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.

Ten comparisons of steroid therapy in the first episode of steroid-sensitive nephrotic syndrome:
1. Comparisons with 2 months therapy (12 studies, 1201 children)*
2. Five to 6 months versus 3 month therapy (9 studies, 913 children)*
3. Less than 2 months versus 2 months (1 study, 61 children)
4. 12 months versus 5 months therapy (1 study, 58 children)
5. Different total doses of prednisone (1 study, 59 children)
6. Steroid therapy and Sairei-to (1 study, 171 children)
7. Steroid therapy and cyclosporin (1 study, 104 children)
8. High dose methylprednisolone and 2 months therapy (1 study, 15 children)
9. Deflazacort with or without prednisone versus prednisone alone (3 studies, 255 children)
10. Weight-based versus BSA-based dosing of prednisolone (1 study, 100 children)

* One study had children in each comparison group

Eleven comparisons in children with frequently relapsing steroid-sensitive nephrotic syndrome:
1. Different prednisone doses (1 study, 30 children)
2. Daily compared with alternate-day prednisone dose for relapsing nephrotic syndrome (1 study, 62 children)
3. Intermittent dose versus alternate-day prednisone dose (1 study, 43 children)
4. Daily versus intermittent prednisone therapy (1 study, 50 children)
5. Single versus divided prednisone dose (2 studies, 138 children)
6. Intravenous versus oral corticosteroid (1 study, 64 children)
7. Prolonged oral versus intermittent therapy (2 months therapy) (1 study, 50 children)
8. Prolonged steroid therapy (7 months) versus 2 months therapy (1 study, 129 children)
9. Daily prednisolone treatment during viral infections (4 studies, 194 children)
10. Cortisol versus placebo (1 study, 26 children)
11. Deflazacort versus methylprednisolone (1 study, 11 children)

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
• 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, 61 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.
• 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 frequent relapsing disease. 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).
  o 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 frequent relapsing disease (RR 0.99, 95%CI 0.82 to 1.19; 4 studies, 585 children). While, in studies with a high risk of bias for allocation concealment, 3 months of therapy compared to 2 months of therapy probably decrease frequent relapse disease (RR 0.45, 95%CI 0.26 to 0.77; 3 studies, 220 children).
• Corticosteroid therapy for 5 to 6 months duration compared to 3 months duration it 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 frequent relapsing disease. 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.
  o 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 frequent relapsing disease (RR 1.00, 95%CI 0.74 to 1.34; 3 studies, 377 children). 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 frequent relapse disease (RR 0.48, 95%CI 0.32 to 0.72; 3 studies, 330 children).
• 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
Corticosteroid dose

Weight-based (1.5mg/kg, maximum 40 mg versus body-surface area-based dosing prednisolone of 40 mg/m²) (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.

High total dose (60 mg/m²/day (max 80 mg) for 6 weeks, 40 mg/m²/day on alternate days for 6 weeks) compared with lower total dose (40 mg/m²/day (max 60 mg) for 6 weeks, 40 mg/m²/day on alternate days for 6 weeks.

- 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.

Other

- 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) and may have little or no effect on complete remission at 6 weeks (RR 1.04, 95%CI 0.89 to 1.23; 1 study, 42 children). Other critical and important outcomes were not reported in RCTs.

- 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.

- 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.

Nephrotic syndrome in children with viral infections

Daily prednisolone compared with placebo or alternate day prednisolone

- 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

- 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 to 12 months (RR 1.20, 95%CI 0.93 to 1.55). Other critical and important outcomes were not reported in RCTs.
• 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.

• 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.

• 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.

• 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**

• 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).

• We are uncertain the effects of prednisone at 60 mg/m²/day for 4 weeks and tapered daily dose for 4 weeks compared to 60 mg/m²/day till remission and 40 mg/m² on 3/7 consecutive days because it has only been examined in one small RCT (50 children), with very serious study limitations.

• Prolonged duration of steroid therapy for 7 months (60 mg/m²/day for 4 weeks, then 60 mg/m² on alternate days. Reducing alternate-day dose by 10 mg/m² every 4 weeks) compared to standard duration of steroid therapy for 2 months (60 mg/m²/day till urine protein-free for 3 days, then 40 mg/m² on alternate days for 4 weeks) probably decreases 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).

**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 (5 studies, 147 children)
2. Alkylating agent (different durations, doses, route) (6 studies, 223 children)
3. Different alkylating agents (1 study, 50 children)
4. Alkylating agent versus vincristine (1 study, 39 children)
5. Calcineurin inhibitor versus prednisone alone (1 study, 127 children)
6. Calcineurin inhibitor versus alkylating agent (2 studies, 95 children)
7. Calcineurin inhibitor versus mycophenolate mofetil (3 studies (1 cross-over study), 89 children)
8. Calcineurin inhibitor (different doses) (2 studies, 188 children)
9. Levamisole versus placebo/prednisone (8 studies, 422 children)
10. Levamisole versus alkylating agent (1 study, 40 children)
11. Levamisole versus alkylating agent vs prednisone (1 study, 85 children)
12. Rituximab versus placebo or control (4 studies, 154 children)
13. Rituximab plus calcineurin inhibitor versus calcineurin inhibitor (1 study, 54 children)
14. Azathioprine versus placebo (2 studies, 60 children)
15. Mizoribine versus placebo (1 study, 197 children)
16. Fucidic acid versus prednisone (1 cross-over study, 18 children)

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.

Alkylating agent versus placebo/prednisone
- 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, the effects of chlorambucil compared with prednisone or placebo are unclear because study limitations and the low number of patients and few events in the 2 RCTs (41 children).
- Other critical and important outcomes were not reported by RCTs.

Alkylating agent (different durations, doses, route)
- 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.
- 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.
- 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.

- 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.
- The effects of an increase chlorambucil dose compared with a stable dose is unclear because of the very low certainty of the evidence.
- 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 steroid-dependent nephrotic syndrome. Other critical and important outcomes were not reported.

**Alkylating agent compared with other therapies**

- 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). 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). 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.
- 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. Other critical and important outcomes were not reported in the RCT.

**Other therapies**

**Levamisole versus other treatment**

- 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.
- Levamisole compared with cyclophosphamide may have little or no effect on relapse at 6 to 9 months, 12 months or 24 months after therapy. The effect on relapse 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**

- 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). Other critical and important outcomes were not reported in RCTs.
  - The use of a 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 to 0.94) (1 study, 44 children).
  - 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.

- Mycophenolate mofetil compared with cyclosporin may decrease 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. It may decrease hypertrichosis (RR 0.23, 95%CI 0.10 to 0.50; 3 studies, 140 children).

**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 probably decreases relapse at 6 months (RR 0.26, 95%CI 0.15 to 0.45; 4 studies, 154 children). However, its effect on relapse at 12 months and other critical and important outcomes are unclear due to very low certainty of the evidence.

**Mizoribine or azathioprine or azithromycin compared with placebo steroids alone**

- Treatment with mizoribine 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.
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

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Explanation/ results</th>
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<tbody>
<tr>
<td>Kidney function (GFR, presence of proteinuria, presence of albuminuria)</td>
<td>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.</td>
</tr>
<tr>
<td>Relapse (infrequent and frequent) and steroid-dependent</td>
<td>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.</td>
</tr>
<tr>
<td>Genetic markers</td>
<td>RCTs did not examine results in regards to genetic markers of disease</td>
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<tr>
<td>Gender</td>
<td>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.</td>
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<tr>
<td></td>
<td>For first relapse HR was 1.19 (95%CI 0.77 to 1.84)</td>
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<td></td>
<td>For clinical frequent relapsing nephrotic syndrome HR 1.77 (95%CI 0.98 to 3.03)</td>
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</tbody>
</table>

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.