**KDIGO GN Guideline update – Evidence summary**

**Immunosuppressive therapy for ANCA associated nephritis**

**PICO question**
In patients with ANCA associated nephritis, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapies improve clinical efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

**Search strategy and selection**
Keywords for ANCA-associated nephritis, renal vasculitis, 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 original Cochrane review was published in 2008. An updated review was published in 2015 identified 31 primary studies (146 reports) with 2217 participants; five (13 reports) ongoing studies were also identified. The 2018 search update identified 63 reports, six reports were excluded because they were not RCTs, did not include patients with ANCA associated nephritis, or the wrong intervention. 13 primary studies (33 reports), one ongoing study, and five studies (six reports) of studies recently completed but with no full-text publication were identified. Overall, the 2018 Cochrane review update identified 39 studies (209 reports) with 3296 participants, four ongoing studies (17 reports) (Figure 1).

**Figure 1. Study flow diagram**

**Induction therapy**
Twelve comparisons for induction therapy were included for the following:

1. Plasma exchange as adjunctive therapy versus usual care (8 studies, 1020 participants; mean follow-up ≈28 months)
2. Pulse versus continuous cyclophosphamide (4 studies, 300 participants; mean follow-up ≈23 months)
3. Rituximab versus IV cyclophosphamide (2 studies, 241 participants; mean follow-up 21 months)
4. Mycophenolate mofetil versus cyclophosphamide (3 studies, 216 participants; mean follow-up 10 months)
5. Methotrexate versus cyclophosphamide (1 study, 95 participants; 18 months follow-up)
6. Avacopan versus prednisolone (1 study, 67 participants; 3 months follow-up)
7. Intravenous immunoglobulin versus placebo (1 study, 34 participants; 12 months follow-up)
8. Etanercept versus placebo (1 study, 180 participants; median follow-up for the etanercept group was 25 months and 19 months for the control group)
9. Plasma exchange versus immunadsorption (1 study, 44 participants; 6 months follow-up)
10. Lymphocytaphaeresis versus control (1 study, 24 participants; 6 months follow-up)
11. Six versus 12 cyclophosphamide pulses (2 studies, 171 participants; mean 36 months follow-up)
12. Reduced dose versus standard dose steroids (1 study, 704 participants; follow-up unclear)

Maintenance therapy

Eleven comparisons for maintenance therapy were included for the following:

1. Azathioprine versus cyclophosphamide (1 study, 155 participants; 18 months follow-up)
2. Mycophenolate mofetil versus azathioprine (1 study, 156 participants; 4 years follow-up)
3. Azathioprine versus methotrexate (1 study, 126 participants; 3 years follow-up)
4. Leflunomide versus methotrexate (1 study, 54 participants; 24 months follow-up)
5. Methotrexate versus cyclophosphamide (1 study, 95 participants; 18 months follow-up)
6. Pre-emptive therapy for relapse versus standard of care (2 studies, 60 participants; follow-up unclear)
7. Antibiotics versus placebo (2 studies, 112 participants; mean follow-up 12.5 months)
8. Cyclosporin versus cyclophosphamide (1 study, 32 participants; 5 years follow-up)
9. Extended versus standard azathioprine (3 studies, 866 participants; mean follow-up ≈32 months)
10. Rituximab versus azathioprine (1 study, 115 participants; 28 months follow-up)
11. Methotrexate versus cyclophosphamide (1 study, 71 participants; 24 months follow-up)

Summary of the main findings

Induction therapy

Plasma exchange as adjunctive therapy versus usual care

- Patients with severe acute kidney injury secondary to vasculitis or rapidly deteriorating kidney function were included in these eight RCTs (1020 participants).
- Compared to usual care, plasma exchange as adjunctive therapy probably has little or no effect on all-cause mortality (RR 0.96, 95%CI 0.72 to 1.29; 6 studies, 957 participants) but it probably decreases end-stage kidney disease at 12 months (RR 0.45, 95%CI 0.29 to 0.72; 6 studies, 235 participants).
• Plasma exchange as adjunctive therapy probably increases infection (RR 1.26, 95%CI 1.03 to 1.54); however may have little or no effect on other serious adverse events and the induction of complete remission, compared to usual care.

*Pulse cyclophosphamide versus continuous cyclophosphamide*

• Patients with systemic rather than specifically renal vasculitis were included in these studies
• Compared to continuous cyclophosphamide, pulse cyclophosphamide may have little or no effect on all-cause mortality, end-stage kidney disease, and infection.
• Pulse cyclophosphamide probably has little or no effect on complete remission at 18 months. Other critical and important outcomes (≥50% loss of GFR, malignancy, and annual loss of GFR) were not reported in RCTs.

*Rituximab versus cyclophosphamide*

• Compared to cyclophosphamide, treatment with rituximab has little or no effect on infection (RR 0.89, 95%CI 0.42 to 1.92; 2 studies, 241 participants) and probably little or no effect on complete remission at 6 months (RR 1.02, 95%CI 0.79 to 1.32; 2 studies, 236 participants).
• Effects on other critical or important outcomes are unclear, as they were not reported in RCTs or due to very low evidence because of study limitations and very serious imprecision.

*Mycophenolate mofetil versus cyclophosphamide*

• The effects of mycophenolate mofetil compared to cyclophosphamide on all-cause mortality and end-stage kidney disease are uncertain because they have only been examined in one RCT with study limitations and few events.
• We cannot be certain of the effect of mycophenolate mofetil on other critical and important outcomes compared to cyclophosphamide as they were not reported in RCTs.
• Azathioprine plus steroids may decrease all-cause mortality, but effects on other critical and important clinical and safety outcomes are uncertain because the certainty of the evidence is very low.

*Intravenous immunoglobulin versus placebo*

• Compared to placebo plus standard of care, IV immunoglobulin may increase the treatment response (BVAS reduction >50%) at three months (RR 2.33, 95%CI 1.18 to 4.61; 1 study, 35 participants). Effects on other critical and important outcomes are unclear as they were not reported by the RCT or due to serious risk of bias and imprecision.

*Other immunosuppressive agents*

• Methotrexate compared to cyclophosphamide may decrease relapse (RR 0.57, 95%CI 0.34 to 0.96; 1 study, 89 participants). However, it may have little or no effect on complete remission at six months (RR 0.96, 95%CI 0.85 to 1.08; 1 study, 95 participants). The effect on other critical and important outcomes are uncertain, as they were not reported or due to very few events.
• Avacopan may improve eGFR compared to prednisolone (MD 3.3 higher, 95%CI 0.57 higher to 6.03 higher; 1 study, 41 participants). The effects on other outcomes are uncertain, as they were not reported in RCTs or due to very serious imprecision and study limitations (complete remission).
• Treatment with etanercept compared to placebo plus standard of care was examined in one RCT (174 participants). The effects on all-cause mortality and relapse are uncertain because of very few events and study limitations. It may have little or no effect on infection (RR 1.00, 95%CI 0.74 to 1.35) and sustained complete remission (RR 0.93, 95%CI 0.77 to 1.11). Other critical and important outcomes were not examined in the RCT.
• The effects of plasma exchange compared with immunoadsorption are very uncertain, as it was only examined in one small RCT (44 participants) and many critical and important outcomes were not reported.
• It is uncertain if lymphocytapheresis compared with standard of care increases or decreases critical or important outcomes because the certainty of the evidence was very low or outcomes were not reported in the small RCT (24 participants).

• The use of six compared with 12 cyclophosphamide pulses may have little or no effect on all-cause mortality and serious adverse events. It probably has little or no effect on complete remission (RR 0.99, 95%CI 0.85 to 1.15; 2 studies, 151 participants), and relapse (RR 1.57, 95%CI 0.96 to 2.56. The effect on other critical and important outcomes are uncertain due to the very low certainty of evidence.

• Reduced dose prednisone compared with standard dose prednisone may have little or no effect on all-cause mortality, end-stage kidney disease, infection, sustained complete remission, and serious adverse events. Other critical and important outcomes were not reported in the RCT (704 participants).

Maintenance therapy

Azathioprine versus cyclophosphamide

• In one RCT (144 participants) azathioprine compared with cyclophosphamide probably has little or no effect on infection (RR 1.03, 95%CI 0.51 to 2.06) and relapse (RR 1.13, 95%CI 0.51 to 2.50). However, it probably decreases leukopenia (RR 0.65, 95%CI 0.42 to 0.99). Other critical and important outcomes were not reported.

Azathioprine versus methotrexate

• One RCT (126 participants) found that azathioprine compared to methotrexate probably has little or no effect on relapse (RR 1.10, 95%CI 0.68 to 1.77) or adverse events resulting in hospitalization or study drug discontinuation (RR 0.58, 95%CI 0.25 to 1.38). Other critical and important outcomes were not reported.

Leflunomide versus methotrexate

• In one small RCT (54 participants), leflunomide compared to methotrexate probably has little or no effect on infection (RR 1.17, 95%CI 0.66 to 2.07), and relapse (RR 0.52, 95%CI 0.22 to 1.11). Other critical and important outcomes were not examined.

Mycophenolate mofetil versus azathioprine

• Compared to azathioprine, mycophenolate mofetil probably increases relapse (RR 1.47, 95%CI 1.04 to 2.09; 1 study, 156 participants). It may have little or no effect on infection, and other critical and important outcomes have not been examined in the RCT.

Antibiotics versus placebo

• The use of trimethoprim/sulfamethoxazole (160/800 mg) compared to placebo may little or no effect on mortality at six months, and complete remission at one and two years. Other critical and important outcomes were not examined in RCTs.

Other immunosuppressive therapy

• Rituximab compared with azathioprine (1 study, 115 participants) probably decreases major relapse (RR 0.18, 95%CI 0.06 to 0.58) while it may have little or no effect on minor relapse (RR 0.68, 95%CI 0.26 to 1.78). The effect on other critical and important outcomes is unclear because of very low certainty of evidence (all-cause mortality, infection) or they were not reported in the RCT.

• Compared to cyclophosphamide, cyclosporin probably has little or no effect on relapse (RR 1.38, 95%CI 0.82 to 2.33; 1 study, 64 participants).

• There was insufficient evidence to assess if methotrexate improves or worsens critical and important outcomes compared to maintenance therapy with cyclophosphamide.

• Extended azathioprine therapy (1.5 to 2.0 mg/kg/d until 4 years after diagnosis, then tapered by 25 mg every 3 months) compared to standard azathioprine therapy (1.5 to 2.0 mg/kg/d until 12 months after diagnosis, then tapered by 25 mg every 3 months)
had uncertain effects on all-cause mortality, end-stage kidney, infection and serious adverse events disease because of study limitations and very serious imprecision. It probably decreases relapse (RR 0.41, 95%CI 0.26 to 0.64; 2 studies, 162 participants).

• We are uncertain of the effects of pre-emptive therapy compared to usual treatment/follow-up because of the very low certainty of the evidence.
Effect modifiers

The following effect modifiers were considered for the comparisons:
Plasma exchange as adjunctive therapy versus usual care (8 studies, 1020 participants)

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Explanation/ results</th>
</tr>
</thead>
</table>
| Kidney function (GFR, proteinuria, presence of albuminuria) | Patients in the RCTs comparing plasma exchange adjunctive therapy to usual care had severe deteriorating kidney function or acute kidney injury.  
• MEPEX 2007 only included patients with serum creatinine > 500 µmol/L  
• Glockner 1988 included patients with >70% crescents  
• Cole 1992 only included patients with crescents <50%  
• Rifle 1980 only included patients with crescents >50%  
Exclusion of the Cole 1992 study to the outcomes all-cause mortality, end-stage kidney disease and infection made no difference to the overall effect estimate, and introduced greater imprecision for the infection outcome and therefore inappropriate to report.  
One study (Szpirt 2011) reported that proteinuria > 1g/day increased relapse (OR 3.7, 95%CI 1.4 to 10.2) and creatinine > 250 µmol/L increased end-stage kidney disease and death (OR 5.3, 95%CI 1.6 to 17.4). |
| Relapse or resistant disease | Trials did not examine the treatment of patients with relapsing or resistant disease. |
| Gender | The trials largely included a majority of male patients (range 57-78%) and did not present results according to gender. |
| Age (adult vs. pediatric) | Two studies included children less than 18 years of age. However, they did not separate the results according to adults and children. |
| Presence of pulmonary hemorrhage | Most RCTs did not provide any data on patients with pulmonary hemorrhage, and some RCTs excluded patients with pulmonary hemorrhage. However, PEXIVAS 2011 included patients with pulmonary hemorrhage but did not separate results for these patients. |
| Serology (Presence of ANCA etc.) | The presence of ANCA is reported in the two more recent studies. The majority of patients in the MEPEX 2007 study are positive for ANCA (94.7%), and all patients in the Szpirt 2011 are ANCA positive. |

There was insufficient data in other comparisons to report on effect modifiers.


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

All RCTs included in the previous guideline evidence summary have been included in this evidence review.
### PICO (21.1)

**Population:** Patients with ANCA associated nephritis and severe kidney disease  
**Intervention:** Plasma exchange as adjunctive therapy  
**Comparator:** Control (usual care)

<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><strong>All-cause mortality</strong></td>
<td>At any time point</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Relative risk: 0.96 (CI 95% 0.72 - 1.29)</td>
<td>157 per 1000</td>
<td>151 per 1000</td>
<td><strong>Moderate</strong> Due to serious risk of bias&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Based on data from 957 patients in 6 studies&lt;sup&gt;1&lt;/sup&gt; Follow up Mean 37 months</td>
<td>Difference: 6 fewer per 1000 (CI 95% 44 fewer - 46 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>End-stage kidney disease</strong></td>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk: 0.45 (CI 95% 0.29 - 0.72)</td>
<td>376 per 1000</td>
<td>169 per 1000</td>
<td><strong>Moderate</strong> Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Based on data from 235 patients in 6 studies&lt;sup&gt;3&lt;/sup&gt; Follow up Mean 36 months</td>
<td>Difference: 207 fewer per 1000 (CI 95% 267 fewer - 105 fewer)</td>
<td></td>
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<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
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<tr>
<td></td>
<td>Follow up Mean 36 months</td>
<td>Difference: fewer per 1000</td>
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<tr>
<td><strong>Infection</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Relative risk: 1.26 (CI 95% 1.03 - 1.54)</td>
<td>253 per 1000</td>
<td>319 per 1000</td>
<td><strong>Moderate</strong> Due to serious risk of bias&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Based on data from 956 patients in 5 studies&lt;sup&gt;9&lt;/sup&gt; Follow up Mean 25 months</td>
<td>Difference: 66 more per 1000 (CI 95% 8 more - 137 more)</td>
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<tr>
<td><strong>Malignancy</strong></td>
<td>Relative risk (CI 95% - -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td></td>
<td>Follow up Mean 36 months</td>
<td>Difference: fewer per 1000</td>
<td></td>
<td></td>
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<tr>
<td><strong>Complete remission sustained remission</strong></td>
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<td></td>
<td>Relative risk: 1.02 (CI 95% 0.89 - 1.16)</td>
<td>560 per 1000</td>
<td>571 per 1000</td>
<td><strong>Low</strong> Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Based on data from 704 patients in 1 studies&lt;sup&gt;8&lt;/sup&gt; Follow up Unclear</td>
<td>Difference: 11 more per 1000 (CI 95% 62 fewer - 90 more)</td>
<td></td>
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<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk: 1.0 (CI 95% 0.89 - 1.11)</td>
<td>639 per 1000</td>
<td>639 per 1000</td>
<td><strong>Low</strong> Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Based on data from 704 patients in 1 studies&lt;sup&gt;10&lt;/sup&gt; Follow up Unclear</td>
<td>Difference: 0 fewer per 1000 (CI 95% 70 fewer - 70 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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 |
   
   **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to one trial taking over 10 years and resulting in change in equipose due to changing physicians, also one study allowed for cross-over one month after therapy.
   
   **Imprecision:** No serious due to [reason];

   
   **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to one trial taking over 10 years and resulting in change in equipose due to changing physicians, Incomplete data and/or large loss to follow up in Mauri 1985;
   
   **Imprecision:** Serious due to few events; **Upgrade:** Large magnitude of effect.

5. Serious infections


7. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to one trial taking over 10 years and resulting in change in equipose due to changing physicians, also one study allowed for cross-over one month after therapy.
   
   **Imprecision:** Serious.


9. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Serious. Only data from one study;

10. Systematic review [48] with included studies: PEXIVAS 2011 **Baseline/comparator:** Control arm of reference used for intervention.

11. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Serious. Only data from one study;

**References**

[48] Interventions for renal vasculitis in adults. 2018;
**PICO (21.2)**

**Population:** Patients with systemic ANCA associated vasculitis  
**Intervention:** Pulse cyclophosphamide  
**Comparator:** Continuous cyclophosphamide

<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**  
At the end of follow-up | Relative risk: 0.77  
(CI 95% 0.44 - 1.32)  
Based on data from 278 patients in 4 studies\(^1\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
206 per 1000 | **Pulse cyclophosphamide**  
159 per 1000 | **Low**  
Due to serious risk of bias, Due to serious imprecision\(^2\) | Pulse compared with continuous cyclophosphamide may have little or no difference on all-cause mortality |
| **End-stage kidney disease**  
At the end of the study | Relative risk: 1.9  
(CI 95% 0.92 - 3.91)  
Based on data from 245 patients in 4 studies\(^3\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
74 per 1000 | **Pulse cyclophosphamide**  
141 per 1000 | **Low**  
Due to serious risk of bias, Due to serious imprecision\(^4\) | Pulse compared with continuous cyclophosphamide may have little or no difference on end-stage kidney disease |
| \(\geq 50\%\) loss of GFR | Relative risk  
(CI 95% - -)  
Based on data from 278 patients in 4 studies\(^6\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
per 1000 | **Pulse cyclophosphamide**  
per 1000 | No studies were found that looked at \(\geq 50\%\) loss of GFR |
| **Infection\(^5\)** | Relative risk: 0.71  
(CI 95% 0.38 - 1.33)  
Based on data from 278 patients in 4 studies\(^4\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
348 per 1000 | **Pulse cyclophosphamide**  
247 per 1000 | **Low**  
Due to serious risk of bias, Due to serious imprecision\(^7\) | Pulse compared with continuous cyclophosphamide may have little or no difference on infection |
| **Malignancy** | Relative risk  
(CI 95% - -)  
Based on data from 116 patients in 1 studies\(^9\)  
Follow up 18 months | **Continuous cyclophosphamide**  
per 1000 | **Pulse cyclophosphamide**  
per 1000 | No studies were found that looked at malignancy |
| **Complete remission**  
18 months | Relative risk: 0.99  
(CI 95% 0.94 - 1.03)  
Based on data from 278 patients in 4 studies\(^8\)  
Follow up 18 months | **Continuous cyclophosphamide**  
1000 per 1000 | **Pulse cyclophosphamide**  
990 per 1000 | **Moderate**  
Due to serious imprecision\(^9\) | Pulse compared to continuous cyclophosphamide probably has little or no difference on complete remission |
| **Relapse** | Relative risk: 1.79  
(CI 95% 1.11 - 2.87)  
Based on data from 235 patients in 4 studies\(^10\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
181 per 1000 | **Pulse cyclophosphamide**  
324 per 1000 | **Moderate**  
Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect\(^11\) | Pulse compared with continuous cyclophosphamide probably increases relapse |
| **Leukopenia** | Relative risk: 0.53  
(CI 95% 0.36 - 0.77)  
Based on data from 278 patients in 4 studies\(^12\)  
Follow up Mean 23 months | **Continuous cyclophosphamide**  
418 per 1000 | **Pulse cyclophosphamide**  
222 per 1000 | **Moderate**  
Due to serious risk of bias\(^13\) | Pulse compared with continuous cyclophosphamide probably decreases leukopenia |
| **Annual GFR loss**  
3 years | Measured by:  
Scale: - Lower better | **Continuous cyclophosphamide**  
Mean | **Pulse cyclophosphamide**  
Mean | No studies were found that looked at annual GFR loss |

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\(^1\) M Fei et al 2013  
\(^2\) Due to serious risk of bias, Due to serious imprecision  
\(^3\) Due to serious risk of bias, Due to serious imprecision  
\(^4\) Due to serious risk of bias, Due to serious imprecision  
\(^5\) Due to serious risk of bias, Due to serious imprecision  
\(^6\) Due to serious risk of bias, Due to serious imprecision  
\(^7\) Due to serious risk of bias, Due to serious imprecision  
\(^8\) Due to serious risk of bias, Due to serious imprecision  
\(^9\) Due to serious risk of bias, Due to serious imprecision  
\(^10\) Due to serious risk of bias, Due to serious imprecision  
\(^11\) Due to serious risk of bias, Due to serious imprecision  
\(^12\) Due to serious risk of bias, Due to serious imprecision  
\(^13\) Due to serious risk of bias, Due to serious imprecision
<table>
<thead>
<tr>
<th>Difference: MD null lower</th>
<th>GFR loss</th>
</tr>
</thead>
</table>


2. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up in one study Haubitz 1998, studies were terminated early in two studies Gullerin 1997 and Haubitz 1998 due to differences between the groups.; **Imprecision:** Serious. Wide confidence intervals;


4. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up in one study Haubitz 1998, studies were terminated early in two studies Gullerin 1997 and Haubitz 1998 due to differences between the groups.; **Imprecision:** Serious. due to few events;

5. Serious infections


7. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up in one study Haubitz 1998, studies were terminated early in two studies Gullerin 1997 and Haubitz 1998 due to differences between the groups.; **Imprecision:** Serious. due to few events;


9. **Imprecision:** Serious. Only data from one study. Low number of patients;


11. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up in one study Haubitz 1998, studies were terminated early in two studies Gullerin 1997 and Haubitz 1998 due to differences between the groups.; **Imprecision:** Serious. due to few events; **Upgrade:** Large magnitude of effect.


13. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up in one study Haubitz 1998, studies were terminated early in two studies Gullerin 1997 and Haubitz 1998 due to differences between the groups.;

**References**

[48] Interventions for renal vasculitis in adults. 2018;
### PICO (21.3)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Rituximab  
**Comparator:** Cyclophosphamide

<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 6 months | Relative risk: 1.0 (CI 95% 0.21 - 4.7) Based on data from 241 patients in 2 studies<sup>1</sup> Follow up Mean 21 months | Cyclophosphamide: 28 per 1000  
Rituximab: 28 per 1000  
Difference: 0 fewer per 1000 (CI 95% 22 fewer - 104 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision<sup>2</sup> | We are uncertain whether rituximab increases or decreases all-cause mortality at 6 months |
| End-stage kidney disease | Relative risk (CI 95% - ) | per 1000  
Difference: fewer per 1000 | | No studies were found that looked at end-stage kidney disease |
| ≥50% loss of GFR | Relative risk (CI 95% - ) | per 1000  
Difference: fewer per 1000 | | No studies were found that looked at ≥50% loss of GFR |
| Infection<sup>3</sup> | Relative risk: 0.89 (CI 95% 0.42 - 1.92) Based on data from 241 patients in 2 studies<sup>4</sup> Follow up Mean 21 months | Cyclophosphamide: 92 per 1000  
Rituximab: 82 per 1000  
Difference: 10 fewer per 1000 (CI 95% 53 fewer - 85 more) | High | Rituximab compared to cyclophosphamide has little or no difference on infection |
| Malignancy | Relative risk (CI 95% - ) | per 1000  
Difference: fewer per 1000 | | No studies were found that looked at malignancy |
| Complete remission 6 months | Relative risk: 1.02 (CI 95% 0.66 - 1.32) Based on data from 236 patients in 2 studies<sup>5</sup> Follow up Mean 21 months | Cyclophosphamide: 661 per 1000  
Rituximab: 674 per 1000  
Difference: 13 more per 1000 (CI 95% 139 fewer - 212 more) | Moderate  
Due to serious imprecision<sup>6</sup> | Rituximab compared to cyclophosphamide probably has little or no difference on complete remission |
| Sustained remission 12 months | Relative risk: 0.93 (CI 95% 0.66 - 1.3) Based on data from 44 patients in 1 studies<sup>7</sup> Follow up 24 months | Cyclophosphamide: 818 per 1000  
Rituximab: 761 per 1000  
Difference: 57 fewer per 1000 (CI 95% 278 fewer - 245 more) | Low  
Due to very serious imprecision<sup>8</sup> | Rituximab compared with cyclophosphamide may have little or no difference on sustained remission |
| Severe adverse events | Relative risk: 0.98 (CI 95% 0.89 - 1.09) Based on data from 242 patients in 2 studies<sup>9</sup> Follow up Mean 21 months | Cyclophosphamide: 818 per 1000  
Rituximab: 802 per 1000  
Difference: 16 fewer per 1000 (CI 95% 90 fewer - 74 more) | Moderate  
Due to serious risk of bias<sup>10</sup> | Rituximab compared with cyclophosphamide probably has little or no difference on severe adverse events |
| Annual GFR loss 3 years | Measured by: Scale: - Lower better | Mean  
Mean | | No studies were found that looked at annual |
Difference: MD null lower


2. Risk of bias: Serious. Unclear of blinding of participants and personnel, resulting in potential for performance bias, unclear of outcome assessors, resulting in potential for detection bias in RAVE 2010; Imprecision: Very Serious. Wide confidence intervals, due to few events;

3. Serious infection


6. Imprecision: Serious. Low number of patients;


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


10. Risk of bias: Serious. Unclear of blinding of participants and personnel, resulting in potential for performance bias, unclear of outcome assessors, resulting in potential for detection bias in RAVE 2010;

References
[49] Interventions for renal vasculitis in adults. 2018;
### PICO (21.4)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Mycophenolate mofetil  
**Comparator:** Cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome</th>
<th>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</td>
<td>~6 months</td>
<td>Relative risk: 1.25 (CI 95% 0.35 - 4.46) Based on data from 140 patients in 1 studies&lt;sup&gt;1&lt;/sup&gt; Follow up 18 months</td>
<td>57 per 1000</td>
<td>71 per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td></td>
<td>Relative risk: 1.0 (CI 95% 0.14 - 6.9) Based on data from 140 patients in 1 studies&lt;sup&gt;3&lt;/sup&gt; Follow up 18 months</td>
<td>29 per 1000</td>
<td>29 per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>Relative risk: 1.34 (CI 95% 0.78 - 2.29) Based on data from 216 patients in 3 studies&lt;sup&gt;5&lt;/sup&gt; Follow up Mean 10 months</td>
<td>174 per 1000</td>
<td>233 per 1000</td>
<td><strong>Low</strong> Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>~6 months</td>
<td>Relative risk: 1.17 (CI 95% 1.01 - 1.35) Based on data from 216 patients in 3 studies&lt;sup&gt;6&lt;/sup&gt; Follow up Mean 10 months</td>
<td>716 per 1000</td>
<td>838 per 1000</td>
<td><strong>High</strong></td>
</tr>
<tr>
<td>Relapse</td>
<td>~18 months</td>
<td>Relative risk: 1.56 (CI 95% 0.84 - 2.87) Based on data from 119 patients in 1 studies&lt;sup&gt;7&lt;/sup&gt; Follow up 18 months</td>
<td>214 per 1000</td>
<td>334 per 1000</td>
<td><strong>Low</strong> Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td>Relative risk: 1.25 (CI 95% 0.86 - 1.81) Based on data from 140 patients in 1 studies&lt;sup&gt;10&lt;/sup&gt; Follow up 18 months</td>
<td>400 per 1000</td>
<td>500 per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>~3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
</tbody>
</table>
Difference: MD null lower

   Risk of bias: Serious. Unclear of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Only data from one study, Low number of patients, Wide confidence intervals;
   Risk of bias: Serious. Unclear of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study;
   Risk of bias: Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Imprecision: Serious. Wide confidence intervals;
   Risk of bias: Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Imprecision: Serious. Wide confidence intervals, Only data from one study;
   Risk of bias: Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Imprecision: Serious. Wide confidence intervals, Only data from one study;
   Risk of bias: Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Imprecision: Serious. Wide confidence intervals;
   Risk of bias: Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Imprecision: Serious. Wide confidence intervals, Only data from one study;
   Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Serious. Only data from one study;
   Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

References
[49] Interventions for renal vasculitis in adults. 2018;
### PICO (21.5)
**Population:** Patients with ANCA associated nephritis  
**Intervention:** Intravenous immunoglobulin  
**Comparator:** Placebo

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| All-cause mortality | Relative risk: 0.2 (CI 95% 0.01 - 3.88)  
Based on data from 34 patients in 1 studies  
Follow up 12 months | Placebo: 118 per 1000 intravenous immunoglobulin: 24 per 1000  
Difference: 94 fewer per 1000 (CI 95% 117 fewer - 340 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision\(^2\) | We are uncertain whether intravenous immunoglobulin compared with placebo increases or decreases all-cause mortality |
| End-stage kidney disease | Relative risk (CI 95%  - )  
Follow up 12 months | Placebo: per 1000  
intravenous immunoglobulin: per 1000  
Difference: fewer per 1000 | | No studies were found that looked at end-stage kidney disease |
| ≥50% loss of GFR | Relative risk (CI 95%  - )  
Follow up 12 months | Placebo: per 1000  
intravenous immunoglobulin: per 1000  
Difference: fewer per 1000 | | No studies were found that looked at ≥50% loss of GFR |
| Infection | Relative risk (CI 95%  - )  
Follow up 12 months | Placebo: per 1000  
intravenous immunoglobulin: per 1000  
Difference: fewer per 1000 | | No studies were found that looked at infection |
| Malignancy | Relative risk (CI 95%  - )  
Follow up 12 months | Placebo: per 1000  
intravenous immunoglobulin: per 1000  
Difference: fewer per 1000 | | No studies were found that looked at malignancy |
| Complete remission | Relative risk (CI 95%  - )  
Follow up 12 months | Placebo: per 1000  
intravenous immunoglobulin: per 1000  
Difference: fewer per 1000 | | No studies were found that looked at complete remission |
| Treatment response\(^3\)  
3 months | Relative risk: 2.33 (CI 95% 1.18 - 4.61)  
Based on data from 34 patients in 1 studies  
Follow up 12 months | Placebo: 353 per 1000  
intravenous immunoglobulin: 822 per 1000  
Difference: 469 more per 1000 (CI 95% 64 more - 1274 more) | Moderate  
Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect\(^5\) | Intravenous immunoglobulin compared with placebo probably increases treatment response |
| Relapse | Relative risk: 1.17 (CI 95% 0.39 - 3.56)  
Based on data from 31 patients in 1 studies  
Follow up 12 months | Placebo: 267 per 1000  
intravenous immunoglobulin: 312 per 1000  
Difference: 45 more per 1000 (CI 95% 163 fewer - 684 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision\(^7\) | We are uncertain whether intravenous immunoglobulin compared with placebo increases or decreases relapse |
| Annual GFR loss  
3 years | Measured by:  
Scale: - Lower better | Mean  
Mean | | No studies were found that looked at annual GFR loss |
### Table 1:  
<table>
<thead>
<tr>
<th>Difference</th>
<th>GFR loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD null lower</td>
<td></td>
</tr>
</tbody>
</table>


2. **Risk of bias**: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias and pharmaceutical sponsor involved in random sequence generation; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

3. Treatment response - BVAS reduction of 50% between entry


5. **Risk of bias**: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias and pharmaceutical sponsor involved in random sequence generation; **Imprecision**: Serious. Only data from one study, Low number of patients; **Upgrade**: Large magnitude of effect.


7. **Risk of bias**: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias and pharmaceutical sponsor involved in random sequence generation; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

### References

[49] Interventions for renal vasculitis in adults, 2018;
### Outcome Timeframe

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Relative risk: 0.94 (CI 95% 0.14 - 6.39) Based on data from 95 patients in 1 studies&lt;sup&gt;1&lt;/sup&gt; Follow up 18 months</td>
<td><strong>43</strong> per 1000</td>
<td><strong>40</strong> per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>18 months</td>
<td></td>
<td>Difference: <strong>3 fewer per 1000</strong> (CI 95% 37 fewer - 232 more)</td>
<td>Very Low</td>
<td>We are uncertain whether methotrexate compared with cyclophosphamide increases or decreases all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk: 0.96 (CI 95% 0.85 - 1.08) Based on data from 95 patients in 1 studies&lt;sup&gt;4&lt;/sup&gt; Follow up 18 months</td>
<td><strong>935</strong> per 1000</td>
<td><strong>898</strong> per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td>Difference: <strong>37 fewer per 1000</strong> (CI 95% 140 fewer - 75 more)</td>
<td>Low</td>
<td>Methotrexate compared with cyclophosphamide may have little or no difference on complete remission</td>
</tr>
<tr>
<td>Relapse</td>
<td>Relative risk: 0.57 (CI 95% 0.34 - 0.96) Based on data from 89 patients in 1 studies&lt;sup&gt;5&lt;/sup&gt; Follow up 18 months</td>
<td><strong>535</strong> per 1000</td>
<td><strong>305</strong> per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>230 fewer per 1000</strong> (CI 95% 353 fewer - 21 fewer)</td>
<td>Low</td>
<td>Methotrexate compared to cyclophosphamide may decrease relapse</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td>Difference: MD null lower</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

2. Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients.
4. Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Serious. Only data from one study, Low number of patients.

6. **Risk of bias:** Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Serious. Only data from one study; Low number of patients;

**References**
[49] Interventions for renal vasculitis in adults. 2018;
## PICO (21.7)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Avacopan  
**Comparator:** Prednisolone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>Avacopan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Relative risk (CI 95%: - ·)</td>
<td>Difference: fewer per 1000</td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95%: - ·)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95%: - ·)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk (CI 95%: - ·)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95%: - ·)</td>
<td>per 1000</td>
<td>per 1000</td>
<td>No studies were found that looked at malignancy</td>
</tr>
</tbody>
</table>
| Complete remission | Relative risk: 0.83 (CI 95%: 0.37 - 1.87) Based on data from 41 patients in 1 studies  
Follow up 3 months | 400 per 1000 | 332 per 1000 | Difference: 68 fewer per 1000 (CI 95%: 252 fewer - 348 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision  
Avacopan compared with prednisolone may improve complete remission |
| Annual GFR loss 3 years | Measured by: Scale: - Lower better  
Follow up 3 months | Mean | Mean | Difference: MD null lower | No studies were found that looked at annual GFR loss |
| eGFR | Measured by: Scale: - High better  
Follow up 3 months | mL/min/1.73 | mL/min/1.73 | Difference: MD 3.3 higher (CI 95%: 0.57 higher - 6.03 higher) | Low  
Due to serious risk of bias, Due to serious imprecision  
Avacopan compared with prednisolone may improve eGFR |

2. Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;  
4. Risk of bias: Serious. Unclear blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Serious. Only data from one study, Low number of patients;
References
[49] Interventions for renal vasculitis in adults. 2018;
### Table: Study results and measurements

<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><strong>All-cause mortality</strong></td>
<td>Relative risk: 1.91 (CI 95% 0.36 - 10.16) Based on data from 174 patients in 1 studies¹ Follow up Median 22 months</td>
<td>24 per 1000 46 per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision²</td>
<td>We are uncertain whether etanercept compared with placebo increases or decreases all-cause mortality</td>
</tr>
<tr>
<td><strong>End-stage kidney disease</strong></td>
<td>Relative risk (CI 95% - -)</td>
<td>per 1000  per 1000</td>
<td>Fewer per 1000</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td><strong>≥50% loss of GFR</strong></td>
<td>Relative risk (CI 95% - -)</td>
<td>per 1000  per 1000</td>
<td>Fewer per 1000</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>Relative risk: 1.0 (CI 95% 0.74 - 1.35)   Based on data from 174 patients in 1 studies³ Follow up Median 22 months</td>
<td>494 per 1000 494 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision⁴</td>
<td>Etanercept compared with placebo may have little or no difference on infection</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>Relative risk: 12.42 (CI 95% 0.71 - 217.18) Based on data from 174 patients in 1 studies⁵ Follow up Median 22 months</td>
<td>0 per 1000  per 1000</td>
<td>Fewer per 1000</td>
<td>Etanercept compared with placebo may have little or no difference on sustained remission</td>
</tr>
<tr>
<td><strong>Complete remission - Sustained</strong></td>
<td>Relative risk: 0.93 (CI 95% 0.77 - 1.11) Based on data from 174 patients in 1 studies⁵ Follow up Median 22 months</td>
<td>753 per 1000 700 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision⁷</td>
<td>Etanercept compared with placebo may have little or no difference on relapse</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>Relative risk: 0.93 (CI 95% 0.56 - 1.56) Based on data from 126 patients in 1 studies⁹ Follow up Median 22 months</td>
<td>328 per 1000 305 per 1000</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision⁹</td>
<td>Etanercept compared with placebo may have little or no difference on relapse</td>
</tr>
<tr>
<td><strong>Annual GFR loss 3 years</strong></td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean  Mean</td>
<td>MD null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

2. Risk of bias: Serious. Inadequate sequence generation/ generation of comparable groups, 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. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; Imprecision: Serious. Only data from one study, Low number of patients;

7. **Risk of bias:** Serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias; **Imprecision:** Serious. Only data from one study. Low number of patients;


9. **Risk of bias:** Serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias; **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

References
[49] Interventions for renal vasculitis in adults. 2018;
<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>All-cause mortality 6 months</td>
<td>Relative risk: 1.64 (CI 95% 0.3 - 8.89) Based on data from 44 patients in 1 studies¹ Follow up 6 months</td>
<td>87 per 1000</td>
<td>143 per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision²</td>
</tr>
<tr>
<td>End-stage kidney disease 6 months</td>
<td>Relative risk: 0.58 (CI 95% 0.12 - 2.62) Based on data from 39 patients in 1 studies³ Follow up 6 months</td>
<td>190 per 1000</td>
<td>110 per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision⁴</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td><strong>No studies were found that looked at ≥50% loss of GFR</strong></td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk (CI 95% -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td><strong>No studies were found that looked at infection</strong></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td><strong>No studies were found that looked at malignancy</strong></td>
</tr>
<tr>
<td>Complete remission</td>
<td>Relative risk (CI 95% -)</td>
<td>per 1000</td>
<td>per 1000</td>
<td><strong>No studies were found that looked at complete remission</strong></td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td><strong>Difference: MD null lower</strong></td>
</tr>
</tbody>
</table>

2. **Risk of bias:** Serious. Unclear sequence generation/ generation of comparable groups, 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. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;

**References**

[49] Interventions for renal vasculitis in adults. 2018;
### PICO (21.10)
Population: Patients with ANCA associated nephritis  
Intervention: Lymphocytapheresis  
Comparator: Standard of care - IV methylprednisone, steroids and cyclophosphamide

<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** 6 months | Relative risk: 0.4 (CI 95% 0.1 - 1.67) Based on data from 24 patients in 1 studies1 Follow up 6 months | **417** per 1000  
**167** per 1000  
Difference: **250 fewer per 1000** (CI 95% 375 fewer - 279 more) | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision2 | We are uncertain whether lymphocytapheresis compared with standard of care increases or decreases all-cause mortality |
| **End-stage kidney disease** 6 months | Relative risk: 0.33 (CI 95% 0.04 - 2.77) Based on data from 24 patients in 1 studies3 Follow up 6 months | **250** per 1000  
**83** per 1000  
Difference: **167 fewer per 1000** (CI 95% 240 fewer - 443 more) | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision4 | We are uncertain whether lymphocytapheresis compared with standard of care increases or 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 malignancy |
| Complete remission | Relative risk (CI 95% - -) | - per 1000  
- per 1000  
Difference: fewer per 1000 | | No studies were found that looked at complete remission |
| 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 |

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2. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear binding of participants and personnel, resulting in potential for performance bias, unclear of binding of outcome assessors, resulting in potential for detection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of binding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of binding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting, Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
4. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, unclear binding of participants and personnel,
resulting in potential for performance bias, unclear 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, Low number of patients;

References
[49] Interventions for renal vasculitis in adults. 2018;
### PICO (21.11)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Six cyclophosphamide pulses  
**Comparator:** Twelve cyclophosphamide pulses

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| **All-cause mortality** | Relative risk: 0.99 (CI 95% 0.51 - 1.89)  
Based on data from 153 patients in 2 studies¹  
Follow up Mean 36 months | Relative risk: 0.99  
(214 per 1000) vs 212 per 1000  
Difference: 2 fewer per 1000  
(CI 95% 105 fewer - 190 more) | Low  
Due to serious risk of bias, Due to serious imprecision² | Six compared to 12 cyclophosphamide pulses may have little or no difference on all-cause mortality |
| **End-stage kidney disease** | Relative risk (CI 95% -)  
(176 per 1000) vs 225 per 1000  
Difference: 49 more per 1000  
(CI 95% 92 fewer - 421 more) | Very Low  
Due to serious risk of bias, Due to very serious imprecision³ | No studies were found that looked at end-stage kidney disease |
| **≥50% loss of GFR** | Relative risk (CI 95% -)  
(261 per 1000) vs 410 per 1000  
Difference: 149 more per 1000  
(CI 95% 10 fewer - 407 more) | Moderate  
Due to serious risk of bias⁶ | No studies were found that looked at ≥50% loss of GFR |
| **Infection** | Relative risk: 1.28 (CI 95% 0.48 - 3.39)  
Based on data from 65 patients in 1 studies³  
Follow up 36 months | Relative risk: 1.28  
(861 per 1000) vs 852 per 1000  
Difference: 9 fewer per 1000  
(CI 95% 129 fewer - 129 more) | Moderate  
Due to serious risk of bias⁸ | We are uncertain whether six compared with 12 cyclophosphamide pulses increases or decreases infection |
| **Malignancy** | Relative risk (CI 95% -)  
(784 per 1000) vs 604 per 1000  
Difference: 180 fewer per 1000  
(CI 95% 321 fewer - 0 fewer) | Low  
Due to serious risk of bias, Due to serious imprecision¹⁰ | Six compared with 12 cyclophosphamide pulses may decrease severe adverse events slightly |
| **Complete remission** | Relative risk: 0.99 (CI 95% 0.85 - 1.15)  
Based on data from 151 patients in 2 studies⁵  
Follow up Mean 36 months | Relative risk: 0.99  
(261 per 1000) vs 410 per 1000  
Difference: 149 more per 1000  
(CI 95% 10 fewer - 407 more) | Moderate  
Due to serious risk of bias⁸ | Six compared to 12 cyclophosphamide pulses probably has little or no difference on complete remission |
| **Relapse** | Relative risk: 1.57 (CI 95% 0.96 - 2.56)  
Based on data from 133 patients in 2 studies⁷  
Follow up 133 | Relative risk: 1.57  
(261 per 1000) vs 410 per 1000  
Difference: 149 more per 1000  
(CI 95% 10 fewer - 407 more) | Moderate  
Due to serious risk of bias⁸ | Six compared with 12 cyclophosphamide pulses probably has little or no difference on relapse |
| **Severe adverse events** | Relative risk: 0.77 (CI 95% 0.59 - 1.0)  
Based on data from 104 patients in 1 studies⁸  
Follow up 36 months | Relative risk: 0.77  
(784 per 1000) vs 604 per 1000  
Difference: 180 fewer per 1000  
(CI 95% 321 fewer - 0 fewer) | Low  
Due to serious risk of bias, Due to serious imprecision¹⁰ | Six compared with 12 cyclophosphamide pulses may decrease severe adverse events slightly |
| **Annual GFR loss 3 years** | Measured by: Scale: - Lower better | Mean | Low  
Due to serious risk of bias, Due to serious imprecision¹⁰ | No studies were found that looked at annual |
2. Risk of bias: Serious. due to the groups in Guillevin 2003 did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant; Imprecision: Serious. Wide confidence intervals;
4. Risk of bias: Serious. due to the groups in Guillevin 2003 did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
6. Risk of bias: Serious. due to the groups in Guillevin 2003 did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant;
8. Risk of bias: Serious. due to the groups in Guillevin 2003 did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant;
10. Risk of bias: Serious. due to the groups in Guillevin 2003 did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant; Imprecision: Serious. Only data from one study;

References
[49] Interventions for renal vasculitis in adults. 2018;
### PICO (21.12)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Reduced dose steroids  
**Comparator:** Standard dose 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>
</table>
| **All-cause mortality** | Relative risk: 0.86 (CI 95% 0.6 - 1.24) Based on data from 704 patients in 1 studies¹ | **151** per 1000 | 130 per 1000 | Low | Reduced dose compared with standard dose corticosteroids may have little or no difference on all-cause mortality.  
**Difference:** 21 fewer per 1000 (CI 95% 60 fewer - 36 more) |
| **End-stage kidney disease** | Relative risk: 1.02 (CI 95% 0.76 - 1.38) Based on data from 704 patients in 1 studies³ | **194** per 1000 | 198 per 1000 | Low | Due to serious risk of bias, Due to serious imprecision  
**Difference:** 4 more per 1000 (CI 95% 47 fewer - 74 more) |
| ≥50% loss of GFR | Relative risk (CI 95% - ) | per 1000 | per 1000 | No studies were found that looked at ≥50% loss of GFR. |
| **Infection⁵** | Relative risk: 0.82 (CI 95% 0.66 - 1.03) Based on data from 704 patients in 1 studies⁶ | **330** per 1000 | 271 per 1000 | Low | Reduced dose compared with standard dose corticosteroids may have little or no difference on infection.  
**Difference:** 59 fewer per 1000 (CI 95% 112 fewer - 10 more) |
| **Malignancy** | Relative risk (CI 95% - ) | per 1000 | per 1000 | No studies were found that looked at malignancy. |
| **Complete remission - sustained remission** | Relative risk: 1.05 (CI 95% 0.92 - 1.2) Based on data from 704 patients in 1 studies⁸ | **550** per 1000 | 577 per 1000 | Low | Reduced dose compared with standard dose corticosteroids may have little or no difference on sustained remission.  
**Difference:** 27 more per 1000 (CI 95% 44 fewer - 110 more) |
| **Severe adverse events** | Relative risk: 1.05 (CI 95% 0.94 - 1.18) Based on data from 704 patients in 1 studies¹⁰ | **621** per 1000 | 652 per 1000 | Low | Reduced dose compared with standard dose corticosteroids may have little or no difference on severe adverse events.  
**Difference:** 31 more per 1000 (CI 95% 37 fewer - 112 more) |
| **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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2. **Risk of bias:** Serious, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Serious, Only data from one study, Low number of patients;  
4. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: Serious. Only data from one study, Low number of patients;

5. Serious infections


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: Serious. Only data from one study, Low number of patients;


9. 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;


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

References

[49] Interventions for renal vasculitis in adults. 2018;
**PICO (21.13)**

Population: Patients with ANCA associated nephritis

Intervention: Maintenance therapy: azathioprine

Comparator: Maintenance therapy: cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates Maintenance therapy: cyclophosphamide</th>
<th>Absolute effect estimates Maintenance therapy: azathioprine</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 (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk: 1.03 (CI 95% 0.51 - 2.06) Based on data from 144 patients in 1 studies Follow up 18 months</td>
<td>178 per 1000</td>
<td>183 per 1000</td>
<td>Moderate Due to serious imprecision²</td>
<td>We are uncertain whether azathioprine compared with cyclophosphamide as maintenance therapy increases or decreases infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000</td>
<td>per 1000</td>
<td></td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td>Relapse</td>
<td>Relative risk: 1.13 (CI 95% 0.51 - 2.5) Based on data from 144 patients in 1 studies Follow up 18 months</td>
<td>137 per 1000</td>
<td>155 per 1000</td>
<td>Moderate Due to serious imprecision⁴</td>
<td>We are uncertain whether azathioprine compared with cyclophosphamide as maintenance therapy increases or decreases relapse</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Relative risk: 0.65 (CI 95% 0.42 - 0.99) Based on data from 144 patients in 1 studies Follow up 18 months</td>
<td>479 per 1000</td>
<td>311 per 1000</td>
<td>Moderate Due to serious imprecision⁶</td>
<td>Azathioprine compared with cyclophosphamide as maintenance therapy may decrease leukopenia</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

2. Imprecision: Serious. Only data from one study, Low number of patients;
4. **Imprecision:** Serious. Only data from one study, Low number of patients;
5. Systematic review [49] with included studies: CYCAZAREM 2003 **Baseline/comparator:** Control arm of reference used for intervention.
6. **Imprecision:** Serious. Only data from one study, Low number of patients;

**References**
[49] Interventions for renal vasculitis in adults. 2018;
### 22 Aug 2018 - KDIGO Clinical Practice Guideline for Glomerulonephritis

**PICO (21.14)**
Population: Patients with ANCA associated nephritis  
Intervention: Maintenance therapy: azathioprine  
Comparator: Maintenance therapy: methotrexate

<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 (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Moderate</td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Moderate</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Moderate</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Moderate</td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Moderate</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td>Relapse</td>
<td>Relative risk: 1.1 (CI 95% 0.68 - 1.77) Based on data from 126 patients in 1 studies¹ Follow up 3 years</td>
<td>333 per 1000 366 per 1000</td>
<td>Moderate Due to serious imprecision² Azathioprine compared with methotrexate as maintenance therapy may have little or no difference on relapse</td>
<td></td>
</tr>
<tr>
<td>Adverse event causing death or study drug discontinuation</td>
<td>Relative risk: 0.58 (CI 95% 0.25 - 1.38) Based on data from 126 patients in 1 studies² Follow up 3 years</td>
<td>190 per 1000 110 per 1000</td>
<td>Moderate Due to very serious imprecision³ Azathioprine compared with methotrexate as maintenance therapy may have little or no difference on adverse events resulting in death or drug discontinuation</td>
<td></td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td>Mean Mean</td>
<td>MD null lower</td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
</tbody>
</table>

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

**References**

[49] Interventions for renal vasculitis in adults, 2018;
## PICO (21.15)
Population: Patients with ANCA associated nephritis
Intervention: Maintenance therapy: mycophenolate mofetil
Comparator: Maintenance therapy: azathioprine

<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>Maintenance therapy: azathioprine</td>
<td>Maintenance therapy: mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Difference: fewer per 1000</td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td><strong>End-stage kidney disease</strong></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Difference: fewer per 1000</td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td><strong>≥50% loss of GFR</strong></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Difference: fewer per 1000</td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>Relative risk (CI 95% - )</td>
<td>per 1000 per 1000</td>
<td>Difference: fewer per 1000</td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>Relative risk: 0.39 (CI 95% 0.11 - 1.43) Based on data from 156 patients in 1 studies Follow up 4 years</td>
<td><strong>100</strong> per 1000 <strong>39</strong> per 1000</td>
<td><strong>Low</strong> Due to very serious imprecision²</td>
<td>Mycophenolate mofetil compared with azathioprine as maintenance therapy may have little or no difference on infection</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>Relative risk: 1.47 (CI 95% 1.04 - 2.09) Based on data from 156 patients in 1 studies Follow up 4 years</td>
<td><strong>375</strong> per 1000 <strong>551</strong> per 1000</td>
<td><strong>Moderate</strong> Due to serious imprecision⁴</td>
<td>Mycophenolate mofetil compared with azathioprine as maintenance therapy probably increases relapse</td>
</tr>
<tr>
<td><strong>Annual GFR loss 3 years</strong></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>
</tbody>
</table>

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

**References**
[49] Interventions for renal vasculitis in adults. 2018;
**PICO (21.16)**

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Maintenance therapy: antibiotics (trimethoprim/sulfamethoxazole)  
**Comparator:** Maintenance therapy: placebo  

<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 6 months** | Relative risk: 0.33 (CI 95% 0.01 - 7.76) Based on data from 81 patients in 1 studies Follow up 6 months | Maintenance therapy: placebo 25 per 1000 Maintenance therapy: antibiotics 8 per 1000 Difference: 17 fewer per 1000 (CI 95% 25 fewer - 169 more) | Low Due to very serious imprecision¹ | Antibiotics compared with placebo in maintenance therapy may have little or no difference on all-cause mortality at 6 months  
| **End-stage kidney disease** | (CI 95% - ) | Difference: fewer |  
| **≥50% loss of GFR** | (CI 95% - ) | Difference: fewer |  
| **Infection** | (CI 95% - ) | Difference: fewer |  
| **Malignancy** | (CI 95% - ) | Difference: fewer |  
| **Complete remission 1 year** | Relative risk: 1.14 (CI 95% 0.98 - 1.33) Based on data from 111 patients in 2 studies² Follow up Mean 12 months | 796 per 1000 Maintenance therapy: placebo 907 per 1000 Difference: 111 more per 1000 (CI 95% 16 fewer - 263 more) | Low Due to serious risk of bias, Due to serious imprecision³ | Antibiotics compared with placebo in maintenance therapy may have little or no difference on complete remission at 1 year  
| **Complete remission 2 years** | Relative risk: 1.28 (CI 95% 0.94 - 1.76) Based on data from 80 patients in 1 studies³ Follow up 6 months | 590 per 1000 Maintenance therapy: placebo 755 per 1000 Difference: 165 more per 1000 (CI 95% 35 fewer - 448 more) | Low Due to serious imprecision, Due to serious risk of bias⁵ | Antibiotics compared to placebo probably has little or no difference on complete remission at 2 years  
| **Annual GFR loss 3 years** | Measured by: Scale: - Lower better | Difference: null lower |  

¹ Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;  
³ Risk of bias: Serious. In Zycinska 2009 the groups were not balanced. Patients in the placebo group were older, had worse kidney function and a higher mean BVAS score at baseline; Imprecision: Serious. Low number of patients;
5. Risk of bias: Serious. Imprecision: Serious. Only data from one study, Low number of patients;

References
[49] Interventions for renal vasculitis in adults. 2018;
## PICO (21.17)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Maintenance therapy: rituximab  
**Comparator:** Maintenance therapy: azathioprine  

<table>
<thead>
<tr>
<th>Outcome/Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| All-cause mortality | Relative risk: 0.2  
(CI 95% 0.01 - 4.15)  
Based on data from 115 patients in 1 studies  
Follow up 28 months | **Maintenance therapy:**  
azathioprine: per 1000  
**Maintenance therapy:**  
rituximab: per 1000  
Difference: **27 fewer per 1000**  
(CI 95% 34 fewer - 107 more) | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision | We are uncertain whether rituximab compared with azathioprine as maintenance therapy increases or decreases all-cause mortality |
| End-stage kidney disease | Relative risk  
(CI 95% - )  
Based on data from 115 patients in 1 studies  
Follow up 28 months | per 1000  
Difference: fewer per 1000 |  
No studies were found that looked at end-stage kidney disease |
| ≥50% loss of GFR | Relative risk  
(CI 95% - )  
Based on data from 115 patients in 1 studies  
Follow up 28 months | per 1000  
Difference: fewer per 1000 |  
No studies were found that looked at ≥50% loss of GFR |
| Infection³ | Relative risk: 1.4  
(CI 95% 0.61 - 3.22)  
Based on data from 115 patients in 1 studies  
Follow up 28 months | **Maintenance therapy:**  
azathioprine: per 1000  
**Maintenance therapy:**  
rituximab: per 1000  
Difference: **55 more per 1000**  
(CI 95% 54 fewer - 306 more) | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision | We are uncertain whether rituximab compared with azathioprine as maintenance therapy increases or decreases infection |
| Malignancy | (CI 95% - )  
Based on data from 115 patients in 1 studies  
Follow up 28 months | Difference: fewer |  
No studies were found that looked at malignancy |
| Major relapse | Relative risk: 0.18  
(CI 95% 0.06 - 0.58)  
Based on data from 115 patients in 1 studies  
Follow up 28 months | **Maintenance therapy:**  
azathioprine: per 1000  
**Maintenance therapy:**  
rituximab: per 1000  
Difference: **240 fewer per 1000**  
(CI 95% 275 fewer - 123 fewer) | **Moderate**  
Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect | Rituximab compared with azathioprine as maintenance therapy probably decreases major relapse |
| Minor relapse | Relative risk: 0.68  
(CI 95% 0.26 - 1.78)  
Based on data from 115 patients in 1 studies  
Follow up 28 months | **Maintenance therapy:**  
azathioprine: per 1000  
**Maintenance therapy:**  
rituximab: per 1000  
Difference: **50 fewer per 1000**  
(CI 95% 115 fewer - 121 more) | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision | We are uncertain whether rituximab compared with azathioprine as maintenance therapy increases or decreases minor relapse |
| 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 MAINRITSAN 2014  
**Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

3. **Serious infections**

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

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

6. Primary study MAINRITSAN 2014 **Baseline/comparator:** Control arm of reference used for intervention.

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;
### PICO (21.18)
- **Population:** Patients with ANCA associated nephritis
- **Intervention:** Maintenance therapy: leflunomide
- **Comparator:** Maintenance therapy: methotrexate

<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% loss of GFR</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>Infection</td>
<td>Relative risk: 1.17 (CI 95% 0.66 - 2.07) Based on data from 54 patients in 1 studies Follow up 24 months</td>
<td>429 per 1000 502 per 1000</td>
<td>Moderate Due to serious imprecision&lt;sup&gt;1&lt;/sup&gt;</td>
<td>We are uncertain whether leflunomide compared with methotrexate as maintenance therapy increases or decreases 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>Relapse</td>
<td>Relative risk: 0.52 (CI 95% 0.22 - 1.11) Based on data from 54 patients in 1 studies Follow up 24 months</td>
<td>464 per 1000 241 per 1000</td>
<td>Moderate Due to serious imprecision&lt;sup&gt;2&lt;/sup&gt;</td>
<td>We are uncertain whether leflunomide compared with methotrexate as maintenance therapy increases or decreases relapse</td>
</tr>
<tr>
<td>Major relapse</td>
<td>Relative risk: 0.15 (CI 95% 0.02 - 1.17) Based on data from 54 patients in 1 studies Follow up 24 months</td>
<td>250 per 1000 38 per 1000</td>
<td>Moderate Due to serious imprecision&lt;sup&gt;4&lt;/sup&gt;</td>
<td>We are uncertain whether leflunomide compared with methotrexate as maintenance therapy increases or decreases major relapse</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Relative risk: 11.81 (CI 95% 0.68 - 203.68) Based on data from 54 patients in 1 studies Follow up 24 months</td>
<td>0 per 1000 0 per 1000</td>
<td>Very Low Due to very serious risk of bias, Due to very serious imprecision&lt;sup&gt;5&lt;/sup&gt;</td>
<td>There were too few who experienced the serious adverse events, to determine whether leflunomide compared with methotrexate as maintenance therapy made a difference</td>
</tr>
</tbody>
</table>

<sup>1</sup> Due to serious imprecision
<sup>2</sup> Due to serious imprecision
<sup>3</sup> Due to serious imprecision
<sup>4</sup> Due to serious imprecision
<sup>5</sup> Due to very serious risk of bias, Due to very serious imprecision
| Annual GFR loss 3 years | Measured by: | Scale: - Lower better | Difference: null lower | No studies were found that looked at annual GFR loss |

1. **Risk of bias**: No serious. Study terminated early due to high rate of relapses in control group; **Imprecision**: Serious. Only data from one study, Low number of patients;
2. **Risk of bias**: No serious. Study terminated early due to high rate of relapses in control group; **Imprecision**: Serious. Only data from one study, Low number of patients, Only data from one study, Low number of patients, Only data from one study, Low number of patients;
3. Primary study Metzler 2007 Baseline/comparator: Control arm of reference used for intervention .
4. **Risk of bias**: No serious. Study terminated early due to high rate of relapses in control group; **Imprecision**: Serious. Only data from one study, Low number of patients;
5. **Risk of bias**: Very Serious. Study terminated early due to high rate of relapses in control group; **Imprecision**: Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
## PICO (21.19)
Population: Patients with ANCA associated nephritis  
Intervention: Maintenance therapy: cyclosporin  
Comparator: Maintenance therapy: cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - -)</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td>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>
</tbody>
</table>
| Relapse | Relative risk: 1.38  
(CI 95% 0.82 - 2.33)  
Based on data from 64 patients in 1 studies  
Follow up 5 years | 406  
per 1000  
(CI 95% 73 fewer - 540 more)  
406  
560  
per 1000  
Moderate  
Due to serious imprecision¹ | Cyclosporin compared with cyclophosphamide as maintenance therapy probably has little or no difference on relapse |
| Annual GFR loss 3 years | Measured by: Scale: - Lower better | Difference: null lower |                                                     | No studies were found that looked at annual GFR loss |

1. Imprecision: Serious. Low number of patients, Only data from one study;
### PICO (21.20)
**Population:** Patients with ANCA associated nephritis  
**Intervention:** Maintenance therapy: methotrexate  
**Comparator:** Maintenance therapy: cyclophosphamide

<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: 0.44 (CI 95% 0.04 - 4.67) Based on data from 68 patients in 1 studies Follow up 24 months</td>
<td><strong>Maintenance therapy:</strong> cyclophosphamide</td>
<td><strong>Maintenance therapy:</strong> methotrexate</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63 per 1000</td>
<td>28 per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>35 fewer per 1000</strong> (CI 95% 60 fewer - 231 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td></td>
<td></td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% loss of GFR</td>
<td>(CI 95% - )</td>
<td></td>
<td></td>
<td>No studies were found that looked at ≥50% loss of GFR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td></td>
<td></td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>(CI 95% - )</td>
<td></td>
<td></td>
<td>No studies were found that looked at malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Relative risk: 1.14 (CI 95% 0.48 - 2.72) Based on data from 68 patients in 1 studies Follow up 24 months</td>
<td><strong>219</strong> per 1000</td>
<td><strong>250</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, Due to very serious imprecision²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>31 more per 1000</strong> (CI 95% 114 fewer - 377 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Measured by: Scale: - Lower better</td>
<td></td>
<td></td>
<td>No studies were found that looked at annual GFR loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference: <strong>null lower</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **Risk of bias:** Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;  
2. **Risk of bias:** Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision:** Very Serious. Wide confidence intervals, Only data from one study, Low number of patients;
### PICO (21.21)

**Population:** Patients with ANCA associated nephritis  
**Intervention:** Maintenance therapy: extended azathioprine  
**Comparator:** Maintenance therapy: standard azathioprine

<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><strong>End-stage kidney disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Relative risk: 0.1 (CI 95% 0.01 - 1.86) Based on data from 117 patients in 1 studies1 Follow up 48 months | Maintenance therapy: standard azathioprine per 1000: 71  
Maintenance therapy: extended azathioprine per 1000: 7 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision2 | We are uncertain whether extended or standard azathioprine as maintenance therapy increases or decreases end-stage kidney disease |
| **≥50% loss of GFR** |
| (CI 95% - ) | | Difference: fewer | No studies were found that looked at ≥50% loss of GFR |
| **Infection³** |
| Relative risk: 1.14 (CI 95% 0.38 - 3.41) Based on data from 45 patients in 1 studies4 Follow up 48 months | Maintenance therapy: standard azathioprine per 1000: 208  
Maintenance therapy: extended azathioprine per 1000: 237 | **Very Low**  
Due to very serious risk of bias, Due to very serious imprecision5 | We are uncertain whether extended or standard azathioprine as maintenance therapy increases or decreases infection |
| **Malignancy** |
| (CI 95% - ) | | Difference: fewer | No studies were found that looked at malignancy |
| **Relapse** |
| Relative risk: 0.41 (CI 95% 0.26 - 0.64) Based on data from 192 patients in 2 studies6 | Maintenance therapy: standard azathioprine per 1000: 538  
Maintenance therapy: extended azathioprine per 1000: 221 | **Moderate**  
Due to very serious risk of bias, Upgraded due to Large magnitude of effect7 | Extended compared with standard azathioprine as maintenance therapy probably decreases relapse |
| **Major relapse** |
| Relative risk: 0.41 (CI 95% 0.19 - 0.86) Based on data from 117 patients in 1 studies8 | Maintenance therapy: standard azathioprine per 1000: 321  
Maintenance therapy: extended azathioprine per 1000: 132 | **Low**  
Due to serious risk of bias, Due to serious imprecision9 | Extended compared with standard azathioprine as maintenance therapy may decrease major relapse |
| **Serious adverse events** |
| Relative risk: 2.75 (CI 95% 0.78 - 9.66) Based on data from 117 patients in 1 studies9 | Maintenance therapy: standard azathioprine per 1000: 54  
Maintenance therapy: extended azathioprine per 1000: 149 | **Very Low**  
Due to serious risk of bias, Due to very serious imprecision10 | We are uncertain whether extended or standard azathioprine as maintenance therapy increases or decreases serious adverse events |
| **All-cause mortality** |
| Relative risk: 2.81 (CI 95% 0.69 - 11.5) Based on data from 162 patients in 2 studies10 Follow up Mean 48 months | Maintenance therapy: standard azathioprine per 1000: 25  
Maintenance therapy: extended azathioprine per 1000: 70 | **Very Low**  
Due to very serious risk of bias, Due to very serious imprecision11 | We are uncertain whether extended or standard azathioprine as maintenance therapy increases or decreases all-cause mortality |
| **Annual GFR loss 3 years** |
| Measured by: Scale: - Lower better | | | No studies were found that looked at annual |

---

1. Studies1  
2. Very Low due to serious risk of bias, due to very serious imprecision.  
3. Infections  
4. Studies4  
5. Very Low due to very serious risk of bias, due to very serious imprecision.  
6. Studies6  
7. Due to very serious risk of bias, upgraded due to large magnitude of effect.  
8. Studies8  
9. Due to serious risk of bias, due to serious imprecision.  
10. Studies9  
11. Due to very serious risk of bias, due to very serious imprecision.  
12. Studies10  
13. Due to very serious risk of bias, due to very serious imprecision.

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

3. Serious Infections


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, due to early termination of the AZA-ANCA due to poor recruitment.; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;


7. **Risk of bias: Very Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to early termination of the AZA-ANCA due to poor recruitment.; **Upgrade: Large magnitude of effect.**


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


11. **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;


13. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to early termination of the AZA-ANCA due to poor recruitment.; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;

References
[49] Interventions for renal vasculitis in adults. 2018;
PICO (21.22)
Population: Patients with ANCA associated nephritis
Intervention: Maintenance therapy: pre-emptive therapy for relapse
Comparator: Standard of care

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
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<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>Relapse</td>
<td>Relative risk: 0.23 (CI 95% 0.03 - 1.59) Based on data from 60 patients in 2 studies¹</td>
<td>677 per 1000 156 per 1000 Difference: 521 fewer per 1000 (CI 95% 657 fewer - 399 more)</td>
<td>Very Low Due to serious risk of bias, Due to very serious imprecision²</td>
<td>We are uncertain whether pre-emptive therapy for relapse compared to standard of care for maintenance therapy increases or decreases relapse</td>
</tr>
<tr>
<td>Annual GFR loss</td>
<td>Measured by: Scale: Lower better</td>
<td>Mean</td>
<td>Mean</td>
<td>Difference: MD null lower</td>
</tr>
</tbody>
</table>

2. Risk of bias: Serious. Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias of Tervaert 1990 and Boomsma 2003 is an abstract only; Imprecision: Very Serious. Low number of patients, Wide confidence intervals;

References
[49] Interventions for renal vasculitis in adults. 2018;