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

| | |
|---|---|
| | 11. or/6-10<br>12. and/5,11<br>13. randomised controlled trial/<br>14. crossover procedure/<br>15. double-blind procedure/<br>16. single-blind procedure/<br>17. random$.tw.<br>18. factorial$.tw.<br>19. crossover$ or cross-over$).tw.<br>20. placebo$.tw.<br>21. (double$ adj blind$).tw.<br>22. (singl$ adj blind$).tw.<br>23. assign$.tw.<br>24. allocat$.tw.<br>25. volunteer$.tw.<br>26. or/13-25<br>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<br>2. (lipoid next nephrosis):ti,ab,kw<br>3. #1 or #2 |
| Search strategy - MEDLINE | 1. nephrotic syndrome/<br>2. nephrosis, lipoid/<br>3. nephrotic syndrome.tw.<br>4. lipoid nephrosis.tw.<br>5. or/1-3<br>6. (exp Adult/ not (exp Aged/ and exp Child/ or exp Infant/ or exp Adolescent/))<br>7. 5 not 6<br>8. (child* or infant* or babies* or boy* or girl* or pediatric* or paediatric* or adolescen*)<br>9. and/5,8<br>10. or/7,9<br>11. randomised controlled trial.pt.<br>12. controlled clinical trial.pt.<br>13. randomized.ab.<br>14. placebo.ab.<br>15. clinical trials as topic/<br>16. randomly.ab.<br>17. (crossover or cross-over).tw.<br>18. Cross-over Studies/<br>19. trial.ti.<br>20. or/11-19<br>21. animals/ not (humans/ and animals/)<br>22. 9 and 20<br>23. 22 not 21 |
| Search strategy - Embase | 1. Nephrotic Syndrome/<br>2. Lipoid Nephrosis/<br>3. nephrotic syndrome.tw.<br>4. lipoid nephrosis.tw.<br>5. or/1-4<br>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<br>8. (child* or infant* or babies* or boy* or girl* or pediatric* or paediatric* or adolescen*)<br>9. and/5,8<br>10. or/7,9<br>11. randomised controlled trial/<br>12. crossover procedure/<br>13. double-blind procedure/<br>14. single-blind procedure/<br>15. random$.tw.<br>16. factorial$.tw.<br>17. crossover$ or cross-over$).tw.<br>18. placebo$.tw.<br>19. (double$ adj blind$).tw.<br>20. (singl$ adj blind$).tw.<br>21. assign$.tw.<br>22. allocat$.tw.<br>23. volunteer$.tw.<br>24. or/12-24<br>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<br>2. MeSH descriptor: [Nephrosis, Lipoid] explode all trees<br>3. nephrotic syndrome:ti,ab,kw (Word variations have been searched)<br>4. lipoid nephrosis:ti,ab,kw (Word variations have been searched)<br>5. minimal change glomerulonephritis:ti,ab,kw (Word variations have been searched)<br>6. minimal change nephr*:ti,ab,kw (Word variations have been searched)<br>7. idiopathic steroid resistant nephrotic syndrome:ti,ab,kw (Word variations have been searched)<br>8. SRNS:ti,ab,kw (Word variations have been searched)<br>9. {or #1-#8} |
| Search strategy - MEDLINE | 1. Nephrotic Syndrome/<br>2. Nephrosis Lipoid/<br>3. nephrotic syndrome.tw.<br>4. lipoid nephrosis.tw.<br>5. minimal change glomerulonephritis.tw.<br>6. minimal change nephr$.tw.<br>7. idiopathic steroid resistant nephrotic syndrome.tw.<br>8. or/1-7<br>9. randomised controlled trial.pt.<br>10. controlled clinical trial.pt.<br>11. randomized.ab.<br>12. placebo.ab.<br>13. clinical trials as topic/<br>14. randomly.ab.<br>15. (crossover or cross-over).tw.<br>16. Cross-over Studies/<br>17. trial.ti.<br>18. or/9-17<br>19. animals/ not (humans/ and animals/) |

| | |
|---|---|
| | 20. 8 and 18<br>21. 20 not 19 |
| Search strategy - Embase | 1. Nephrotic Syndrome/<br>2. Lipoid Nephrosis/<br>3. nephrotic syndrome.tw.<br>4. lipoid nephrosis.tw.<br>5. minimal change glomerulonephritis.tw.<br>6. minimal change nephropathy.tw.<br>7. idiopathic steroid resistant nephrotic syndrome.tw.<br>8. or/1-7<br>9. randomised controlled trial/<br>10. crossover procedure/<br>11. double-blind procedure/<br>12. single-blind procedure/<br>13. random$.tw.<br>14. factorial$.tw.<br>15. crossover$ or cross-over$).tw.<br>16. placebo$.tw.<br>17. (double$ adj blind$).tw.<br>18. (singl$ adj blind$).tw.<br>19. assign$.tw.<br>20. allocat$.tw.<br>21. volunteer$.tw.<br>22. or/9-21<br>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 KDIGO 2025 Neptrotic syndrome 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<br>The processes of guideline development are transparent and allow for involvement of all Work Group Members | For guideline group composition – see *Work Group Membership*<br>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 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] Mean follow up 18 months | **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] Mean follow up 19 months | **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] Mean follow up 21 months | **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] Mean follow up 20.5 months | **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] Mean follow up 20 months | **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] Mean follow up 18 months | **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] Mean follow up 19.7 months | **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.

**References**

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[331] Webb NJA, Woolley RL, Lambe T, Frew E, Brettell EA, Barsoum EN, Tormpeter RS, Cummins C, Deeks JJ, Wheatley K, IVes NJ. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. BMJ 2019;365(1800)

**Table S5.**
Population: Children with nephrotic syndrome and upper respiratory infection
Intervention: Prednisolone 15 mg/m$^2$ daily (maximum 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<br>3 years | (95% CI - ) | Difference: | | No studies looked annual GFR loss at 3 years |

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

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**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Glucocorticoids or placebo or both | <br>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 complete remission |
| ≥50% GFR loss | (95% CI: - ) | Difference: | | | No studies were found that looked at ≥50% GFR loss |
| Relapse - Cyclophosphamide versus prednisone<br>6–12 months | Relative risk: 0.47<br>(95% CI: 0.33 - 0.66)<br>Based on data from 157 patients in 4 studies[1]<br>Mean follow up 17.8 months | **713**<br>per 1000 | **335**<br>per 1000<br>Difference: **378 fewer per 1000**<br>(95% CI: 478 fewer - 242 fewer) | **Moderate**<br>Due to serious risk of bias[2] | Cyclophosphamide probably decreases relapse at 6–12 months |

| | | | | |
|---|---|---|---|---|
| Relapse - Chlorambucil versus prednisone or placebo<br>6–12 months | Relative risk: 0.19<br>(95% CI: 0.03 - 1.09)<br>Based on data from 41 patients in 2 studies[3]<br>Mean follow up 14.5 months | **850** per 1000 **161** per 1000<br>Difference: **689 fewer per 1000**<br>(95% CI: 825 fewer - 77 more) | **Moderate**<br>Due to serious risk of bias[4] | Chlorambucil probably has little or no difference on relapse at 6–12 months |
| Relapse - Cyclophosphamide versus prednisone<br>12–24 months | Relative risk: 0.21<br>(95% CI: 0.07 - 0.65)<br>Based on data from 27 patients in 2 studies[5]<br>Mean follow up 19 months | **929** per 1000 **195** per 1000<br>Difference: **734 fewer per 1000**<br>(95% CI: 864 fewer - 325 fewer) | **Low**<br>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<br>12 months | Relative risk: 0.15<br>(95% CI: 0.02 - 0.95)<br>Based on data from 32 patients in 2 studies[7]<br>Mean follow up 19 months | **1000** per 1000 **150** per 1000<br>Difference: **850 fewer per 1000**<br>(95% CI: 980 fewer - 50 fewer) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[8] | Chlorambucil may decrease relapse at 12 months |
| Annual GFR loss | Measured by:<br>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, 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] Mean follow up 11.3 months | **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<br>6–12 months | Relative risk: 0.65<br>(95% CI: 0.48 - 0.88)<br>Based on data from 462 patients in 8 studies[3]<br>Mean follow up 11.3 months | **862** per 1000<br>**560** per 1000<br><br>Difference: **302 fewer per 1000**<br>(95% CI: 448 fewer - 103 fewer) | **Low**<br>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<br>(95% CI: 0.33 - 0.98)<br>Based on data from 31 patients in 1 study[5]<br>Follow up 12 months | **882** per 1000<br>**503** per 1000<br><br>Difference: **379 fewer per 1000**<br>(95% CI: 591 fewer - 18 fewer) | **Moderate**<br>Due to serious imprecision[6] | Levamisole probably decreases relapse in children with frequently relapsing nephrotic syndrome. |
| Relapse - children with steroid-dependent nephrotic syndrome | Relative risk: 0.86<br>(95% CI: 0.67 - 1.1)<br>Based on data from 68 patients in 1 study[7]<br>Follow up 12 months | **844** per 1000<br>**726** per 1000<br><br>Difference: **118 fewer per 1000**<br>(95% CI: 279 fewer - 84 more) | **Moderate**<br>Due to serious imprecision[8] | Levamisole probably has little or no difference on relapse in children with steroid-dependent nephrotic syndrome. |
| Annual GFR loss | Measured by:<br>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 (MMF)
Comparator: Levamisole

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Levamisole 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 |
| 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] Median follow up 43 months | **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 MMF 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] Median follow up 43 months | **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 MMF 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] Median follow up 43 months | **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] | MMF may have little or no difference on infrequent relapse |

| | | | | |
|---|---|---|---|---|
| Infrequent relapse | Relative risk: 0.88 (95% CI: 0.41 - 1.87) Based on data from 149 patients in 1 study[7] Median follow up 43 months | **165** per 1000 **145** per 1000<br>Difference: **20 fewer per 1000** (95% CI: 97 fewer - 144 more) | **Low** Due to serious risk of bias, Due to serious imprecision[8] | MMF 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] Median follow up 43 months | **14** per 1000 **4** per 1000<br>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 MMF increases or decreases treatment failure |
| Annual GFR loss | Measured by: Scale: - Lower better | Mean Mean<br>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 at 6 months |
| 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) | Due to serious imprecision, Due to serious indirectness[4] | little or no difference on relapse at 12 months |
| | | Difference: **MD 2 higher** (95% CI: 2.44 lower - 6.44 higher) | | |
| 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] Mean follow up 12 months | **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] Mean follow up 3 months | **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<br>6 months | Relative risk: 0.23<br>(95% CI: 0.12 - 0.43)<br>Based on data from 271 patients in 5 studies[5]<br>Mean follow up 6 months | **540** per 1000 **124** per 1000<br>Difference: **416 fewer per 1000**<br>(95% CI: 475 fewer - 308 fewer) | **Moderate**<br>Due to serious risk of bias[6] | Rituximab probably decreases relapse at 6 months |
| Relapse<br>12 months | Relative risk: 0.38<br>(95% CI: 0.13 - 1.09)<br>Based on data from 108 patients in 3 studies[7]<br>Mean follow up 12 months | **974** per 1000 **526** per 1000<br>Difference: **448 fewer per 1000**<br>(95% CI: 740 fewer – 205 more) | **Low**<br>Due to serious risk of bias; Due to serious imprecision[8] | Rituximab may decrease relapse at 12 months. |
| Annual GFR loss | Measured by:<br>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 × 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<br>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<br>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<br>3 years | Measured by:<br>Scale: - Lower better | Difference: | | No studies were found that looked annual GFR loss |
| Relapse<br>6 months | Relative risk: 0.73 (95% CI 0.46 – 1.16)<br>Based on data from 78 patients in 1 study[5]<br>Follow up 12 months | **575** per 1000 **421** per 1000<br><br>Difference:**154 fewer per 1000** (95% CI 371 fewer - 63 more) | **Low**<br>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 complete remission |
| 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 time to relapse |
| Annual GFR loss 3 years | Measured by: Scale: - Lower better | | | | No studies were found that looked |

| | | | | |
|---|---|---|---|---|
| | | Difference: | | annual GFR loss at 3 years |
| Frequent relapse | 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<br><br>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 S14.**
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 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 at 3 years |

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 S15.**
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Mycophenolate mofetil (MMF) for 17 months after rituximab treatment
Comparator: Placebo for 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 complete remission |
| 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 (95% CI: 0.37 – 1.04)<br>Scale: - Higher better<br>Based on data from 78 patients in 1 study[3]<br>Follow up 17 months | **320 days** (median) **654 days** (median)<br><br>Median difference: **334 days longer**<br>(95% CI - ) | **Low**<br>Due to serious imprecision[4] | MMF may increase time to relapse |
| Annual GFR loss<br>3 years | Measured by:<br>Scale: - Lower better | | | No studies were found that looked at annual GFR loss at 3 years |

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: | | 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] Mean follow up 7 months | **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

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

[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 at 3–6 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: [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**

[350] Plank C, Kalb V, Hinkes B, Hildebrandt F, Gefeller O, Rascher W, et al. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome-a randomized controlled multicentre trial by the Arbeitgemeinschaft fur Padiatrische Nephrologie. Pediatric Nephrology 2008;23(9):1483-1493
[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 (MMF) with dexamethasone

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** MMF 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 at 12 months |
| 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<br>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] Mean follow up 12 months | **500** per 1000 **400** per 1000<br>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 at 3 years |

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 (MMF) to maintain remission

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** MMF 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 | Measured by: Scale: - Lower better | Mean Mean | **Low** | Tacrolimus may have little or no |

| | | | | |
|---|---|---|---|---|
| 12 months | 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) | Due to serious risk of bias, Due to serious imprecision[8] | difference on annual 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.

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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** |
|---|---|---|---|---|---|
| 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: 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)<br>Based on data from 60 patients in 1 study[3]<br>Follow up 24 months | **552** per 1000 **806** per 1000<br><br>Difference: **254 more per 1000**<br>(95% CI: 6 more - 618 more) | **Low**<br>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 12–24 months in children with first episode steroid-sensitive nephrotic syndrome |
| Frequent relapses | Relative risk: 1.48 (95% CI: 0.85 - 2.59)<br>Based on data from 61 patients in 1 studies[5]<br>Follow up 24 months | **379** per 1000 **561** per 1000<br><br>Difference: **182 more per 1000**<br>(95% CI: 57 fewer - 603 more) | **Very Low**<br>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:<br>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**

[247] Bagga A., Hari P., Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatric Nephrology 1999;13(9):824-827
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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 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 (4–6 months in 1 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] Mean follow up 19.8 months | **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] Mean follow up 21 months | **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] Mean follow up 22 months | (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] Mean follow up 18.4 months | **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 at 12–24 months |
| 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 at 12–24 months |
| 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] Mean follow up 25 months | **438** per 1000 **438** per 1000 Difference: **0 per 1000** (95% CI: 114 fewer - 149 more) | **High** | 5- or 6-month glucocorticoid therapy duration makes little or no difference to frequent relapses at 12–24 months |
| 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] Mean follow up 12 months | **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 at 12–24 months |
| 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.

**References**

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[253] Hiraoka M., Tsukahara H., Haruki S., Hayashi S., Takeda N., Miyagawa K., et al. Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome. The West Japan Cooperative Study of Kidney Disease in Children. Kidney International 2000;58(3):1247-1252

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[Jamshaid 2022 PMID 35576290] Jamshaid, A. A.; Akhtar, N.; Adnan, A.; Perveen, S.; Chaudhry, A.; Fatima, T.. Outcome Of Short And Long Duration Steroid Therapy In Childhood Nephrotic Syndrome In Terms Of Frequency Of Relapse Rate. J Ayub Med Coll Abbottabad 2022;34:300-303. [PubMed: 35576290]

**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$^2$) | Weight-based prednisolone (1.5 mg/kg [maximum 40 mg]) | **Certainty of the evidence** | **Plain text summary** |
|---|---|---|---|---|---|
| Glucocorticoid-related adverse effects - Cushingoid features | Relative risk: 1.26 (95% CI: 0.61 - 2.59) Based on data from 84 patients in 1 study[1] Follow up 6 months | **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 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 [maximum 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 [maximum 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<br>12 months | Relative risk: 0.63<br>(95% CI: 0.42 - 0.94)<br>Based on data from 59 patients in 1 study[3]<br>Follow up 24 months | **793** per 1000<br>**500** per 1000<br><br>Difference: **293 fewer per 1000**<br>(95% CI: 460 fewer - 48 fewer) | **Low**<br>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<br>(95% CI: 0.35 - 1.37)<br>Based on data from 60 patients in 1 study[5]<br>Follow up 24 months | **433** per 1000<br>**299** per 1000<br><br>Difference: **134 fewer per 1000**<br>(95% CI: 281 fewer - 160 more) | **Very Low**<br>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:<br>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**

[253] Hiraoka M., Tsukahara H., Haruki S., Hayashi S., Takeda N., Miyagawa K., et al. Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome. The West Japan Cooperative Study of Kidney Disease in Children. Kidney International 2000;58(3):1247-1252

[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 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 complete 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] Mean follow up 9 months | **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:<br>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**

[249] Broyer M., Terzi F., Lehnert A., Gagnadoux MF, Guest G., Niaudet P. A controlled study of deflazacort in the treatment of idiopathic nephrotic syndrome. Pediatric Nephrology 1997;11(4):418-422
[273] Singhal R., Pandit S., Dhawan N. Deflazacort versus prednisolone: randomized controlled trial in treatment of children with Idiopathic nephrotic syndrome. Iranian Journal of Pediatrics 2015;25(2): e510-e510
[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 S26.**
Population: First episode of nephrotic syndrome in children
Intervention: High-dose methylprednisolone
Comparator: Prednisolone or prednisone, oral

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Prednisolone (2-month of therapy) | **Absolute effect estimates** 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 | Relative risk: 1.50 (95% CI: 0.47 – 4.78) Based on data from 60 patients in 1 study[1] Follow up 4 weeks | **133** per 1000 | **200** per 1000 Difference: **67 more per 1000** (95% CI: 121 fewer - 255 more) | **Very low** Due to very serious imprecision[2] | We are uncertain whether high-dose methylprednisolone increases or decrease 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 | **10.2** Mean days | **4.8** Mean days | **Moderate** | High-dose methylprednisolone |

| | | | | |
|---|---|---|---|---|
| | Based on data from 75 patients in 2 studies[3] Follow up 1 month | Difference: **MD 5.1 days shorter** (95% CI: 8.2 lower - 2.1 lower) | Due to very serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effect[4] | probably decreases time to remission |
| Time to first relapse | Measured by: Months Scale: - High better Based on data from 15 patients in 1 study[2] Mean follow up 40 months | Mean Mean<br><br>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. Primary study [Liu 2024 38607215] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Not serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study
3. Primary study [265] [Liu 2024 38607215] **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 25%, Selective outcome reporting; **Imprecision: Not serious. Upgrade: Large magnitude of effect.**
5. Primary study [265] **Baseline/comparator:** Control arm of reference used for intervention.
6. **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**

[265] Mocan H., Erduran E., Karaguzel G. High dose methylprednisolone therapy in nephrotic syndrome. Indian Journal of Pediatrics 1999;66(2):171-174

[Liu 2024 38607215] Liu M, Cai Y. Efficacy and Safety of Methylprednisolone Pulse Therapy and Conventional Oral Prednisone for Pediatric Patients With Nephrotic Syndrome. Altern Ther Health Med. 2024:AT10400. Online ahead of print. PMID: 38607215.

[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: | | | 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 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<br>2 years | Relative risk: 1.12<br>(95% CI: 0.64 - 1.94)<br>Based on data from 171 patients in 1 study[3]<br>Follow up 24 months | **216** per 1000 **242** per 1000<br><br>Difference: **26 more per 1000**<br>(95% CI: 78 fewer - 203 more) | **Very Low**<br>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:<br>Scale: - Lower better | Difference: | | 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 first episode of nephrotic syndrome
Intervention: Single daily dose of prednisolone
Comparator: Divided (twice) daily dose of prednisone

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Divided (twice) daily dose | Single-daily 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 |
| Relapse | Relative risk: 0.84 (95% CI: 0.40 - 1.74) Based on data from 56 patients in 1 study[1] Follow up 12 weeks | **370** per 1000 | **310** per 1000 Difference: **60 fewer per 1000** (95% CI: 188 fewer - 308 more) | **Low** Due to serious risk of bias, Due to serious imprecision[2] | Single compared with divided daily prednisolone dose may have little or no difference on relapse within 12 weeks |
| Complete remission | (95% CI: - ) | Difference: | | | No studies were found that looked at complete remission |

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

1. Primary study [Khan 2023 37335578] **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.

**References**

[Khan 2023 37335578] Khan T, Akhtar S, Mukherjee D, Basu S, Tse Y, Sinha R. Single- versus Divided-Dose Prednisolone for the First Episode of Nephrotic Syndrome in Children: An Open-Label RCT. Clin J Am Soc Nephrol. 2023;18(10):1294-1299. doi: 10.2215/CJN.0000000000000216. PMID: 37335578.

**Table S29.**
Population: Children with relapsing nephrotic syndrome
Intervention: Intermittent dose of prednisone
Comparator: Alternate-day dose of 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 slightly decrease relapsing during 6 months of therapy |
| 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 9–12 months |

| | | | | |
|---|---|---|---|---|
| Complete remission | (95% CI: - ) | Difference: | | No studies were found that looked at complete remission |
| Annual GFR | Measured by:<br>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 S30.**
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:<br>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 S31.**
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:<br>Scale: - Lower better | Difference: | | | No studies were found that looked at annual GFR loss |
| Relapse rate per year<br>12 months | Measured by:<br>Scale: - Lower better<br>Based on data from 62 patients in 1 study[1] | Mean | Mean<br>Difference: **MD 0.90 lower** (95% CI: 1.33 lower - 0.47 lower) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[2] | Daily prednisone for relapsing nephrotic syndrome may decrease the annual rate of relapse at 12 months |

| | | | | |
|---|---|---|---|---|
| | 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 S32.**
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 | **Absolute effect estimates** 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] Mean follow up 18 months | **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:<br>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 S33.**
Population: Children with relapsing nephrotic syndrome
Intervention: Single glucocorticoid dose
Comparator: Divided-dose glucocorticoid therapy (3 doses/d)

| **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 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)<br>Based on data from 138 patients in 2 studies[3]<br>Mean follow up 7.5 months | Difference: **164 fewer per 1000**<br>(95% CI: 228 fewer - 25 fewer) | Due to very serious risk of bias[4] | may decrease serious adverse events |
| Annual GFR loss | Measured by:<br>Scale: - Lower better | Difference: | | No studies were found that looked at annual GFR loss |
| Mean time to relapse<br>2 months therapy | Measured by: Months<br>Scale: - Lower better<br>Based on data from 94 patients in 1 study[5]<br>Follow up 9 months | Mean Mean<br>Difference: **MD 0.30 shorter**<br>(95% CI: 1.64 lower - 1.04 higher) | **Low**<br>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 S34.**
Population: Children with relapsing nephrotic syndrome
Intervention: Single glucocorticoid dose (60 mg/d)
Comparator: Divided-dose glucocorticoid therapy (40 mg/d AM, 20 mg/d 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 |
| Serious adverse events | Relative risk: Not estimable (95% CI -) | **0** per 1000 | **0** per 1000 Difference: **0 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 therapy makes a |

| | | | | |
|---|---|---|---|---|
| | Based on data from 104 patients in 2 studies[1] Follow up 12 months | | | 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 at 3 years |
| 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<br><br>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 S35.**
Population: Children with relapsing nephrotic syndrome
Intervention: 1 mg/kg of glucocorticoid
Comparator: 2 mg/kg of 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<br>Scale: - Lower better<br>Based on data from 79 patients in 2 studies[1]<br>Follow up 3-12 months | Mean Mean<br><br>Difference: **MD 0.53 months longer**<br>(95% CI: 0.43 shorter – 1.49 longer) | **Low**<br>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:<br>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)<br>Based on data from 76 patients in 3 studies[5]<br>Mean follow up 7 months | **464** per 1000 **544** per 1000<br><br>Difference: **74 more per 1000**<br>(95% CI 55 fewer - 241 more) | **Low**<br>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 S36.**
Population: Children with relapsing nephrotic syndrome
Intervention: 1 mg/kg of alternate-day prednisolone
Comparator: 1.5 mg/kg of alternate-day 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 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<br>3 months | Relative risk: 1.24<br>(95% CI 0.34 – 4.46)<br>Based on data from 40 patients in 1 study[3]<br>Follow up 3 months | **350** per 1000 **400** per 1000<br><br>Difference: **50 more per 1000**<br>(95% CI: 250 fewer - 350 more) | **Very Low**<br>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 at 3 months |

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 S37.**
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 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:<br>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 S38.**
Population: Children with relapsing nephrotic syndrome
Intervention: Prolonged glucocorticoid therapy (7 months): 60 mg/m$^2$ per day for 4 weeks and 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 and then 40 mg/m$^2$ on alternate days for 4 weeks

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Standard duration (2 months) | **Absolute effect estimates** 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<br>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 at 6 months |
| 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 S39.**
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** | Cyclophosphamide may have little or no |

| | | | | |
|---|---|---|---|---|
| | Based on data from 50 patients in 1 study<br>Follow up 24 months | Difference: **155 more per 1000**<br>(95% CI: 100 fewer - 565 more) | Due to serious risk of bias, Due to serious imprecision[3] | difference on relapse at 24 months |
| Annual GFR loss | Measured by:<br>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 S40.**
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] Mean follow up 28 months | **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 at 12 months |

| | | | | |
|---|---|---|---|---|
| Annual GFR loss | Measured by:<br>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 S41.**
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 | 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<br>12 months | Relative risk: 1.01 (95% CI: 0.73 - 1.39)<br>Based on data from 72 patients in 1 study[3]<br>Mean follow up 42 months | **677** per 1000 **684** per 1000<br><br>Difference: **7 more per 1000**<br>(95% CI: 183 fewer - 264 more) | **Low**<br>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<br>24 months | Relative risk: 0.98 (95% CI: 0.74 - 1.28)<br>Based on data from 73 patients in 1 study[5]<br>Mean follow up 42 months | **750** per 1000 **735** per 1000<br><br>Difference: **15 fewer per 1000**<br>(95% CI: 195 fewer - 210 more) | **Low**<br>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<br>12 months | Relative risk: 0.25 (95% CI: 0.07 - 0.92)<br>Based on data from 22 patients in 1 study[7]<br>Follow up 5–26 months | **727** per 1000 **182** per 1000<br><br>Difference: **545 fewer per 1000**<br>(95% CI: 676 fewer - 58 fewer) | **Low**<br>Due to very serious risk of bias[8] | Cyclophosphamide duration for 8 weeks may decrease relapse at 12 months |
| Annual GFR loss | Measured by:<br>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 S42.**
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) | 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 per 1000** (95% CI: 0 - 0) | **Very Low** Due to very serious risk of bias, Due to very serious imprecision[2] | There were too few who experienced the relapse at 12 months to determine whether low dose cyclophosphamide made a difference |

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|---|---|---|---|---|
| Annual GFR loss | Measured by:<br>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 S43.**
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Intravenous cyclophosphamide
Comparator: Oral cyclophosphamide

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Oral cyclophosphamide | <br>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)<br>Based on data from 83 patients in 2 studies[1]<br>Mean follow up 17 months | **238** per 1000 | **33** per 1000<br>Difference: **205 fewer per 1000** (95% CI: 231 fewer - 67 fewer) | **Low**<br>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<br>6 months | Relative risk: 0.54 (95% CI: 0.34 - 0.88)<br>Based on data from 83 patients in 2 studies[3] | **524** per 1000 | **283** per 1000<br>Difference: **241 fewer per 1000** (95% CI: 346 fewer - 63 fewer) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[4] | Intravenous cyclophosphamide may decrease relapse at 6 months |

| | | | | |
|---|---|---|---|---|
| | Mean follow up 17 months | | | |
| Continuing frequently relapsing or steroid-dependent nephrotic syndrome<br>6 months | Relative risk: 0.4 (95% CI: 0.18 - 0.89)<br>Based on data from 47 patients in 1 study[5]<br>Follow up 22.5 months (mean) | **571** per 1000 **228** per 1000<br><br>Difference: **343 fewer per 1000**<br>(95% CI: 468 fewer - 63 fewer) | **Low**<br>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:<br>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 S44.**
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 at 24 months |

| | | | | |
|---|---|---|---|---|
| | Follow up 24 months | | | |
| Annual GFR loss | Measured by:<br>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 S45.**
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 t 6–9 months |
| Relapse- chlorambucil | Relative risk: 0.47 | **950** per 1000 | **447** per 1000 | **Low** | |

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

| | | | | |
|---|---|---|---|---|
| Annual GFR loss | Measured by:<br>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**

[302] Edefonti A., Ghio L., Bettinelli A., Paterlini G., Giani M., Nebbia G., et al. Unconjugated hyperbilirubinemia due to ciclosporin administration in children with nephrotic syndrome. Contributions to Nephrology 1988;67 121-124

[322] Niaudet P. Comparison of cyclosporin and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: a multicentre randomized controlled trial. The French Society of Paediatric Nephrology. Pediatric nephrology (Berlin, Germany) 1992;6(1):1-3

[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 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)<br>Based on data from 39 patients in 1 study[3]<br>Follow up 24 months | Difference: **206 fewer per 1000**<br>(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:<br>Scale: - Lower better | Difference: | | 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**

[283] Abeyagunawardena A. Intravenous pulsed cyclophosphamide versus vincristine therapy in steroid dependent nephrotic syndrome: a randomised controlled trial [abstract]. Pediatric Nephrology 2007;22(9):1547-1547
[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: Levamisole daily
Comparator: Levamisole alternate day

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Levamisole alternate-day dose | Levamisole daily 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 |
| Relapse | Relative risk: 0.75 (95% CI: 0.52 - 1.09) Based on data from 190 patients in 1 study[1] Follow up 12 months | **438** per 1000 | **330** per 1000 Difference: **108 fewer per 1000** (95% CI: 245 fewer - 29 more) | **Very low** Due to very serious risk of bias, Due to serious imprecision[2] | We are uncertain whether daily compared with alternative-day levamisole increases or decreases relapse at 12 months |
| Sustained remission | Relative risk: 1.34 (95% CI: 0.87 – 2.04) Based on data from 190 patients in 1 study[3] | **271** per 1000 | **362** per 1000 Difference: **91 more per 1000** (95% CI: 41 fewer - 222 more) | **Very low** Due to very serious risk of bias, Due to serious imprecision[4] | We are uncertain whether daily compared with alternative-day levamisole increases or decreases sustained |

| | | | | |
|---|---|---|---|---|
| | Follow up 12 months | | | remission at 12 months |
| Annual GFR | Measured by:<br>Scale: - Lower better | Difference: | | No studies were found that looked at annual GFR loss |

1. Primary study [Banerjee 2024 38822220] **Baseline/comparator:** Control arm of reference used for intervention. Results calculated from inverse reported in study (no or infrequent relapses).
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
3. Primary study [Banerjee 2024 38822220] **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: Serious.** Only data from one study

**References**

[Banerjee 2024 38822220] Banerjee S, Sengupta J, Sinha R, Chatterjee S, Sarkar S, Akhtar S, Saha R, Pahari A. Daily compared with alternate-day levamisole in pediatric nephrotic syndrome: an open-label randomized controlled study. Pediatr Nephrol. 2024;39(10):2969-2977. doi: 10.1007/s00467-024-06402-9. PMID: 38822220.

**Table S48.**
Population: Children with frequently relapsing nephrotic syndrome during infections
Intervention: Levamisole, oral
Comparator: Prednisone, oral

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Prednisone 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 | (95% CI: - ) | Difference: | | No studies were found that looked at infection |
| Malignancy | (95% CI: - ) | Difference: | | No studies were found that looked at malignancy |
| Frequent relapses | Relative risk: 0.56 (95% CI: 0.35 – 0.92) Based on data from 160 patients in 1 study[1] Follow up 12 months | **400** per 1000 **225** per 1000 Difference: **175 fewer per 1000** (95% CI: 316 fewer - 34 fewer) | **Low** Due to serious risk of bias, Due to serious imprecision[2] | Levamisole may decrease frequent relapses compared to prednisone at 12 months |
| Relapse | Relative risk: 1.15 (95% CI: 0.94 – 1.40) Based on data from 160 patients in 1 study[1] Follow up 12 months | **663** per 1000 **763** per 1000 Difference: **100 more per 1000** (95% CI: 39 fewer - 239 more) | **Low** Due to serious risk of bias, Due to serious imprecision[2] | Compared with prednisone, levamisole may have little or no difference on relapse |

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

1. Primary study [Sinha 2024 38360110] **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study
3. Primary study [Sinha 2024 38360110] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants, resulting in potential for performance bias; **Imprecision: Serious.** Only data from one study

**References**

[Sinha 2024 38360110] Sinha A, Devi KG, Kalra S, Mani K, Hari P, Bagga A. An open label non-inferiority randomized controlled trial evaluated alternate day prednisolone given daily during infections vs. levamisole in frequently relapsing nephrotic syndrome. Kidney Int. 2024;105(5):1113-1123. doi: 10.1016/j.kint.2024.01.028. PMID: 38360110.

**Table S49.**
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 at 6–9 months |
| 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] | 12 months after 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<br>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 24 months after 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<br>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**

[300] Donia AF, Ammar HM, El Agroudy A., Moustafa F., Sobh MA. Long-term results of two unconventional agents in steroid-dependent nephrotic children. Pediatric Nephrology 2005;20(10):1420-1425
[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 S50.**
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Mycophenolate mofetil (MMF)
Comparator: Cyclosporine

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Cyclosporine 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 |
| 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 per 1000** (95% CI: 0 - 0) | **Very Low** Due to serious risk of bias, Due to very serious imprecision[2] | We are uncertain whether MMF 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 12 months | Relative risk: 1.9 (95% CI: 0.66 - 5.46) Based on data from 82 patients in 2 studies[3] Mean follow up 12 months | **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 MMF 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] Mean follow up 10 months | **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] | MMF 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] | MMF 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**

[301] Dorresteijn E., Van ER, Nauta J., van der Heijden B. Intestinal permeability in patients treated with mycophenolate mofetil (MMF) for nephrotic syndrome (NS) [abstract]. Pediatric Nephrology 2010;25(9):1865-1866
[316] Uddin GM, Rahman MA, Rahman MH, Roy RR, Begum A., Huque SS. Comparative efficacy of mycophenolate mofetil and cyclosporine in children with frequent relapse nephrotic syndrome [abstract]. Pediatric Nephrology 2016;31(10):1852-1853
[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
[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 frequently relapsing steroid-sensitive nephrotic syndrome
Intervention: Changing cyclosporine dose
Comparator: Fixed cyclosporine dose

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Fixed cyclosporine dose | <br>Changing cyclosporine dose | **Certainty of the evidence** | **Plain text summary** |
|---|---|---|---|---|---|
| Relapse<br>24 months | Relative risk: 0.65 (95% CI: 0.45 - 0.94)<br>Based on data from 44 patients in 1 study[1]<br>Follow up 24 months | **900**<br>per 1000 | **585**<br>per 1000<br><br>Difference: **315 fewer per 1000**<br>(95% CI: 495 fewer - 54 fewer) | **Low**<br>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 |

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|---|---|---|---|---|
| Relapse<br>6 months | Relative risk: 0.31<br>(95% CI: 0.1 - 1.02)<br>Based on data from 44 patients in 1 study[3]<br>Follow up 24 months | **400** per 1000 **124** per 1000<br>Difference: **276 fewer per 1000**<br>(95% CI: 360 fewer - 8 more) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[4] | Changing cyclosporine dose may have little or no difference on relapse at 6 months |
| Relapse<br>12 months | Relative risk: 0.33<br>(95% CI: 0.16 - 0.7)<br>Based on data from 44 patients in 1 study[5]<br>Follow up 24 months | **750** per 1000 **248** per 1000<br>Difference: **502 fewer per 1000**<br>(95% CI: 630 fewer - 225 fewer) | **Low**<br>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:<br>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**

[310] Ishikura K., Ikeda M., Hattori S., Yoshikawa N., Sasaki S., Ijima K., et al. A 2-year, prospective, randomized, multicenter trial of cyclosporine in children with frequently relapsing nephrotic syndrome [abstract]. Pediatric Nephrology 2007;22(9):1531-1531

[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 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<br>2 years | Relative risk: 0.74<br>(95% CI: 0.45 - 1.22)<br>Based on data from 85 patients in 1 study[5]<br>Follow up 24 months | **500** per 1000 **370** per 1000<br><br>Difference: **130 fewer per 1000**<br>(95% CI: 275 fewer - 110 more) | **Low**<br>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<br>2 years | Relative risk: 0.42<br>(95% CI: 0.18 - 0.99)<br>Based on data from 85 patients in 1 study[7]<br>Follow up 24 months | **334** per 1000 **140** per 1000<br><br>Difference: **194 fewer per 1000**<br>(95% CI: 274 fewer - 3 fewer) | **Low**<br>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:<br>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**

[308] Iijima K., Sako M., Oba MS, Ito S., Hataya H., Tanaka R., et al. Cyclosporine C2 monitoring for the treatment of frequently relapsing nephrotic syndrome in children: a multicenter randomized phase II trial. Clinical Journal of the American Society of Nephrology: CJASN 2014;9(2):271-278

[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 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 at 6 months |
| 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**

[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

[293] Barratt TM, Cameron JS, Chantler C., Counahan R., Ogg CS, Soothill JF. Controlled trial of azathioprine in treatment of steroid-responsive nephrotic syndrome of childhood. Archives of Disease in Childhood 1977;52(6):462-463

[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 S54.**
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 S55.**
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**

[320] Zhang B., Liu T., Wang W., Zhang X., Fan S., Liu Z., et al. A prospective randomly controlled clinical trial on azithromycin therapy for induction treatment of children with nephrotic syndrome. European Journal of Pediatrics 2014;173(4):509-515

[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 S56.**
Population: Children with relapsing steroid-dependent nephrotic syndrome or frequent relapsing nephrotic syndrome
Intervention: Rituximab (lower dosing regimen)
Comparator: Rituximab (standard dosing regimen)

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Rituximab standard dose | Rituximab lower 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: 0.51 (95% CI: 0.26-1.00) Based on data from 29 patients in 1 study[1] Follow up ~20 months | **786** per 1000 | **400** per 1000 Difference: **386 fewer per 1000** (95% CI: 714 fewer – 58 fewer) | **Low** Due to serious risk of bias, Due to serious imprecision[2] | Low dose rituximab may decrease the rate of infection |
| Malignancy | (95% CI: - ) | Difference: | | | No studies were found that looked at malignancy |
| Relapse | Relative risk: Not estimable (95% CI - ) Based on data from 29 patients in 1 study[3] Follow up ~ 20 months | **0** per 1000 | **0** per 1000 Difference: **0 per 1000** (95% CI: 60 fewer - 60 more) | **Very low** Due to serious risk of bias, Due to very serious imprecision[4] | We are uncertain whether lower dose rituximab increases or decreases relapse compared with standard dose |
| Complete remission | (95% CI: - ) | | | | No studies were found that looked at complete remission |

| | | | | |
|---|---|---|---|---|
| Annual GFR | Measured by:<br>Scale: - Lower better | | | No studies were found that looked at annual GFR loss |

1. Primary study [Zhu 2023 37382130] **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. Primary study [Zhu 2023 37382130] **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.** No events so no estimate possible, Only data from one study

[Zhu 2023 37382130] Zhu Y, Wu L, Wang Y, Zhu YF, Peng Y, Fang SH, Zhang LD, Deng F. Efficacy and safety of low-dose rituximab in treatment of pediatric nephrotic syndrome: a prospective randomized controlled trial. Zhongguo Dang Dai Er Ke Za Zhi. 2023;25(6):606-611. doi: 10.7499/j.issn.1008-8830.2301026. PMID: 37382130.

**Table S57.**
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Rituximab, single dose
Comparator: Mycophenolate mofetil (MMF) 350 mg/d twice daily (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 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 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 complete remission |
| 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 decreases relapse at 12 months |

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

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 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 S58.**
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<br>Scale: - Lower better<br>Based on data from 34 patients in 1 study[1]<br>Follow up 12 months | **1.6** per patient/year **1.1** per patient/year<br>Difference: **0.5 fewer infections per patient/year** (95% CI: 1.1 fewer – 0.1 more) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[2] | Rituximab may have little or no difference on infection |
| 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)<br>Based on data from 40 patients in 1 study[3]<br>Follow up 12 months | **550** per 1000 **550** per 1000<br>Difference: **0 per 1000** (95% CI: 310 fewer - 310 more) | **Very Low**<br>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 |
| Relapse | Relative risk: 0.85 (95% CI: 0.47 – 1.54)<br>Based on data from 74 patients in 2 studies[5] | **405** per 1000 **324** per 1000<br>Difference: **61 fewer per 1000** (95% CI: 215 fewer - 219 more) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[6] | Rituximab may have little or no different effect on relapse |

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

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 S59.**
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<br>Scale: - Lower better<br>Based on data from 34 patients in 1 study[1]<br>Follow up 12 months | **2.6** per patient/year **1.1** per patient/year<br>Difference: **1.5 fewer infections per patient/year** (95% CI: 2.2 fewer – 0.8 more) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[2] | Rituximab may have little or no difference on infections |
| Malignancy | (95% CI - ) | Difference: | | No studies were found that looked at malignancy |
| Complete remission | (95% CI - ) | Difference: | | No studies were found that looked complete remission |
| Relapse | Relative risk: 0.20 (95% CI: 0.07 – 0.57)<br>Based on data from 34 patients in 1 study[3]<br>Follow up 12 months | **882** per 1000 **176** per 1000<br>Difference: **706 fewer per 1000** (95% CI: 943 fewer - 469 fewer) | **Moderate**<br>Due to serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effec[4] | Rituximab probably reduces relapse |

| | | | | |
|---|---|---|---|---|
| Time to relapse | Measured by:<br>Scale – Higher better<br>Based on data from 34 patients in 1 study[5]<br>Follow up 12 months | **3.3 months** **8.3 months**<br><br>Mean difference:**5.0 months longer**<br>(statistically significant) | **Moderate**<br>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 |
| Annual GFR loss<br>3 years | Measured by:<br>Scale: - Lower better | Annual GFR loss<br>3 years | | No studies were found that looked at annual GFR loss at 3 years |

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 S60.**
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<br>Scale: - Lower better<br>Based on data from 34 patients in 1 study[1]<br>Follow up 12 months | **2.6** per patient/year **1.6** per patient/year<br>Difference: **1.0 fewer infections per patient/year** (95% CI: 1.8 fewer – 0.2 fewer) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[2] | Tacrolimus may result in a lower infection rate |
| 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 | Relative risk: 0.40 (95% CI: 0.21 – 0.78)<br>Based on data from 34 patients in 1 study[3] | **882** per 1000 **353** per 1000<br>Difference: **529 fewer per 1000** (95% CI: 803 fewer - 256 fewer) | **Moderate**<br>Due to serious risk of bias, Due to serious imprecision, Upgraded due to | Tacrolimus probably reduces relapse |

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

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 S61.**
Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: Adrenocorticotropic hormone (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 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 at 6 months |
| 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

*Steroid-resistant nephrotic syndrome in children*

**Table S62.**
Population: Children with steroid-resistant nephrotic syndrome after 6 months of cyclosporine or mycophenolate mofetil (MMF)
Intervention: Cyclosporine 2.5 mg/kg twice daily x 12 months (without steroids)
Comparator: MMF 0.5 g/m$^2$ twice daily x 12 months (without steroids)

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** MMF 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 4 (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 cyclosporine increases or decreases grade 4 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] | Cyclosporine may have a lower complete remission rate |

| | | | | |
|---|---|---|---|---|
| Time to relapse | 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 | **10.8 months** median **8 months** median<br>Median difference: **2.8 months fewer** (95% CI - ) | **Low** Due to serious risk of bias; Due to serious imprecision[6] | Cyclosporine may have shorter time to relapse |
| Annual GFR loss 3 years | Measured by: Scale: - Lower better | Difference: | | No studies were found that looked at annual GFR loss at 3 years |

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 S63.**
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] Mean follow up 37 months | **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] Mean follow up 30.5 months | **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 | | | | No studies were found that looked |

| | | | | |
|---|---|---|---|---|
| 3 years | | Difference: | | at annual GFR loss at 3 years |

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 S64.**
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 S65.**
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/pneumonia |
| 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<br><br>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 at 3 years |

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 S66.**
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: | | | 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: [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 S67.**
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Mycophenolate mofetil (MMF)
Comparator: Cyclophosphamide

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Cyclophosphamide / 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 |
| 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] | MMF may have little or no difference on complete remission at 6 months |
| 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] | MMF may have little or no difference on complete remission at 12 months |

| | | | | |
|---|---|---|---|---|
| Annual GFR loss | Measured by:<br>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 S68.**
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Leflunomide
Comparator: Mycophenolate mofetil (MMF)

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** MMF 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 at 6–12 months |
| 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 S69.**
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 at 6 months |
| 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:<br>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 S70.**
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] Mean follow up 9 months | **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] Mean follow up 9 months | **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 S71.**
Population: Children with steroid-resistant nephrotic syndrome
Intervention: Intravenous cyclophosphamide
Comparator: Oral cyclophosphamide plus intravenous dexamethasone

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Oral cyclophosphamide plus IV dexamethasone | <br>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)<br>Based on data from 46 patients in 1 study[1]<br>Follow up 18 months | **740** per 1000 | **577** per 1000<br>Difference: **163 fewer per 1000** (95% CI: 355 fewer - 126 more) | **Low**<br>Due to very serious imprecision[2] | Intravenous cyclophosphamide may have little or no difference on cushingoid features |
| Complete remission<br>6 months | Relative risk: 1.13 (95% CI: 0.65 - 1.96)<br>Based on data from 49 patients in 1 study[3]<br>Follow up 18 months | **479** per 1000 | **541** per 1000<br>Difference: **62 more per 1000** (95% CI: 168 fewer - 460 more) | **Low**<br>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<br>18 months | Relative risk: 1.13 (95% CI: 0.65 - 1.96)<br>Based on data from 49 patients in 1 study[5]<br>Follow up 18 months | **479** per 1000 | **541** per 1000<br>Difference: **62 more per 1000** (95% CI: 168 fewer - 460 more) | **Low**<br>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)<br>Based on data from 46 patients in 1 study[7]<br>Follow up 18 months | **434** per 1000 | **17** per 1000<br>Difference: **417 fewer per 1000** (95% CI: 434 fewer - 139 fewer) | **Moderate**<br>Due to serious imprecision[8] | Intravenous cyclophosphamide may decrease hypertension |
| Hypokalemia | Relative risk: 0.06 (95% CI: 0.0 - 0.98)<br>Based on data from 46 patients in 1 study[9] | **305** per 1000 | **18** per 1000<br>Difference: **287 fewer per 1000** | **Moderate**<br>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 per 1000** (95% CI: 0 - 0) | **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)<br>Based on data from 46 patients in 1 study[17]<br>Follow up 18 months | Difference: **34 more per 1000**<br>(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:<br>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 S72.**
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 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 S73.**
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 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 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]