – 0.8 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Rituximab may have little or no different effect on infection rate than cyclophosphamide
Malignancy	(95% CI -)	Difference:		No studies were found that looked at malignancy
Complete remission	(95% CI -)	Difference:		No studies were found that looked at relapse
Relapse	Relative risk: 0.20 (95% CI: 0.07 – 0.57) Based on data from 34 patients in 1 study[3] Follow up 12 months	**882** per 1000 **176** per 1000 Difference: **706 fewer per 1000** (95% CI: 943 fewer - 469 fewer)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effec[4]	Rituximab probably reduces relapse compared with cyclophosphamide

Time to relapse	Measured by: Scale – Higher better Based on data from 34 patients in 1 study[5] Follow up 12 months	**3.3 months** **8.3 months** Mean difference:**5.0 months longer** (statistically significant)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effect[6]	Rituximab probably results in a longer time to relapse than cyclophospham ide
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Annual GFR loss 3 years		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study.
3. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study. **Upgrade: Large magnitude of effect.**
5. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study. **Upgrade: Large magnitude of effect.**

References

[Wang 2022 PMID 35154548] Wang, L.; Zhu, J.; Xia, M.; Hua, R.; Deng, F.. Comparison of rituximab, cyclophosphamide, and tacrolimus as first steroid-sparing agents for complicated relapsing/steroid-dependent nephrotic syndrome in children: an evaluation of the health-related quality of life. Arch Med Sci 2022;1:275-278. [PubMed: 35154548]

Table S56.
Population: Children with frequently relapsing or steroid-dependent, but difficult to treat nephrotic syndrome
Intervention: Tacrolimus
Comparator: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide	Tacrolimus	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Measured by: infections/patient Scale: - Lower better Based on data from 34 patients in 1 study[1] Follow up 12 months	**2.6** per patient/year	**1.6** per patient/year Difference: **1.0 fewer** infections per patient/year (95% CI: 1.8 fewer – 0.2 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Tacrolimus may result in a lower infection rate than cyclophosphamide
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission	95% CI -)	Difference:			No studies were found that looked at relapse
Relapse	Relative risk: 0.40 (95% CI: 0.21 – 0.78) Based on data from 34 patients in 1 study[3]	**882** per 1000	**353** per 1000 Difference: **529 fewer per 1000** (95% CI: 803 fewer - 256 fewer)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to	Tacrolimus probably reduces relapse compared with cyclophosphamide

	Follow up 12 months		large magnitude of effec[4]	
Time to relapse	Measured by: Scale – Higher better Based on data from 34 patients in 1 study[5] Follow up 12 months	**3.3 months** **4.6 months** Mean difference:**1.3 months longer** (statistically significant, implied)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Tacrolimus may result in a longer time to relapse than cyclophosphamide
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Annual GFR loss 3 years		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study.
3. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study. **Upgrade: Large magnitude of effect.**
5. Systematic review with included studies: [Wang 2022 PMID 35154548] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only one study.

References

[Wang 2022 PMID 35154548] Wang, L.; Zhu, J.; Xia, M.; Hua, R.; Deng, F.. Comparison of rituximab, cyclophosphamide, and tacrolimus as first steroid-sparing agents for complicated relapsing/steroid-dependent nephrotic syndrome in children: an evaluation of the health-related quality of life. Arch Med Sci 2022;1:275-278. [PubMed: 35154548]

Table S57.
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: ACTH
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo ACTH	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:		No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Relapse 6 months	Relative risk: 1.0 (95% CI: 0.83 - 1.2) Based on data from 31 patients in 1 study[1] Follow up 6 months	**938** per 1000 **938** per 1000 Difference: **0 fewer per 1000** (95% CI: 159 fewer - 188 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether ACTH increases or decreases relapse
Complete remission	(95% CI: -)	Difference:		No studies were found that looked at complete remission
Annual GFR loss	Measured by: Scale: -	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [333] **Baseline/comparator** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to the study was stopped at a preplanned interim analysis after enrolment of 31 participants because of a lack of treatment efficacy; **Imprecision: Serious.** Only data from one study.

References

[332] Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2020;4 CD002290

[333] Wang C-S, Travers C, McCracken C, Leong T, Gbadegesin R, Quiroga A, Benfield MR, Hidalgo G, Srivastava T, Lo M, Yadin O, Mathias R, Araya CE, Khalid M, Orjuela A, Zaritsky J, Al-Akash S, Kamel M, Greenbaum LA: Adrenocorticotropic Hormone for Childhood Nephrotic Syndrome: The ATLANTIS Randomized Trial. Clinical journal of the American Society of Nephrology: CJASN 2018;13(12):1859-1865

Table 58.
Population: Children with steroid-resistant nephrotic syndrome, after 6 months of CYC or MMF
Intervention: Cyclosporin 2.5 mg/kg twice daily x 12 months (without steroids)
Comparator: Mycophenolate mofetil 0.5 g/m^2 twice daily x 12 months (without steroids)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Mycophenolate mofetil	Cyclosporin	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI -)	Difference:			No studies were found that looked at mortality
Kidney failure	(95% CI -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at ≥50% GFR loss
Adverse events, grade IV (Bacterial pneumonia, hypoglobulinemia)	Relative risk: 1.57 (95% CI: 0.41 – 6.04) Based on data from 66 patients in 1 study[1] Follow up 12 months	**94** per 1000	**147** per 1000 Difference: **53 more per 1000** (95% CI: 100 fewer – 210 more)	**Very Low** Due to serious risk of bias; Due to very serious imprecision[2]	We are uncertain whether cyclosporin compared with mycophenolate mofetil increases or decreases grade IV adverse events
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 0.76 (95% CI: 0.56 – 1.04) Based on data from 66 patients in 1 study[3] Follow up 12 months	**813** per 1000	**618** per 1000 Difference: **195 fewer per 1000** (95% CI: 410 fewer - 20 more)	**Low** Due to serious risk of bias; Due to serious imprecision[4]	Cyclosporin may have lower complete remission than MMF
Time to relapse		**10.8 months** median	**8 months** median		Cyclosporin may have shorter time to

	Hazard ratio [of MMF vs. CYC]: 1.31 (95% CI: 1.12 – 1.54) Based on data from 66 patients in 1 study[5] Follow up 12 months	Median difference: **2.8 months fewer** (95% CI -)	**Low** Due to serious risk of bias; Due to serious imprecision[6]	relapse compared with MMF
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Assadi 2022 PMID 35869690]. **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very serious.** Only data from one study, very wide confidence interval;
3. Systematic review with included studies: [Assadi 2022 PMID 35869690]. **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study, moderately large effect size, but not statistically significant;
5. Systematic review with included studies: [Assadi 2022 PMID 35869690]. **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study;

References

[Assadi 2022 PMID 35869690] Assadi F, Mazaheri M, Sadeghi-Bodj S.. Randomized controlled trial to compare safety and efficacy of mycophenolate vs. cyclosporine after rituximab in children with steroid-resistant nephrotic syndrome. Pharmacotherapy 2022;42(9):690-696. [PubMed: 35869690]

Table S59.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Oral cyclophosphamide
Comparator: Prednisone or placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisone or placebo	Oral cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	Relative risk: 1.07 (95% CI: 0.19 - 5.95) Based on data from 60 patients in 1 study[1] Follow up 37 months (mean)	**80** per 1000	**86** per 1000 Difference: **6 more per 1000** (95% CI: 65 fewer - 396 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether oral cyclophosphamide increases or decreases all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 1.06 (95% CI: 0.61 - 1.87) Based on data from 84 patients in 2 studies[3] Follow up 30.5 months (mean)	**353** per 1000	**374** per 1000 Difference: **21 more per 1000** (95% CI: 138 fewer - 307 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Oral cyclophosphamide may have little or no difference on complete remission
Annual GFR loss	Measured by: Scale: - Lower better				

3 years		Difference: **null lower**		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [342] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [364] with included studies: [355] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Selective outcome reporting, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Low number of patients and few events, Only data from one study

References

[342] Gipson DS, Trachtman H., Kaskel FJ, Greene TH, Radeva MK, Gassman JJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney International 2011;80(8):868-878
[355] Tarshish P., Tobin JN, Bernstein J., Edelmann Cm JR. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatric Nephrology 1996;10(5):590-593
[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S60.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Azathioprine
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo Azathioprine	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:		No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission	Relative risk: 0.94 (95% CI: 0.15 - 5.84) Based on data from 30 patients in 1 study[1] Follow up 3 months	**134** per 1000 **126** per 1000 Difference: **8 fewer per 1000** (95% CI: 114 fewer - 649 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether chlorambucil increases or decreases complete remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies found that looked at annual GFR loss

1. Systematic review [364] with included studies: [286] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study, Wide confidence intervals

References

[286] Abramowicz M., Barnett HL, Edelmann Cm JR, Greifer I., Kobayashi O., Arneil GC, et al. Controlled trial of azathioprine in children with nephrotic syndrome. Lancet 1970;1(7654):959-961

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S61.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Tacrolimus
Comparator: Cyclosporine

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporine Tacrolimus	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection - sepsis/pneumonia	Relative risk: 0.95 (95% CI: 0.06 - 14.22) Based on data from 41 patients in 1 study[1] Follow up 12 months	**50** per 1000 **48** per 1000 Difference: **2 fewer per 1000** (95% CI: 47 fewer - 661 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether tacrolimus increases or decreases infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission 6 months	Relative risk: 1.14 (95% CI: 0.64 - 2.03) Based on data from 41 patients in 1 study[3] Follow up 12 months	**500** per 1000 **570** per 1000 Difference: **70 more per 1000** (95% CI: 180 fewer - 515 more)	**Low** Due to very serious imprecision[4]	Tacrolimus may have little or no difference on complete remission at 6 months
Complete remission 12 months	Relative risk: 0.8 (95% CI: 0.45 - 1.42)	**500** per 1000 **400** per 1000 Difference: **100 fewer per 1000**	**Low** Due to very serious imprecision[6]	Tacrolimus may have little or no difference on complete remission at 12 months

	Based on data from 58 patients in 2 studies[5] Follow up 12 months (mean)	(95% CI: 275 fewer - 210 more)		
Annual GFR loss 3 years	Measured by: Scale: - Lower better Based on data from 35 patients in 1 study[7] Follow up 12 months	Mean Mean Difference: **MD 0.7 lower** (95% CI: 16.71 lower - 15.31 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether tacrolimus increases or decreases annual GFR loss

1. Primary study [339] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Primary study [339] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
5. Systematic review with included studies: [357], [339] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
7. Systematic review with included studies: [339] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients

References

[339] Choudhry S., Bagga A., Hari P., Sharma S., Kalaivani M., Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. American Journal of Kidney Diseases 2009;53(5):760-769

[357] Valverde S., Hernandez AM, Velasquez L., Romero B., Mendoza A., Ramon G., et al. Efficacy of prednisone-tacrolimus vs. prednisone-cyclosporine in steroid-resistant nephrotic syndrome [abstract]. Pediatric Nephrology 2010;25(9):1804-1804

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S62.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Rituximab plus cyclosporine plus prednisolone
Comparator: Cyclosporine plus prednisolone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporine plus prednisolone	**Absolute effect estimates** Rituximab plus cyclosporine plus prednisolone	**Certainty of the evidence**	**Plain text summary**
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 0.94 (95% CI: 0.22 - 3.94) Based on data from 31 patients in 1 study[1] Follow up 18 months	**200** per 1000	**188** per 1000 Difference: **12 fewer per 1000** (95% CI: 156 fewer - 588 more)	**Low** Due to very serious imprecision[2]	Rituximab plus cyclosporine plus prednisolone may have little or no difference on complete remission
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference: **more**			No studies were found that looked at ≥50% GFR loss
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**			No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [349] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study

References

[349] Magnasco A., Ravani P., Edefonti A., Murer L., Ghio L., Belingheri M., et al. Rituximab in children with resistant idiopathic nephrotic syndrome. Journal of the American Society of Nephrology 2012;23(6):1117-1124
[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S63.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Mycophenolate mofetil
Comparator: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide	Mycophenolate mofetil	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission 6 months	Relative risk: 0.9 (95% CI: 0.36 - 2.24) Based on data from 11 patients in 1 study[1] Follow up 6-12 months	**667** per 1000	**600** per 1000 Difference: **67 fewer per 1000** (95% CI: 427 fewer - 827 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Mycophenolate mofetil may have little or no difference on complete remission
Complete remission 12 months	Relative risk: 1.2 (95% CI: 0.41 - 3.51) Based on data from 11 patients in 1 study[3] Follow up 12 months	**500** per 1000	**600** per 1000 Difference: **100 more per 1000** (95% CI: 295 fewer - 1255 more)	**Low** Due to very serious imprecision[4]	Mycophenolate mofetil may have little or no difference on complete remission at 12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Low number of patients and few events, Only data from one study
3. Systematic review with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study

References

[358] Wu B., Mao J., Shen H., Fu H., Wang J., Liu A., et al. Triple immunosuppressive therapy in steroid-resistant nephrotic syndrome children with tacrolimus resistance or tacrolimus sensitivity but frequently relapsing. Nephrology 2015;20(1):18-24

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S64.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Leflunomide
Comparator: Mycophenolate mofetil

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Mycophenolate mofetil	Leflunomide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 1.61 (95% CI: 0.8 - 3.23) Based on data from 12 patients in 1 study[1] Follow up 6-12 months	**600** per 1000	**966** per 1000 Difference: **366 more per 1000** (95% CI: 120 fewer - 1338 more)	**Low** Due to very serious imprecision[2]	Leflunomide may have little or no difference on complete remission
Complete remission 12 months	Relative risk: 1.19 (95% CI: 0.51 - 2.8) Based on data from 12 patients in 1 study[3] Follow up 12 months	**600** per 1000	**714** per 1000 Difference: **114 more per 1000** (95% CI: 294 fewer - 1080 more)	**Low** Due to very serious imprecision[4]	Leflunomide may have little or no difference on complete remission at 12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
3. Systematic review [364] with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study

References

[358] Wu B., Mao J., Shen H., Fu H., Wang J., Liu A., et al. Triple immunosuppressive therapy in steroid-resistant nephrotic syndrome children with tacrolimus resistance or tacrolimus sensitivity but frequently relapsing. Nephrology 2015;20(1):18-24

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S65.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Leflunomide
Comparator: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide	Leflunomide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:			No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission 6 months	Relative risk: 1.46 (95% CI: 0.82 - 2.61) Based on data from 13 patients in 1 study[1] Follow up 6-12 months	**667** per 1000	**974** per 1000 Difference: **307 more per 1000** (95% CI: 120 fewer - 1074 more)	**Low** Due to very serious imprecision[2]	Leflunomide may have little or no difference on complete remission
Complete remission 12 months	Relative risk: 1.19 (95% CI: 0.51 - 2.8) Based on data from 12 patients in 1 study[3] Follow up 12 months	**600** per 1000	**714** per 1000 Difference: **114 more per 1000** (95% CI: 294 fewer - 1080 more)	**Low** Due to very serious imprecision[4]	Leflunomide may have little or no difference on complete remission at 12 months

Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
3. Systematic review [364] with included studies: [358] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study

References

[358] Wu B., Mao J., Shen H., Fu H., Wang J., Liu A., et al. Triple immunosuppressive therapy in steroid-resistant nephrotic syndrome children with tacrolimus resistance or tacrolimus sensitivity but frequently relapsing. Nephrology 2015;20(1):18-24

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S66.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Intravenous cyclophosphamide
Comparator: Oral cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral cyclophosphamide	**Absolute effect estimates** Intravenous cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:			No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:			No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 1.41 (95% CI: 0.05 - 41.41) Based on data from 46 patients in 2 studies[1] Follow up 9 months (mean)	**93** per 1000	**131** per 1000 Difference: **38 more per 1000** (95% CI: 88 fewer - 3758 more)	**Low** Due to serious inconsistency, Due to serious imprecision[2]	Intravenous cyclophosphamide may have little or no difference on infection
Malignancy	(95% CI: -)	Difference:			No studies were found that looked at malignancy
Complete remission	Relative risk: 1.68 (95% CI: 0.79 - 3.58) Based on data from 46 patients in 2 studies[3] Follow up 9 months (mean)	**667** per 1000	**974** per 1000 Difference: **307 more per 1000** (95% CI: 120 fewer - 1074 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Intravenous cyclophosphamide may have little or no difference on complete remission
Annual GFR loss	Measured by: Scale: - Lower better				

		Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [351], [340] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious.** Point estimates vary widely, the direction of the effect is not consistent between the included studies; **Imprecision: Serious.** Low number of patients
3. Systematic review [364] with included studies: [340], [351] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: Serious.** Low number of patients and few events, Only data from one study

References

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

[351] Ohri A., Phatarpekar A., Ali U., Tembekar Y. Randomized controlled trial of oral versus intravenous cyclophosphamide in idiopathic steroid resistant nephrotic syndrome [abstract]. Pediatric Nephrology 2010;25(9):1879-1879

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S67.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Intravenous cyclophosphamide
Comparator: Oral cyclophosphamide plus intravenous dexamethasone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral cyclophosphamide plus IV dexamethasone	**Absolute effect estimates** Intravenous cyclophosphamide	**Certainty of the evidence**	**Plain text summary**
Glucocorticoid-related adverse events - Cushingoid features	Relative risk: 0.78 (95% CI: 0.52 - 1.17) Based on data from 46 patients in 1 study[1] Follow up 18 months	**740** per 1000	**577** per 1000 Difference: **163 fewer per 1000** (95% CI: 355 fewer - 126 more)	**Low** Due to very serious imprecision[2]	Intravenous cyclophosphamide may have little or no difference on cushingoid features
Complete remission 6 months	Relative risk: 1.13 (95% CI: 0.65 - 1.96) Based on data from 49 patients in 1 study[3] Follow up 18 months	**479** per 1000	**541** per 1000 Difference: **62 more per 1000** (95% CI: 168 fewer - 460 more)	**Low** Due to very serious imprecision[4]	Intravenous cyclophosphamide may have little or no difference on complete remission at 6 months
Sustained remission/steroid-sensitive relapses 18 months	Relative risk: 1.13 (95% CI: 0.65 - 1.96) Based on data from 49 patients in 1 study[5] Follow up 18 months	**479** per 1000	**541** per 1000 Difference: **62 more per 1000** (95% CI: 168 fewer - 460 more)	**Low** Due to very serious imprecision[6]	Intravenous cyclophosphamide may have little or no difference on sustained remission/steroid-sensitive relapses
Hypertension	Relative risk: 0.04 (95% CI: 0.0 - 0.68) Based on data from 46 patients in 1 study[7] Follow up 18 months	**434** per 1000	**17** per 1000 Difference: **417 fewer per 1000** (95% CI: 434 fewer - 139 fewer)	**Moderate** Due to serious imprecision[8]	Intravenous cyclophosphamide may decrease hypertension
Hypokalemia	Relative risk: 0.06 (95% CI: 0.0 - 0.98) Based on data from 46 patients in 1 study[9]	**305** per 1000	**18** per 1000 Difference: **287 fewer per 1000**	**Moderate** Due to serious imprecision[10]	Intravenous cyclophosphamide may decrease hypokalemia

	Follow up 18 months	(95% CI: 305 fewer - 6 fewer)		
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	(95% CI: -)	Difference:		No studies were found that looked at kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection - Bacterial infections	Relative risk: 0.66 (95% CI: 0.27 - 1.26) Based on data from 46 patients in 1 study[11] Follow up 18 months	**348** per 1000 **230** per 1000 Difference: **118 fewer per 1000** (95% CI: 254 fewer - 90 more)	**Low** Due to very serious imprecision[12]	Intravenous cyclophosphamide may have little or no difference on bacterial infections
Infection - Urinary tract infections	Relative risk: 4.44 (95% CI: 0.22 - 88.04) Based on data from 46 patients in 1 study[13] Follow up 18 months	**0** per 1000 **0** per 1000 Difference: **0 fewer per 1000** (95% CI: 0 fewer - 0 fewer)	**Low** Due to very serious imprecision[14]	Intravenous cyclophosphamide may have little or no difference on urinary tract infections
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Glucocorticoid-related adverse events - Steroid encephalopathy	Relative risk: 0.3 (95% CI: 0.01 - 6.94) Based on data from 46 patients in 1 study[15] Follow up 18 months	**44** per 1000 **13** per 1000 Difference: **31 fewer per 1000** (95% CI: 44 fewer - 261 more)	**Low** Due to very serious imprecision[16]	Intravenous cyclophosphamide may have little or no difference on steroid encephalopathy
Glucocorticoid-related adverse	Relative risk: 1.77	**44** per 1000 **78** per 1000	**Low**	Intravenous cyclophosphamide

events - cataract/glaucoma	(95% CI: 0.17 - 18.26) Based on data from 46 patients in 1 study[17] Follow up 18 months	Difference: **34 more per 1000** (95% CI: 37 fewer - 759 more)	Due to very serious imprecision[18]	may have little or no difference on cataract/glaucoma
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Imprecision: Very Serious.** Low number of patients
3. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
5. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study
7. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Imprecision: Serious.** Low number of patients
9. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Imprecision: Serious.** Low number of patients
11. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Imprecision: Very Serious.** Low number of patients
13. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Imprecision: Very Serious.** Low number of patients
15. Systematic review [364] with included studies: [350] **Baseline/comparator:** Control arm of reference used for intervention.
16. **Imprecision: Very Serious.** Low number of patients
17. Primary study [350] **Baseline/comparator:** Control arm of reference used for intervention.
18. **Imprecision: Very Serious.** Low number of patients

References

[350] Mantan M., Sriram CS, Hari P., Dinda A., Bagga A. Efficacy of intravenous pulse cyclophosphamide treatment versus combination of intravenous dexamethasone and oral cyclophosphamide treatment in steroid-resistant nephrotic syndrome. Pediatric Nephrology 2008;23(9):1495-1502

[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Table S68.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Chlorambucil
Comparator: Indomethacin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Indomethacin Chlorambucil	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	(95% CI: -)	Difference:		No studies were found that looked at all-cause mortality
Kidney failure	Relative risk: 0.2 (95% CI: 0.01 - 3.85) Based on data from 30 patients in 1 study[1] Follow up ≥6 months	**133** per 1000 **27** per 1000 Difference: **106 fewer per 1000** (95% CI: 132 fewer - 379 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether chlorambucil increases or decreases kidney failure
≥50% GFR loss	(95% CI: -)	Difference:		No studies were found that looked at ≥50% GFR loss
Infection	(95% CI: -)	Difference:		No studies were found that looked at infection
Malignancy	(95% CI: -)	Difference:		No studies were found that looked at malignancy
Complete remission	Relative risk: 1.0 (95% CI: 0.42 - 2.4) Based on data from 30 patients in 1 study[3] Follow up ≥6 months	**400** per 1000 **400** per 1000 Difference: **0 fewer per 1000** (95% CI: 232 fewer - 560 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias[4]	We are uncertain whether chlorambucil increases or decreases complete remission
Annual GFR loss	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review [364] with included studies: [360] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients
3. Systematic review [364] with included studies: [360] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Low number of patients and few events, Only data from one study, Wide confidence intervals

References

[360] Kleinknecht C, Broyer M, Gubler MC, Palcoux JB. Irreversible renal failure after indomethacin in steroid-resistant nephrosis. The New England journal of medicine 1980;302(12):691
[364] Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane Database of Systematic Reviews. 2019;2019(11): CD003594

Tables S69.
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Ofatumumab
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Ofatumumab	**Certainty of the evidence**	**Plain text summary**
All-cause mortality	Relative risk: 2.63 (95% CI: 0.13 – 54.64) Based on data from 13 patients in 1 study[1] Follow up 12 months	**0** per 1000	**141** per 1000 Difference: **141 more per 1000** (95% CI: 190 fewer - 470 more)	**Very Low** Due to very serious imprecision[2]	We are uncertain whether ofatumumab increases or decreases mortality
Kidney failure	Relative risk: 0.57 (95% CI: 0.14 – 2.36) Based on data from 13 patients in 1 study[3] Follow up 12 months	**500** per 1000	**286** per 1000 Difference: **214 fewer per 1000** (95% CI: 740 fewer - 310 more)	**Very Low** Due to very serious imprecision[4]	We are uncertain whether ofatumumab increases or decreases kidney failure
≥50% GFR loss	(95% CI -)	Difference:			No studies were found that looked at ≥50% GFR loss
Serious adverse event	Relative risk: not estimable (95% CI -) Based on data from 13 patients in 1 study[5] Follow up 12 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (95% CI: 250 fewer - 250 more)	**Very Low** Due to very serious imprecision[6]	We are uncertain whether ofatumumab increases or decreases serious adverse events
Malignancy	(95% CI -)	Difference:			No studies were found that looked at malignancy
Complete or partial remission	Relative risk: not estimable (95% CI -) Based on data from 13 patients in 1 study[7]	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (95% CI: 250 fewer - 250 more)	**Very Low** Due to very serious imprecision[8]	We are uncertain whether ofatumumab increases or decreases complete or partial remission

	Follow up 12 months			
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference:		No studies were found that looked at annual GFR loss

1. Systematic review with included studies: [Ravani 2020b PMID 31993781] **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Not serious. Imprecision**; but study terminated for futility**: Very Serious.** Very wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review with included studies: [Ravani 2020b PMID 31993781] **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Not serious. Imprecision**; but study terminated for futility**: Very Serious.** Very wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review with included studies: [Ravani 2020b PMID 31993781] **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Not serious. Imprecision**; but study terminated for futility**: Very Serious.** Very wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review with included studies: [Ravani 2020b PMID 31993781] **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Not serious. Imprecision**; but study terminated for futility**: Very Serious.** Very wide confidence intervals, Only data from one study, Low number of patients;

References

[Ravani 2020b PMID 31993781] Ravani P, Pisani I, Bodria M, Caridi G, Degl'Innocenti ML, Ghiggeri GM. Low-dose ofatumumab for multidrug-resistant nephrotic syndrome in children: a randomized placebo-controlled trial. Pediatric Nephrology 2020;35:997-1003. [DOI: 10.1007/s00467-020-04481-y; Other: NCT02394106; PubMed: 31993781]