Minimal change disease

Immunosuppressive therapy of adults with minimal change disease

PICO question
In patients with biopsy-proven minimal change disease, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapy improves efficacy outcomes (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) and reduce adverse effects (malignancy and infection)?

Search strategy and selection
Keywords for minimal change disease, and immunosuppressive therapy were used to search the Cochrane Kidney and Transplant Specialized Registry of studies for all randomized controlled trials (RCTs) published up to May 2018.

Search results
The 2008 Cochrane review search strategy found 3845 studies from relevant medical databases (Medline, EMBASE, CENTRAL). Studies were excluded because they were duplicates, not RCTs, not focused on patients with minimal change disease, including mixed etiology of nephrotic syndrome. There were three primary studies (68 participants included) in this review.

The May 2018 search identified 11 relevant reports, four reports were excluded and five primary studies (7 reports) (276 participants) were identified.

Overall eight primary studies (10 reports) with a total of 344 participants were included in the 2018 Cochrane systematic review update.

There were six ongoing RCTs identified from clinical trials registries and published protocols.

RCTs examined three comparisons
1. Steroid versus placebo or no treatment (one study, 28 participants)
2. Intravenous with or without oral steroids vs. oral steroids alone (two studies, 40 participants)
3. Calcineurin inhibitors with or without oral steroids vs. oral steroids alone (four studies, 252 participants)

Summary of the main findings

Steroid versus placebo or no treatment (one study, 28 participants)

- Steroid compared with placebo/no treatment may have little or no effect on complete remission (RR 1.44, CI 95% 0.95 to 2.19).
- For corticosteroid related adverse events, in particular avascular necrosis, steroid compared with placebo/no treatment may have little or no effect (RR 1.21, 95%CI 0.89 to 1.66).
- We are uncertain whether steroid compared with placebo increases or decrease doubling of serum creatinine and end-stage kidney disease due to the very low certainty of the evidence. Other critical and important outcomes (malignancy, ≥50% loss of GFR, infection, malignancy, annual GFR loss) were not reported in the RCT.

Intravenous with or without oral steroids versus oral steroids alone
• Intravenous steroids with or without oral steroids compared with oral steroids alone may have little or no effect on all-cause mortality (RR 0.3, 95% CI 0.02 to 7.39), from 22 patients in one study.
• We are uncertain if intravenous steroids with or without oral steroids compared with oral steroids alone has any effect on complete remission, due to study limitations, statistical heterogeneity ($I^2 = 90\%$) and very serious imprecision. For sustained remission there may be little or no difference (RR 0.50, 95% CI 0.11 to 2.19; 1 study, 22 participants) and relapse (RR 1.18, 95% CI 0.65 to 2.15; 1 study, 19 participants).
• Other critical and important outcomes (end-stage kidney disease, ≥50% loss of GFR, infection, malignancy, and annual GFR loss) were not reported in RCTs.

Calcineurin inhibitors with or without oral steroids vs. Oral steroids alone
• The use of calcineurin inhibitors effect on corticosteroid-related adverse events: decreases obesity (RR 0.05, 95% CI 0.00 to 0.41; 2 studies, 81 participants), probably decreases Cushing's syndrome (RR 0.02, 95% CI 0.00 to 0.35; 1 study, 119 participants), and may have little or no effect on acne (95% CI 0.01 to 1.03; 2 studies, 82 participants). Effects on other corticosteroid-related adverse events, induction of diabetes mellitus, hyperglycemia, osteoporosis are unclear because the certainty of the evidence was very low due to study limitations and very wide confidence intervals that indicate both appreciable benefit and harm.
• Calcineurin inhibitors with or without oral steroids compared with oral steroids alone probably has little or no effect on complete remission (RR 1.00 CI 95% 0.94 to 1.06; 4 studies, 242 participants), relapse at 6 to 9 months (RR 0.89, 95% CI 0.56 to 1.41; 3 studies, 179 participants) and 25-30 months (RR 0.92, 95% CI 0.66 to 1.29; 2 studies, 127 participants).
• Calcineurin inhibitors with or without oral steroids probably decreases the development of frequent relapsing and drug dependence minimal change disease (RR 0.31, 95% CI 0.11 to 0.90; 1 study, 106 participants).
• We are uncertain of the effects on respiratory infections due to very low certainty of the evidence. Other critical and important outcomes (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, malignancy, and annual GFR loss) were not reported in RCTs.

Effect modifiers
The following effect modifiers were considered:
• Kidney function (GFR, presence of proteinuria, presence of albuminuria)
• Relapse or steroid dependent minimal change disease
• Primary vs. secondary forms of disease
• Gender
There was insufficient data to allow for the assessment of effect modifiers.

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

No studies were found in the 2012 guideline that were not included in the 2018 review.
**PICO (13.1)**

**Population:** First episode of minimal change disease in adults with nephrotic syndrome  
**Intervention:** Steroid  
**Comparator:** Placebo or no treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo or no treatment</td>
<td>Steroid</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Very Low</td>
<td>We are uncertain whether steroid compared with placebo increases or decreases all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk: 0.33 (CI 95% 0.01 - 7.55) Based on data from 28 patients in 1 studies Follow up 77 months</td>
<td>Difference: 48 fewer per 1000 (CI 95% 70 fewer - 465 more)</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Very Low</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Very Low</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Very Low</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 1.44 (CI 95% 0.95 - 2.19) Based on data from 28 patients in 1 studies Follow up 77 months</td>
<td>Difference: 283 more per 1000 (CI 95% 32 fewer - 765 more)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Steroid compared with placebo/ no treatment may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Doubling serum creatinine</td>
<td>Relative risk: 0.11 (CI 95% 0.01 - 1.89) Based on data from 28 patients in 1 studies Follow up 77 months</td>
<td>Difference: 255 fewer per 1000 (CI 95% 283 fewer - 255 more)</td>
<td>Very Low Due to very serious imprecision Due to serious risk of bias</td>
<td>We are uncertain whether steroid compared with placebo increases or decreases doubling serum creatinine</td>
</tr>
<tr>
<td>Corticosteroid related adverse event - Avascular necrosis</td>
<td>Relative risk: 1.21 (CI 95% 0.89 - 1.66) Based on data from 28 patients in 1 studies Follow up 77 months</td>
<td>Difference: 172 more per 1000 (CI 95% 90 fewer - 541 more)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Steroid compared with placebo/ no treatment may have little or no difference on avascular necrosis</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td></td>
<td></td>
<td>No studies were found that looked at annual</td>
</tr>
</tbody>
</table>

2. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear blinding of participants and personnel, resulting in potential for performance bias, unclear blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

3. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear blinding of participants and personnel, resulting in potential for performance bias, unclear 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, Only data from one study, Low number of patients;

4. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear blinding of participants and personnel, resulting in potential for performance bias, unclear blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

5. Primary study Coggins 1985 Baseline/comparator: Control arm of reference used for intervention.

6. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear blinding of participants and personnel, resulting in potential for performance bias, unclear blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Only data from one study, Low number of patients;

**References**

[15] Interventions for minimal change disease in adults with nephrotic syndrome. 2018;
### PICO (13.2)
**Population:** First episode of minimal change disease in adults with nephrotic syndrome  
**Intervention:** Intravenous steroids with or without oral steroids  
**Comparator:** Oral steroids alone

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| All-cause mortality        | Relative risk: 0.33 (CI 95% 0.02 - 7.39)  
Based on data from 22 patients in 1 studies  
Follow up 12 - 24 months | Oral steroids alone: 91 per 1000  
Intravenous steroids ± oral steroids: 30 per 1000  
Difference: 61 fewer per 1000 (CI 95% 89 fewer - 581 more) | Low  
Due to very serious imprecision | Intravenous steroids with or without oral steroids compared with oral steroids alone may have little or no difference on all-cause mortality |
| End-stage kidney disease   | (CI 95% - )                    | Difference: fewer         |                                                    | No studies were found that looked at end-stage kidney disease |
| ≥50% loss of GFR           | (CI 95% - )                    | Difference: fewer         |                                                    | No studies were found that looked at ≥50% loss of GFR |
| 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         | Relative risk: 1.76 (CI 95% 0.17 - 18.32)  
Based on data from 35 patients in 2 studies  
Follow up Mean 22 months | Oral steroids alone: 667 per 1000  
Intravenous steroids ± oral steroids: 1174 per 1000  
Difference: 507 more per 1000 (CI 95% 554 fewer - 11552 more) | Very Low  
Due to serious risk of bias, Due to very serious inconsistency, Due to very serious imprecision | We are uncertain whether intravenous with or without oral steroids compared with oral steroids alone may increase or decrease complete remission |
| Sustained remission        | Relative risk: 0.5 (CI 95% 0.11 - 2.19)  
Based on data from 22 patients in 1 studies  
Follow up 12 - 24 months | Oral steroids alone: 364 per 1000  
Intravenous steroids ± oral steroids: 182 per 1000  
Difference: 182 fewer per 1000 (CI 95% 324 fewer - 433 more) | Low  
Due to very serious imprecision | Intravenous steroids with or without oral steroids compared with oral steroids alone may have little or no difference on sustained remission |
| Relapse                    | Relative risk: 1.18 (CI 95% 0.65 - 2.15)  
Based on data from 19 patients in 1 studies  
Follow up 12 - 24 months | Oral steroids alone: 636 per 1000  
Intravenous steroids ± oral steroids: 750 per 1000  
Difference: 114 more per 1000 (CI 95% 223 fewer - 731 more) | Low  
Due to very serious imprecision | Intravenous with or without oral steroids compared with oral steroids alone may have little or no difference on relapse |
| Annual GFR loss 3 years    | Measured by: Scale: - Lower better |                                |                                                    | No studies were found that looked at annual |
1. **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients and few events;

2. Primary study Imbasciati 1985, Yeung 1983 **Baseline/comparator:** Control arm of reference used for intervention.

3. **Risk of bias:** Serious. Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias; **Inconsistency:** Very Serious. Point estimates vary widely. The magnitude of statistical heterogeneity was high, with I^2: 90%; **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients;

4. **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

5. **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
### PICO (13.3)

**Population:** First episode of minimal change disease in adults with nephrotic syndrome  
**Intervention:** Calcineurin inhibitors with or without oral steroids  
**Comparator:** Oral steroids alone  

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at malignancy</td>
</tr>
</tbody>
</table>
| **Corticosteroid related adverse effects - Obesity** | Relative risk: 0.05  
(CI 95% 0.0 - 0.41)  
Based on data from 81 patients in 2 studies<sup>1</sup>  
Follow up Mean 6.5 months | 825 per 1000  
41 per 1000 | High  
Due to serious risk of bias, Due to serious imprecision, Upgraded due to Very large magnitude of effect<sup>2</sup>  
Calcineurin inhibitors with or without oral steroids compared with oral steroids alone decreases obesity |  |  
| Infections - Respiratory infections requiring antibiotics | Relative risk: 0.33  
(CI 95% 0.01 - 7.87)  
Based on data from 60 patients in 1 studies<sup>3</sup>  
Follow up 6 months | 33 per 1000  
11 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>4</sup>  
We are uncertain whether calcineurin inhibitors with or without oral steroids compared with oral steroids alone increases or decreases respiratory infections requiring antibiotics |  |  
| **Corticosteroid related adverse effects - Diabetes mellitus** | Relative risk: 0.13  
(CI 95% 0.01 - 2.41)  
Based on data from 119 patients in 1 studies<sup>5</sup>  
Follow up 25 months | 54 per 1000  
7 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>6</sup>  
We are uncertain whether calcineurin inhibitors with or without oral steroids compared with oral steroids alone increases or decreases induction of diabetes mellitus |  |  
| **Corticosteroid related adverse effects - Hyperglycaemia** | Relative risk: 0.95  
(CI 95% 0.14 - 6.33)  
Based on data from 81 patients in 2 studies<sup>7</sup>  
Follow up Mean 6.5 months | 50 per 1000  
47 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>11</sup>  
We are uncertain whether calcineurin inhibitors with or without oral steroids compared with oral steroids alone increases or decreases hyperglycemia |  |  

<sup>1</sup>Reference 1: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)  
<sup>2</sup>Reference 2: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)  
<sup>4</sup>Reference 4: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)  
<sup>5</sup>Reference 5: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)  
<sup>6</sup>Reference 6: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)  
<sup>7</sup>Reference 7: KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)
<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Baseline/comparator:</th>
<th>Relative Risk</th>
<th>Difference</th>
<th>Risk of Bias</th>
<th>Risk of Imprecision</th>
<th>Risk of Measurement Bias</th>
<th>Risk of Publication Bias</th>
<th>Study Quality</th>
<th>Prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid related adverse effects - Osteoporosis</td>
<td>Control arm of reference used for intervention</td>
<td>Relative risk: 0.18 (CI 95% 0.02 - 1.48)</td>
<td>73 fewer per 1000 (CI 95% 87 fewer - 43 more)</td>
<td>Low</td>
<td>Very Low</td>
<td>Serious</td>
<td>Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>We are uncertain whether calcineurin inhibitors with or without oral steroids compared with oral steroids alone increases or decreases osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Control arm of reference used for intervention</td>
<td>Relative risk: 0.02 (CI 95% 0.0 - 0.35)</td>
<td>350 fewer per 1000 (CI 95% 357 fewer - 322 fewer)</td>
<td>Low</td>
<td>Moderate</td>
<td>Very Serious</td>
<td>Very Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone probably decreases cushing's syndrome</td>
</tr>
<tr>
<td></td>
<td>Control arm of reference used for intervention</td>
<td>Relative risk: 0.1 (CI 95% 0.01 - 1.03)</td>
<td>329 fewer per 1000 (CI 95% 362 fewer - 11 more)</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone may have little or no difference on acne</td>
</tr>
<tr>
<td>Complete remission 3 to 6 months</td>
<td></td>
<td>Relative risk: 1.0 (CI 95% 0.94 - 1.06)</td>
<td>0 fewer per 1000 (CI 95% 56 fewer - 56 more)</td>
<td>Low</td>
<td>Low</td>
<td>Very Serious</td>
<td>Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Relapse 6 to 9 months</td>
<td></td>
<td>Relative risk: 0.89 (CI 95% 0.56 - 1.41)</td>
<td>32 fewer per 1000 (CI 95% 126 fewer - 118 more)</td>
<td>Low</td>
<td>Low</td>
<td>Very Serious</td>
<td>Very Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone may have little or no difference on relapse at 6 to 9 months</td>
</tr>
<tr>
<td>Relapse 25 to 30 months</td>
<td></td>
<td>Relative risk: 0.92 (CI 95% 0.66 - 1.29)</td>
<td>42 fewer per 1000 (CI 95% 178 fewer - 152 more)</td>
<td>Low</td>
<td>Low</td>
<td>Very Serious</td>
<td>Very Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone may have little or no difference on relapse at 25 to 30 months</td>
</tr>
<tr>
<td>Frequent relapses or drug dependence</td>
<td></td>
<td>Relative risk: 0.31 (CI 95% 0.11 - 0.9)</td>
<td>162 fewer per 1000 (CI 95% 209 fewer - 24 fewer)</td>
<td>Low</td>
<td>Low</td>
<td>Very Serious</td>
<td>Very Serious</td>
<td>Adequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;</td>
<td>Calcineurin inhibitors with or without oral steroids compared with oral steroids alone probably decreases frequent relapses or drug dependence</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td></td>
<td>Measured by: Scale: - Lower better</td>
<td>Difference: null lower</td>
<td>Null</td>
<td>Null</td>
<td>Null</td>
<td>Null</td>
<td>Null</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

2. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; | Imprecision: Serious. Low number of patients; Upgrade: Very large magnitude of effect.
4. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; | Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
5. Primary study Li 2017b Baseline/comparator: Control arm of reference used for intervention.
6. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; | Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
8. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; | Imprecision: Very Serious. Wide confidence intervals, Low number of patients and few events;
9. Primary study Li 2017b **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:** **Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

11. Primary study Li 2017b **Baseline/comparator:** Control arm of reference used for intervention .

12. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** **Very Serious.** Wide confidence intervals, Only data from one study; **Upgrade:** Very large magnitude of effect.


14. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** **Serious.** Low number of patients;


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; **Imprecision:** **Very Serious.** Wide confidence intervals;


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; **Imprecision:** **Serious.** Wide confidence intervals, Low number of patients;

19. Systematic review [16] with included studies: Li 2017b, Shirai 2017 **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.** Wide confidence intervals;

21. **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

[16] Interventions for minimal change disease in adults with nephrotic syndrome. 2018;
[17] Interventions for minimal change disease in adults with nephrotic syndrome. 2018;