KDIGO GN Guideline update – Evidence summary

IgA nephropathy and IgA vasculitis - IgA nephropathy

Non-immunosuppressive therapy for IgA nephropathy

PICO question
In patients with biopsy-proven IgA nephropathy, what non-immunosuppressive agents (fish oil, anticoagulants/antiplatelet, antioxidant, tonsillectomy, statins, traditional Chinese medicine, vitamin D, vitamin E, allopurinol, etc.) compared to no treatment/placebo or standard of care improve efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

* Note – antihypertensive medication was not covered in this review

Search strategy and selection
Keywords for IgA nephropathy and fish oil, anticoagulant agents, tonsillectomy and other non-immunosuppressive treatments were used to search the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials (RCTs) published up to May 2018.

Search results
The non-immunosuppressive Cochrane review published in 2011, identified 2872 relevant citations with 433 duplicate reports, 2305 citations were excluded because they were not RCTs, did not include patients with biopsy-proven IgA nephropathy, had less than 75% of patients with IgA nephropathy in the trial, or were the wrong intervention. The review identified 56 primary studies with 56 secondary publications (112 reports) with 2838 participants.

The May 2018 search update for the Cochrane Kidney and Transplant Specialized Register identified 51 citations, of which 15 were excluded because they were not RCTs, did not include patients with biopsy-proven IgA nephropathy, had less than 75% of patients with IgA nephropathy in the trial, or were the wrong intervention. Thirty-six reports were included, of these four reports were of antihypertensive therapy leaving 31 reports (19 primary studies and 12 secondary publications) with 1210 participants that were included in the update for this review.

Overall 75 primary studies (68 secondary publications) with 4048 participants were included.

There were six ongoing studies identified from clinicaltrials.gov

Twenty-one comparisons for induction therapy were included for the following:
1. Fish oil versus placebo (5 studies, 169 participants)
2. Fish oil versus symptomatic treatment (1 study, 34 participants)
3. High dose fish oil versus low dose fish oil (1 study, 73 participants)
4. Anticoagulant versus placebo or no treatment (3 studies, 110 participants)
5. Anticoagulant versus other treatment (2 studies, 52 participants)
6. Anticoagulant plus angiotensin receptor blocker (ARB) versus ARB alone (3 studies, 331 participants)
7. Anticoagulant plus prednisone versus prednisone alone (1 study, 20 participants)
8. Antioxidant versus ARB (1 study, 68 participants)
9. Tonsillectomy plus standard of care versus standard of care alone (3 studies, 177 participants)
10. Statins versus placebo (1 study, 21 participants)
11. Statins plus antiplatelet therapy versus antiplatelet therapy alone (1 study 30 participants)
12. Phenytoin versus no treatment (2 studies, 83 participants)
13. Herbal medicine versus placebo or no treatment (3 studies, 176 participants)
14. Traditional Chinese medicine versus western medicine (3 studies, 205 participants)
15. Traditional Chinese medicine plus western medicine versus western medicine alone (2 studies, 157 participants)
16. Urokinase plus angiotensin converting enzyme inhibitor (ACEi) versus ACEi alone (1 study, 71 participants)
17. Vitamin D versus no treatment (1 study, 50 participants)
18. Vitamin E versus placebo (1 study, 55 participants)
19. Sodium cromoglycate versus placebo/no treatment (1 study, 30 participants)
20. Low-calorie diet versus usual diet (1 study, 26 participants)
21. Allopurinol versus no treatment (1 study, 40 participants)

**Summary of the main findings**

**Fish oil**
- Compared with placebo or no treatment, treatment with fish oil may decrease a >50% increase in serum creatinine. There were uncertain effects on other critical and important outcomes because the certainty of the evidence was very low due to study limitations and imprecise effect estimates.
  - The effects of high versus low dose fish oil were uncertain as only end-stage kidney disease was examined in RCTs and the certainty of the evidence was very low.
- Fish oil compared to symptomatic treatment, may slightly decrease the >50% loss in GFR slightly. However, the effect estimate crosses the line of no effect (RR 0.14, 95%CI 0.02 to 1.01; 1 study, 28 participants).
- Fish oil combined with antihypertensive medication compared to antihypertensive medication alone may improve creatinine clearance (ml/min) (MD 26.20, 95%CI 1.01 to 51.39; 1 study, 30 participants).
  - We are uncertain if fish oil compared to symptomatic treatment increases or decreases other critical or important outcomes, as they were not examined in studies or the certainty of the evidence was very low due to study limitations and imprecise effect estimates.

**Anticoagulant therapy**
- We are uncertain if treatment with an anticoagulant compared to placebo or no treatment improves critical or important outcomes because the certainty of the evidence is very low (study limitations and imprecision in the effect estimate).
- Compared to hirudin, dipryidamole may increase complete remission (RR 0.27, 95% CI 0.16 to 0.46) but it may decrease creatinine clearance (ml/min) (MD 15.90, 95%CI 19.9 to 11.81 lower). However, its effects on other critical or important outcomes are unclear because the certainty of the evidence was very low, due to study limitations and very serious imprecision (1 study, 262 participants).
- Similarly, we are uncertain if the use of dipyridamole combined with aspirin compared to vitamin B increased or decreased critical or important outcomes because the certainty of the evidence was very low (1 study, 38 participants).
- Compared to treatment with ACEi or ARB alone, the addition of an ACEi or ARB to anticoagulant therapy may have little or no difference on end-stage kidney disease and eGFR. However, the effects on other critical and important outcomes are unclear because the certainty of the evidence is very low.

**Antioxidant therapy**
• Treatment with an antioxidant (probucol) compared to ARB alone may increase the annual loss of GFR (ml/min/1.73m²) at three years (MD 1.36 higher, 95%CI 0.32 to 2.40 higher). RCTs did not report other critical, or important outcomes or there were too few events.

Tonsillectomy
• The addition of tonsillectomy to standard of care may increase the remission of proteinuria (RR 1.90, 95%CI 1.45 to 2.47) compared to standard of care alone. It may also increase the remission of microscopic hematuria (RR 1.93 95%CI 1.47 to 2.53) (2 studies, 143 participants). Tonsillectomy may also decrease relapse of proteinuria and hematuria. These trials have only been conducted in patients of Asian ethnicity, and hence the generalizability of these findings are unclear.
  o RCTs did not examine other critical or important outcomes.

Herbal medicine
• Treatment with Huai Qi Huang compared to no treatment may increase remission of proteinuria (RR 2.35, 95%CI 1.30 to 4.26; 1 study, 45 participants). There were uncertain effects on the remission of hematuria and other critical and important outcomes were not examined.
• Traditional Chinese medicine compared to western medicine had uncertain effects on critical and important outcomes because the certainty of the evidence was very low due to study limitations and imprecise effect estimates.

Effect modifiers
The following effect modifiers were considered
  • Kidney function (GFR, proteinuria, the presence of albuminuria, the presence of macroscopic hematuria)
  • Histopathological class of disease
  • Relapse
  • Primary versus secondary forms of the disease
  • Age (adult versus pediatric)

However, because of a lack of data, subgroup analyses were not possible.

Immunosuppressive therapy of IgA nephropathy

PICO question
In patients with biopsy-proven IgA nephropathy, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapies 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 IgA 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 immunosuppressive treatment Cochrane review published in 2011, identified 1196 relevant citations from relevant medical databases, 1159 citations were excluded because they were not RCTs, did not include patients with biopsy-proven IgA nephropathy, had less than 75% of patients with IgA nephropathy in the trial, or were the wrong intervention. The review identified 13 primary studies (21 reports). The 2015 Cochrane review update identified 103 relevant reports from the Cochrane Kidney and Transplant Specialized Register, 19 primary studies (41 reports) were included.
The May 2018 search update for the Cochrane Kidney and Transplant Specialized Register identified 68 reports, seven were excluded because they were duplicates, not RCTs, did not include patients with biopsy-proven IgA nephropathy, had less than 75% of patients with IgA nephropathy in the trial, or were the wrong intervention. The 2018 review update found 22 primary studies (46 reports), four reports of studies already included in the previous Cochrane review, and ten reports of ongoing studies.

Overall 53 primary studies (132 reports) with 3690 participants were included. There were ten ongoing studies identified from clinicaltrials.gov

Twenty comparisons for induction therapy were included for the following:

1. Steroids (oral, oral + IV, oral + RASi) versus no steroid regimen (placebo/no treatment, usual care) (13 studies, 1110 participants)
2. Steroids plus non-immunosuppressive (RAS, RAS + tonsillectomy) versus steroid (2 studies, 117 participants)
3. Cyclophosphamide then azathioprine plus steroid versus usual care (2 studies, 200 participants)
4. Cyclophosphamide plus steroid versus steroid alone (1 study, 24 participants)
5. Cyclophosphamide plus antiplatelet/anticoagulant versus usual care (3 studies, 178 participants)
6. Azathioprine plus steroids versus placebo/usual care (1 study, 43 participants)
7. Azathioprine plus steroids versus steroids alone (2 studies, 68 participants)
8. Azathioprine plus anticoagulant/antiplatelet versus anticoagulant/antiplatelet (1 study, 78 participants)
9. Calcineurin inhibitors plus steroids versus steroid alone (1 study, 51 participants)
10. Cyclosporin versus placebo/usual care (1 study, 22 participants)
11. Mycophenolate mofetil versus placebo/usual care (3 studies, 118 participants)
12. Mycophenolate mofetil plus steroids versus steroid alone (1 study, 176 participants)
13. Mycophenolate mofetil plus RASi versus RASi alone (1 study, 40 participants)
14. Mizoribine versus placebo/usual care (1 study, 42 participants)
15. Mizoribine plus steroid versus steroid alone (1 study, 40 participants)
16. Mizoribine plus RASi versus RASi alone (1 study, 99 participants)
17. Leflunomide versus placebo (1 study, 360 participants)
18. Leflunomide plus steroid versus steroid alone (2 studies, 85 participants)
19. Leflunomide plus low dose steroid versus high dose steroid alone (2 studies, 192 participants)
20. Leflunomide versus RASi alone (1 study, 49 participants)

Summary of the main findings

Steroid versus no steroid regimen

- Compared to no steroid regimen, treatment with steroids probably decreased end-stage kidney disease (RR 0.41, 95%CI 0.26 to 0.65; 10 studies, 825 participants) and annual GFR loss (ml/min) (MD 5.40 lower, 95%CI 2.25 lower to 8.55 lower; 2 studies, 359 participants). Also, steroid treatment compared with no steroid treatment may increase complete remission (RR 1.76, 95%CI 1.03 to 3.01). The effects on other critical and important outcomes are unclear because studies did not examine these outcomes or due to study limitations or imprecision in the effect estimate.
  - The protective effects of steroid use on end-stage kidney disease are seen in the use of oral steroids compared to placebo/usual care (RR 0.48, 95%CI 0.29 to 0.79; 7 studies,
579 participants) and steroid plus RASi compared with RASi alone (RR 0.16, 95%CI 0.04 to 0.59; 2 studies, 160 participants).

- An increase in complete remission was not observed in the comparison of oral steroid with placebo or usual care or steroid plus RASi versus RASi alone. Although, it may decrease annual GFR loss.
- The use of oral steroids compared with placebo / usual care may decrease doubling serum creatinine (RR 0.45, 95%CI 0.29 to 0.69; 6 studies, 341 participants).
- Only one study examined the use of oral plus IV steroids compared to no treatment, and the effects were uncertain because studies did not examine critical or important outcomes or due to study limitations and imprecision.

Cytotoxic regimens versus non-cytotoxic regimens

Cyclophosphamide

- The use of cyclophosphamide then azathioprine plus corticosteroids versus supportive therapy may make no difference on end-stage kidney disease or annual loss of GFR, although it increases complete remission (RR 3.41, 95%CI 1.17 to 9.93; 1 study, 162 participants). The effect on other critical and important outcomes are unclear because either RCTs did not look at these outcomes or due to imprecision in the effect estimate and study limitations.
  - Treatment with cyclophosphamide plus steroid compared to steroids alone made no difference to complete remission and we are uncertain about the other critical and important outcomes because the certainty of the evidence was very low.
  - Treatment with cyclophosphamide plus antiplatelet/anticoagulant compared to usual care made no difference to end-stage kidney disease and we are uncertain about the other critical and important outcomes because the certainty of the evidence was very low.

Azathioprine

- The use of azathioprine combined with steroids compared to placebo or usual care increases complete remission (RR 5.94, 95%CI 2.03 to 17.34; 1 study, 43 participants) but we are uncertain of the effects on other critical and important outcomes as RCTs did not examine these outcomes or due to study limitations or two few events.
  - Azathioprine plus steroids plus anticoagulant/antiplatelet therapy compared to anticoagulant/antiplatelet alone may have little or no difference to end-stage kidney disease or complete remission. However, compared to steroids alone it probably increases complete remission (RR 1.24, 95%CI 1.01 to 1.52; 1 study, 78 participants). The effects on other outcomes are unclear because the certainty of the evidence is so low.

Calcineurin inhibitors

- Calcineurin inhibitors plus steroids compared with steroids alone may make little or no difference to complete remission (RR 0.91, 95%CI 0.60 to 1.39; 2 studies, 72 participants). The effects on other critical and important outcomes are unclear because the certainty of the evidence is very low due to study limitations and imprecision in the effect estimates.

Mycophenolate mofetil

- Mycophenolate mofetil with or without steroids compared to either steroid or usual care has only been examined in a few small studies and the effects on critical and important outcomes are mostly uncertain.
  - Mycophenolate mofetil plus steroids compared with steroids alone may have little or no difference on infection (RR 1.37, 95%CI 0.83 to 2.24; 1 study. 175 participants) and complete remission (RR 0.99, 95%CI 0.68 to 1.46; 1 study, 174 participants).
• Mycophenolate mofetil plus a RASi compared with a RASi alone may decrease end-stage kidney disease (RR 0.22, 95%CI 0.05 to 0.90; 1 study, 40 participants) but the effects on other outcomes are uncertain as other critical and important outcomes were not examined.

Other immunosuppressive agents

• The effects of a mizoribine regimen compared with no mizoribine on critical and important outcomes are uncertain because there have only been a few small RCTs.
• The effects of leflunomide with or without low dose steroids compared to a non-leflunomide regimen are uncertain due to study limitations and imprecision in the effect estimates. Many critical and important outcomes were not examined in these RCTs.

Effect modifiers

The following table lists the effect modifiers considered for comparisons. Only one comparison, steroid versus no steroid had sufficient data (13 trials, 1110 participants).

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<tr>
<th>Effect modifier</th>
<th>Explanation/ results</th>
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| Kidney function (GFR, presence of proteinuria, presence of albuminuria) | Subgroups determined by kidney function were not examined in many of the RCTs. However the TESTING 2017 (1) study had pre-specified subgroups for composite outcome (≥40% GFR loss, ESKD, death due to kidney failure):  
  • Proteinuria - <3.0 g/day proteinuria (RR 0.2 95%CI 0.05 to 0.9); ≥3.0 g/day proteinuria (RR 0.4, 95%CI 0.17 to 0.97)  
  • Baseline eGFR – <50 ml/min/1.73m² (RR 0.60, 95%CI 0.25 to 1.40); ≥50 ml/min/1.73m² (RR 0.12, 95%CI 0.02 to 0.97) |
| Relapse or resistant disease                         | RCTs did not examine the treatment of patients with relapsing or resistant IgA nephropathy.                                                             |
| Histopathological class of disease                   | RCTs did not examine results in regards to the class of IgA nephropathy.                                                                                |
| Gender                                               | The RCTs similarly included around 65% of male.                                                                                                       |
| Age (adult vs. pediatric)                            | One trial Kobayashi 1996 (2), included children <15 years of age. Similar results to the overall effect estimate (included both adults and children) were reported. That treatment with steroids (oral) decreased ESKD and doubling serum creatinine compared to placebo or usual care. |

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

Non-immunosuppressive therapy

All RCTs included in the previous guideline evidence summary have been included in this evidence review, except for Walker RG et al 1990 (1) as this has been covered included in the immunosuppressive treatment for IgA nephropathy review.


Immunosuppressive therapy

Steroid versus no steroid regimen

1. Pozzi 2004 – Long-term follow-up study of Pozzi 1999 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.


2. Manno 2009 - Long-term follow-up study of Manno 2001 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.

Manno C et al. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. NDT. 2009;24(12):3694-701