**KDIGO GN Guideline update – Evidence summary**

**Infection-related glomerulonephritis**

**Immunosuppressive therapy of hepatitis B or C related glomerulonephritis**

**PICO question**
In adult patients with hepatitis B or C related glomerulonephritis, what antiviral treatment therapy compared to no treatment/placebo or standard of care improves efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduces adverse effects (infection, and malignancy)?

**Search strategy and selection**
The Cochrane Kidney and Transplant Specialized Register was searched for all randomized control trials (RCTs) examining hepatitis B and C infection-related glomerulonephritis and antiviral therapy, published up to June 2018.

**Search results**
The June 2018 search identified 33 relevant citations, 32 of these were excluded because they were not RCTs, or did not include participants with hepatitis related glomerulonephritis, or not on antiviral therapy. There were no studies found regarding hepatitis B infection-related glomerulonephritis. one RCTs found on antiviral therapy in patients with hepatitis C infection-related glomerulonephritis, and two RCTs in patients with severe cryoglobulinemic vasculitis either HCV related or unrelated.

**Summary of the main findings**

**Hepatitis B infection-related glomerulonephritis**
- No RCT were identified

**Hepatitis C infection-related glomerulonephritis**

**PICO 17.1 – Interferon therapy versus prednisone** (1 study, 13 participants)
- Critical and important outcomes (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, infection malignancy, annual loss of GFR) were not reported in RCTs or there were too few who experienced events to be certain of the effect (complete remission).
- Interferon therapy compared with prednisone probably decreases liver function (ALT (U/I)) after 6 months of therapy. (MD 33 lower, 95%CI 58.5 lower to 7.5 lower) and at 18 months of therapy (MD 25 lower, 95%CI 49.39 lower to 0.61 lower).
- Interferon therapy compared with prednisone may have little or no effect on kidney function (serum creatinine after 6 months of therapy (MD 0.30 lower, 95%CI 0.97 lower to 0.37 higher), and at 18 months of therapy (MD 0.20 higher, 95%CI 1.21 lower to 1.61 higher); daily proteinuria after 6 months of therapy (MD 0.0, 95%CI 1.10 lower to 1.61 higher) and after 18 months (MD 0.0, 95%CI 1.75 lower to 1.75 higher).

**PICO 17.2 – Patients with severe cryoglobulinemic vasculitis either HCV-related and HCV unrelated**
- Rituximab versus standard of care (1 study, 59 participants)
• Compared to standard of care, it is not clear if rituximab improved or worsen critical and important outcomes (all-cause mortality, infection, cardiovascular events, treatment survival) because of very low certainty in the evidence (study limitations, very serious imprecision, due to serious indirectness).

**PICO 17.3 - Patients with HCV-related cryoglobulinemic vasculitis that have failed treatment with interferon-alpha and ribavirin – Rituximab versus standard of care (1 study, 24 participants)**

• In patients that failed treatment with interferon-alpha and ribavirin, the use of rituximab compared to standard of care may increase complete remission (RR 55, 95%CI 4.3, 703.43) (low certainty of the evidence) and probably decreases GFR decline (RR 0.01, 95%CI 0.00, 0.77) (moderate certainty of the evidence).
**Immunosuppressive therapy of HIV associated nephropathy**

**PICO question**
In patients with HIV-associated nephropathy, what antiretroviral treatment (HAART alone or combined with antihypertensive agents, corticosteroids and immunosuppressive therapies) compared to no treatment/placebo or standard of care improves 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**
Medline, EMBASE, Central, and AIDSEARCH and the Cochrane renal register were searched in 2009. The Cochrane Kidney and Transplant Specialized Register was searched for all randomized control trials (RCTs) examining anti-viral therapy, published up to May 2018.

**Search results**
The 2009 search of Medline, EMBASE, Central, AIDSEARCH and the Cochrane renal register found 893 studies. A total of 878 studies were excluded due to being the wrong population or intervention or for not being a RCT or Quasi-RCT, and from the remaining 15 studies, four were eligible. Out of these four studies, two were ongoing and two were suspended and therefore excluded. There was updated searched in 2018 found one additional study by Abgrall, 2015, this was also excluded because it was the wrong intervention. The previous two on-going studies (NCT00000819 – completed in 1996; NCT00089518 – completed in 2005) identified in the 2009 search have been completed according to clinical trials.gov but have not been published and therefore have been included as studies awaiting classification.

**Summary of the main findings**
No studies were found

**Effect modifiers**
The following effect modifiers were considered:
- Kidney function (GFR, proteinuria, presence of albuminuria)
- Gender
- Age (adults vs. pediatrics)
- Presence of cryoglobulinemia in patients with hepatitis C

There was insufficient data to allow for the assessment of effect modifiers.

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

No studies were identified for the infection-related glomerulonephritis chapter for the 2012 KDIGO GN guideline.
KDIGO Glomerulonephritis guideline update – Evidence review team response – work group comments

Hepatitis C related-glomerulonephritis

1. The Evidence Review team missed several RCT in HCV related GN. This may not be a problem as we plan to use the KDIGO-HCV-CPG (2018) as the CPG for this section. But for completeness sake the Evidence Review Team should conduct a Review of the following RCTs and large open label cohort studies:

The following randomized controlled trial (RCT) and long-term following study of this RCT included patients with type II cryoglobulins both HCV-related or unrelated, and not all patients had nephropathy. As a result, the review original evidence review did not include these studies. However, we have updated the evidence review to include this study.

The De Vita study (59 participants) is examined in MAGICapp PICO 17.2 Patients with severe cryoglobulinemic vasculitis either HCV-related or HCV-unrelated rituximab versus standard of care. Highlights that rituximab may decrease the number of patients that remain on treatment compared to patients treated with standard immunosuppressive therapy at 12 months (RR 47.45, 95%CI 5.64, 399.29, 1 study, 59 participants) and 24 months (RR 41.08, 95%CI 4.90, 344.34), and other little or no difference between other outcomes all-cause mortality, infection, and cardiovascular events. However, the certainty of this evidence has been graded as very low, as this is the only RCT examining rituximab versus standard of care in this population and because of study limitations, with the trial being stopped early which may overestimate the effects of the therapy, although, the trial was stopped early because the increased efficacy of the rituximab treatment compared to standard of care. Also, this evidence could be considered indirect because 29% of participants had nephritis, and the data is not reported separately for participants with nephritis.

The long-term follow-up study (Quartuccio et al. 2015) only reported data on the standard of care arm, which had been switch over to rituximab therapy because of relapse, so data could not be meta-analysed. However, this study found in 57% of participants retreated with rituximab achieved complete disease remission, and 24% achieved partial response to therapy. This study has been included in the reference list in the Infection-related Glomerulonephritis chapter in MAGICapp and can be referred to in the chain of logic.
The above study (Sneller study (24 participants)) included patients with HCV-related cryoglobulinemic vasculitis who had failed treatment with interferon-alpha and ribavirin. Only 67% of patients in this study had nephritis. PICO 17.3 has been included in MAGICapp to demonstrate that treatment with rituximab compared to standard of care in this population may increase complete remission at 6 months (RR 55.00, 95%CI 4.30, 703.43) but its effect on relapse and infection are unclear because the certainty of evidence is very low (due to indirectness – not all patients having nephritis, and very serious imprecision with confidence intervals that indicate both appreciable benefit and harm). However, in patients with nephritis, rituximab compared to standard of care probably decreases a decline in GFR (RR 0.01, 95%CI 0.00, 0.77; 1 study, 8 participants). This outcome was not quantified or defined in the study.

We have only included randomized controlled trials (RCTs) and hence the observational studies listed below were not included in the evidence review. However, we have added the following studies in the reference list on MAGICapp and can be referred to in the rationale for guideline recommendations.


Hepatitis B related-glomerulonephritis

2. We will be referring to the European Association for Liver Disease published CPG (2017) on Hepatitis B viral infection related kidney disease in our Chain of Logic - but neither this CPG or my own review has identified ant RCT germane to this topic.

Great, thank you for reviewing the evidence.

Bacterial, helminthic, protozoal and fungal related glomerulonephritis

3. I can confirm the absence of any published RCT in bacterial, helminthic, protozoal and fungal related GN.

Great, thank you for reviewing the evidence.

HIV-associated nephropathy

4. No additional RCT in HIV associated GN have been identified

Great, thank you for reviewing the evidence.
## PICO Evidence Tables

**PICO (17.1)**  
Population: Patients with hepatitis C associated glomerulonephritis  
Intervention: Interferon therapy  
Comparator: Prednisone

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at end-stage kidney disease</td>
</tr>
<tr>
<td>≥50% GFR loss</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at ≥50% GFR loss</td>
</tr>
<tr>
<td>Infection</td>
<td>(CI 95% - )</td>
<td>Difference: fewer</td>
<td></td>
<td>No studies were found that looked at infection</td>
</tr>
<tr>
<td>Measure</td>
<td>Description</td>
<td>Difference</td>
<td>Evidence Quality</td>
<td>Risk of Bias/Imprecision</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Complete remission was measured in 13 patients from 1 studies. Follow up 18 months</td>
<td>fewer per 1000</td>
<td>Very Low</td>
<td>Due to serious risk of bias, Due to very serious imprecision</td>
</tr>
<tr>
<td>Daily proteinuria (g/day) End of therapy (6 months)</td>
<td>Daily proteinuria was measured in 13 patients from 1 studies. Follow up 18 months</td>
<td>Mean</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
</tr>
<tr>
<td>Daily proteinuria (g/day) End of follow-up (18 months)</td>
<td>Daily proteinuria was measured in 13 patients from 1 studies. Follow up 18 months</td>
<td>Mean</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
</tr>
<tr>
<td>Liver function (ALT) (U/I) End of therapy (6 months)</td>
<td>Liver function was measured in 13 patients from 1 studies. Follow up 18 months</td>
<td>Mean</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
</tr>
<tr>
<td>Liver function (ALT) (U/I) End of follow-up (18 months)</td>
<td>Liver function was measured in 13 patients from 1 studies. Follow up 18 months</td>
<td>Mean</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
</tr>
<tr>
<td>Annual GFR loss 3 years</td>
<td>Annual GFR loss was measured over 3 years.</td>
<td>null lower</td>
<td>Low</td>
<td>Due to serious imprecision, Due to serious risk of bias</td>
</tr>
</tbody>
</table>
### Serum creatinine

| End of therapy (6 months) | Measured by: mg/dL  
Scale: - Lower better  
Based on data from 13 patients in 1 studies  
Follow up 18 months | Mean | Mean  
Difference: MD 0.30 lower  
(CI 95% 0.97 lower - 0.37 higher) | Low  
Due to serious risk of bias, Due to serious imprecision  
IFN compared with prednisone may have little or no difference on serum creatinine after 6 months of therapy |
|---|---|---|---|
| End of follow-up (18 months) | Measured by: mg/dL  
Scale: - Lower better  
Based on data from 13 patients in 1 studies  
Follow up 18 months | Mean | Mean  
Difference: MD 0.20 higher  
(CI 95% 1.21 lower - 1.61 higher) | Low  
Due to serious risk of bias, Due to serious imprecision  
IFN compared with prednisone may have little or no difference on serum creatinine after 18 months |

1. Systematic review with included studies: [240] **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, Incomplete data and/or large loss to follow up, Selective outcome reporting; **Imprecision:** Very Serious. Only data from one study, Low number of patients;  
3. Systematic review with included studies: [240] **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;  
5. Systematic review with included studies: [240] **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;  
7. Systematic review with included studies: [240] **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;  
9. Systematic review with included studies: [240] **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;  
11. Systematic review with included studies: [240] **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;  
13. Primary study [240] **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up; **Imprecision:** Serious. Only data from one study, Low number of patients;

### References

### PICO (17.2)

**Population:** Patients with severe cryoglobulinemic vasculitis either HCV-related or HCV-unrelated  
**Intervention:** Rituximab  
**Comparator:** Standard of care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
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</table>
| **All-cause mortality** | Relative risk: 0.52  
(CI 95% 0.1 - 2.61)  
Based on data from 59 patients in 1 study1  
Follow up 24 months | 133 per 1000  
69 per 1000  
Difference: **64 fewer per 1000**  
(CI 95% 120 fewer - 214 more) | **Very Low**  
Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision2 | We are uncertain whether rituximab increases or decreases all-cause mortality |
| **≥50% GFR loss** | (CI 95% - -) |  |  | No studies were found that looked at ≥50% GFR loss |
| **Infection** | Relative risk: 0.5  
(CI 95% 0.04 - 5.83)  
Based on data from 59 patients in 1 study1  
Follow up 24 months | 67 per 1000  
34 per 1000  
Difference: **33 fewer per 1000**  
(CI 95% 64 fewer - 324 more) | **Very Low**  
Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision2 | We are uncertain whether rituximab increases or decreases infection |
| **Malignancy** | (CI 95% - -) |  |  | No studies were found that looked at malignancy |
| **Cardiovascular events** | Relative risk: 0.48  
(CI 95% 0.08 - 2.86)  
Based on data from 59 patients in 1 study1  
Follow up 24 months | 33 per 1000  
16 per 1000  
Difference: **17 fewer per 1000**  
(CI 95% 50 fewer - 214 more) | **Very Low**  
Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision2 | We are uncertain whether rituximab increases or decreases cardiovascular events |
| **End-stage kidney disease** | (CI 95% - -) |  |  | No studies were found that looked at end-stage kidney disease |
Complete remission

Difference: fewer

No studies were found that looked at complete remission

Treatment survival 12 months

Relative risk: 47.45
(CI 95% 3.64 - 399.29)
Based on data from 59 patients in 1 studies’
Follow up 12 months

33 per 1000

Difference: 1533 more per 1000
(CI 95% 153 more - 13144 more)

Very Low
Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision

We are uncertain whether rituximab increases or decreases treatment survival at 12 months

Annual loss of GFR

Measured by:
Scale: - Lower better

Difference: null lower

No studies were found that looked at annual loss of GFR

15. Systematic review with included studies: [244] Baseline/comparator: Control arm of reference used for intervention.
16. 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 overestimating benefit; Indirectness: Serious. Differences between the population of interest and those studied - not all participants had nephropathy; Imprecision: Very Serious. Wide confidence intervals, Only data from one study, Only data from one study, Only data from one study, Low number of patients;
17. Systematic review with included studies: [244] Baseline/comparator: Control arm of reference used for intervention.
18. 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 overestimating benefit; Indirectness: Serious. Differences between the population of interest and those studied - not all participants had nephropathy; Imprecision: Very Serious. Only data from one study, Low number of patients;
19. Systematic review with included studies: [244] Baseline/comparator: Control arm of reference used for intervention.
20. 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 overestimating benefit; Indirectness: Serious. Differences between the population of interest and those studied - not all participants had nephropathy; Imprecision: Very Serious. Only data from one study, Low number of patients;
22. 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 overestimating benefit; Indirectness: Serious. Differences between the population of interest and those studied - not all participants had nephropathy; Imprecision: Very Serious. Only data from one study, Low number of patients;

References
**PICO (17.3)**  
Population: Patients with HCV-related cryoglobulinemic vasculitis that have failed treatment with interferon-alpha and ribavirin  
Intervention: Rituximab  
Comparator: Standard of care

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<td></td>
<td>No studies were found that looked at ≥50% GFR loss</td>
</tr>
</tbody>
</table>
| Infection | Relative risk: 0.0  
(CI 95% 0.0 - 0.0)  
Based on data from 24 patients in 1 studies  
Follow up 12 months | per 1000 | per 1000 | Difference: fewer per 1000 | There were too few who experienced the infection, to determine whether rituximab made a difference |
| Malignancy | (CI 95% - ) | Difference: fewer | | No studies were found that looked at malignancy |
| Complete remission 6 months | Relative risk: 55.0  
(CI 95% 4.3 - 703.43) | 83 per 1000 | 4565 per 1000 | Low  
Due to serious imprecision, Due to | Rituximab may increase complete remission at 6 months |
Based on data from 24 patients in 1 studies
Follow up 12 months
Difference: 4482 more per 1000
(CI 95% 274 more - 58302 more)
serious indirectness

Relapse
Relative risk: 1.4
(CI 95% 0.04 - 43.79)
Follow up 12 months
0 per 1000
0 per 1000
Difference: 0 fewer per 1000
(CI 95% 0 fewer - 0 fewer)
Very Low
Due to serious indirectness, Due to very serious imprecision
We are uncertain whether rituximab increases or decreases relapse

Adverse events
Relative risk: 3.26
(CI 95% 0.12 - 88.35)
Follow up 12 months
0 per 1000
0 per 1000
Difference: fewer per 1000
Very Low
Due to serious indirectness, Due to very serious imprecision
We are uncertain whether rituximab increases or decreases adverse events

GFR decline
Relative risk: 0.01
(CI 95% 0.01 - 0.77)
Follow up 12 months
1000 per 1000
10 per 1000
Difference: 990 fewer per 1000
(CI 95% 990 fewer - 230 fewer)
Moderate
Due to serious imprecision
Rituximab probably decreases the number of patients who experience a decline in GFR

Annual GFR loss
Measured by:
Scale: - Lower better
Difference: null lower
No studies were found that looked at annual GFR loss

References