KDIGO GN Guideline update – Evidence summary

Idiopathic membranous nephropathy

Immunosuppressive therapy of idiopathic membranous nephropathy

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

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

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

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

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

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

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

Summary of the main findings
Steroid versus placebo or no treatment

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

Alkylating agents versus placebo/no treatment or steroids

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

Calcinuerin inhibitors
versus placebo/no treatment or steroids

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

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

**versus alkylating agents**

- The effects on all-cause mortality, end-stage kidney disease, and doubling serum creatinine are uncertain because of study limitations, heterogeneity, and imprecision.
- Compared to alkylating agents, calcineurin inhibitors may have little or no effect on infection (RR 0.55, 95%CI 0.25 to 1.23; 3 studies, 218 participants) and complete remission (RR 1.28, 95%CI 0.71 to 2.32; 4 studies, 176 participants). However, it probably slightly increase a ≥20% loss of GFR (RR 0.71, 95%CI 0.51 to 1.00; 1 study, 69 participants).

**Azathioprine versus placebo or no treatment**

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

**Mycophenolate mofetil (MMF) versus other**

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

**Cyclophosphamide plus steroids versus chlorambucil plus steroids**

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

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

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

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

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

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

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

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

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

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

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


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

Alkylating agents versus placebo/no treatment or steroids
1. Ponticelli 1995 – This is a long-term follow-up study of Ponticelli 1983 that has been included in the meta-analysis. All data from long-term follow-up studies are included in the meta-analysis if an attrition rate over 70% is maintained. Ponticelli C, et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney International*. 1995;48(5):1600-4