KDIGO GN Guideline update – Evidence summary

Steroid-sensitive nephrotic syndrome

Corticosteroid therapy for nephrotic syndrome in children

PICO question

In children (aged 3 to 18 years of age) with steroid-sensitive nephrotic syndrome, what corticosteroid therapy regimens compared with no treatment/placebo or standard of care improve efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

Search strategy and selection

Keywords for steroid-sensitive nephrotic syndrome, and corticosteroids were used to search the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials (RCTs) published up to April 2018.

Search results

The corticosteroid therapy Cochrane review was originally published in 2000, and updates published in 2003, 2005, 2007 and 2015. The previous searches of relevant medical literature databases for previous Cochrane reviews identified 519 reports. The 2015 update search identified 48 relevant reports and the April 2018 search identified 20 reports from the Cochrane Kidney and Transplant Specialized Register.

Overall, 45 primary studies (79 reports) with 3901 participants were included.

Four ongoing studies were also identified from the Indian clinical trials registry and published protocols.

Nine comparisons of steroid therapy in the first episode of steroid-sensitive nephrotic syndrome:

1. 1 month corticosteroid therapy compared with 2 months therapy (12 studies, 1201 children)* (1-10)
2. Five to 6 months versus 3 month therapy (9 studies, 913 children)* (11-17)
3. Less than 2 months versus 2 months (1 study, 61 children) (3)
4. 12 months versus 5 months therapy (1 study, 58 children) (18)
5. Different total doses of prednisone (1 study, 59 children) (19)
6. Steroid therapy and Sairei-to (1 study, 171 children) (20)
7. High dose methylprednisolone and 2 months therapy (1 study, 15 children) (21)
8. Deflazacort with or without prednisone versus prednisone alone (2 studies, 65 children) (22, 23)
9. Weight-based versus BSA-based dosing of prednisolone (1 study, 100 children) (24)

* One study had children in each comparison group

Ten comparisons in children with frequently relapsing steroid-sensitive nephrotic syndrome:

1. Daily compared with alternate-day prednisone dose for relapsing nephrotic syndrome (1 study, 62 children) (25)
2. Intermittent dose versus alternate-day prednisone dose (1 study, 43 children) (26)
3. Daily versus intermittent prednisone therapy (1 study, 50 children) (19)
4. Single versus divided prednisone dose (2 studies, 138 children) (27, 28)

5. Intravenous versus oral corticosteroid (1 study, 64 children) (29)
6. Prolonged oral versus intermittent therapy (2 months therapy) (1 study, 50 children) (4)
7. Prolonged steroid therapy (7 months) versus 2 months therapy (1 study, 129 children) (30)
8. Daily prednisolone treatment during viral infections (3 studies, 194 children) (31-33)
9. Cortisol versus placebo (1 study, 26 children) (34)
10. Deflazacort versus methylprednisolone (1 study, 11 children) (35)

Summary of the main findings

- RCTs did not report on all-cause mortality, end-stage kidney disease or malignancy as these outcomes rarely occur in children with nephrotic syndrome.
- Children with nephrotic syndrome largely maintain normal GFR hence annual GFR loss is rarely reported.

Treatment of the first episode of steroid-sensitive nephrotic syndrome

Duration of corticosteroid therapy

Compared with 2 months duration

- PICO 11.1 - The use of corticosteroid therapy for 1 month compared to 2 months may increase relapse at 6 months (RR 1.60, 95%CI 1.01 to 2.54; 1 study, 61 participants), and 12 to 24 months (RR 1.46, 95%CI 1.01 to 2.12, 1 study, 60 participants). However, the effect on the number of children developing frequent relapsing disease is unclear due to study limitations and serious imprecision. Other critical and important outcomes were not reported in RCTs.
- PICO 11.2 - Corticosteroid therapy for 3 months or more compared to 2 months of therapy may have little or no effect on infection. Other critical outcomes are not reported in RCTs. It may decrease relapse at 12 to 24 months (RR 0.79, 95%CI 0.65 to 0.95; 11 studies, 1108 children), and have little or no effect on the number of children developing frequenting relapsing disease (RR 0.79, 95%CI 0.59, 1.06; 7 studies, 805 participants) (low certainty evidence – very serious study limitations).
    - When studies are stratified according to study limitations, in studies with low risk of bias for allocation concealment, there was little or no difference in the number of children developing frequenting relapsing disease (RR 0.99, 95%CI 0.82 to 1.19; 4 studies, 585 children) (high certainty in the evidence). In studies with a high risk of bias for allocation concealment, 3 months of therapy compared to 2 months of therapy probably decrease frequenting relapse disease (RR 0.45, 95%CI 0.26 to 0.77; 3 studies, 220 children).
- There was low to very low certainty of the evidence of 3 months or more compared to 2 months duration on corticosteroid-related adverse events. However, it probably made little or no difference to Cushing's syndrome (RR 1.29, 95%CI 0.87 to 1.90; 5 studies, 417 children).
- PICO 11.3 - Corticosteroid therapy for 5 to 6 months duration compared to 3 months duration may decrease relapse at 12 to 24 months (RR 0.62, 95%CI 0.45 to 0.85; 7 studies, 763 children), and have little or no effect on the number of children developing frequenting relapsing disease (RR 0.73, 95%CI 0.49, 1.09) (low certainty of the evidence – study limitations and serious inconsistency). The longer duration of steroids probably had little or no effect on corticosteroid-related adverse events and may have little or no effect on infection compared to the shorter 3 months duration of therapy.
    - When studies are stratified according to study limitations, in studies with low risk of bias for allocation concealment, there was little or no difference in the number of children developing frequenting relapsing disease (RR 1.00, 95%CI 0.74 to 1.34; 3 studies, 377 children) (High certainty of the evidence). While, in studies with a high risk of bias for allocation concealment, 5 or 6 months of therapy compared to 3

months of therapy probably decrease frequenting relapse disease (RR 0.48, 95%CI 0.32 to 0.72; 3 studies, 330 children) (moderate certainty in the evidence)

- 12 months compared to 5 months duration of corticosteroid therapy was examined in one study (58 children), it found the longer duration of therapy had little or no effect on relapse (RR 0.76. 95%CI 0.51 to 1.13). Other critical and important outcomes were not examined in RCTs.

Corticosteroid dose

PICO 11.5 - Weight-based (1.5mg/kg, maximum 40 mg versus body-surface area-based dosing prednisolone of 40 mg/m^2) (1 study, 100 children)

- We are uncertain if weight based dosing compared to BSA-based dosing of prednisolone increases or decreases infection, and Cushingoid features due to study limitations and effect estimates that cross the null with appreciable benefit and harm. It may make little or no difference to relapse at 6 months. Other critical and important outcomes were not reported in the RCT.

PICO 11.6 - High total dose (60 mg/m^2/day (max 80 mg) for 6 weeks, 40 mg/m^2/day on alternate days for 6 weeks) compared with lower total dose (40 mg/m^2/day (max 60 mg) for 6 weeks, 40 mg/m^2/day on alternate days for 6 weeks. (1 study, 60 participants)

- Higher total dose compared to lower total dose prednisone may decrease relapse at 12 months (RR 0.63, 95%CI 0.42 to 0.94; 1 study, 59 children). Effects on the development of frequently relapsing nephrotic syndrome is unclear, likewise for Cushing's syndrome, as this has only been examined in one small RCT and the certainty of the evidence is very low (study limitations and serious imprecision).

Other

- PICO 11.7 (2 studies, 65 participants) - Deflazacort compared to prednisolone probably decreases relapse at 9 to 12 months (RR 0.47. 95%CI 0.28 to 0.79; 2 studies, 65 children) (moderate certainty of the evidence – study limitations) and may have little or no effect on complete remission at 6 weeks (RR 1.17, 95%CI 0.90 to 1.53; 1 study, 25 children) (low certainty of the evidence – study limitations and serious imprecision). Other critical and important outcomes were not reported in RCTs.
- PICO 11.8 – We are uncertain if the use of high dose methylprednisone compared to prednisone alone may decrease the time to remission (days) (MD 5.54 lower, 95%CI 8.46 lower to 2.61 lower; 2 studies, 38 children). We are uncertain of the effect on time to first relapse (months) due to study limitations and effect estimates that cross the null with both appreciable benefit and harm. No other critical or important outcomes were examined in RCTs.
- PICO 11.9 - We are unable to determine the effect of long prednisone duration plus Sairei-to compared with standard prednisone duration and Sairei-to on critical and important outcomes as they were not reported or because the certainty of the evidence is very low for the outcomes relapse and the development of frequently relapsing nephrotic syndrome.

<u>Nephrotic syndrome in children with viral infections</u>

PICO 11.10 - *Daily prednisolone compared with placebo or alternate day prednisolone (4 studies,)*

- Daily prednisolone may have little or no effect on the number of relapses with infection (RR 0.49, 95%CI 0.18 to 1.30; 1 study, 40 children) compared to alternate-day prednisolone.
    - However, its use may decrease the rate of infection-related relapses (MD 0.7 lower, 95%CI 0.87 lower to 0.53 lower) (relapses/patient/year), and the rate of infection-related relapses per patient at 2 years (MD 3.3 lower, 95%CI 4.03 lower to 2.57 lower).
- Other critical and important outcomes were not reported in RCTs

Children with relapsing nephrotic syndrome

Type of steroid therapy

- PICO 11.11 - Intermittent dose versus alternate-day therapy (1 study, 48 children) may have little or no difference on relapse during 6 months of therapy (RR 0.60, 95%CI 0.36 to 1.02), and 9 to12 months (RR 1.20, 95%CI 0.93 to 1.55). Other critical and important outcomes were not reported in RCTs.
- PICO 11.12 - Daily steroid therapy compared to intermittent steroid therapy may decrease relapse (RR 0.20, 95%CI 0.05 to 0.82; 1 study, 50 children). Other critical and important outcomes were not reported in RCTs.
- PICO 11.13 - The use of daily steroid therapy compared to alternate day steroid therapy may decrease the annual relapse rate (MD 0.90 lower, 95%CI 1.33 lower to 0.47 lower; 1 study, 62 children). Other critical and important outcomes were not reported in RCTs.
- PICO 11.14 - Compared to divided corticosteroid dose, single corticosteroid dose may have little or no effect on relapse (RR 1.07, 95%CI 0.93 to 1.55; 1 study, 94 children). However, it may decrease mean time (months) to relapse (MD 0.30 lower, 95%CI 1.64 lower to 1.04 lower; 1 study, 94 children). A single corticosteroid dose may decrease serious adverse effects compared to divided corticosteroid dose (RR 0.41, 95%CI 0.18 to 0.91). Other critical and important outcomes were not reported in RCTs.
- PICO 11.15 - Intravenous steroid therapy compared with oral steroid therapy may have little or no effect on relapse at 9 to 12 months (RR 1.06, 95%CI 0.75 to 1.52; 1 study. 64 children). Other critical and important outcomes were not reported in RCTs.

Dose and duration of steroid therapy

- PICO 11.16 - The use of lower dose (1 mg/kg) corticosteroid compared with higher dose (2 mg/kg) corticosteroid may have little or no effect on time to remission. Other critical and important outcomes were not reported in the small RCT (20 children)
- PICO 11.17 - We are uncertain the effects of prednisone at 60 mg/m^2/day for 4 weeks and tapered daily dose for 4 weeks compared to 60 mg/m^2/day till remission and 40 mg/m^2 on 3/7 consecutive days because it has only been examined in one small RCT (50 children), with very serious study limitations.
- PICO 11.18 - Prolonged duration of steroid therapy for 7 months (60 mg/m^2/day for 4 weeks, then 60 mg/m^2 on alternate days. Reducing alternate-day dose by 10 mg/m^2 every 4 weeks) compared to standard duration of steroid therapy for 2 months (60 mg/m^2/day till urine protein-free for 3 days, then 40 mg/m^2 on alternate days for 4 weeks) may decrease relapse at 6 months (RR 0.04, 95%CI 0.01 to 0.25), and may decrease relapse at 1 year (RR 0.43, 95%CI 0.29 to 0.65), 2 years (RR 0.60, 95%CI 0.45 to 0.80), and 3 years (RR 0.71, 95%CI 0.56 to 0.90). It may also decrease the development of frequently relapsing or steroid-dependent nephrotic syndrome (RR 0.43, 95%CI 0.19 to 0.95) (low certainty of the evidence – study limitations, serious imprecision).

Non-corticosteroid immunosuppressive therapy of steroid-sensitive nephrotic syndrome

PICO question

In children (aged 3 to 18 years of age) with steroid-sensitive nephrotic syndrome, what non-corticosteroid immunosuppressive regimens compared to no treatment/placebo or standard of care improve efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

Search strategy and selection

Keywords for steroid-sensitive nephrotic syndrome, and immunosuppressive therapy were used to search the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials (RCTs) published up to April 2018.

Search results

The corticosteroid therapy Cochrane review was originally published in 2001, and updates published in 2005, 2008 and 2013. The previous searches of relevant medical literature databases for previous Cochrane reviews identified 832 reports. The 2013 update search identified 30 relevant reports and the April 2018 search identified 38 reports from the Cochrane Kidney and Transplant Specialized Register. Eight primary studies (23 reports), eight reports of included studies in the previous Cochrane reviews. Four studies (7 reports) from the 2018 search were excluded as they were not RCTs, were not non-corticosteroid immunosuppressive therapy, the wrong population, or have been withdrawn by the journal because of forgery.

Overall, there was 40 primary studies (67 reports) with 1990 participants were included.

Seven ongoing studies were also identified from the clinicaltrials.gov and published protocols.

Sixteen comparisons for induction therapy were included:

1. Alkylating agent versus placebo/prednisone (7 studies, 210 children) (36-42)
2. Alkylating agent (different durations, doses, route) (6 studies, 219 children) (43-48)
3. Different alkylating agents (1 study, 50 children) (49)
4. Alkylating agent versus vincristine (1 study, 39 children) (50)
5. Calcineurin inhibitor versus prednisone alone (1 study, 127 children) (51)
6. Calcineurin inhibitor versus alkylating agent (2 studies, 95 children) (52, 53)
7. Calcineurin inhibitor versus mycophenolate mofetil (3 studies (1 cross-over study), 89 children) (54-56)
8. Calcineurin inhibitor (different doses) (2 studies, 188 children) (57, 58)
9. Levamisole versus placebo/prednisone (8 studies, 422 children) (42, 59-65)
10. Levamisone versus alkylating agent (1 study, 40 children) (42)
11. Levamisole versus alkylating agent vs prednisone (1 study, 85 children) (66)
12. Rituximab versus placebo or control (4 studies, 154 children) (67-69)
13. Rituximab + calcineurin inhibitor versus calcineurin inhibitor (1 study, 54 children) (69)
14. Azathioprine versus placebo (2 studies, 60 children) (36, 70)
15. Mizoribine versus placebo (1 study, 197 children) (71)
16. Fucidic acid versus prednisone (1 cross-over study, 18 children) (72)

Summary of the main findings

- RCTs did not report on all-cause mortality, end-stage kidney disease and malignancy as these outcomes rarely occur in children with nephrotic syndrome.
- Children with nephrotic syndrome largely maintain normal GFR hence annual GFR loss is rarely reported.

PICO 11.19 - Alkylating agent versus placebo/prednisone (5 studies, 147 participants)

- Cyclophosphamide compared with prednisone or placebo probably decreases relapse at 6 to 12 months (RR 0.47, 95%CI 0.33 to 0.66; 4 studies, 157 children) and 12 to 24 months (RR 0.21, 95%CI 0.07 to 0.65; 2 studies, 27 children)
- However, chlorambucil compared with prednisone or placebo probably make little or no effect on relapse after 6 to 12 months (RR 0.19, 95%CI 0.03, 1.09, 2 studies, 41 participants), and may decrease relapse at 12 months (RR 0.15, 95%CI 0.02, 0.95)
- Other critical and important outcomes were not reported by RCTs.

Alkylating agent (different durations, doses, route)

- *PICO 11.20* - Cyclophosphamide compared to chlorambucil was examined in one RCT (50 children), it may have little or no effect on relapse at 24 months (RR 1.31, 95%CI 0.80 to 2.13). However, its effect on relapse at 12 months is unclear because of study limitations, and an effect estimate that crosses the null with appreciable benefits and harm.

- PICO 11.21 - Intravenous compared with oral cyclophosphamide probably decrease infection (RR 0.14, 95%CI 0.03 to 0.72; 2 studies, 83 participants), it may also decrease relapse at six months (RR 0.54, 95%CI 0.34 to 0.88), and the development of frequently relapsing or steroid- dependent nephrotic syndrome (RR 0.40, 95%CI 0.18 to 0.89; 1 study, 47 participants). Other critical and important outcomes were not reported in RCTs.
- PICO 11.22 Two RCTs examined longer versus shorter duration cyclophosphamide. One study compared 12 weeks versus 8 weeks duration (50 children), the longer duration therapy may have little or no effect on relapse at 12 months (RR 1.01, 95%CI 0.73 to 1.39), and 24 months (RR 0.98, 95%CI 0.74 to 1.28). The other RCT found (29 children), that cyclophosphamide therapy for 8 weeks compared to 2 weeks may decrease relapse at 12 months (RR 0.25, 95%CI 0.07 to 0.92), its effects on relapse at 6 months are uncertain because of very low certainty of the evidence. Other critical and important outcomes were not reported in RCTs.
- PICO 11.23 - We are unable to be certain of the effects of lower (2.5 mg/kg/day) compared with higher (5 mg/kg/day) or increasing compared with stable chlorambucil dose because of very low certainty of the evidence.
- PICO 11.24 (1 study, 28 participants) - The effects of an increase chlorambucil dose compared with a stable dose is unclear because of the very low certainty of the evidence.
- PICO 11.25 children with frequently and steroid-dependent patients - One post-hoc analysis of the APN 1982 study (50 children), identified that the use of an alkylating agent in children with frequently-relapsing nephrotic syndrome may decrease relapse at 24 months (RR 0.35, 95%CI 0.15 to 0.85) compared to use in children with frequently relapsing or steroid-dependent nephrotic syndrome. Other critical and important outcomes were not reported.

Alkylating agent compared with other therapies

- PICO 11.26 - Compared to cyclosporin, cyclophosphamide probably decrease relapse at 12 to 24 months (RR 0.40, 95%CI 0.22 to 0.73; 1 study, 55 children) (low certainty of the evidence). Chlorambucil (1 RCT, 40 children) may decrease relapse at 12 months (RR 0.47, 95%CI 0.29 to 0.78) and 24 months (RR 0.58, 95%CI 0.38 to 0.87) (low certainty of the evidence). The use of either cyclophosphamide or chlorambucil decreases hypertrichosis (RR 0.05, 95%CI 0.01 to 0.36; 2 studies, 112 children). Effects on other critical and important outcomes is not clear due to very low certainty of the evidence or because it was not reported in RCTs.
- PICO 11.27 - Cyclophosphamide was compared to vincristine in one small RCT (39 children), it may have little or no effect on relapse at 12 and 24 months (low certainty of the evidence). Other critical and important outcomes were not reported in the RCT.

<u>Other therapies</u>

Levamisole versus other treatment

- PICO 11.28 - Levamisole compared with placebo/no treatment or steroids alone may decrease relapse at 4 to 12 months (RR 0.52, 95%CI 0.33 to 0.82; 8 studies, 474 children) and 6 to 12 months (RR 0.65, 95%CI 0.48 to 0.88; 8 studies, 462 children). It also decreases relapse for patients with frequently relapsing nephrotic syndrome (RR 0.57, 95%CI 0.33 to 0.98; 1 study, 31 children) and it may have little or no effect on relapse for children with steroid-dependent nephrotic syndrome (RR 0.86, 95%CI 0.67 to 1.10; 1 study, 68 children). Other critical and important outcomes were not reported in RCTs.
- PICO 11.29 Children with frequently or steroid-dependent nephrotic syndrome (2 studies, 97 participants) - Levamisole compared with cyclophosphamide may have little or no effect on relapse at 12 months (RR 0.39, 95%CI 0.68, 1.16) or 24 months after therapy (RR 0.89, 95%CI 0.73, 1.10). However, the effect on relapse after 6 months of therapy and at the end of treatment was unclear because very low certainty of the evidence (study limitations, serious imprecision, serious inconsistency) and infection after therapy was unclear due to study

limitations and wide confidence intervals that cross the null with both appreciable benefit and harm. Other critical and important outcomes were not reported in RCTs.

Cyclosporin

- PICO 11.30 Cyclosporin combined with prednisone versus prednisone alone may decrease relapse at 6 months (RR 0.13, 95%CI 0.13 to 0.83; 1 study, 104 children), but may have little or no effect on relapse at 12 months (RR 0.72, 95%CI 0.46, 1.13). Other critical and important outcomes were not reported in RCTs.
    - PICO 11.32 – In children with frequently relapsing or steroid-dependent disease changing cyclosporin dose compared to a fixed cyclosporin dose may decrease relapse at 12 months (RR 0.33, 95%CI 0.16 to 0.70) and 24 months (RR 0.65, 95%CI 0.45, 0.94) but may have little or no effect on relapse at 6 months (RR 0.31, 95%CI 0.10 to 1.02) (1 study, 44 children) in children with relapsing disease.
    - PICO 11.33 - A higher cyclosporin dose (starting at 3-4mg/kg/day in 2 divided doses, dose titrated for whole-blood C2 level between 600 and 700 ng/mL for the first 6 months and then between 450 and 550 ng/mL for the next 18 months) compared to a lower cyclosporin dose (starting at 3-4 mg/kg/day in 2 divided doses, dose titrated for whole-blood C2 level between 450 and 550 ng/mL for the first 6 months and then 300-400 ng/mL for the next 18 months) may decrease the development of frequent relapsing and steroid-dependent nephrotic syndrome (RR 0.42, 95%CI 0.18 to 0.99; 1 study, 85 children), and have little or no effect on relapse (RR 0.74, 95%CI 0.45 to 1.22). Its effect on other critical and important outcomes is unclear as they were not reported in RCTs or the certainty of the evidence was very low.
- PICO 11.31 - Mycophenolate mofetil compared with cyclosporin may improve annual GFR loss (MD 20 higher, 95%CI 5.49 to 34.51 higher; 1 study, 24 children). With uncertain effects on relapse, infection (pneumonia) because of very low certainty of evidence but it may decrease hypertrichoposis (RR 0.23, 95%CI 0.10 to 0.50; 3 studies, 140 children) (low certainty om the evidence).

PICO 11.34 – Children with frequently relapsing or steroid-dependent nephrotic syndrome - Rituximab versus placebo or control

- Rituximab compared with placebo or control may decrease relapse at 3 months (RR 0.32, 95%CI 0.14 to 0.70; 3 studies, 132 children) and decreases relapse at 6 months (RR 0.26, 95%CI 0.15 to 0.45; 4 studies, 154 children) ((low certainty of the evidence). However, its effect on relapse at 12 months and other critical and important outcomes are unclear due to very low certainty of the evidence.

PICO 11.35 – 11.37 - Mizoribine or azathioprine or azithromycin compared with placebo or steroids alone

- Treatment with or azathioprine or azithromycin was compared in small RCTs. The effects are uncertain because of very low certainty of evidence and RCTs not reporting the majority of critical and important outcomes. Treatment with mizoribine compared with placebo may have little or no effect on adverse effects (RR 1.59, 95%CI 0.97, 2.49; 1 study, 197 participants

Effect modifiers

The following table lists the effect modifiers considered for comparisons. Only two comparisons were considered appropriate to examine for effect modifiers in the corticosteroid therapy review

1. Comparisons with 2 months therapy (12 studies, 1201 children)
2. Five to 6 months versus 3 month therapy (9 studies, 913 children)

There was insufficient data to examine effect modifiers in the non-corticosteroid therapy review

Effect modifier	Explanation/ results
Kidney function (GFR, presence of proteinuria, presence of albuminuria)	RCTs did not provide separate data for the measures of kidney function. Trials of patients with initial episodes of steroid-sensitive nephrotic syndrome largely included patients with stable kidney function and excluded patients with deteriorating kidney function.
Relapse (infrequent and frequent) and steroid-dependent	We have presented results separately for patients with initial episode of steroid-sensitive nephrotic syndrome to frequent-relapsing or steroid-dependent nephrotic syndrome in the MAGICapp evidence tables and the summary of findings.
Genetic markers	RCTs did not examine results in regards to genetic markers of disease
Gender	The RCTs included a majority of male (range 60% to 72). One study examining treatment with steroids for 6 months compared to 3 months of steroid therapy (Teeninga 2013) reported hazard ratios according to gender in a multivariate analysis. For first relapse HR was 1.19 (95%CI 0.77 to 1.84) For clinical frequent relapsing nephrotic syndrome HR 1.77 (95%CI 0.98 to 3.03)

1. Teeninga N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *JASN*. 2013;24(1):149-59.

Studies from the 2012 KDIGO GN guideline evidence tables not included in 2018 evidence review.

All RCTs included in the previous guideline evidence summary have been included in this evidence review.

KDIGO Glomerulonephritis guideline update – Evidence review team response – work group comments

Chapter 3 and 4. Steroid-sensitive and steroid-resistant nephrotic syndrome

Marina Vivarelli comments

General comment:

1. **At least for me, it would be really helpful if for each PICO question the relevant bibliography were listed, instead of having it in alphabetical order in the Dropbox file**

Thank you for your patience, we are still learning how best to use MAGICapp. We have now updated MAGICapp to cite references for each outcome and PICO table.

PICO (11.10) Population: Children with nephrotic syndrome and viral infections Intervention: Daily prednisolone Comparator: Placebo or alternate day prednisolone

2. **Comment: the table lists only one study, included I believe in the 2 sequential publications, both by Abeyagunawardeena. However, as far as I can see it omits this study, which is a RCT, and which is in the Dropbox file (has it been included in the analysis?):**

Gulati A, Sinha A, Sreenivas V, Math A, Hari P, Bagga A. Clin J Am Soc Nephrol. 2011 Jan;6(1):63-9. doi: 10.2215/CJN.01850310. Epub 2010 Sep 16.Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial.

This study was previously included in the evidence review but was not linked to MAGICapp. The PICO 11.10 has been updated to include the studies Gulati 2011 (32) and Mattoo 2000 (33), and they have been linked them to the relevant outcome - infection-related relapse.

3. **Moreover, the PREDNOS 2 trial is a UK multicentre double blind randomised controlled trial of short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome (SSNS). It started in 2013 and preliminary results may have been presented at scientific meetings. If possible, this would be worth checking as it is large (360 pts) and certainly well-conducted. Otherwise, it should be earmarked for future updates. This is the publication of the protocol:**

Webb NJ, Frew E, Brettell EA, Milford DV, Bockenhauer D, Saleem MA, Christian M, Hall AS, Koziell A, Maxwell H, Hegde S, Finlay ER, Gilbert RD, Booth J, Jones C, McKeever K, Cook W, Ives NJ; PREDNOS 2 study group. Trials. 2014 Apr 27;15:147. doi: 10.1186/1745-6215-15-147. Short course daily prednisolone therapy during an upper respiratory tract

infection in children with relapsing steroid-sensitive nephrotic syndrome (PREDNOS 2): protocol for a randomised controlled trial.

The PREDNOS 2 trial (9) has been included in the evidence review in PICO 11.2 – corticosteroid therapy 3 months or more duration versus 2 months duration for the outcomes: relapse, frequent relapse and frequent relapse (low risk of bias for allocation concealment). This reference has been cited and linked to PICO.

PICO (11.11 – 11.18) Population: Children with relapses of nephrotic syndrome, different interventions and comparators

4. **Comment: the recommmendation can in my opinion remain as in the 2012 KDIGO guidelines for IRNS and for the use of prednisone in FRNS. However, for the use of prednisone in FRNS, a very recent RCT should be added and evaluated, if possible:**

Yadav M, Sinha A, Khandelwal P, Hari P, Bagga A. Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Pediatr Nephrol. 2018 Sep 7. doi: 10.1007/s00467-018-4071-7

The search for the evidence review for the KDIGO glomerulonephritis guideline update was conducted in April 2018 . Following KDIGO practice, the search will be updated during the public comment period, and relevant studies published since April 2018 will be included.

5. **I would add as something to watch for future updates 2 studies, the first ongoing and the second completed:**

- **Schijvens AM, Dorresteijn EM, Roeleveld N, Ter Heine R, van Wijk JAE, Bouts AHM, Keijzer-Veen MG, van de Kar NCAJ, van den Heuvel LPWJ, Schreuder MF. BMJ Open. 2017 Sep 27;7(9):e018148. doi: 10.1136/bmjopen-2017-018148. REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study- protocol of a national, double-blind, randomised, placebo-controlled, non-inferiority intervention study.**
- **EudraCT Number: 2012-004326-16, PROPINE Study "A Prospective Randomized study to Optimize Prednisone therapy for relapses of Idiopathic NEphrotic syndrome in children (PROPINE study)"**

Thank you for highlighting these ongoing trials. They have been flagged in the Cochrane reviews and will be incorporated when they are published.

Bibliography suggestions for other chapters

6. **Suggested bibliography that can guide practice point statements regarding the use of vitamin D and calcium in children that require prolonged treatment with prednisone/prednisolone (TO BE INCLUDED IN THE GENERAL MANGEMENT CHAPTER ?):**

- **Singh DN, Krishnamurthy S, Kamalanathan SK, Harichandrakumar KT, Sivamurukan P. Three-monthly bolus vitamin D supplements (1000 vs 400 IU/day) for prevention of bone loss in children with difficult-to-treat nephrotic syndrome: a randomised clinical trial. Paediatr Int Child Health. 2018 Aug 9:1-10. doi: 10.1080/20469047.2018.1505589.**
- **Muske S, Krishnamurthy S, Kamalanathan SK, Rajappa M, Harichandrakumar KT, Sivamurukan P. Effect of two prophylactic bolus vitamin D dosing regimens (1000 IU/day vs. 400 IU/day) on bone mineral content in new-onset and infrequently-relapsing nephrotic syndrome: a randomised clinical trial. Paediatr Int Child Health. 2018 Feb;38(1):23-33. doi: 10.1080/20469047.2017.1319528**
- **Yadav VK, Sharma S, Debata PK, Patel S, Kabi BC, Aggrawal KC. Change in Bone Mineral Density and Role of Vitamin D and Calcium Supplementation During**

Treatment of First Episode Nephrotic Syndrome. J Clin Diagn Res. 2017 Sep;11(9):SC18-SC21. doi: 10.7860/JCDR/2017/27030.10657

- **Gruppen MP, Davin JC, Oosterveld MJ, Schreuder MF, Dorresteijn EM, Kramer SP, Bouts AH. Prevention of steroid-induced low bone mineral density in children with renal diseases: a systematic review. Nephrol Dial Transplant. 2013 Aug;28(8):2099-106. doi: 10.1093/ndt/gft090**
- **Choudhary S, Agarwal I, Seshadri MS. Calcium and vitamin D for osteoprotection in children with new-onset nephrotic syndrome treated with steroids: a prospective, randomized, controlled, interventional study. Pediatr Nephrol. 2014 Jun;29(6):1025-32. doi: 10.1007/s00467-013-2720-4**
- **Banerjee S, Basu S, Sen A, Sengupta J. The effect of vitamin D and calcium supplementation in pediatric steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2017 Nov;32(11):2063-2070. doi: 10.1007/s00467-017-3716-2**
- **Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vitamin D treatments in steroid-treated children with nephrotic syndrome. Pediatr Nephrol. 2006 Mar;21(3):350-4.**

These references have been included in the bibliography for the Chapter 2 General principles in the management of glomerular disease.

7. **Suggested bibliography that can guide practice point statements regarding the use of gastroprotection in children that require prolonged treatment with prednisone/prednisolone (TO BE INCLUDED IN THE GENERAL MANGEMENT CHAPTER ?):**

- **Guslandi M. Steroid ulcers: Any news? World J Gastrointest Pharmacol Ther. 2013 Aug 6;4(3):39-40**
- **Dorlo TP1, Jager NG, Beijnen JH, Schellens JH Ned Tijdschr Geneeskd. 2013;157(19):A5540. [Concomitant use of proton pump inhibitors and systemic corticosteroids]. [Article in Dutch]**

Comment: a very scanty find, if the team can do better, that would be great!

Thank you for the suggestions, they have been included in the bibliography for the Chapter 2 General principles in the management of glomerular disease. However, this topic was outside the original scope of the guideline and a systematic search has not been completed for this topic.

8. **Suggested bibliography after 2012 for a clinical practice point regarding special considerations for IgA nephropathy in children, to be included in the IgA nephropathy chapter:**

- **Halling SE, NDT 2013**

Edström Halling S, Söderberg MP, Berg UB. Predictors of outcome in paediatric IgA nephropathy with regard to clinical and histopathological variables (Oxford classification). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2012;27(2):715-722

- **Tesar V, JASN 2015**

Tesar V, Troyanov S, Bellur S et al. Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study. Journal of the American Society of Nephrology : JASN 2015;26(9):2248-2258

- **Coppo R, Ped Neph 2017**

Coppo R. Biomarkers and targeted new therapies for IgA nephropathy. Pediatric Nephrology 2017;32(5):725-731

- **Shima Ped Neph 2017**

Shima Y, Nakanishi K, Sato M et al : IgA nephropathy with presentation of nephrotic syndrome at onset in children. Pediatric nephrology 2017;32(3):457-465

- **Cambier A, KI Reports 2018**

Cambier A, Rabant M, Peuchmaur M et al : Immunosuppressive Treatment in Children With IgA Nephropathy and the Clinical Value of Podocytopathic Features. Kidney international reports 2018;3(4):916-925

- **Shima Ped Neph 2018**

Shima Y, Nakanishi K, Kaku Y et al : Combination therapy with or without warfarin and dipyridamole for severe childhood IgA nephropathy: an RCT. Pediatric Nephrology 2018;

We have included these studies in Chapter 10. IgA nephropathy, and have cited the relevant studies below each bullet point, please let us know if they are incorrect.

9. **Suggested bibliography after 2012 for a clinical practice point regarding special considerations for IMN in children, to be included in the IMN chapter:**

- **Dettmar AK, Wiech T, Kemper MJ, Soave A, Rink M, Oh J, Stahl RAK, Hoxha E; Pediatric MN Study Group. Immunohistochemical and serological characterization of membranous nephropathy in children and adolescents. Pediatr Nephrol. 2018 Mar;33(3):463-472. doi: 10.1007/s00467-017-3817-y**
- **Kumar V, Varma AK, Nada R, Ghosh R, Suri D, Gupta A, Kumar V, Rathi M, Kohli H, Jha V, Gupta K, Ramachandran R. Primary membranous nephropathy in adolescence: A prospective study. Nephrology (Carlton). 2017 Sep;22(9):678-683. doi: 10.1111/nep.12835**
- **Vivarelli M, Emma F, Pellé T, Gerken C, Pedicelli S, Diomedi-Camassei F, Klaus G, Waldegger S, Ronco P, Debiec H. Genetic homogeneity but IgG subclass-dependent clinical variability of alloimmune membranous nephropathy with anti-neutral endopeptidase antibodies. Kidney Int. 2015 Mar;87(3):602-9. doi: 10.1038/ki.2014.381**
- **Ayalon R, Beck LH Jr. Membranous nephropathy: not just a disease for adults. Pediatr Nephrol. 2015 Jan;30(1):31-9. doi: 10.1007/s00467-013-2717-z.**
- **Cossey LN, Walker PD, Larsen CP. Phospholipase A2 receptor staining in pediatric idiopathic membranous glomerulopathy. Pediatr Nephrol. 2013 Dec;28(12):2307-11. doi: 10.1007/s00467-013-2574-9**
- **Debiec H, Lefeu F, Kemper MJ, Niaudet P, Deschênes G, Remuzzi G, Ulinski T, Ronco P. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med. 2011 Jun 2;364(22):2101-10. doi: 10.1056/NEJMoa1013792**

These references have been included in the bibliography for the Chapter 7 Idiopathic membranous nephropathy.

Keisha Gibson comments

PICO (11.31) Population: Children with steroid sensitive nephrotic syndrome Intervention: MMF Comparator: cyclosporine

10. **This below study is listed in MagicApp as a 2011 abstract. I do not see that the actual manuscript has been included listed below.**

Gellerman J, Weber L, Pape L, et al. Mycophenolate mofetil versus Cyclosporin A in children with frequently relapsing nephrotic syndrome. J Am Soc Nephrol. 2013 Oct;24(10): 1689-97.

Thank you for noticing this error. We have updated the reference list on MAGICapp to include this publication and removed reference to the abstract publication. Please note, the data for this trial came from this publication. The study name for this trial is Gellerman 2011 within the Cochrane Kidney and Transplant Registry of Clinical Trials until the next update publication of the Cochrane review. The study name will then be Gellerman 2013.

PICO (11.34) Population: Children with steroid sensitive nephrotic syndrome Intervention: Rituximab Comparator: Placebo or control

11. **I don't think the below reference is included. It is a follow-up to the trial initially published in 2010.**

Kamei K, Ishikura K, Sako M. Et al. Long-term outcome of childhood-onset complicated nephrotic syndrome after a multicenter, double-blind, randomized, placebo-controlled trial of rituximab. Pediatr Nephrol. 2017 Nov;32(11):2071-2078.

This study has been included as a secondary publication for the Iijima 2010 study in the evidence review. As this long-term follow-up study does not include patients treated with the comparator (placebo) no data could be abstracted for meta-analysis. Not all secondary publications for trials have been included in the reference list on MAGICapp. However, this study has been added to the reference list and can be cited in the rationale for guideline recommendations.

Please note, this study and secondary publication has been added to the Dropbox

Bibliography suggestions for other chapters

12. **Suggested bibliography after 2012 for a clinical practice point regarding special considerations for Lupus nephritis in children, to be included in the Lupus chapter:**
    - **Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis. 2017 Dec; 76(12): 1965-1973.**
    - **Tian SY, Silverman ED, Pullenayegum E., et al. Comparative Effectiveness of Mycophenolate Mofetil for the Treatment of Juvenile-Onset Proliferative Lupus Nephritis. Arthritis Care Res. 2017 Dec; 69(12): 1887-1894.**
    - **Basu B, Roy B, Babu BG. Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis. Pediatr Nephrol. 2017 Jun; 32(6): 1013-1021.**
    - **Ruggiero B, Vivarelli M, Gianviti A, et al. Lupus nephritis in children and adolescents: results of the Italian Collaborative Study. Nephrol Dial Transplant. 2013 Jun;28(6): 1487-96.**

Thank you for identifying these studies, they have been added to the reference list of the lupus nephritis chapter and can be cited in the rationale for guideline recommendations.

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3. Ehrich JHftAfPN. Short initial prednisone therapy versus standard prednisone therapy in the steroid responsive nephrotic syndrome [abstract]. Pediatric Nephrology. 1987;1(1):C28-C.
4. Jayantha UK. Prolong versus standard steroid therapy for children with relapsing course of nephrotic syndrome [abstract no: P026]. Pediatric Nephrology. 2004;19(9):C99-C.
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11. Al Talhi A, Al Saran K, Osman ET, Al Shatri A, Osman M, Mirza K. A randomized study on a 3-month versus a 7-month prednisolone regimen for the initial episode of childhood idiopathic nephrotic syndrome at a large Saudi center. International Journal of Pediatrics and Adolescent Medicine. 2018;5(1):18-23.
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multicenter controlled trial for the French Society of Pediatric Nephrology [abstract]. International Journal of Pediatric Nephrology. 1982;3(1):45-.
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PICO evidence tables

PICO (11.1)
Population: First episode of nephrotic syndrome in children
Intervention: Corticosteroid therapy 1 month duration
Comparator: Corticosteroid therapy 2 months duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Corticosteroid therapy 2 months duration	Corticosteroid therapy 1 month duration	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Complete remission	(CI 95% -)	Difference: **fewer**			No studies were found that looked at complete remission
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)				No studies were found that looked at infection

		Difference: **fewer**		
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Relapse 6 months	Relative risk: 1.6 (CI 95% 1.01 - 2.54) Based on data from 61 patients in 1 studies[1] Follow up 24 months	**448** per 1000 **717** per 1000 Difference: **269 more per 1000** (CI 95% 4 more - 690 more)	**Low** Due to serious risk of bias, Due to serious imprecision, Due to serious risk of bias[2]	Compared with 2 months, 1 month corticosteroid therapy may increase relapse at 6 months in children with first episode steroid-sensitive nephrotic syndrome
Relapse 12 to 24 months	Relative risk: 1.46 (CI 95% 1.01 - 2.12) Based on data from 60 patients in 1 studies[3] Follow up 24 months	**552** per 1000 **806** per 1000 Difference: **254 more per 1000** (CI 95% 6 more - 618 more)	**Low** Due to very serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect[4]	Compared with 2 months, 1 month corticosteroid therapy may increase relapse at 12 months in children with first episode steroid-sensitive nephrotic syndrome
Frequent relapses	Relative risk: 1.48 (CI 95% 0.85 - 2.59) Based on data from 61 patients in 1 studies[5] Follow up 24 months	**379** per 1000 **561** per 1000 Difference: **182 more per 1000** (CI 95% 57 fewer - 603 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether steroid therapy for 1 month compared to two months makes little or no difference in the frequent relapses
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

1. Primary study [28] **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 [28] **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 [28] **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;

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PICO (11.2)

Population: First episode of nephrotic syndrome in children
Intervention: Corticosteroid therapy 3 months or more duration
Comparator: Corticosteroid therapy 2 months duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Corticosteroid therapy 2 month Corticosteroid therapy 3 months duration	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Infection	Relative risk: 0.87 (CI 95% 0.62 - 1.22) Based on data from 265 patients in 3 studies[1] Follow up Mean 18 months	**342** per 1000 **298** per 1000 Difference: **44 fewer per 1000** (CI 95% 130 fewer - 75 more)	**Low** Due to very serious risk of bias[2]	Compared with 2 months, 3 month or more of corticosteroid therapy in children with a first episode of nephrotic syndrome may have little or no difference on infection

Corticosteroid-related adverse events - Ophthalmological disorders	Relative risk: 0.46 (CI 95% 0.12 - 1.76) Based on data from 472 patients in 6 studies[3] Follow up Mean 15.4 months	**38** per 1000 **17** per 1000 Difference: **21 fewer per 1000** (CI 95% 33 fewer - 29 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[4]	We are uncertain whether 3 months or more duration of steroid therapy compared with 2 months duration in first episode of nephrotic syndrome increases or decreases ophthalmological disorders
Corticosteroid-related adverse events - Retarded growth	Relative risk: 0.54 (CI 95% 0.25 - 1.18) Based on data from 354 patients in 4 studies[5] Follow up Mean 21 months	**112** per 1000 **60** per 1000 Difference: **52 fewer per 1000** (CI 95% 84 fewer - 20 more)	**Low** Due to very serious risk of bias[6]	Compared with 2 months, 3 month or more of corticosteroid therapy in children with a first episode of nephrotic syndrome may have little or no difference on retarded growth
Corticosteroid-related adverse events - Cushing's syndrome	Relative risk: 1.29 (CI 95% 0.87 - 1.9) Based on data from 417 patients in 5 studies[7] Follow up Mean 14.4 months	**276** per 1000 **356** per 1000 Difference: **80 more per 1000** (CI 95% 36 fewer - 248 more)	**Moderate** Due to serious risk of bias[8]	Compared with 2 months, 3 month or more of corticosteroid therapy in children with a first episode of nephrotic syndrome probably makes little or no difference on cushing's syndrome
Corticosteroid-related adverse events - Osteoporosis	Relative risk: 0.47 (CI 95% 0.06 - 3.38) Based on data from 233 patients in 3 studies[9] Follow up Mean 20 months	**45** per 1000 **21** per 1000 Difference: **24 fewer per 1000** (CI 95% 42 fewer - 107 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether 3 months or more duration of steroid therapy compared with 2 months duration in first episode of nephrotic syndrome increases or decreases osteoporosis
Relapse 12 to 24 months	Relative risk: 0.79 (CI 95% 0.65 - 0.95) Based on data from 1108 patients in 11 studies[11] Follow up Mean 18 months	**701** per 1000 **554** per 1000 Difference: **147 fewer per 1000** (CI 95% 245 fewer - 35 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[12]	Three months or more duration compared to 2 months duration of steroid therapy may decrease relapse in children with a first episode of nephrotic syndrome
Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Frequent relapses 12 to 24 months	Relative risk: 0.79 (CI 95% 0.59 - 1.06)	**396** per 1000 **313** per 1000	**Low** Due to very serious risk of bias[14]	Three months or more duration compared to 2 months duration of steroid therapy may make little or no difference to frequents relapses in children

	Based on data from 805 patients in 7 studies[13] Follow up Mean 19.7 months	Difference: **83 fewer per 1000** (CI 95% 162 fewer - 24 more)		with a first episode of nephrotic syndrome
Frequent relapses - stratified low risk of bias for allocation concealment 12 to 24 months	Relative risk: 0.99 (CI 95% 0.82 - 1.19) Based on data from 585 patients in 4 studies[15] Follow up Mean 21 months	**413** per 1000 **409** per 1000 Difference: **4 fewer per 1000** (CI 95% 74 fewer - 78 more)	**High**	Three months or more duration compared to 2 months duration of steroid therapy may make no difference to frequents relapses in children with a first episode of nephrotic syndrome
Frequent relapses - stratified unclear or high risk of bias for allocation concealment 12 to 24 months	Relative risk: 0.45 (CI 95% 0.26 - 0.77) Based on data from 220 patients in 3 studies[16] Follow up Mean 18 months	**357** per 1000 **161** per 1000 Difference: **196 fewer per 1000** (CI 95% 264 fewer - 82 fewer)	**Moderate** Due to serious risk of bias[17]	Three months or more duration compared to 2 months duration of steroid therapy probably decreases frequents relapses in children with a first episode of nephrotic syndrome
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies comparing duration of corticosteroid therapy were found that looked at annual GFR loss

7. Systematic review with included studies: [45], [44], [36] **Baseline/comparator:** Control arm of reference used for intervention .
8. **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;
9. Systematic review with included studies: [24], [53], [27], [33], [36], [45] **Baseline/comparator:** Control arm of reference used for intervention .
10. **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;
11. Systematic review with included studies: [36], [24], [27], [33] **Baseline/comparator:** Control arm of reference used for intervention .
12. **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;
13. Systematic review with included studies: [24], [27], [36], [43], [45] **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 concealment of allocation during randomization process, resulting in potential for selection bias, Selective outcome reporting;
15. Systematic review with included studies: [27], [36], [53] **Baseline/comparator:** Control arm of reference used for intervention .
16. **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;
17. Systematic review with included studies: [54], [57], [101], [36], [43], [48], [44], [53], [24], [27], [33] **Baseline/comparator:** Control arm of reference used for intervention .
18. **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%.;
19. Systematic review with included studies: [44], [57], [101], [24], [33], [53], [27] **Baseline/comparator:** Control arm of reference used for intervention .
20. **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;
21. Systematic review with included studies: [27], [57], [101], [24] **Baseline/comparator:** Control arm of reference used for intervention .
22. Systematic review with included studies: [44], [53], [33] **Baseline/comparator:** Control arm of reference used for intervention .

23. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias;

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PICO (11.3)

Population: First episode of nephrotic syndrome in children
Intervention: Corticosteroid therapy 5 or 6 months duration
Comparator: Corticosteroid therapy 3 months duration

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Corticosteroid therapy 3 months duration	Corticosteroid therapy 5 or 6 months duration	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.98 (CI 95% 0.65 - 1.46) Based on data from 702 patients in 5 studies Follow up Mean 19.8 months	**185** per 1000 Difference: **4 fewer per 1000** (CI 95% 65 fewer - 85 more)	**181** per 1000	**Low** Due to very serious risk of bias[1]	5 or 6 months compared with 3 months corticosteroid therapy duration may have little or no difference on infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies were found that looked at malignancy

Corticosteroid-related adverse events - Cushingoid appearance	Relative risk: 0.86 (CI 95% 0.6 - 1.23) Based on data from 762 patients in 6 studies Follow up Mean 21 months	**375** per 1000 **323** per 1000 Difference: **52 fewer per 1000** (CI 95% 150 fewer - 86 more)	**Moderate** Due to serious risk of bias[2]	5 or 6 months compared with 3 months corticosteroid therapy duration probably has little or no difference on cushingoid appearance
Corticosteroid-related adverse events - Eye complications	Relative risk: 0.46 (CI 95% 0.18 - 1.17) Based on data from 614 patients in 5 studies Follow up Mean 22 months	**36** per 1000 **17** per 1000 Difference: **19 fewer per 1000** (CI 95% 30 fewer - 6 more)	**Moderate** Due to serious risk of bias[3]	5 or 6 months compared with 3 months corticosteroid therapy duration probably has little or no difference to eye complications
Relapse 12 to 24 months	Relative risk: 0.62 (CI 95% 0.45 - 0.85) Based on data from 763 patients in 7 studies Follow up Mean 19.3 months	**694** per 1000 **430** per 1000 Difference: **264 fewer per 1000** (CI 95% 382 fewer - 104 fewer)	**Low** Due to very serious risk of bias, Due to serious inconsistency, Upgraded due to Large magnitude of effect[4]	5 or 6 months compared with 3 months corticosteroid therapy duration may decrease relapse
Frequent relapses 12 to 24 months	Relative risk: 0.73 (CI 95% 0.49 - 1.09) Based on data from 707 patients in 6 studies Follow up Mean 18.5 months	**386** per 1000 **282** per 1000 Difference: **104 fewer per 1000** (CI 95% 197 fewer - 35 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[5]	5 or 6 months compared with 3 months corticosteroid therapy duration may have little or no difference on frequent relapses
Frequent relapses - stratified by low risk of bias for allocation concealment 12 to 24 months	Relative risk: 1.0 (CI 95% 0.74 - 1.34) Based on data from 377 patients in 3 studies Follow up Mean 25 months	**438** per 1000 **438** per 1000 Difference: **0 fewer per 1000** (CI 95% 114 fewer - 149 more)	**High**	5 or 6 months compared with 3 months corticosteroid therapy duration makes little or no difference to frequent relapses
Frequent relapses - stratified by high or unclear risk of bias for allocation concealment 12 to 24 months	Relative risk: 0.48 (CI 95% 0.32 - 0.72) Based on data from 330 patients in 3 studies Follow up Mean 12 months	**327** per 1000 **157** per 1000 Difference: **170 fewer per 1000** (CI 95% 222 fewer - 92 fewer)	**Moderate** Due to serious risk of bias[6]	In studies of high or unclear risk of bias for allocation concealment, 5 or 6 months compared with 3 months corticosteroid therapy duration probably decreases frequent relapses
Complete remission	(CI 95% -)			No studies were found that looked at complete remission

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

24. **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;
25. **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;
26. **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;
27. **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, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:83%.; **Upgrade: Large magnitude of effect.**
28. **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%.;
29. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias;

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PICO (11.5)

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 (40mg/m2)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** BSA-based dosing of prednisone (40mg/m2)	 Weight-based prednisolone (1.5 mg/kg (maximum 40 mg))	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Corticsteroid-relarted adverse effects - Cushingoid features	Relative risk: 1.26 (CI 95% 0.61 - 2.59) Based on data from 84 patients in 1 studies[1] Follow up 6 months	**233** per 1000	**294** per 1000 Difference: **61 more per 1000** (CI 95% 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)) compared with BSA-based dosing prednisone (40mg/m2) increases or decreases cushingoid features
Complete remission	(CI 95% -)	Difference: **fewer**			No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 1.0 (CI 95% 0.66 - 1.53) Based on data from 86 patients in 1 studies[3] Follow up 6 months	**500** per 1000	**500** per 1000 Difference: **0 fewer per 1000** (CI 95% 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)) compared with BSA based prednisone (40mg/m2) may have little or no difference on relapse at 6 months
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease

≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infections	Relative risk: 0.79 (CI 95% 0.19 - 3.3) Based on data from 84 patients in 1 studies[5] Follow up 6 months	**93** per 1000 **73** per 1000 Difference: **20 fewer per 1000** (CI 95% 75 fewer - 214 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether weight-based (1.5 mg/kg (maximum 40 mg)) compared with BSA-based dosing prednisone (40mg/m2) increases or decreases infections
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

30. Primary study [47] **Baseline/comparator:** Control arm of reference used for intervention .
31. **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;
32. Primary study [47] **Baseline/comparator:** Control arm of reference used for intervention .
33. **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;
34. Primary study [47] **Baseline/comparator:** Control arm of reference used for intervention .
35. **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;

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PICO (11.6)

Population: First episode of nephrotic syndrome in children
Intervention: Higher total dose (60 mg/m2/d (max 80 mg) for 6 weeks, 40 mg/m2 on alternate days for 6 weeks) prednisone

Comparator: Lower total dose (40 mg/m2/d (max 60 mg) for 6 weeks, 40 mg/m2 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** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**			No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies were found that looked at malignancy
Corticosteroid-related adverse effects -	Relative risk: 3.0 (CI 95% 0.9 - 10.01)	**100** per 1000	**300** per 1000	**Very Low** Due to serious risk of bias, Due to very	We are uncertain whether higher total dose compared to lower total dose prednisone increases or decreases cushing's syndrome

Cushing's Syndrome	Based on data from 60 patients in 1 studies[1] Follow up 24 months	Difference: **200 more per 1000** (CI 95% 10 fewer - 901 more)	serious imprecision[2]	
Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 0.63 (CI 95% 0.42 - 0.94) Based on data from 59 patients in 1 studies[3] Follow up 24 months	**793** per 1000 **500** per 1000 Difference: **293 fewer per 1000** (CI 95% 460 fewer - 48 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Higher total dose compared with lower total dose of prednisone may decrease relapse at 12 months
Frequently relapsing nephrotic syndrome	Relative risk: 0.69 (CI 95% 0.35 - 1.37) Based on data from 60 patients in 1 studies[5] Follow up 24 months	**433** per 1000 **299** per 1000 Difference: **134 fewer per 1000** (CI 95% 281 fewer - 160 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether higher total dose compared to lower total dose prednisone increases or decreases frequently relapsing nephrotic syndrome
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

36. Primary study [30] **Baseline/comparator:** Control arm of reference used for intervention .
37. **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;
38. Primary study [30] **Baseline/comparator:** Control arm of reference used for intervention .
39. **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;
40. Primary study [30] **Baseline/comparator:** Control arm of reference used for intervention .
41. **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

[30] 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

[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

PICO (11.7)

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** (Quality of evidence)	**Plain text summary**
All cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all cause mortality
End stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Complete remission 6 weeks	Relative risk: 1.17 (CI 95% 0.9 - 1.53)	**846** **990** per 1000 per 1000	**Low** Due to serious risk of bias, Due to serious	We are uncertain whether deflazacort compared with prednisolone increases or decreases remission at 6 weeks

	Based on data from 25 patients in 1 studies[1] Follow up 6 weeks	Difference: **144 more per 1000** (CI 95% 85 fewer - 448 more)	imprecision[2]	
Relapse 9-12 Months	Relative risk: 0.47 (CI 95% 0.28 - 0.79) Based on data from 65 patients in 2 studies[3] Follow up 9 Months (mean)	**636** per 1000 **299** per 1000 Difference: **337 fewer per 1000** (CI 95% 458 fewer - 134 fewer)	**Moderate** Due to serious risk of bias[4]	Deflazacort compared with prednisolone probably decreases relapse at 9-12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked annual GFR loss

42. Primary study [50] **Baseline/comparator:** Control arm of reference used for intervention .
43. **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;
44. Systematic review with included studies: [50], [26] **Baseline/comparator:** Control arm of reference used for intervention .
45. **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

[26] 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
[50] 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
[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

PICO (11.8)

Population: First episode of nephrotic syndrome in children
Intervention: High dose methylprednisone
Comparator: Prednisolone (2 month therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone (2 month therapy) high dose methylprednisone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥ 50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss
Time to remission	Measured by: days Scale: - Lower better Based on data from 38 patients in 2 studies Follow up 23 Months (mean)	DaysMean DaysMean Difference: **MD 5.54 lower** (CI 95% 8.46 lower - 2.61 lower)	**Very Low** Due to very serious risk of bias, Due to serious imprecision,	We are uncertain if high dose methylprednisone increases or decreases time to remission
Time to first relapse	Measured by: Months Scale: - High better Based on data from 15 patients in 1 studies[2] Follow up 40 Months (mean)	Mean Mean Difference: **MD 8.10 lower** (CI 95% 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 methylprednisone compared with 2 month prenisolone therapy in the first episode of nephrotic syndrome increases or decreases time to first relapse

46. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up 25%, Selective outcome reporting; **Imprecision: Serious.** Low number of patients, due to few events; **Upgrade: Large magnitude of effect.**
47. Primary study [42] **Baseline/comparator:** Control arm of reference used for intervention .
48. **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

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

PICO (11.10)

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** (Quality of evidence)	**Plain text summary**
All cause mortality	(CI 95% -)	Difference: **fewer**		No studies for looked at all cause mortality
End stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies looked at end stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies looked at complete remission
Relapse with infection	Relative risk: 0.49 (CI 95% 0.18 - 1.3) Based on data from 40 patients in 1 studies[1] Follow up until child had two upper respiratory tract infections	**455** per 1000 **223** per 1000 Difference: **232 fewer per 1000** (CI 95% 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 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies looked at annual GFR loss
Rate of infection-related relapse[3]	Measured by: relapses/patient/year Scale: - Lower better Based on data from 95 patients in 1 studies[4] Follow up 24 months	Mean Mean Difference: **MD 3.3 lower** (CI 95% 4.03 lower - 2.57 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Daily prednisolone compared with alternate day prednisolone may decrease rate of relapse at 1 year in patients with nephrotic syndrome with viral infections
Rate of infection-related relapse[6] 2 years	Measured by: relapses/patient/year Scale: - Lower better Based on data from 36 patients in 1 studies[7] Follow up 24 months	Mean Mean Difference: **MD 3.3 lower** (CI 95% 4.03 lower - 2.57 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Daily prednisolone compared with alternate day prednisolone may decrease rate of relapse at 2 years in patients with nephrotic syndrome with viral infections

49. Primary study [17] **Baseline/comparator:** Control arm of reference used for intervention .
50. **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;
51. (Number of relapses/patient at 2 years)
52. Primary study [29] **Baseline/comparator:** Control arm of reference used for intervention .
53. **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;
54. (Number of relapses/patient at 2 years)
55. Primary study [40] **Baseline/comparator:** Control arm of reference used for intervention .
56. **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;

References

[17] Abeyagunawardena AS, Trompeter RS : Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial. Archives of Disease in Childhood 2008;93(3):226-228

[23] Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, Abeyagunawardena S, Illangasekera YA, Karunadasa UI, Trompeter RS : Short courses of daily prednisolone during upper respiratorytract infections reduce relapse frequency in childhood nephrotic syndrome. Pediatric Nephrology 2017;32(8):1377-1382

[29] Gulati A., Sinha A., Sreenivas V., Math A., Hari P., Bagga A. : Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clinical Journal of The American Society of Nephrology: CJASN 2011;6(1):63-69

[40] Mattoo TK, Mahmoud MA : Increased maintenance corticosteroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. Nephron 2000;85(4):343-345

[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

PICO (11.11)

Population: Children with relapsing nephrotic syndrome
Intervention: Intermittent dose versus
Comparator: Alternate-day therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alternate-day therapy Intermittent dose versus	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥ 50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥ 50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Relapsing during therapy 6 Month therapy	Relative risk: 0.6 (CI 95% 0.36 - 1.02) Based on data from 48 patients in 1 studies[1] Follow up 6 Months	**720** per 1000 **432** per 1000 Difference: **288 fewer per 1000** (CI 95% 461 fewer - 14 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroid therapy in relapse of nephrotic syndrome vs standard therapy may decrease relapsing during therapy slightly
Relapse 9 -12 months	Relative risk: 1.2 (CI 95% 0.93 - 1.55) Based on data from 48 patients in 1 studies[3] Follow up 9-12 Months	**760** per 1000 **912** per 1000 Difference: **152 more per 1000** (CI 95% 53 fewer - 418 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	We are uncertain whether intermitten steroid comapred with alternate-day therapy increases or decreases relapse at 9 to 12 months
Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Annual GFR 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

57. Primary study [22] **Baseline/comparator:** Control arm of reference used for intervention .
58. **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;
59. Primary study [22] **Baseline/comparator:** Control arm of reference used for intervention .
60. **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

[22] 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
[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

PICO (11.12)

Population: Children with relapsing nephrotic syndrome
Intervention: Daily steroid therapy
Comparator: Intermittent steroid therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Intermittent steroid therapy	Daily steroid therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥ 50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥ 50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**			No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies were found that looked at malignancy
Complete remission	(CI 95% -)	Difference: **fewer**			No studies were found that looked at complete remission

Relapse	Relative risk: 0.2 (CI 95% 0.05 - 0.82) Based on data from 50 patients in 1 studies[1] Follow up At least 8 Months	**400** per 1000 **80** per 1000 Difference: **320 fewer per 1000** (CI 95% 380 fewer - 72 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision,[2]	Daily steroid therapy compared with intermitten steroid therapy may decrease relapse
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked all-cause mortality
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

61. Primary study [21] **Baseline/comparator:** Control arm of reference used for intervention .
62. **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

[21] 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

[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

PICO (11.13)
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** (Quality of evidence)	**Plain text summary**
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
All-cause mortality	(CI 95% -)			No studies were found that looked at all-cause mortality

		Difference: **fewer**		
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥ 50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥ 50% GFR loss
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss
Relapse rate per year 12 months	Measured by: Scale: - Lower better Based on data from 62 patients in 1 studies[1] Follow up 12 Months	Mean Mean Difference: **MD 0.90 lower** (CI 95% 1.33 lower - 0.47 lower)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Daily prednisone compared with alternate day prednisone for relapsing nephrotic syndrome may decrease the annual rate of relapse

1. Primary study [55] **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

[55] 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

[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

PICO (11.14)

Population: Children with relapsing nephrotic syndrome
Intervention: Single corticosteroid dose
Comparator: Divided dose steroid therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Divided dose steroid therapy Single corticosteroid dose	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ccomplete remission
Relapse 9 to 12 months	Relative risk: 1.07 (CI 95% 0.93 - 1.55) Based on data from 94 patients in 1 studies[1] Follow up 9 Months	**574** per 1000 **614** per 1000 Difference: **40 more per 1000** (CI 95% 40 fewer - 316 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Single steroid dose compared with divided steroid dose may have little or no difference on further relapse by 9-12 months
Serious adverse events	Relative risk: 0.41 (CI 95% 0.18 - 0.91) Based on data from 138 patients in 2 studies[3] Follow up 7.5 Months (mean)	**278** per 1000 **114** per 1000 Difference: **164 fewer per 1000** (CI 95% 228 fewer - 25 fewer)	**Low** Due to very serious risk of bias[4]	Single steroid dose compared with divided steroid dose may decrease serious adverse events
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss
Mean time to relapse 2 month therapy	Measured by: Months Scale: - Lower better Based on data from 94 patients in 1 studies[5] Follow up 9 Months	Mean Mean Difference: **MD 0.30 lower** (CI 95% 1.64 lower - 1.04 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Steroid therapy in relapse of nephrotic syndrome vs standard therapy may have little or no difference on mean time to relapse

3. Primary study [59] **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.** Wide confidence intervals, Only data from one study;
5. Systematic review with included studies: [38], [59] **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, Selective outcome reporting;
7. Primary study [59] **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 large loss to follow up; **Imprecision: Serious.** Wide confidence intervals, Only data from one study;

References

[38] Li X., Li Z., Cheng Z. : Treatment of children with simple nephrotic syndrom using prednison once per day. Acta Academiae Medicinae Hubei 1994;15(4):386-388
[59] Ekka BK, Bagga A., Srivastava RN : Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatric Nephrology 1997;11(5):597-599
[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

PICO (11.15)
Population: Children with relapsing nephrotic syndrome
Intervention: Intravenous steroid therapy
Comparator: Oral steroid therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral steroid therapy	Intravenous steroid therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥ 50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥ 50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**			No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies were found that looked at malignancy
Complete remission	(CI 95% -)				No studies were found that looked at complete remission

		Difference: **fewer**		
Relapse 9 to 12 months	Relative risk: 1.06 (CI 95% 0.75 - 1.52) Based on data from 64 patients in 1 studies[1] Follow up Mean 18 Months	**636** per 1000 **674** per 1000 Difference: **38 more per 1000** (CI 95% 159 fewer - 331 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroid therapy in relapse of nephrotic syndrome vs standard therapy may have little or no difference on further relapses by 9 to 12 months
Annual GFR loss 3 Years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

9. Primary study [32] **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.** Wide confidence intervals, Only data from one study;

References

[32] 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

[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

PICO (11.16)

Population: Children with relapsing nephrotic syndrome
Intervention: 1 mg/kg corticosteroid
Comparator: 2 mg/kg corticosteroid

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** 2 mg/kg corticosteroid 1 mg/kg corticosteroid	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked all cause mortality
End stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked end stage kidney disease
> 50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at >50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Time to remission	Measured by: Scale: - Lower better Based on data from 20 patients in 1 studies[1] Follow up 3 Months	Mean Mean Difference: **MD 0.90 higher** (CI 95% 0.96 lower - 2.76 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	1 mg/kg corticosteroid compared with 2 mg/kg corticosteroid may have little or no difference on time to remission
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked annual GFR loss

11. Systematic review with included studies: [25] **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, Selective outcome reporting (no report of adverse events); **Imprecision: Serious.** Only data from one study;

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

PICO (11.17)
Population: Children with relapsing nephrotic syndrome
Intervention: Prednisone: 60 mg/m2/d for 4 weeks and tapered daily dose for 4 weeks
Comparator: Prednisone: 60 mg/m2/d till remission and 40 mg/m2 on 3/7 consecutive days

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Intermitten oral steroid therapy Prolonged oral steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
End stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked a all-cause mortality
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Complete remission	(CI 95% -)			No studies were found that looked at complete remission

		Difference: **fewer**		
Relapse 9 to 12 months	Relative risk: 1.0 (CI 95% 0.89 - 1.12) Based on data from 50 patients in 1 studies[1] Follow up 8 Months	**960** per 1000 **960** per 1000 Difference: **0 fewer per 1000** (CI 95% 106 fewer - 115 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether prelonged steroid therapy compared with intermitten steroid therapy decreases further relapses at 9 to 12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

13. Primary study [21] **Baseline/comparator:** Control arm of reference used for intervention .
14. **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

[21] 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

[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

PICO (11.19)
Population: Children with frequently relapsing steroid-sensitive nephrotic syndrome
Intervention: Alkylating agents
Comparator: Steroids or placebo or both

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Steroids or placebo or both Alkylating agents	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
≥50% GFR loss	(CI 95% -)			No studies were found that looked at ≥50% GFR loss

		Difference: **fewer**		
Relapse - Cyclophosphamide versus prednisone 6 to 12 months	Relative risk: 0.47 (CI 95% 0.33 - 0.66) Based on data from 157 patients in 4 studies[1] Follow up Mean 17.8 months	**713** per 1000 **335** per 1000 Difference: **378 fewer per 1000** (CI 95% 478 fewer - 242 fewer)	**Moderate** Due to serious risk of bias[2]	Cyclophosphamide compared with prednisone probably decreases relapse at 6 to 12 months
Relapse - Chlorambucil versus prednisone or placebo 6 to 12 months	Relative risk: 0.19 (CI 95% 0.03 - 1.09) Based on data from 41 patients in 2 studies[3] Follow up Mean 14.5 months	**850** per 1000 **161** per 1000 Difference: **689 fewer per 1000** (CI 95% 825 fewer - 77 more)	**Moderate** Due to serious risk of bias[4]	Chlorambucil probably has little or no difference on relapse at 6 to 12 months
Relapse - Cyclophosphamide versus prednisone 12 to 24 months	Relative risk: 0.21 (CI 95% 0.07 - 0.65) Based on data from 27 patients in 2 studies[5] Follow up Mean 19 months	**929** per 1000 **195** per 1000 Difference: **734 fewer per 1000** (CI 95% 864 fewer - 325 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Cyclophosphamide compared with prednisone may decrease relapse at 12 to 24 months
Relapse - Chlorambucil versus prednisone or placebo 12 months	Relative risk: 0.15 (CI 95% 0.02 - 0.95) Based on data from 32 patients in 2 studies[7] Follow up Mean 19 months	**1000** per 1000 **150** per 1000 Difference: **850 fewer per 1000** (CI 95% 980 fewer - 50 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Chlorambucil may decrease relapse at 12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

15. Systematic review with included studies: [67], [75], [92], [72] **Baseline/comparator:** Control arm of reference used for intervention .
16. **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;
17. Systematic review with included studies: [81], [64] **Baseline/comparator:** Control arm of reference used for intervention .
18. **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;
19. Systematic review with included studies: [75], [72] **Baseline/comparator:** Control arm of reference used for intervention .
20. **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;
21. Systematic review with included studies: [81], [64] **Baseline/comparator:** Control arm of reference used for intervention .

22. **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;

References

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[75] Chiu J., McLaine PN, Drummond KN : A controlled prospective study of cyclophosphamide in relapsing, corticosteroid-responsive, minimal-lesion nephrotic syndrome in childhood. Journal of Pediatrics 1973;82(4):607-613

[81] Grupe WE, Makker SP, Ingelfinger JR : Chlorambucil treatment of frequently relapsing nephrotic syndrome. New England Journal of Medicine 1976;295(14):746-749

[92] 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

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PICO (11.21)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Oral cyclophosphamide Intravenous cyclophosphamide	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 0.14 (CI 95% 0.03 - 0.72) Based on data from 83 patients in 2 studies[1] Follow up Mean 17 months	**238** per 1000 **33** per 1000 Difference: **205 fewer per 1000** (CI 95% 231 fewer - 67 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Intravenous compared with oral cyclophosphamide may decrease infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 0.54 (CI 95% 0.34 - 0.88) Based on data from 83 patients in 2 studies[3] Follow up Mean 17 months	**524** per 1000 **283** per 1000 Difference: **241 fewer per 1000** (CI 95% 346 fewer - 63 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Intravenous cyclophosphamide compared with oral cyclophosphamide may decrease relapse
Continuing frequently relapsing or steroid-dependent nephrotic syndrome 6 months	Relative risk: 0.4 (CI 95% 0.18 - 0.89) Based on data from 47 patients in 1 studies[5] Follow up Mean 22.5 months	**571** per 1000 **228** per 1000 Difference: **343 fewer per 1000** (CI 95% 468 fewer - 63 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Intravenous cyclophosphamide compared with oral cyclophosphamide may decrease continuing frequently relapsing or steroid-dependent nephrotic syndrome
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

23. Systematic review with included studies: [88], [62] **Baseline/comparator:** Control arm of reference used for intervention .
24. **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;
25. Systematic review with included studies: [62], [88] **Baseline/comparator:** Control arm of reference used for intervention .
26. **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;
27. Systematic review with included studies: [88] **Baseline/comparator:** Control arm of reference used for intervention .
28. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

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PICO (11.23)

Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Cyclophosphamide low dose (2.5 mg/kg/d)
Comparator: Cyclophosphamide high dose (5 mg/kg/d)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclophosphamide high dose (5 mg/kg/d) Cyclophosphamide low dose (2.5 mg/kg/d)	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 2.33 (CI 95% 0.11 - 48.99) Based on data from 14 patients in 1 studies[1] Follow up 18 months	**0** per 1000 **0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	There were too few who experienced the relapse, to determine whether cyclophosphamide low dose compared with high dose made a difference
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

29. Systematic review with included studies: [98] **Baseline/comparator:** Control arm of reference used for intervention .
30. **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

[98] 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
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PICO (11.24)

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** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 0.18 (CI 95% 0.01 - 3.41) Based on data from 21 patients in 1 studies[1] Follow up Mean 28 months	**200** per 1000 **36** per 1000 Difference: **164 fewer per 1000** (CI 95% 198 fewer - 482 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether increasing or stable chlorambucil dose increases or decreases relapse
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

31. Primary study [69] **Baseline/comparator:** Control arm of reference used for intervention .
32. **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

[69] 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
[105] Pravitsitthikul N, Willis NS, Hodson EM, Craig JC : Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. 2013;CD002290

PICO (11.25)

Population: Post-hoc analysis: Children with frequently relapsing and steroid-dependent patients
Intervention: Alkylating agents in frequently relapsing
Comparator: Alkylating agents in steroid-dependent patients

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alkylating agents in steroid-dependent patients Alkylating agents	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 24 months	Relative risk: 0.35 (CI 95% 0.15 - 0.85) Based on data from 50 patients in 1 studies[1] Follow up 24 months	**706** per 1000 **247** per 1000 Difference: **459 fewer per 1000** (CI 95% 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 compared with steroid-dependent nephrotic syndrome may decrease relapse
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

33. Primary study [68] **Baseline/comparator:** Control arm of reference used for intervention .
34. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

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[105] Pravitsitthikul N, Willis NS, Hodson EM, Craig JC : Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. 2013;CD002290

PICO (11.26)

Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Alkylating agents
Comparator: Cyclosporin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporin Alkylating agents	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse - Chlorambucil versus cyclosporin 6 to 9 months	Relative risk: 0.82 (CI 95% 0.44 - 1.53) Based on data from 40 patients in 1 studies[1] Follow up 2 to 3 years	**550** per 1000 **451** per 1000 Difference: **99 fewer per 1000** (CI 95% 308 fewer - 291 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether chlorambucil versus cyclosporin increases or decreases relapse
Relapse- Chlorambucil versus cyclosporin 12 months	Relative risk: 0.47 (CI 95% 0.29 - 0.78) Based on data from 40 patients in 1 studies[3] Follow up Mean 30 months	**950** per 1000 **447** per 1000 Difference: **503 fewer per 1000** (CI 95% 674 fewer - 209 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Chlorambucil compared with cyclosporin may decrease relapse at 12 months
Relapse - Chlorambucil versus cyclosporin 12 to 24 months	Relative risk: 0.58 (CI 95% 0.38 - 0.87) Based on data from 40 patients in 1 studies[5] Follow up Mean 30 months	**950** per 1000 **551** per 1000 Difference: **399 fewer per 1000** (CI 95% 589 fewer - 123 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Chlorambucil compared with cyclosporin may decrease relapse at 12 to 24 months
Relapse - Cyclophosphamide versus cyclosporin 6 to 9 months	Relative risk: 1.07 (CI 95% 0.48 - 2.35) Based on data from 55 patients in 1 studies[7] Follow up Mean 30 months	**300** per 1000 **321** per 1000 Difference: **21 more per 1000** (CI 95% 156 fewer - 405 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether cyclophosphamide versus cyclosporin increases or decreases relapse
Hypertrichosis	Relative risk: 0.05 (CI 95% 0.01 - 0.36) Based on data from 112 patients in 2 studies[9] Follow up Mean 22 months	**339** per 1000 **17** per 1000 Difference: **322 fewer per 1000** (CI 95% 336 fewer - 217 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[10]	Alkylating agents compared with cyclosporin may decrease hypertrichosis
Serum creatinine increase >30%	Relative risk: 0.18 (CI 95% 0.02 - 1.54)	**89** per 1000 **16** per 1000	**Very Low** Due to serious risk of bias, Due to	We are uncertain whether alkylating agents versus cyclosporin increases or decreases serum creatinine

	Based on data from 112 patients in 2 studies[11] Follow up Mean 22 months	Difference: **73 fewer per 1000** (CI 95% 87 fewer - 48 more)	very serious imprecision[12]	increases >30%
Relapse - Cyclophosphamide versus cyclosporin 12 to 24 months	Relative risk: 0.4 (CI 95% 0.22 - 0.73) Based on data from 55 patients in 1 studies[13] Follow up 3 months to 2 years	**800** per 1000 **320** per 1000 Difference: **480 fewer per 1000** (CI 95% 624 fewer - 216 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[14]	Cyclophosphamide compared with cyclosporin may decrease relapse
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

35. Systematic review with included studies: [99] **Baseline/comparator:** Control arm of reference used for intervention .
36. **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;
37. Systematic review with included studies: [99] **Baseline/comparator:** Control arm of reference used for intervention .
38. **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;
39. Primary study [99] **Baseline/comparator:** Control arm of reference used for intervention .
40. **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;
41. Systematic review with included studies: [99] **Baseline/comparator:** Control arm of reference used for intervention .
42. **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;
43. Systematic review with included studies: [99], [79] **Baseline/comparator:** Control arm of reference used for intervention .
44. **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;
45. Systematic review with included studies: [79], [99] **Baseline/comparator:** Control arm of reference used for intervention .
46. **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;
47. Systematic review with included studies: [79] **Baseline/comparator:** Control arm of reference used for intervention .
48. **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

[79] 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

[99] 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

[105] Pravitsitthikul N, Willis NS, Hodson EM, Craig JC : Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. 2013;CD002290

PICO (11.27)

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** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies vincristine were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 12 months	Relative risk: 0.54 (CI 95% 0.26 - 1.16) Based on data from 39 patients in 1 studies[1] Follow up 24 months	**619** per 1000 **334** per 1000 Difference: **285 fewer per 1000** (CI 95% 458 fewer - 99 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Cyclophosphamide compared with vincristine may have little or no difference on relapse at 12 months
Relapse 24 months	Relative risk: 0.73 (CI 95% 0.45 - 1.18) Based on data from 39 patients in 1 studies[3] Follow up 24 months	**762** per 1000 **556** per 1000 Difference: **206 fewer per 1000** (CI 95% 419 fewer - 137 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Cyclophosphamide compared with vincristine may have little or no difference on relapse at 24 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at complete remission

49. Systematic review with included studies: [61] **Baseline/comparator:** Control arm of reference used for intervention .
50. **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;
51. Systematic review with included studies: [61] **Baseline/comparator:** Control arm of reference used for intervention .
52. **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;

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[60] Abeyagunawardena A. : Intravenous pulsed cyclophosphamide versus vincristine therapy in steroid dependant nephrotic syndrome: a randomised controlled trial [abstract]. Pediatric Nephrology 2007;22(9):1547-1547

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PICO (11.28)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Steroids or placebo or both, or no treatment — Levamisole	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Relapse 4 to 12 months	Relative risk: 0.52 (CI 95% 0.33 - 0.82) Based on data from 474 patients in 8 studies[1] Follow up Mean 11.3 months	**764** per 1000 **397** per 1000 Difference: **367 fewer per 1000** (CI 95% 512 fewer - 138 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[2]	Levamisole compared with steroids, placebo or no treatment may decrease relapse at 4 to 12 months
Relapse 6 to 12 months	Relative risk: 0.65 (CI 95% 0.48 - 0.88) Based on data from 462 patients in 8 studies[3] Follow up Mean 11.3 months	**862** per 1000 **560** per 1000 Difference: **302 fewer per 1000** (CI 95% 448 fewer - 103 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency[4]	Levamisole compared with steroids, placebo or no treatment may decrease relapse at 6 to 12 months
Relapse - children with frequently relapsing nephrotic syndrome	Relative risk: 0.57 (CI 95% 0.33 - 0.98) Based on data from 31 patients in 1 studies[5] Follow up 12 months	**882** per 1000 **503** per 1000 Difference: **379 fewer per 1000** (CI 95% 591 fewer - 18 fewer)	**Moderate** Due to serious imprecision[6]	In patients with frequently relapsing nephrotic syndrome, levamisole compared with steroids, placebo or no treatment probably decreases relapse
Relapse - children with steroid-dependent nephrotic syndrome	Relative risk: 0.86 (CI 95% 0.67 - 1.1) Based on data from 68 patients in 1 studies[7] Follow up 12 months	**844** per 1000 **726** per 1000 Difference: **118 fewer per 1000** (CI 95% 279 fewer - 84 more)	**Moderate** Due to serious imprecision[8]	In patients with frequently relapsing nephrotic syndrome, levamisole probably has little or no difference on relapse - children with steroid-dependent nephrotic syndrome
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

53. Systematic review with included studies: [76], [61], [74], [95], [82], [65], [92], [89] **Baseline/comparator:** Control arm of reference used for intervention .
54. **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%.;
55. Primary study [65], [95], [82], [92], [76], [61], [89], [74] **Baseline/comparator:** Control arm of reference used for intervention .
56. **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%.;
57. Systematic review with included studies: [82] **Baseline/comparator:** Control arm of reference used for intervention .

58. **Imprecision: Serious.** Only data from one study, Low number of patients;
59. Primary study [82] **Baseline/comparator:** Control arm of reference used for intervention .
60. **Imprecision: Serious.** Only data from one study, Low number of patients;

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PICO (11.29)

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** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies comparing levamisole with cyclophosphamide were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies comparing levamisole with cyclophosphamide were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies comparing levamisole with cyclophosphamide were found that looked at ≥50% GFR loss
Infection	Relative risk: 1.08 (CI 95% 0.67 - 1.75) Based on data from 40 patients in 1 studies[1] Follow up 24 months	**600** per 1000 **648** per 1000 Difference: **48 more per 1000** (CI 95% 198 fewer - 450 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether levamisole compared with cyclophosphamide increases or decreases infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies comparing levamisole with cyclophosphamide were found that looked at malignacy

Relapse 6 to 9 months after therapy	Relative risk: 1.17 (CI 95% 0.76 - 1.81) Based on data from 97 patients in 2 studies[3] Follow up Mean 18 months	**532** per 1000 **622** per 1000 Difference: **90 more per 1000** (CI 95% 128 fewer - 431 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	Levamisole compared with cyclophosphamide may have little or no difference on relapse
Relapse 12 months after therapy	Relative risk: 0.89 (CI 95% 0.68 - 1.16) Based on data from 40 patients in 1 studies[5] Follow up 24 months	**900** per 1000 **801** per 1000 Difference: **99 fewer per 1000** (CI 95% 288 fewer - 144 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Levamisole compared with cyclophosphamide may have little or no difference on relapse after 12 months of therapy
Relapse 24 months after therapy	Relative risk: 0.89 (CI 95% 0.73 - 1.1) Based on data from 40 patients in 1 studies[7] Follow up 24 months	**950** per 1000 **845** per 1000 Difference: **105 fewer per 1000** (CI 95% 256 fewer - 95 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Levamisole compared with cyclophosphamide may have little or no difference on relapse after 24 months of therapy
Complete remission	(CI 95% -)	Difference: **fewer**		No studies comparing levamisole with cyclophosphamide were found that looked at complete remission
Relapse End of therapy	Relative risk: 2.14 (CI 95% 0.22 - 20.95) Based on data from 97 patients in 2 studies[9] Follow up Mean 18 months	**255** per 1000 **546** per 1000 Difference: **291 more per 1000** (CI 95% 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 compared with cyclophosphamide increases or decreases relapse at the end of therapy
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

61. Systematic review with included studies: [77] **Baseline/comparator:** Control arm of reference used for intervention .
62. **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;
63. Systematic review with included studies: [77], [92] **Baseline/comparator:** Control arm of reference used for intervention .
64. **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;
65. Systematic review with included studies: [77] **Baseline/comparator:** Control arm of reference used for intervention .

66. **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;
67. Systematic review with included studies: [77] **Baseline/comparator:** Control arm of reference used for intervention .
68. **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;
69. Primary study [92], [77] **Baseline/comparator:** Control arm of reference used for intervention .
70. **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;

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PICO (11.30)
Population: Children with steroid-sensitive nephrotic syndrome in children
Intervention: Cyclosporin and prednisone
Comparator: Prednisone alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisolone alone	Cyclosporin and prednisone	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**			No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies were found that looked at malignancy
Complete remission	(CI 95% -)				No studies were found that looked at complete remission

		Difference: **fewer**		
Relapse 6 months	Relative risk: 0.33 (CI 95% 0.13 - 0.83) Based on data from 104 patients in 1 studies[1] Follow up 24 months	**309** per 1000 **102** per 1000 Difference: **207 fewer per 1000** (CI 95% 269 fewer - 53 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Cyclosporin and prednisone compared with prednisone alone may decrease relapse
Relapse 12 months	Relative risk: 0.72 (CI 95% 0.46 - 1.13) Based on data from 104 patients in 1 studies[3] Follow up 24 months	**509** per 1000 **366** per 1000 Difference: **143 fewer per 1000** (CI 95% 275 fewer - 66 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Cyclosporin and prednisone may have little or no difference on relapse at 12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss
Creatinine clearance (mL/min)	Measured by: Scale: - High better Based on data from 87 patients in 1 studies[5] Follow up 24 months	mL/minMean mL/minMean Difference: **MD 2 higher** (CI 95% 2.44 lower - 6.44 higher)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[6]	We are uncertain whether cyclosporin and prednisone compared with prednisone alone increases or decreases creatinine clearance

71. Primary study [84] **Baseline/comparator:** Control arm of reference used for intervention .
72. **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, Low number of patients;
73. Primary study [84] **Baseline/comparator:** Control arm of reference used for intervention .
74. **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.** Wide confidence intervals, Only data from one study, Low number of patients;
75. Primary study [84] **Baseline/comparator:** Control arm of reference used for intervention .
76. **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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PICO (11.31)
Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Mycophenolate mofetil
Comparator: Cyclosporin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporin Mycophenolate mofetil	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection - Pneumonia	Relative risk: 3.0 (CI 95% 0.13 - 67.06) Based on data from 24 patients in 1 studies[1] Follow up 12 months	**0** per 1000 **0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil compared with cyclosporin increases or decreases relapse at infection - pneumonia
Malignancy	(CI 95% -)	Difference: **fewer**		No studies comparing mycophenolate mofetil with cyclosporin were found that looked at ≥50% GFR loss
Complete remission	(CI 95% -)			No studies comparing mycophenolate mofetil with cyclosporin were found that looked at complete remission

		Difference: **fewer**		
Relapse 12 months	Relative risk: 1.9 (CI 95% 0.66 - 5.46) Based on data from 82 patients in 2 studies[3] Follow up Mean 12 months	**238** per 1000 **452** per 1000 Difference: **214 more per 1000** (CI 95% 81 fewer - 1061 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether mycophenolate mofetil compared with cyclosporin increases or decreases relapse at 12 months
Hypertrichosis	Relative risk: 0.23 (CI 95% 0.1 - 0.5) Based on data from 140 patients in 3 studies[5] Follow up Mean 10 months	**426** per 1000 **98** per 1000 Difference: **328 fewer per 1000** (CI 95% 383 fewer - 213 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Mycophenolate mofetil compared with cyclosporin may decrease hypertrichosis
Annual GFR loss	Measured by: Scale: - Lower better Based on data from 24 patients in 1 studies[7] Follow up 12 months	mL/min/1.73m^2Mean mL/min/1.73m^2Mean Difference: **MD 20 higher** (CI 95% 5.49 higher - 34.51 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Mycophenolate mofetil compared with cyclosporin may improve annual GFR loss

77. Primary study [78] **Baseline/comparator:** Control arm of reference used for intervention .
78. **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;
79. Systematic review with included studies: [102], [78] **Baseline/comparator:** Control arm of reference used for intervention .
80. **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;
81. Systematic review with included studies: [78], [93], [102] **Baseline/comparator:** Control arm of reference used for intervention .
82. **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;
83. Primary study [78] **Baseline/comparator:** Control arm of reference used for intervention .
84. **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;

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PICO (11.32)
Population: Children with frequently relapsing steroid-sensitive nephrotic syndrome
Intervention: Changing cyclosporin dose
Comparator: Fixed cyclosporin dose

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

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

85. Primary study [87] **Baseline/comparator:** Control arm of reference used for intervention .
86. **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.**
87. Primary study [87] **Baseline/comparator:** Control arm of reference used for intervention .
88. **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;
89. Primary study [87] **Baseline/comparator:** Control arm of reference used for intervention .
90. **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;

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PICO (11.33)

Population: Children with frequently relapsing or steroid-dependent nephrotic syndrome
Intervention: High cyclosporin dose
Comparator: Low dose cyclosporin dose

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

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

91. Primary study [85] **Baseline/comparator:** Control arm of reference used for intervention .
92. **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;
93. Primary study [85] **Baseline/comparator:** Control arm of reference used for intervention .
94. **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;
95. Primary study [85] **Baseline/comparator:** Control arm of reference used for intervention .
96. **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;
97. Primary study [85] **Baseline/comparator:** Control arm of reference used for intervention .
98. **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;

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PICO (11.34)

Population: Children with frequently replapsing or steroid-dependent nephrotic syndrome
Intervention: Rituximab
Comparator: Placebo or control

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or control Rituximab	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	Relative risk: 2.01 (CI 95% 0.46 - 8.8) Based on data from 102 patients in 2 studies[1] Follow up Mean 12 months	**39** per 1000 **78** per 1000 Difference: **39 more per 1000** (CI 95% 21 fewer - 304 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether rituximab compared with placebo or control increases or decreases infections
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy
Relapse 3 months	Relative risk: 0.32 (CI 95% 0.14 - 0.7) Based on data from 132 patients in 3 studies[3] Follow up Mean 15 months	**530** per 1000 **170** per 1000 Difference: **360 fewer per 1000** (CI 95% 456 fewer - 159 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Rituximab compared with placebo or control may decrease relapse at 3 months
Relapse 6 months	Relative risk: 0.26 (CI 95% 0.15 - 0.45) Based on data from 154 patients in 4 studies[5] Follow up Mean 11.5 months	**843** per 1000 **219** per 1000 Difference: **624 fewer per 1000** (CI 95% 717 fewer - 464 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Rituximab compared with placebo or control probably decreases relapse at 6 months
Relapse 12 months	Relative risk: 0.54 (CI 95% 0.24 - 1.21) Based on data from 78 patients in 2 studies[7] Follow up Mean 17 months	**974** per 1000 **526** per 1000 Difference: **448 fewer per 1000** (CI 95% 740 fewer - 205 more)	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[8]	We are uncertain whether rituximab compared with placebo or control increases or decreases relapse at 12 months
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

99. Systematic review with included studies: [90], [86] **Baseline/comparator:** Control arm of reference used for intervention .
100. **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;
101. Systematic review with included studies: [91], [90], [86] **Baseline/comparator:** Control arm of reference used for intervention .
102. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Serious.** Low number of patients;
103. Systematic review with included studies: [91], [86], [73], [66] **Baseline/comparator:** Control arm of reference used for intervention .
104. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Imprecision: Serious.** Low number of patients;
105. Systematic review with included studies: [91], [86] **Baseline/comparator:** Control arm of reference used for intervention .
106. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 80%.; **Imprecision: Serious.** Wide confidence intervals;

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PICO (11.35)

Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Azathioprine
Comparator: Steroids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Steroids Azathioprine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Relapse 6 months	Relative risk: 0.9 (CI 95% 0.59 - 1.38) Based on data from 60 patients in 2 studies[1] Follow up Mean 7 months	**567** per 1000 **510** per 1000 Difference: **57 fewer per 1000** (CI 95% 232 fewer - 215 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether azathioprine compared with steroids increases or decreases relapse
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies were found that looked at annual GFR loss

107. Systematic review with included studies: [63], [70] **Baseline/comparator:** Control arm of reference used for intervention .
108. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: Serious.** Wide confidence intervals;

References

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PICO (11.36)

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** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Complete remission	(CI 95% -)	Difference: **fewer**		No studies were found that looked at complete remission
Adverse effects	Relative risk: 1.56 (CI 95% 0.97 - 2.49) Based on data from 197 patients in 1 studies[1] Follow up 18 months	**214** per 1000 **334** per 1000 Difference: **120 more per 1000** (CI 95% 6 fewer - 319 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Mizoribine compared with placebo may have little or no difference on adverse effects
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

109. Primary study [96] **Baseline/comparator:** Control arm of reference used for intervention .
110. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

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PICO (11.37)

Population: Children with steroid-sensitive nephrotic syndrome
Intervention: Azithromycin
Comparator: Steroids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Steroids Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at End-stage kidney disease
≥50% GFR loss	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% GFR loss
Infection	(CI 95% -)	Difference: **fewer**		No studies were found that looked at infection
Malignancy	(CI 95% -)	Difference: **fewer**		No studies were found that looked at malignancy

Relapse 6 months	Relative risk: 0.59 (CI 95% 0.33 - 1.07) Based on data from 189 patients in 1 studies[1] Follow up 6 months	**253** per 1000 **149** per 1000 Difference: **104 fewer per 1000** (CI 95% 170 fewer - 18 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	We are uncertain whether azithromycin compared with steroids increases or decreases relapse at 6 months
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

111. Systematic review with included studies: [97] **Baseline/comparator:** Control arm of reference used for intervention .
112. **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;

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