KDIGO GN Guideline update – Evidence summary

Idiopathic membranous nephropathy

Immunosuppressive therapy of idiopathic membranous nephropathy

PICO question
In adults with biopsy-proven idiopathic membranous nephropathy, what immunosuppressive agents compared to placebo no treatment or other immunosuppressive therapies improve efficacy outcomes (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) and reduce adverse effects (infection, and malignancy)?

Search strategy and selection
Keywords for idiopathic membranous nephropathy and immunosuppressive therapy were used to search the Cochrane Kidney and Transplant Specialized Register for all RCTs published up to May 2018.

Search results
The Cochrane review published in 2004, identified 943 relevant citations from medical databases, 917 citations were excluded because they were not RCTs, did not include patients with biopsy-proven idiopathic membranous nephropathy, or were not on immunosuppressive therapy. The review identified 18 primary studies (19 reports). The 2014 Cochrane review update identified 244 relevant reports from the Cochrane Kidney and Transplant Specialized Register, 21 primary studies (33 reports), and 25 reports of existing studies were included. Overall there were 39 primary studies identified (77 reports).

The May 2018 search update of the Cochrane Kidney and Transplant Specialized Register identified 48 reports, seven were excluded because they were duplicates, not RCTs, did not include patients with biopsy-proven idiopathic membranous nephropathy, or were the wrong intervention. The 2018 review update found 20 primary studies (29 reports), five reports of studies already included in the previous Cochrane review, and ten reports of ongoing studies.

Overall 60 primary studies (109 reports) with 3356 participants were included.

There were 23 ongoing studies identified from clinicaltrials.gov, Chinese clinical trials registry, and the European clinical trials registry.

Nineteen comparisons were included:
1. Steroids versus placebo/no treatment (5 studies, 395 participants)
2. Alkylating agents versus placebo/no treatment or steroids (12 studies, 773 participants)
3. Calcineurin inhibitors versus placebo/no treatment (8 studies, 440 participants)
4. Calcineurin inhibitors versus alkylating agents (7 studies, 502 participants)
5. Azathioprine versus placebo/no treatment (2 studies, 39 participants)
6. Mycophenolate mofetil versus alkylating agents (2 studies, 41 participants)
7. Mycophenolate mofetil versus calcineurin inhibitors (2 studies, 129 participants)
8. Mycophenolate mofetil versus supportive therapy (1 study, 36 participants)
9. Mycophenolate mofetil plus cyclosporin versus cyclosporin alone (1 study, 18 participants)
10. Cyclophosphamide plus steroids versus chlorambucil plus steroids (3 studies, 145 participants)
11. Cyclophosphamide versus leflunomide (1 study, 48 participants)
12. Cyclophosphamide plus leflunomide versus leflunomide alone (1 study, 48 participants)
13. Cyclophosphamide plus leflunomide versus cyclophosphamide alone (1 study, 48 participants)
14. Mizoribine versus placebo/no treatment or steroids (3 studies, 150 participants)
15. Mizoribine (150 mg) once daily versus mizoribine (50 mg) three times daily (1 study, 37 participants)
16. Rituximab plus ACEi/ARB versus ACEi/ARB alone (1 study, 77 participants)
17. Tacrolimus plus steroids for 6 months versus tacrolimus versus 24 months (1 study, 42 participants)
18. Cyclosporin (1.5 mg/kg twice daily) versus cyclosporin (3.0 mg/kg once daily) (1 study, 33 participants)
19. Early (immediate) treatment - cyclophosphamide plus steroids versus late treatment (when serum creatinine > 25%) - cyclophosphamide plus steroids (1 study, 26 participants)

Summary of the main findings

Steroid versus placebo or no treatment

- Compared to no steroid regimen, treatment with steroids may make little or no difference to all-cause mortality (RR 0.58, 95% CI 0.11 to 2.98; 3 studies, 295 participants), or end-stage kidney disease (RR 0.80, 95%CI 0.33 to 1.94; 3 studies, 295 participants).
- Compared to no steroid regimen, treatment with steroids may make little or no difference to complete remission (RR 0.64, 95%CI 0.29 to 1.42; 2 studies, 196 participants).
- Steroid treatment may make no difference to doubling serum creatinine (RR 0.41, 95%CI 0.11 to 1.53; 3 studies, 130 participants), but may decrease 50% increase in serum creatinine (RR 0.57, 95%CI 0.34 to 0.94; 1 study, 103 participants).
- Other critical and important outcomes (≥50% loss of GFR, infection, malignancy, and annual loss of GFR) were not examined in RCTs.

Alkylating agents versus placebo/no treatment or steroids

- Compared to placebo/no treatment or steroids alone, treatment with an alkylating agent (cyclophosphamide or chlorambucil) may have little or no difference on all-cause mortality (RR 0.67, 95%CI 0.25 to 1.81; 8 studies, 445 participants).
- Alkylating agents probably decrease end-stage kidney disease compared to placebo/no treatment or steroids alone (RR 0.31, 95%CI 0.15 to 0.61; 8 studies; 392 participants).
- Compared to placebo/no treatment or steroids alone, treatment with an alkylating agent may increase complete remission at 9 to 30 months (RR 2.32, 95%CI 1.60 to 3.36; 7 studies, 422 participants).
- Alkylating agents probably decrease doubling serum creatinine compared to placebo/no treatment or steroids alone (RR 0.43, 95%CI 0.17 to 0.55; 5 studies, 257 participants) and 50% increase in serum creatinine (RR 0.51, 95%CI 0.32 to 0.80; 4 studies, 289 participants). However, alkylating agents increase serious adverse events (RR 2.62, 95%CI 1.48 to 4.64; 4 studies, 173 participants).
- Other critical and important outcomes were not reported in RCTs (≥50% loss of GFR, malignancy, annual loss of GFR)

Calcinuerin inhibitors

versus placebo/no treatment or steroids

- We are uncertain of the effects of calcineurin inhibitors on all-cause mortality, end-stage kidney disease, complete remission, lower respiratory infections, doubling serum creatinine
and >50% increase in serum creatinine because the certainty of the evidence is very low (study limitations and very serious imprecision).

- Compared to placebo or no treatment, treatment with calcineurin inhibitors may have little or no effect on serious adverse events (RR 1.66, 95%CI 0.91 to 3.02).
- Other critical and important outcomes (malignancy and annual GFR loss) were not reported in RCTs.

versus alkylating agents

- The effects on all-cause mortality, end-stage kidney disease, and doubling serum creatinine are uncertain because of study limitations, heterogeneity, and imprecision.
- Compared to alkylating agents, calcineurin inhibitors may have little or no effect on infection (RR 0.55, 95%CI 0.25 to 1.23; 3 studies, 218 participants) and complete remission (RR 1.28, 95%CI 0.71 to 2.32; 4 studies, 176 participants). However, it probably slightly increase a ≥20% loss of GFR (RR 1.4, 95%CI 1.0 to 1.95; 1 study, 69 participants).

Azathioprine versus placebo or no treatment

- We are uncertain about the effect of azathioprine compared with placebo or no treatment on all-cause mortality as studies did not look at this critical outcome. There too few events to examine the effect on end-stage kidney disease, and due to study limitations and imprecision in the effect estimates we are unable to determine the effect on complete remission.
- Azathioprine compared with placebo or no treatment may have little or no effect on doubling serum creatinine and eGFR at 12 months.

Mycophenolate mofetil (MMF) versus other

- Only one small RCT compared MMF to supportive therapy, due to study limitations and imprecision, the effects on critical and important outcomes are uncertain.
- There were too few events to examine all-cause mortality and end-stage kidney disease for the comparison of MMF and an alkylating agent. MMF compared with an alkylating agent may have little or no effect on complete remission (RR 1.16, 95%CI 0.29 to 4.69; 2 studies, 41 participants) and eGFR (MD 5 higher, 95%CI 6 lower to 6 higher). Other critical and important outcomes were not reported in RCTs.
- The effects of MMF compared with calcineurin inhibitors on all-cause mortality, infection, and malignancy were uncertain because there was study limitations and imprecision in the effect estimate. The critical and important outcomes (end-stage kidney disease, ≥50% GFR loss) were not reported in RCTs. It may have little or no effect on complete remission (RR 0.86, 95%CI 0.4 to 1.85; 2 studies, 99 participants) and eGFR at 11 months (MD 13.9 lower, 95%CI 31.05 lower to 3.25 higher).
- One small RCT examined the addition of cyclosporin to MMF compared with cyclosporin alone, that did not report on many critical and important outcome and the effect on complete remission is uncertain due to study limitations and very serious imprecision.

Cyclophosphamide plus steroids versus chlorambucil plus steroids

- The effects on all-cause mortality, doubling serum creatinine, and end-stage kidney disease at 15 months are uncertain as they have only been reported in one small RCT with study limitations. However, cyclophosphamide plus steroids compared to chlorambucil plus steroids may have little or no effect on end-stage kidney disease at 32 to 39 months (RR 0.40, 95%CI 0.08 to 2.09; 2 studies, 127 participants).
- Compared with chlorambucil plus steroids, cyclophosphamide plus steroids may have little or no effect on complete remission (RR 2.22, 95%CI 0.76 to 6.47; 3 studies, 147 participants). However, it probably decreases adverse events leading to treatment discontinuation or hospitalization (RR 0.48, 95%CI 0.26 to 0.90; 3 studies, 147 participants).

Other immunosuppressive agents
• Cyclophosphamide versus leflunomide or the combination of cyclophosphamide with leflunomide compared with cyclophosphamide or leflunomide alone may have little or no difference on complete remission. Other critical and important outcomes were not examined in the small RCT.

• The effects of mizoribine compared to placebo/no treatment or steroids alone are uncertain as many critical or important outcomes were not examined in RCTs. Due to the very low certainty of the evidence the effects on complete and partial remission are unclear. The use of mizoribine in one daily dose (150 mg once daily) compared to three doses (50 mg) daily may have little or no difference on induction of complete remission (RR 1.35, 95%CI 0.66 to 2.78; 1 study, 37 participants).

• Treatment with rituximab plus ACEi/ARB effects on critical and important outcomes are unclear as the one RCT (75 participants) did not report these outcomes, or due to a low number of patients and few events and study limitations (malignancy, serious adverse events, and complete remission). However, it probably increases the induction of partial remission (RR 3.08, 95%CI 1.25 to 7.62).

• Treatment with tacrolimus plus steroids for 6 months compared with tacrolimus plus steroids for 24 months (1 study, 42 participants) may have little or no effect on infection (urinary tract infection and upper respiratory tract infection), hyperglycemia, and induction of complete remission at 6 months and 24 months. Other critical and important outcomes were not examined.

• One small RCT (33 participants) examined cyclosporin twice daily (1.5 mg/kg) compared with cyclosporin once daily (3.0 mg/kg). Effects on critical and important outcomes are uncertain, as many were not reported or due to study limitations and imprecision in the effect estimate, but it may decrease proteinuria at 12 months (MD 0.7 lower, 95%CI 0.96 to 0.44 lower).

• Immediate treatment with cyclophosphamide plus steroids compared to late treatment (when serum creatinine >25% of baseline) with cyclophosphamide plus steroids was examined in on small RCT (26 participants) and it had uncertain effects on all-cause mortality and end-stage kidney disease due to study limitations, wide confidence intervals and a low number of patients and few events. Other critical and important outcomes were not reported. It may have little or no difference on complete remission (RR 0.75, 95%CI 0.39 to 1.45) or adverse effects requiring treatment discontinuation or hospitalization (RR 0.29, 95%CI 0.07 to 1.16).

• The effects of adrenocorticotrophic hormone compared with an alkylating agent plus steroids are unclear, as this was only examined in one small RCT (32 participants) and there were few events in critical and important outcomes.
Effect modifiers

The following table lists the effect modifiers considered for all comparisons. Only sufficient data were available for the following comparisons:

1. Steroids versus no placebo/no treatment (5 studies, 395 participants)
2. Alkylating agents versus placebo/no treatment or steroids (12 studies, 773 participants)
3. Calcineurin inhibitors versus placebo/no treatment (8 studies, 440 participants)
4. Calcineurin inhibitors versus alkylating agents (7 studies, 502 participants)

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Explanation/ results</th>
</tr>
</thead>
</table>
| Kidney function (GFR, presence of proteinuria, presence of albuminuria) | For the comparisons 1, 3, and 4 RCTs did not separate results according to kidney function parameters. The majority of participants had nephrotic syndrome. For comparison 2 – alkylating agents versus placebo/no treatment or steroids subgroups determined by kidney function were not examined in many of the RCTs. Ponticelli 1992 (1) had pre-specified subgroups:  
  • Proteinuria - \(\leq 5.0 \text{ g/day}\) versus \(>5.0 \text{ g/day}\) increases complete or partial remission at year 1 (OR 3.5, 95%CI 1.2 to 10.5); and year 2 (OR 3.1, 95%CI 1.1 to 8.8), with no difference at year 3 and 4.  
  • Serum creatinine \(\leq 1.0 \text{ mg/dl}\) versus \(>1.0 \text{ mg/dl}\) increases complete remission at year three (OR 2.8, 95%CI 1.0 to 8.0) with no difference at year 1, 2 or 4. |
| Relapse                                              | For comparisons 1, 2 and 4 RCTs did not examine the treatment of patients with relapsing idiopathic membranous nephropathy. In the calcineurin inhibitors versus placebo/no treatment comparison, one RCT (2) examined patients who failed to meet remission after 8 weeks of corticosteroid therapy. However, this exhibited similar effects to other studies and its exclusion did not change the overall effect estimate of the meta-analysis. |
| Primary versus secondary forms of disease            | RCTs did not provide separate results according to the primary or secondary idiopathic membranous nephropathy. Some studies excluded patients with secondary forms of idiopathic membranous nephropathy. |
| Gender                                               | In included studies for comparisons 1, 2 and 3, male participants were in the majority (60 to 80%). The comparison of calcineurin inhibitors versus alkylating agents, one RCT had 43% male participants (3), and effects were not different to the trials with a majority of male participants. |
| Age (adult vs. pediatric)                            | The RCTs mainly included adults, some studies included adolescent participants (\(>15 \text{ years of age}\)) but did not provide results for this subgroup. |


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

Alkylating agents versus placebo/no treatment or steroids

1. Ponticelli 1995 – This is a long-term follow-up study of Ponticelli 1983 that has been included in the meta-analysis. All data from long-term follow-up studies are included in the meta-analysis if an attrition rate over 70% is maintained.
### PICO (15.1)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Corticosteroids  
**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>
</table>
| **All-cause mortality** | Relative risk: 0.58  
(CI 95% 0.11 - 2.98)  
Based on data from 295 patients in 3 studies  
Follow up Mean 40.3 months | Placebo or no treatment: 48 per 1000  
Corticosteroids: 28 per 1000  
Difference: 20 fewer per 1000  
(CI 95% 43 fewer - 95 more) | Low  
Due to serious risk of bias, Due to serious imprecision | Corticosteroids compared to placebo or no treatment may have little or no difference on all-cause mortality |
| **End-stage kidney disease** | Relative risk: 0.8  
(CI 95% 0.33 - 1.94)  
Based on data from 295 patients in 3 studies  
Follow up Mean 40.3 months | Placebo or no treatment: 103 per 1000  
Corticosteroids: 82 per 1000  
Difference: 21 fewer per 1000  
(CI 95% 69 fewer - 97 more) | Low  
Due to serious risk of bias, Due to serious imprecision | Corticosteroids compared to placebo or no treatment may have little or no difference on end-stage kidney disease |
| ≥50% loss of GFR | (CI 95% - ) | | | No studies comparing corticosteroids with placebo or no treatment were found that looked at ≥50% loss of GFR |
| Infection | (CI 95% - ) | | | No studies comparing corticosteroids with placebo or no treatment were found that looked at infection |
| Malignancy | (CI 95% - ) | | | No studies comparing corticosteroids with placebo or no treatment were found that looked at malignancy |
| Complete remission | Relative risk: 0.64  
(CI 95% 0.29 - 1.42)  
Based on data from 192 patients in 2 studies  
Follow up Mean 36 months | Placebo or no treatment: 160 per 1000  
Corticosteroids: 102 per 1000  
Difference: 58 fewer per 1000  
(CI 95% 114 fewer - 67 more) | Low  
Due to serious risk of bias, Due to serious imprecision | Corticosteroids compared to placebo or no treatment may have little or no difference on complete remission |
| Doubling serum creatinine | Relative risk: 0.41  
(CI 95% 0.11 - 1.53)  
Based on data from 120 patients in 3 studies  
Follow up Mean 20 months | Placebo or no treatment: 210 per 1000  
Corticosteroids: 86 per 1000  
Difference: 124 fewer per 1000  
(CI 95% 187 fewer - 111 more) | Low  
Due to serious risk of bias, Due to serious imprecision | Corticosteroids compared to placebo or no treatment may have little or no difference on doubling serum creatinine. However, exclusion of one study (Murphy 1992) with few events result indicates that corticosteroid may decrease doubling serum creatinine compared with placebo or no treatment |
| 50% increase in serum creatinine | Relative risk: 0.57  
(CI 95% 0.34 - 0.94) | Placebo or no treatment: 510 per 1000  
Corticosteroids: 291 per 1000  | Low  
Due to very serious risk of bias, | Corticosteroids compared to placebo or no treatment |
<table>
<thead>
<tr>
<th>Annual GFR loss 3 years</th>
<th>Measured by: Scale: - Lower better</th>
<th>Difference: <strong>null lower</strong></th>
<th>Due to serious imprecision, Upgraded due to Large magnitude of effect(^9)</th>
<th>no treatment may decrease 50% increase in serum creatinine</th>
</tr>
</thead>
</table>

| 2. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision**: **Serious**. Wide confidence intervals, Low number of patients and events; |
| 4. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision**: **Serious**. Wide confidence intervals, Low number of patients; |
| 6. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and large loss to follow up; **Imprecision**: **Serious**. Low number of patients and few events; |
| 8. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision**: **Serious**. Low number of patients and few events; **Publication bias**: **No serious**. The Systematic review used did not search for gray literature; |
| 10. **Risk of bias**: **Very Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision**: **Serious**. Only data from one study; **Upgrade**: **Large magnitude of effect**. |

References

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
# KDIGO Clinical Practice Guideline for Glomerulonephritis

## PICO (15.2)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Alkylating agents  
**Comparator:** Placebo or no treatment or steroids  

<table>
<thead>
<tr>
<th>Outcome</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></td>
<td></td>
<td>Placebo/no treatment/steroids</td>
<td>Alkylating agents</td>
<td></td>
</tr>
</tbody>
</table>
| All-cause mortality | Relative risk: 0.67 (CI 95% 0.25 - 1.81)  
Follow up Mean 46 months | 45 per 1000 | 30 per 1000 | Low  
Due to serious risk of bias, Due to serious imprecision | Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids may have little or no difference on all-cause mortality |
| End-stage kidney disease | Relative risk: 0.31 (CI 95% 0.15 - 0.61)  
Follow up Mean 43 months | 158 per 1000 | 49 per 1000 | Moderate  
Due to serious risk of bias, Upgraded due to Very large magnitude of effect, Due to serious indirectness | Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids probably decreases end-stage kidney disease |
| ≥50% loss of GFR | Relative risk (CI 95% - ) | per 1000 | per 1000 | Difference: fewer per 1000 | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk (CI 95% - ) | per 1000 | per 1000 | Difference: fewer per 1000 | No studies were found that looked at infection |
| Malignancy | Relative risk (CI 95% - ) | per 1000 | per 1000 | Difference: fewer per 1000 | No studies were found that looked at infection |
| Complete remission 9 to 30 months | Relative risk: 2.32 (CI 95% 1.6 - 3.36)  
Follow up Mean 50 months | 174 per 1000 | 404 per 1000 | High  
Due to serious risk of bias, Upgraded due to Large magnitude of effect | Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids increases complete remission at 9 to 30 months |
| Doubling serum creatinine 15 to 120 months | Relative risk: 0.43 (CI 95% 0.17 - 0.65)  
Follow up Mean 59 months | 413 per 1000 | 179 per 1000 | Moderate  
Due to serious risk of bias, Due to Large magnitude of effect | Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids probably decreases doubling serum creatinine |
| 50% increase in serum creatinine | Relative risk: 0.51 (CI 95% 0.32 - 0.8) | 279 per 1000 | 142 per 1000 | Low  
Due to serious risk of bias, Due to | Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids may have little or no difference on all-cause mortality |
<table>
<thead>
<tr>
<th>Duration of Follow-up</th>
<th>Patients</th>
<th>Difference in Mean Change in GFR</th>
<th>Significance</th>
<th>Chlorambucil Compared to Placebo or No Treatment</th>
<th>Risk of Bias</th>
<th>Risk of Inconsistency</th>
<th>Risk of Imprecision</th>
<th>Indirectness</th>
<th>Upgrade</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 120 months</td>
<td>289</td>
<td><strong>137 fewer per 1000</strong> (CI 95% 190 fewer - 56 fewer)</td>
<td>Serious inconsistency, Due to serious imprecision, Upgraded due to Large magnitude of effect</td>
<td>Chlorambucil compared with placebo or no treatment or steroids may decrease 50% increase in serum creatinine</td>
<td>Serious</td>
<td>Serious</td>
<td>Due to serious imprecision, Due to serious imprecision, Upgraded due to Large magnitude of effect</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Serious adverse events

<table>
<thead>
<tr>
<th>Events</th>
<th>Relative Risk</th>
<th>Difference in Mean Change in GFR</th>
<th>Significance</th>
<th>Alkylating agents, cyclophosphamide or chlorambucil compared with placebo or no treatment or steroids increases serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 per 1000</td>
<td>325 per 1000</td>
<td><strong>201 more per 1000</strong> (CI 95% 60 more - 451 more)</td>
<td>High</td>
<td>Due to serious risk of bias, Due to serious imprecision, Upgraded due to Very large magnitude of effect</td>
</tr>
</tbody>
</table>

### Annual GFR loss 3 years

<table>
<thead>
<tr>
<th>Measured by:</th>
<th>Scale: - Lower better</th>
<th>Difference in Mean Change in GFR</th>
<th>Significance</th>
<th>No studies were found that looked at annual GFR loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean</td>
<td><strong>MD null lower</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Risk of bias: Serious. Incomplete data and/or large loss to follow up; Imprecision: Serious. Due to few events;
4. Risk of bias: Serious. Incomplete data and/or large loss to follow up; Indirectness: Serious. The outcome time frame in studies were insufficient; Imprecision: Serious. Due to few events; Upgrade: Very large magnitude of effect.
6. Risk of bias: Serious. Incomplete data and/or large loss to follow up; Upgrade: Large magnitude of effect.
8. Risk of bias: Serious. Incomplete data and/or large loss to follow up; Inconsistency: Serious. Point estimates vary widely; Upgrade: Large magnitude of effect.
10. Risk of bias: Serious. Unclear for most domains in one study (Ponticelli 1983); Inconsistency: Serious. Point estimates vary widely; Imprecision: Serious. Due to few events; Upgrade: Large magnitude of effect.
12. Risk of bias: Serious. Incomplete data and/or large loss to follow up; Imprecision: Serious. Low number of patients and few events; Upgrade: Very large magnitude of effect.

References
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
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<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk: 1.54 (CI 95% 0.42 - 5.65)</td>
<td>Placebo/no treatment or steroids</td>
<td>17 per 1000</td>
<td>26 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 9 more per 1000 (CI 95% 10 fewer - 79 more)</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk: 1.21 (CI 95% 0.52 - 2.79)</td>
<td>Placebo/no treatment or steroids</td>
<td>85 per 1000</td>
<td>103 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 18 more per 1000 (CI 95% 41 fewer - 152 more)</td>
<td></td>
</tr>
<tr>
<td>Infection - Lower</td>
<td>Relative risk: 5.0 (CI 95% 0.25 - 100.53)</td>
<td>Placebo/no treatment or steroids</td>
<td>0 per 1000</td>
<td>0 per 1000</td>
</tr>
<tr>
<td>respiratory infection</td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>Placebo/no treatment or steroids</td>
<td>per 1000</td>
<td>per 1000</td>
</tr>
<tr>
<td>Complete</td>
<td>Relative risk: 1.13 (CI 95% 0.35 - 3.57)</td>
<td>Placebo/no treatment or steroids</td>
<td>80 per 1000</td>
<td>90 per 1000</td>
</tr>
<tr>
<td>remission</td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 10 more per 1000 (CI 95% 52 fewer - 206 more)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse</td>
<td>Relative risk: 1.66 (CI 95% 0.91 - 3.02)</td>
<td>Placebo/no treatment or steroids</td>
<td>151 per 1000</td>
<td>251 per 1000</td>
</tr>
<tr>
<td>effects</td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 100 more per 1000 (CI 95% 14 fewer - 305 more)</td>
<td></td>
</tr>
<tr>
<td>Doubling serum</td>
<td>Relative risk: 0.96 (CI 95% 0.35 - 2.64)</td>
<td>Placebo/no treatment or steroids</td>
<td>147 per 1000</td>
<td>141 per 1000</td>
</tr>
<tr>
<td>creatinine</td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 6 fewer per 1000 (CI 95% 96 fewer - 241 more)</td>
<td></td>
</tr>
<tr>
<td>50% increase in</td>
<td>Relative risk: 0.55 (CI 95% 0.05 - 5.75)</td>
<td>Placebo/no treatment or steroids</td>
<td>174 per 1000</td>
<td>96 per 1000</td>
</tr>
<tr>
<td>serum creatinine</td>
<td></td>
<td>Calcineurin inhibitors</td>
<td>Difference: 78 fewer per 1000 (CI 95% 165 fewer - 827 more)</td>
<td></td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by:</td>
<td>Mean</td>
<td>Mean Difference: MD null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Scale: - Lower better</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** **Very Serious.** Wide confidence intervals, due to few events;


4. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Indirectness:** **Serious.** The outcome time frame in studies were insufficient; **Imprecision:** **Serious.** Wide confidence intervals;

5. Systematic review [22] with included studies: Ramachandran 2016 **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of bias:** **Serious.** **Imprecision:** **Very Serious.** Wide confidence intervals, Only data from one study;


8. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** **Very Serious.** Wide confidence intervals, Low number of patients and few events;


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


12. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** **Very Serious.** Wide confidence intervals, Low number of patients and few events;


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:** **Very Serious.** Wide confidence intervals, Low number of patients and few events;

References

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.4)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Calcineurin inhibitors  
**Comparator:** Alkylating agents

<table>
<thead>
<tr>
<th>Outcome</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: 1.04  
(CI 95% 0.21 - 5.16)  
Based on data from 238 patients in 5 studies  
Follow up Mean 20 months | 18 per 1000  
19 per 1000 | Very Low  
Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision | We are uncertain whether calcineurin inhibitors compared with alkylating agents increases or decreases all-cause mortality |
| End-stage kidney disease | Relative risk: 1.45  
(CI 95% 0.14 - 14.69)  
Based on data from 178 patients in 4 studies  
Follow up Mean 23 months | 12 per 1000  
17 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness | We are uncertain whether calcineurin inhibitors compared with alkylating agents increases or decreases end-stage kidney disease |
| ≥50% loss of GFR | Relative risk  
(CI 95% - -) | per 1000  
per 1000 | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk: 0.55  
(CI 95% 0.25 - 1.23)  
Based on data from 218 patients in 3 studies  
Follow up Mean 13 months | 145 per 1000  
80 per 1000 | Low  
Due to serious risk of bias, Due to serious imprecision | Calcineurin inhibitors compared with alkylating agents may have little or no difference on infection |
| Malignancy | Relative risk: 0.0  
(CI 95% 0.0 - 0.0)  
Based on data from 58 patients in 1 studies | 0 per 1000  
0 per 1000 | There were too few who experienced the malignancy, to determine whether calcineurin inhibitors compared to alkylating agents made a difference |
| Complete remission | Relative risk: 1.28  
(CI 95% 0.71 - 2.32)  
Based on data from 176 patients in 4 studies  
Follow up Mean 23 months | 280 per 1000  
358 per 1000 | Low  
Due to serious risk of bias, Due to serious imprecision | Calcineurin inhibitors compared with alkylating agents may have little or no difference on complete remission |
| ≥ 20% loss of GFR | Relative risk: 1.4  
(CI 95% 1.0 - 1.95)  
Based on data from 69 patients in 1 studies  
Follow up 12 months | 576 per 1000  
806 per 1000 | Moderate  
Due to serious imprecision | Calcineurin inhibitors compared with alkylating agents probably increase ≥ 20% loss of GFR slightly |
| Doubling serum creatinine | Relative risk: 0.73  
(CI 95% 0.21 - 2.48)  
Based on data from 38 patients in 1 studies  
Follow up 60 months | 250 per 1000  
183 per 1000 | Very Low  
Due to very serious imprecision, Due to serious risk of bias | We are uncertain whether calcineurin inhibitors compared with alkylating agents increases or decreases doubling serum creatinine |
| Annual GFR loss 3 years | Measured by:  
Scale: - Lower better | Mean  
Mean | No studies were found that looked at annual GFR loss |

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1.  
2.  
3.  
4.  
5.  
6.  
7.  
8.  
9.  
10.  
11.  
12.  
13.
Difference: MD null lower

   Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, unclear sequence, allocation concealment and blinding for two studies (Cheng 2010a, Peng 2016); Inconsistency: Serious. Point estimates vary widely; Imprecision: Very Serious. Due to few events, wide confidence intervals.
   Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, unclear sequence, allocation concealment and blinding for two studies (Cheng 2010a); Indirectness: Serious. The outcome time frame in studies were insufficient; Imprecision: Very Serious. Wide confidence intervals, low number of patients and few events.
   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 and unclear sequence generation, allocation concealment and blinding in the Xu 2013a study; Imprecision: Serious. Due to few events.
   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 and unclear sequence generation, allocation concealment and blinding in the Xu 2013a study; Imprecision: Serious. Due to few events.
   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.
   Risk of bias: Serious. Only data from one study, low number of patients; Imprecision: Serious. Only data from one study, low number of patients.

References
### PICO (15.5)
Population: Adults with idiopathic membranous nephropathy with nephrotic syndrome  
Intervention: Azathioprine  
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>All-cause mortality</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td><strong>Very Low</strong></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>fewer per 1000</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| End-stage kidney disease¹       | Relative risk (CI 95% - )  
(0 per 1000 per 1000)  
Based on data from 9 patients in 1 studies  
Follow up 12 Months | 0  
(per 1000 per 1000)  
(Difference: **fewer per 1000**  
(CI 95% 0 fewer - fewer)) | **Very Low**  
Due to very serious imprecision,  
Due to serious indirectness² | There were too few who experienced end stage kidney disease to determine whether azathioprine vs placebo or no treatment made a difference |
| Malignancy                      | Relative risk (CI 95% - )                                                                       | per 1000 per 1000         |                                | No studies were found that looked at malignancy                                      |
| ≥50% GFR loss                   | Relative risk (CI 95% - )                                                                       | per 1000 per 1000         |                                | No studies were found that looked at ≥50% GFR loss                                   |
| Infection                       | Relative risk (CI 95% - )                                                                       | per 1000 per 1000         |                                | No studies were found that looked at infection                                       |
| Complete remission              | Relative risk: 1.19 (CI 95% 0.07 - 19.05)  
Based on data from 39 patients in 2 studies³  
Follow up 9 months  
(mean) | 71  
(per 1000 per 1000)  
(Difference: **13 more per 1000**  
(CI 95% 66 fewer - 1282 more)) | **Very Low**  
Due to serious risk of bias,  
Due to serious inconsistency,Due to very serious imprecision³ | We are uncertain whether azathioprine vs placebo or no treatment increases or decreases complete remission |
| Doubling serum creatinine⁵ 12 Months | Relative risk: 0.8 (CI 95% 0.07 - 9.18)  
Based on data from 9 patients in 1 studies  
Follow up 12 Months | 250  
(per 1000 per 1000)  
(Difference: **50 fewer per 1000**  
(CI 95% 232 fewer - 2045 more)) | **Low**  
Due to very serious imprecision⁶ | There were too few patients who experienced 100% increase in serum creatinine, to determine whether azathioprine vs placebo or no treatment made a difference |
| Annual GFR loss 3 years         | Measured by:  
Scale: - Lower better  
Based on data from 9 | Mean | Mean |                                | No studies were found that looked at annual GFR loss                                 |
| eGFR⁷ 12 Months                 | Measured by:  
Scale: - High better  
Based on data from 9 | mL/min/1.73 m²Mean | mL/min/1.73 m²Mean | **Low**  
Due to very serious imprecision⁸ | Azathioprine vs placebo or no treatment may have little or no |

¹ End-stage kidney disease includes ESKD and death.  
² End-stage kidney disease is not currently considered one of the primary outcomes.  
³ Number of patients is the total number of patients in whom at least one outcome was observed.  
⁴ There were too few patients who experienced ≥50% GFR loss.  
⁵ Doubling serum creatinine is defined as a ≥40% increase in serum creatinine.  
⁶ There were too few patients who experienced ≥50% GFR loss.  
⁷ Estimated glomerular filtration rate (gFR) is defined as eGFR.  
⁸ There were too few patients who experienced ≥50% GFR loss.
<table>
<thead>
<tr>
<th>patients in 1 studies</th>
<th>Difference: MD 33.00 higher (CI 95% 19.01 lower - 85.01 higher)</th>
<th>difference on eGFR at 12 months</th>
</tr>
</thead>
</table>

1. End stage kidney disease (dialysis/transplantation) (Intention to treat analysis) - Azathioprine versus placebo/no treatment at final follow-up (12 months)
2. **Indirectness:** Serious. The outcome time frame in studies were insufficient; **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to no patients with end stage kidney disease;
4. **Risk of bias:** Serious. Selective outcome reporting, due to poorly reported study, many uncertainties (Sharma 2009); **Inconsistency:** Serious. Point estimates vary widely; **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients, Only data from one study, due to few events;
5. 100% increase in serum creatinine - Azathioprine versus placebo/no treatment at final follow-up (12 months) (Intention to treat analysis)
6. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to few patients with 100% increase in serum creatinine;
7. Final GFR [mL/min/1.73 m²] - Azathioprine versus placebo/no treatment at 12 months
8. **Imprecision:** Very Serious. Low number of patients, only data from one study;
### Outcomes and Timeframe

<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>Infection</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td><strong>Very Low</strong></td>
<td>No studies were found that looked at infection.</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Relative risk (CI 95% - )</td>
<td>0 per 1000 per 1000</td>
<td><strong>Low</strong></td>
<td>There were too few who experienced the all-cause mortality, to determine whether mycophenolate mofetil compared to alkylating agents made a difference.</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td><strong>Low</strong></td>
<td>No studies were found that looked at ≥50% loss of GFR.</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95% - )</td>
<td>0 per 1000 per 1000</td>
<td><strong>Low</strong></td>
<td>There were too few who experienced the end-stage kidney disease, to determine whether mycophenolate mofetil compared to alkylating agents made a difference.</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td><strong>Low</strong></td>
<td>No studies were found that looked at malignancy.</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 1.16 (CI 95% 0.29 - 4.69)</td>
<td>263 per 1000 305 per 1000</td>
<td><strong>Low</strong></td>
<td>Mycophenolate mofetil compared to alkylating agents may have little or no difference on complete remission.</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean Mean</td>
<td><strong>Low</strong></td>
<td>No studies were found that looked at annual GFR loss.</td>
</tr>
<tr>
<td>GFR</td>
<td>Measured by: Scale: - High better</td>
<td>ml/min Mean ml/min Mean</td>
<td><strong>Low</strong></td>
<td>Mycophenolate mofetil compared with alkylating agents may have little or no difference on GFR at the end of the study.</td>
</tr>
</tbody>
</table>

2. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and no events;


4. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and no events;


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

7. Systematic review [22] with included studies: Senthil Nayagam 2008 **Baseline/comparator:** Control arm of reference used for intervention.

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

**References**

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.7)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Mycophenolate mofetil  
**Comparator:** Calcineurin inhibitors

<table>
<thead>
<tr>
<th>Outcome</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: 3.0 (CI 95% 0.13 - 70.83)  
Based on data from 60 patients in 1 studies  
Follow up 9 months | 0  
per 1000  
per 1000 | Very Low  
Due to very serious imprecision | There were too few who died to determine whether mycophenolate vs calcineurin inhibitors made a difference |
| End-stage kidney disease | Relative risk  
(CI 95% -)  
Based on data from 0 patients in 0 studies | 0  
per 1000  
per 1000 | No studies were found that looked at end-stage kidney disease |
| ≥50% loss of GFR | Relative risk  
(CI 95% -) | per 1000  
per 1000 | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk: 1.0  
(CI 95% 0.28 - 3.63)  
Based on data from 60 patients in 1 studies  
Follow up 9 months | 133  
per 1000  
per 1000 | Very Low  
Due to very serious imprecision | We are uncertain whether mycophenolate mofetil compared with calcineurin inhibitors increases or decreases infection |
| Malignancy | Relative risk: 0.86  
(CI 95% 0.4 - 1.85)  
Based on data from 39 patients in 1 studies  
Follow up 11 months | 56  
per 1000  
per 1000 | Very Low  
Due to very serious imprecision | We are uncertain whether mycophenolate mofetil compared with calcineurin inhibitors increases or decreases malignancy |
| Complete remission | Relative risk: 0.86  
(CI 95% 0.53 - 0.93)  
Based on data from 99 patients in 2 studies  
Follow up Mean 10 months | 229  
per 1000  
per 1000 | Low  
Due to serious risk of bias | Mycophenolate mofetil compared with calcineurin inhibitors may have little or no difference on complete remission |
| Adverse events | Relative risk: 1.14  
(CI 95% 0.63 - 2.07)  
Based on data from 39 patients in 1 studies  
Follow up 11 months | 500  
per 1000  
per 1000 | Very Low  
Due to very serious imprecision | We are uncertain whether mycophenolate mofetil compared with calcineurin inhibitors increases or decreases malignancy |
| Annual GFR loss | Measured by:  
Scale: - Lower better | Mean  
Mean | No studies were found that looked at annual GFR loss |
| eGFR 11 months | Measured by:  
Scale: - High better  
Based on data from 39 | mL/min/1.73m\(^2\) Mean  
mL/min/1.73m\(^2\) Mean | Low  
Due to serious risk of bias | Mycophenolate mofetil compared with calcineurin inhibitors |
<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Serious. Selective outcome reporting; Imprecision: Very Serious. Only data from one study, due to low number of patients who died;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary study</td>
<td>Control arm of reference used for intervention.</td>
</tr>
<tr>
<td>Systematic review</td>
<td>Peng 2016 Baseline/comparator: Control arm of reference used for intervention.</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>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 binding of participants and personnel, resulting in potential for performance bias, unclear binding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Serious. Unclear binding of outcome assessors, resulting in potential for detection bias, unclear binding of participants and personnel, resulting in potential for performance bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;</td>
</tr>
<tr>
<td>Systematic review</td>
<td>[20] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;</td>
</tr>
<tr>
<td>Systematic review</td>
<td>[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;</td>
</tr>
</tbody>
</table>
**PICO (15.8)**
Population: Adults with idiopathic membranous nephropathy with nephrotic syndrome  
Intervention: Mycophenolate mofetil  
Comparator: Supportive therapy  

<table>
<thead>
<tr>
<th>Outcome</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: 0.0 (CI 95% 0.0 - 0.0) Based on data from 36 patients in 1 studies<sup>1</sup> Follow up 12 months | 0 per 1000 0 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>2</sup> | There were too few who experienced the all-cause mortality, to determine whether mycophenolate mofetil compared with supportive therapy made a difference |
| End-stage kidney disease | Relative risk (CI 95% - -) Based on data from 36 patients in 1 studies<sup>3</sup> Follow up 12 months | 0 per 1000 0 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness<sup>4</sup> | There were too few who experienced the end-stage kidney disease, to determine whether mycophenolate mofetil compared with supportive therapy made a difference |
| ≥50% loss of GFR | Relative risk (CI 95% - -) | per 1000 per 1000 | | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk (CI 95% - -) | per 1000 per 1000 | | No studies were found that looked at infection |
| Malignancy | Relative risk (CI 95% - -) | per 1000 per 1000 | | No studies were found that looked at malignancy |
| Complete remission | Relative risk: 0.45 (CI 95% 0.04 - 4.5) Based on data from 36 patients in 1 studies<sup>5</sup> Follow up 12 months | 118 per 1000 53 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>6</sup> | We are uncertain whether mycophenolate mofetil compared with supportive therapy increases or decreases complete remission |
| Doubling serum creatinine | Relative risk (CI 95% - -) Based on data from 36 patients in 1 studies<sup>7</sup> Follow up 12 months | 0 per 1000 0 per 1000 | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>8</sup> | There were too few who experienced the doubling serum creatinine, to determine whether mycophenolate mofetil compared with supportive therapy made a difference |
<p>| Annual GFR loss 3 years | Measured by: Scale: - Lower better | Mean Mean | | No studies were found that looked at annual GFR loss |</p>
<table>
<thead>
<tr>
<th>eGFR 12 months</th>
<th>Measured by: Scale: - High better Based on data from 35 patients in 1 studies9 Follow up 12 months</th>
<th>mL/min/1.73 m/L/min/1.73 m² Mean</th>
<th>Very Low Due to serious risk of bias, Due to very serious imprecision10</th>
<th>We are uncertain whether mycophenolate mofetil compared with supportive therapy increases or decreases eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference: MD 12.17 higher (CI 95% 4.10 lower - 28.44 higher)</td>
<td></td>
<td></td>
<td></td>
<td></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: Very Serious. Only data from one study, Low number of patients and no events;
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; Indirectness: Serious. The outcome time frame in studies were insufficient; Imprecision: Very Serious. Only data from one study, Low number of patients and no events;
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; Indirectness: Serious. The outcome time frame in studies were insufficient; Imprecision: Very Serious. 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, Only data from one study, Low number of patients and no events;
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;

References
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### Outcome

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>All-cause mortality</td>
<td>Relative risk (CI 95% - )</td>
<td>Cyclosporin alone: per 1000</td>
<td>Mycophenolate mofetil plus cyclosporin: per 1000</td>
<td>Difference: fewer per 1000</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95% - )</td>
<td>Cyclosporin alone: per 1000</td>
<td>Mycophenolate mofetil plus cyclosporin: per 1000</td>
<td>Difference: fewer per 1000</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - )</td>
<td>Cyclosporin alone: per 1000</td>
<td>Mycophenolate mofetil plus cyclosporin: per 1000</td>
<td>Difference: fewer per 1000</td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk (CI 95% - )</td>
<td>Cyclosporin alone: per 1000</td>
<td>Mycophenolate mofetil plus cyclosporin: per 1000</td>
<td>Difference: fewer per 1000</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>Cyclosporin alone: per 1000</td>
<td>Mycophenolate mofetil plus cyclosporin: per 1000</td>
<td>Difference: fewer per 1000</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 1.33 (CI 95% 0.41 - 4.33) Based on data from 18 patients in 1 studies¹ Follow up 12 months</td>
<td>333 per 1000</td>
<td>443 per 1000</td>
<td>Difference: 110 more per 1000 (CI 95% 196 fewer - 1109 more)</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td>Difference: MD null lower</td>
</tr>
</tbody>
</table>

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2. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

References

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.10)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Cyclophosphamide plus steroids  
**Comparator:** Chlorambucil plus steroids

<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: 3.0 (CI 95% 0.14 - 65.9)  
Based on data from 20 patients in 1 studies | Chlorambucil plus steroids: 0 per 1000  
Cyclophosphamide plus steroids: 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 imprecision2 | We are uncertain whether cyclophosphamide plus steroids compared with chlorambucil plus steroids increases or decreases all-cause mortality |
| **End-stage kidney disease 15 months** | Relative risk: 5.0 (CI 95% 0.7 - 35.5)  
Based on data from 20 patients in 1 studies | Chlorambucil plus steroids: 100 per 1000  
Cyclophosphamide plus steroids: 500 per 1000  
Difference: 400 more per 1000 (CI 95% 30 fewer - 3450 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision4 | We are uncertain whether cyclophosphamide plus steroids compared with chlorambucil plus steroids increases or decreases end-stage kidney disease at 15 months |
| **End-stage kidney disease 32 to 39 months** | Relative risk: 0.4 (CI 95% 0.08 - 2.09)  
Based on data from 127 patients in 2 studies | Chlorambucil plus steroids: 77 per 1000  
Cyclophosphamide plus steroids: 31 per 1000  
Difference: 46 fewer per 1000 (CI 95% 71 fewer - 84 more) | Low  
Due to very serious imprecision6 | Cyclophosphamide plus steroids compared with chlorambucil plus steroids may have little or no difference on end-stage kidney disease at 32 to 39 months |
| ≥50% loss of GFR | Relative risk (CI 95%  - ) | Chlorambucil plus steroids:  per 1000  
Cyclophosphamide plus steroids:  per 1000  
Difference: fewer per 1000 |  | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk (CI 95%  - ) | Chlorambucil plus steroids:  per 1000  
Cyclophosphamide plus steroids:  per 1000  
Difference: fewer per 1000 |  | No studies were found that looked at infection |
| Malignancy | Relative risk (CI 95%  - ) | Chlorambucil plus steroids:  per 1000  
Cyclophosphamide plus steroids:  per 1000  
Difference: fewer per 1000 |  | No studies were found that looked at malignancy |
| Complete remission | Relative risk: 2.22 (CI 95% 0.76 - 6.47)  
Based on data from 147 patients in 3 studies | Chlorambucil plus steroids: 160 per 1000  
Cyclophosphamide plus steroids: 355 per 1000  
Difference: 195 more per 1000 (CI 95% 38 fewer - 875 more) | Low  
Due to very serious imprecision8 | Cyclophosphamide plus steroids compared with chlorambucil plus steroids may have little or no difference on complete remission |
| Doubling serum creatinine | Relative risk: 0.82 (CI 95% 0.02 - 41.02)  
Based on data from 52 patients in 2 studies | Chlorambucil plus steroids: 360 per 1000  
Cyclophosphamide plus steroids: 295 per 1000  
Difference: 65 fewer per 1000 (CI 95% 353 fewer - 14407 more) | Very Low  
Due to very serious inconsistency, Due to very serious imprecision10 | We are uncertain whether cyclophosphamide plus steroids compared with chlorambucil plus steroids increases or decreases doubling serum creatinine |
| Adverse events - treatment discontinuation or hospitalization | Relative risk: 0.48 (CI 95% 0.26 - 0.9) Based on data from 147 patients in 3 studies\(^1\) Follow up Mean 29 months | 240 per 1000 | 115 per 1000 | Moderate | Due to serious imprecision\(^12\) | Cyclophosphamide plus steroids compared with chlorambucil plus steroids probably decreases adverse events resulting in treatment discontinuation or hospitalization |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------|----------------|-----------------|-------------------------------------------------------------------------------------------------|
| 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 |

2. **Risk of bias:** Serious. **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
4. **Risk of bias:** Serious. **Indirectness:** Serious. The outcome time frame in studies were insufficient; **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
6. **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients;
8. **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients;
10. **Inconsistency:** Very Serious. Point estimates vary widely, The magnitude of statistical heterogeneity was high, with I\(^2\): 88%; **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients;
12. **Imprecision:** Serious. Low number of patients;

**References**

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
## PICO (15.11)
Population: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome
Intervention: Cyclophosphamide
Comparator: Leflunomide

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>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% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at &gt;50% GFR loss</td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></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></td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 0.93 (CI 95% 0.59 - 1.48) Based on data from 48 patients in 1 studies Follow up 12 Months</td>
<td>625 per 1000 581 per 1000 Difference: 44 fewer per 1000 (CI 95% 256 fewer - 300 more)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Cyclophosphamide compared with leflunomide may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>Measured by: Scale: - Lower better</td>
<td>Difference: null lower</td>
<td></td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

1. **Risk of bias:** Serious. **Selective outcome reporting; Imprecision:** Serious. Only data from one study;
### PICO (15.12)
**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Cyclophosphamide plus leflunomide  
**Comparator:** Leflunomide alone

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at end-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>≥50% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at ≥50% GFR loss</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at malignancy</td>
<td></td>
</tr>
</tbody>
</table>
| Complete remission | Relative risk: 1.4  
(CI 95% 0.99 - 1.98)  
Based on data from 48 patients in 1 study\(^1\)  
Follow up 12 Months | 625 per 1000  
875 per 1000  
Difference: 250 more per 1000  
(CI 95% 6 fewer - 613 more) | Low  
Due to serious risk of bias, Due to serious imprecision\(^2\)  
Cyclophosphamide plus leflunomide compared to leflunomide alone may have little or no difference on 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 |

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1. **Primary study.**  
   **Baseline/comparator:** Control arm of reference used for intervention.  
   **Risk of bias:** Serious. Selective outcome reporting (many outcomes are not reported); **Imprecision:** Serious. Only data from one study;  

**References**

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
## PICO (15.13)
Population: Adults with idiopathic membranous nephropathy with nephrotic syndrome  
Intervention: Cyclophosphamide plus leflunomide  
Comparator: Cyclophosphamide alone

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at end-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>≥50% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at ≥50% GFR loss</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at malignancy</td>
<td></td>
</tr>
</tbody>
</table>
| Complete remission | Relative risk: 1.5  
(CI 95% 1.04 - 2.17)  
Based on data from 48 patients in 1 studies¹  
Follow up 12 Months | 583 per 1000  
875 per 1000  
Difference: 292 more per 1000  
(CI 95% 23 more - 682 more) | Low  
Due to serious risk of bias, Due to serious imprecision² | Cyclophosphamide plus leflunomide compared with cyclophosphamide alone may increase 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 |

1. Primary study. Baseline/comparator: Control arm of reference used for intervention.
2. Risk of bias: Serious. Incomplete data and/or large loss to follow up, Selective outcome reporting (many outcomes not reported); Imprecision: Serious. Only data from one study.

### References
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.14)

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Mizoribine  
**Comparator:** placebo or no treatment or corticosteroids 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>No studies were found that looked at all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found end-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found ≥50% loss of GFR</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at malignancy</td>
<td></td>
</tr>
</tbody>
</table>
| Complete remission¹     | Relative risk: 1.63 (CI 95% 0.69 - 3.84)  
Based on data from 150 patients in 3 studies²  
Follow up Mean 14 months | 86 per 1000  
140 per 1000  
Difference: 54 more per 1000  
(CI 95% 27 fewer - 244 more) | Very Low  
Due to very serious risk of bias,  
Due to serious imprecision³ | We are uncertain whether mizoribine vs placebo/no treatment/corticosteroids increases or decreases complete remission |
| Partial remission       | Relative risk: 1.89 (CI 95% 0.9 - 3.97)  
Based on data from 114 patients in 2 studies⁴  
Follow up 15 Months (Mean) | 154 per 1000  
291 per 1000  
Difference: 137 more per 1000  
(CI 95% 15 fewer - 457 more) | Very Low  
Due to very serious risk of bias,  
Due to serious imprecision⁵ | Mizoribine vs placebo/no treatment/corticosteroids may have little or no difference on partial remission |
| Serious adverse effects⁶ | Relative risk: 4.29 (CI 95% 0.21 - 86.8)  
Based on data from 89 patients in 1 studies  
Follow up 6 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 serious imprecision⁷ | There were too few who experienced serious adverse effects, to determine whether mizoribine vs placebo/no treatment/corticosteroids 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 |

1. **Number with complete or partial remission** - Complete remission
3. **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, Selective outcome reporting, due to other bias (the data was abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant primary nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathological diagnosis);
   **Imprecision: Very Serious.** Due to few patients having complete remission;
5. **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, Selective outcome reporting, due to other bias: The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathologic diagnosis;
   **Imprecision: Serious.** Wide confidence intervals;
6. **Serious adverse effects leading to discontinuation of therapy**
7. **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, Selective outcome reporting, due to other bias; **Imprecision: Serious.** Only data from one study, Low number of patients;

**References**

[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.15)
**Population:** Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome
**Intervention:** Mizoribine (150mg) once a day
**Comparator:** Mizoribine (50mg) 3 times a day

<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% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at ≥50% GFR loss</td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk: 4.75</td>
<td>0 per 1000</td>
<td>0 per 1000</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>(CI 95% 0.24 - 92.65)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, Due to very serious imprecision¹</td>
</tr>
<tr>
<td></td>
<td>Based on data from 37 patients in 1 studies Follow up 24 Months</td>
<td>Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)</td>
<td></td>
<td>There were too few who experienced malignancy, to determine whether mizoribine (150mg) once a day vs three times a day (50mg) made a difference</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 1.35</td>
<td>389 per 1000</td>
<td>525 per 1000</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>(CI 95% 0.66 - 2.78)</td>
<td></td>
<td></td>
<td>Due to serious risk of bias, Due to serious imprecision²</td>
</tr>
<tr>
<td></td>
<td>Based on data from 37 patients in 1 studies Follow up 24 Months</td>
<td>Difference: 136 more per 1000 (CI 95% 132 fewer - 692 more)</td>
<td></td>
<td>Mizoribine (150mg) once a day vs three times day (50mg) may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>Measured by: Scale: - Lower better</td>
<td>Difference: null lower</td>
<td></td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

1. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision:** Very Serious. Only data from one study, due to few patients with malignancy.
2. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision:** Serious. Only data from one study.
### 22 Aug 2018 - KDIGO Clinical Practice Guideline for Glomerulonephritis

#### PICO (15.16)
Population: Adults with idiopathic membranous nephropathy with nephrotic syndrome  
Intervention: Rituximab plus ACEi/ARB  
Comparator: ACEi/ARB

<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>All-cause mortality</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at end-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
<td></td>
</tr>
</tbody>
</table>
| Malignancy               | Relative risk: 0.34 (CI 95% 0.01 - 8.14)  
Based on data from 75 patients in 1 studies2  
Follow up 6 Months | 26 per 1000  
9 per 1000  
Difference: 17 fewer per 1000 (CI 95% 26 fewer - 186 more)  
Very Low  
Due to very serious risk of bias, Due to very serious imprecision3 | We are uncertain whether rituximab plus ACEi/ARB versus ACEi/ARB alone increases or decreases malignancy |
| Complete remission       | Relative risk: 1.67 (CI 95% 0.78 - 3.55)  
Based on data from 75 patients in 1 studies  
Follow up 6 Months | 211 per 1000  
352 per 1000  
Difference: 141 more per 1000 (CI 95% 46 fewer - 538 more)  
Very Low  
Due to very serious risk of bias, Due to serious imprecision4 | We are uncertain if rituximab plus ACEi/ARB versus ACEi/ARB increases or decreases complete remission |
| Partial remission        | Relative risk: 3.08 (CI 95% 1.25 - 7.62)  
Based on data from 75 patients in 1 studies  
Follow up 6 Months | 132.0  
407.0  
Difference: 275.0 more (CI 95% 33.0 more - 874.0 more)  
Moderate  
Due to very serious risk of bias, Due to serious imprecision,  
Upgraded due to Very large magnitude of effect5 | Rituximab plus ACEi/ARB compared with ACEi/ARB alone probably increases partial remission |
| Serious adverse events   | Relative risk: 1.23 (CI 95% 0.41 - 3.69)  
Based on data from 75 patients in 1 studies6  
Follow up 2 Months | 132 per 1000  
162 per 1000  
Difference: 30 more per 1000 (CI 95% 78 fewer - 355 more)  
Very Low  
Due to very serious risk of bias, Due to very serious imprecision7 | We are uncertain whether rituximab plus ACEi/ARB vs ACEi/ARB increases or decreases serious adverse events |
| Annual GFR loss 3 years  | Measured by: Scale: - Lower better | | No studies were found that looked at |
1. No studies available. **Baseline/comparator:** Control arm of reference used for intervention.
2. Primary study. **Baseline/comparator:** Control arm of reference used for intervention.
3. **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:** Very Serious. Wide confidence intervals. Only data from one study, due to few patients with malignancy;
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. Selective outcome reporting; **Imprecision:** Serious. Only data from one study;
5. **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. Only data from one study; **Upgrade:** Very large magnitude of effect.
6. Primary study. **Baseline/comparator:** Control arm of reference used for intervention.
7. **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:** Very Serious. Only data from one study, due to few patients with serious adverse events;

**References**
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### Table 1: Outcome Timeframe, Study results and measurements, Absolute effect estimates, Certainty in effect estimates, Plain text summary

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>All-cause mortality</td>
<td>Relative risk (CI 95% - )</td>
<td>Tacrolimus plus steroids 24 months 0 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>There were too few who experienced the all-cause mortality, to determine whether tacrolimus for 6 months compared to 24 months made a difference</td>
</tr>
<tr>
<td>End stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer 1000</td>
<td>Low</td>
<td>No studies were found that looked at end stage kidney disease</td>
</tr>
<tr>
<td>≥50% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Low</td>
<td>No studies were found that looked at ≥50% GFR loss</td>
</tr>
<tr>
<td>Infection - Urinary tract infection</td>
<td>Relative risk: 0.73 (CI 95% 0.14 - 3.95)</td>
<td>Tacrolimus plus steroids 24 months 136 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>Tacrolimus plus steroids for 6 months compared to 24 months may have little or no difference on urinary tract infection</td>
</tr>
<tr>
<td>Infection - Upper respiratory infection</td>
<td>Relative risk: 1.1 (CI 95% 0.07 - 16.45)</td>
<td>Tacrolimus plus steroids 24 months 45 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>Tacrolimus plus steroids for 6 months compared to 24 months may have little or no difference on upper respiratory infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>Low</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td>Corticosteroid-related adverse events - Hyperglycemia</td>
<td>Relative risk: 0.55 (CI 95% 0.05 - 5.61)</td>
<td>Tacrolimus plus steroids 24 months 91 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>Tacrolimus plus steroids for 6 months compared to 24 months may have little or no difference on hyperglycemia</td>
</tr>
<tr>
<td>Complete remission 6 Months</td>
<td>Relative risk: 1.47 (CI 95% 0.62 - 3.49)</td>
<td>Tacrolimus plus steroids 24 months 273 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>Tacrolimus plus steroids for 6 months compared to 24 months may have little or no difference on complete remission at 6 months</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 0.66 (CI 95% 0.18 - 2.41)</td>
<td>Tacrolimus plus steroids 24 months 227 per 1000 Tacrolimus plus steroids 6 months per 1000</td>
<td>Low</td>
<td>Tacrolimus plus steroids for 6 months compared to 24 months may have little or no difference on complete remission at 6 months</td>
</tr>
</tbody>
</table>
### 24 Months
Based on data from 42 patients in 1 studies\(^8\)  
Follow up 18 Months  
Difference: **77 fewer per 1000**  
(CI 95% 186 fewer - 320 more)  
to 24 months may have little or no difference on complete remission at 24 months

<table>
<thead>
<tr>
<th>Annual GFR loss</th>
<th>Measured by: Scale: - Lower better</th>
<th>Difference: <strong>null lower</strong></th>
<th>No studies were found that looked at annual GFR loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision**: Very Serious. Only data from one study, due to few events;  
3. **Risk of bias**: No serious. Selective outcome reporting; **Imprecision**: Very Serious. Only data from one study, due to events;  
4. Primary study . **Baseline/comparator**: Control arm of reference used for intervention.  
5. **Risk of bias**: No serious. Selective outcome reporting; **Imprecision**: Very Serious. Only data from one study, due to few events;  
6. Primary study . **Baseline/comparator**: Control arm of reference used for intervention.  
7. **Risk of bias**: No serious. Selective outcome reporting; **Imprecision**: Very Serious. Only data from one study, due to few events;  
9. **Risk of bias**: No serious. Selective outcome reporting; **Imprecision**: Very Serious. Only data from one study, due to few events;  

**References**  
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
## PICO (15.18)
**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Cyclosporin (1.5 mg/kg, twice daily)  
**Comparator:** Cyclosporin (3.0 mg/kg, once daily)

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at end-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td>No studies were found that looked at malignancy</td>
<td></td>
</tr>
<tr>
<td>Complete remission 12 months</td>
<td>647 per 1000</td>
<td>686 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether cyclosporin twice daily compared with cyclosporin once daily increases or decreases complete remission</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Difference: null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
<td></td>
</tr>
<tr>
<td>Proteinuria 12 months</td>
<td>g/24hrMean</td>
<td>g/24hrMean</td>
<td>Low</td>
<td>Cyclosporin twice daily compared with cyclosporin once daily may decrease proteinuria</td>
</tr>
</tbody>
</table>

2. **Risk of bias:** Very 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, inadequate/lack of blinding of participants and
personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

3. Risk of bias: Very 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, Inadequate/lack of 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; Upgrade: Large magnitude of effect.

References
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### PICO (15.19)
Population: Adults with idiopathic membranous nephropathy with nephrotic syndrome
Intervention: Early (immediate) treatment cyclophosphamide plus steroids
Comparator: Late treatment (when serum creatinine increases > 25%) cyclophosphamide plus steroids

<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>Relative risk: 0.29 (CI 95% 0.01 - 6.5) Based on data from 26 patients in 1 studies1 Follow up Mean 72 months</td>
<td>late treatment (when Scr incr &gt; 25%) CPA + steroids Early (immediate) treatment CPA + steroids</td>
<td>Difference: 59 fewer per 1000 (CI 95% 82 fewer - 457 more)</td>
<td>We are uncertain whether early compared with late therapy increases or decreases all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk: 2.6 (CI 95% 0.12 - 58.48) Based on data from 26 patients in 1 studies3 Follow up Mean 72 months</td>
<td>0 per 1000 0 per 1000</td>
<td>Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)</td>
<td>We are uncertain whether early compared with late therapy increases or decreases end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td></td>
<td>Difference: fewer</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td></td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td></td>
<td>Difference: fewer</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 0.75 (CI 95% 0.39 - 1.45) Based on data from 26 patients in 1 studies5 Follow up Mean 72 months</td>
<td>667 per 1000 500 per 1000</td>
<td>Difference: 167 fewer per 1000 (CI 95% 407 fewer - 300 more)</td>
<td>Early compared with late cyclosporin plus steroids may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Adverse effects - treatment discontinuation or hospitalization</td>
<td>Relative risk: 0.29 (CI 95% 0.07 - 1.16) Based on data from 26 patients in 1 studies7 Follow up Mean 72 months</td>
<td>500 per 1000 145 per 1000</td>
<td>Difference: 355 fewer per 1000 (CI 95% 465 fewer - 80 more)</td>
<td>Early compared with late cyclosporin plus steroids may have little or no difference on adverse effects causing treatment discontinuation or hospitalizations</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean Mean</td>
<td>Difference: MD null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
<tr>
<td>eGFR</td>
<td>Measured by: Scale: - High better Based on data from 26 patients in 1 studies Follow up Mean 72 months</td>
<td>mL/min/1.73 m/L/min/1.73 m²Mean m²Mean</td>
<td>Difference: MD 8 higher (CI 95% 8.59 lower - 24.59 higher)</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision9</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
</tbody>
</table>

2. **Risk of bias**: Serious. Unclear concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
4. **Risk of bias**: Serious. Unclear concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
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8. **Risk of bias**: Serious. Unclear concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision**: Serious. Only data from one study, Low number of patients;
9. **Risk of bias**: Serious. Unclear concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

**References**
[22] Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. 2018;
### 22 Aug 2018 - KDIGO Clinical Practice Guideline for Glomerulonephritis

**PICO (15.20)**

**Population:** Adults with idiopathic membranous nephropathy with nephrotic syndrome  
**Intervention:** Adrenocorticotropic hormone  
**Comparator:** Alkylating agents plus steroids

<table>
<thead>
<tr>
<th>Outcome Timeframe</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>
</table>
| **All-cause mortality**<sup>1</sup> 22 Months | Relative risk (CI 95% - )  
Based on data from 32 patients in 1 studies  
Follow up 22 Months | 0  
per 1000  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness<sup>3</sup> | There were too few who experienced the all-cause mortality, to determine whether adrenocorticotropic hormone compared with alkylating agent plus steroids made a difference |
| **End-stage kidney disease** | Relative risk: 3.0  
(CI 95%: 0.13 - 68.57)  
Based on data from 32 patients in 1 studies<sup>4</sup>  
Follow up Mean 22 months | 0  
per 1000  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness<sup>3</sup> | We are uncertain whether adrenocorticotropic hormone compared with alkylating agents plus steroids increases or decreases end-stage kidney disease |
| ≥50% loss of GFR | (CI 95% - ) | 0  
per 1000  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision, Due to serious indirectness<sup>3</sup> | 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: 2.0  
(CI 95%: 0.75 - 5.33)  
Based on data from 32 patients in 1 studies<sup>5</sup>  
Follow up Mean 22 months | 250  
per 1000  
500  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision<sup>5</sup> | Adrenocorticotropic hormone compared with alkylating agents plus steroids may have little or no difference on complete remission |
| Doubling serum creatinine | Relative risk: 3.0  
(CI 95%: 0.13 - 68.57)  
Based on data from 32 patients in 1 studies<sup>6</sup>  
Follow up Mean 22 months | 0  
per 1000  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision<sup>7</sup> | We are uncertain whether adrenocorticotropic hormone compared with alkylating agents plus steroids increases or decreases doubling serum creatinine |
| Adverse events - treatment | Relative risk: 0.5  
(CI 95%: 0.05 - 4.98) | 125  
per 1000  
63  
per 1000 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision<sup>7</sup> | We are uncertain whether |
| Discontinuation or Hospitalization | Based on data from 32 patients in 1 studies Follow up Mean 22 months | Difference: 62 fewer per 1000 (CI 95% 119 fewer - 498 more) | Very serious imprecision

Adrenocorticotropic hormone compared with alkylating agents plus steroids increases or decreases adverse events resulting in treatment discontinuation or hospitalization |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Difference: null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

1. Intention to treat analysis
3. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Indirectness: Serious. The outcome time frame in studies was insufficient; Imprecision: Very Serious. Wide confidence intervals, Only data from one study;
5. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Only data from one study, Low number of patients;
7. 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, Only data from one study, Low number of patients;