KDIGO 2021 Guidelines for Treatment of Glomerular Diseases

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George Institute for Global Health
KDIGO GN guidelines

2012 KDIGO guideline document on GNs

2017 Controversies conference on GNs (Singapore)
Published 2018
**Key Question:** Which of the 2012 Glomerular Disease Guideline Recommendations Need Revision?
## Timeline of Guideline for Management of GD

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Controversies Conference</td>
<td>Nov 17</td>
</tr>
<tr>
<td>2017</td>
<td>Meeting 0</td>
<td>Feb 13</td>
</tr>
<tr>
<td>2017</td>
<td>WG Meeting 1</td>
<td>Aug 29</td>
</tr>
<tr>
<td>2017</td>
<td>WG Meeting 2</td>
<td>Jun 18</td>
</tr>
<tr>
<td>2018</td>
<td>Evidence review</td>
<td>Mar 1 - Oct 31</td>
</tr>
<tr>
<td>2018</td>
<td>Guideline draft</td>
<td>Aug 19 - May 15</td>
</tr>
<tr>
<td>2019</td>
<td>Public Review of guideline</td>
<td>Jun 1 - Jul 15</td>
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<tr>
<td>2019</td>
<td>Updated evidence review</td>
<td>Jun 1 - Sep 30</td>
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<tr>
<td>2020</td>
<td>Guideline revision</td>
<td>Aug 1 - Feb 28</td>
</tr>
<tr>
<td>2021</td>
<td>Online publication</td>
<td>Sep 20</td>
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<tr>
<td>2021</td>
<td>Print publication</td>
<td>Oct 1</td>
</tr>
<tr>
<td>2022</td>
<td>Journal submission</td>
<td>Mar 14</td>
</tr>
<tr>
<td>2022</td>
<td>Guideline update kick-off</td>
<td>Feb 15</td>
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</table>
WORK GROUP
WHAT IS NEW SINCE THE 2012 KDIGO GUIDELINE

• General principles chapter discusses supportive therapies appropriate for all GD that supplement the more specific immunosuppressive treatments for each disease.

• Membranous nephropathy chapter now provides an in-depth discussion of monitoring pathogenic autoantibodies in disease management.

• MPGN chapter was replaced with a new chapter entitled *Immunoglobulin- and complement-mediated glomerular diseases with an MPGN pattern of injury*.

• ANCA-associated vasculitis chapter compares and contrasts B cell–targeted therapies with traditional cytotoxic drugs.

• FSGS chapter has been reorganized to help clinicians more accurately differentiate between FSGS mediated by a soluble factor that may be amenable to immunosuppression, and conditions with FSGS-like histology, for which immunosuppression should not be used.

• Chapter on nephrotic syndrome in children takes advantage of several new trials that have defined duration of immunosuppression, and has been written to closely align with the International Pediatric Nephrology Association (IPNA) guideline.
GUIDELINE FORMAT

• KDIGO guidelines continue to use the Grading of Recommendations Assessment, Development, Evaluation (GRADE) methodology, but we have strengthened the link between the recommendation statements and underlying evidence base.

• Guidelines now include a mix of recommendations and “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group.

• All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

• Practice points are a new addition to KDIGO guidance, and may be formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.
GUIDELINE FORMAT

How should I use practice points when caring for my patients?

- Practice points are consensus statements about a specific aspect of care and supplement recommendations for which a systematic review was conducted.
- Note that practice points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, practice points are not graded for strength of recommendation or quality of the evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.
GENERAL MANAGEMENT

• Kidney biopsy remains the cornerstone + likely to expand significantly in the near-term
• need for electron microscopy for every biopsy remains controversial

• ACR and PCR helpful in general clinical management
• not sufficiently accurate for therapeut. decisions when using high-risk medications

• eGFR equations not validated in specific glomerular diseases and patient populations
**General Management**

- **Patient engagement** in determining clinical trial eligibility
- Patient-related outcomes and measurements rapidly evolving

- **Newer determinants of progression**: prematurity, sleep disturbances, obesity, genetics

- **Hypertension + proteinuria**: important
- **Uncertain**: aldosterone or SGLT2 blockers; PCSK9 inhibitors and NOAC in nephrotic pts.
- **Multidisciplinary support, infection control**
- **Role of prophylactic anticoagulation discussed**
OVERVIEW OF GENERAL MANAGEMENT

Lifestyle modifications:
- Sodium restriction
- Moderate protein restriction
- Heart-healthy diet
- Target ideal body weight
- Increased physical activity
- Smoking cessation
- Reduce alcohol consumption

Renin-angiotensin-aldosterone system inhibitors
- Diuretics
- Non-renin-angiotensin-aldosterone system blockade (e.g., calcium channel blockers)

Other considerations:
- Anticoagulation
- Contraception
- Immunizations
- Management of cardiovascular risk factors

Supportive GN treatment

Disease-specific therapy

Infection screen (prior to treatment):
- Tuberculosis
- Hepatitis B
- Hepatitis C
- Human immunodeficiency virus
- Strongyloides (geography-specific)

Immunosuppression:
- Glucocorticoids
- Calcineurin inhibitors
- Mycophenolic acid/mycophenolate mofetil/azathioprine
- Mammalian target of rapamycin inhibitors
- Cyclophosphamide
- B-cell depleting agents
- Plasmapheresis/low-density lipoprotein apheresis

Chemoprophylaxis:
- Trimethoprim-sulfamethoxazole
- Histamine 2 receptor blockers/proton pump inhibitors
- Bisphosphonates
- Gonadal protection
Some specific glomerulonephritides
**IGA-Nephropathy**

[Image of pathological features of IgA nephropathy, including glomerular changes.]
Management of patients at risk of progressive disease

- Proteinuria >1 g/d despite at least 3 months of optimized supportive care:
  - BP management
  - Maximally tolerated dose of ACEI/ARB
  - Lifestyle modification
  - Address cardiovascular risk

- Not applicable to variant forms of IgA:
  - IgA deposition with minimal change disease
  - IgAN with acute kidney injury
  - IgAN with a rapidly progressive glomerulonephritis

- Consider enrollment in a clinical trial

- eGFR <30 ml/min/1.73 m²
  - Toxicity risk stratification:
    - Advanced age
    - Metabolic syndrome
    - Obesity
    - Latent infection (TB, HIV, HBV, HCV)

- eGFR ≥30 ml/min/1.73 m²
  - Consider maximal supportive care
  - Risk/benefit profile of glucocorticoids should be individually discussed

- Not applicable to:
  - IgA vasculitis
  - IgA nephropathy secondary to:
    - Viral (HIV, hepatitis)
    - Inflammatory bowel disease
    - Autoimmune disease
    - Cirrhosis
  - IgA-dominant postinfectious GN

- Specific populations:
  - Japanese – consider tonsillectomy
  - Chinese – consider mycophenolate mofetil as a glucocorticoid-sparing agent
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Catrnan, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group
A) Primary outcome in all patients

B) Kidney failure requiring dialysis or transplant

C) Primary outcome in full-dose cohort

D) Primary outcome in reduced-dose cohort
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators
MEMBRANOUS NEPHROPATHY - DIAGNOSIS

Practice Point 3.1.1: A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive antiPLA2R antibody test.
Risk-based initial treatment of MN

Risk evaluation*
Thromboembolic event
Proteinuria: duration, magnitude
eGFR
Urinary LMWP
Anti-PLA2R

LOW
Wait and see

MODERATE
Wait and see
Rituximab
CNI

HIGH
Rituximab
CP+Steroids
CNI+Ritux

VERY HIGH
CP+Steroids
High dose
Rituximab?

*at BL, 1 and 3 mo

Wait and see down to 1-3 mo in very high risk

Wetzels J, Ronco P, Jha V. KIS Sep 2021
Simplified 2021 KDIGO algorithm for monitoring:
Adjust treatment according to aPLA2R trajectory

Measure aPLA2R at 6 mo

- **Absent***
  - Ritux – Stop
  - CP+Pred – Stop
  - CNI - taper

- **Decreased (<50 RU/ml)**
  - Ritux – continue w/2 G
  - CP+Pred – Stop, watch
  - CNI – continue x 6 mo

- **High**
  - Ritux – reinfuse 2 g
  - CP+Pred – Stop, add Ritux
  - CNI – taper, add Ritux/CP

*Some centers will measure at 3 mo and stop
Response at 3 mo in most cases

Wetzels J, Ronco P, Jha V. KIS Sep 2021
MINIMAL CHANGE NEPHROPATHY

FOCAL SEGMENTAL GLOMERULO-SCLEROSIS

Parietal cell activation
**Minimal Change GN & FSGS**

- “Steroid sensitive” and “steroid-resistant NS” should remain
- Term “primary/idiopathic FSGS” may require revision.
- **Genetic testing:** patients with congenital/infantile forms of nephrotic syndrome, syndromic features, familial forms
- **Children:** Steroids first in all nephrotic pts; need for a global definition of “steroid resistance,” precise order of CYC, MMF, CNI and rituximab not well determined.
- **Adults:** minimum 16 weeks of high-dose steroids as first-line therapy for FSGS or MCD controversial. Several studies indicate that > 8-12 weeks steroids does not reduce relapse. CNIs or CYC second-line agents in adults with MCD. RTX emerging second-line therapy in MCD. CNIs and MMF second- and third-line treatments, resp., for FSGS.
MCD IN ADULTS - TREATMENT

Recommendation 5.3.1: We recommend high-dose oral glucocorticoids for initial treatment of MCD (1C).

Practice Point 5.3.1: Algorithm for the initial treatment of MCD in adults

Practice Point 5.3.2: High-dose glucocorticoid treatment for MCD should be given for no longer than 16 weeks.
FSGS IN ADULTS - CLASSIFICATION

FSGS lesions on light microscopy

- Primary FSGS
  - FSGS with diffuse foot process effacement and nephrotic syndrome (often sudden onset, amenable to therapy)

- Genetic FSGS
  - Familial
  - Syndromic
  - Sporadic

- Secondary FSGS
  - Viral
  - Drug-induced
  - Adaptive changes to glomerular hyperfiltration (normal or reduced nephron mass; segmental foot process effacement; proteinuria without nephrotic syndrome)

- FSGS of undetermined cause (FSGS–UC)
  - Segmental foot process effacement
  - Proteinuria without nephrotic syndrome
  - No evidence of secondary cause
LUPUS ERYTHEMATOSUS
**Lupus Nephritis**

<table>
<thead>
<tr>
<th>ISN/RPS classification</th>
<th>• does not consider tubulointerstitial injury, vascular lesions, or podocytopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing</td>
<td>• no clear clinical benefits</td>
</tr>
<tr>
<td></td>
<td>• risks &amp; benefits of <em>APOL1</em> testing to be clarified</td>
</tr>
<tr>
<td>Repeat renal biopsy</td>
<td>• patients with clinical remission can still have histologic activity and vice versa</td>
</tr>
<tr>
<td>Prediction &amp; Monitoring</td>
<td>• proteinuria at 1 year best predictor of long term renal outcome</td>
</tr>
<tr>
<td></td>
<td>• biomarker panels will be required to accurately stratify risk, predict flare, determine + monitor treatment, and predict prognosis</td>
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# Lupus Nephritis

<table>
<thead>
<tr>
<th><strong>Antimalarials</strong></th>
<th>• recommended for all patients with LN</th>
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</thead>
</table>
| **Corticosteroids** | • use at lowest possible dose during maintenance  
|                    | • Low/zero-steroids protocols under investigation |
| **CYC-/MMF-regimens** | • remain the gold standard therapy for remission induction |
| **Calcineurin-inhibitors** | • Ongoing studies address role and toxicity in ethnically diverse populations |
| **Maintenance Therapy** | • minimum of 3 years, prolonged B-cell depletion with a RTX plus CYC may reduce the duration  
|                        | • A repeat kidney biopsy may be helpful |
Lupus Nephritis — Treatment: Class III or Class IV LN: Initial Therapy

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or MPAA (1B).
Practice Point 10.2.4.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in the figure.

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>Verify adherence to treatment</td>
</tr>
<tr>
<td>2</td>
<td>Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)</td>
</tr>
<tr>
<td>3</td>
<td>Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)</td>
</tr>
<tr>
<td>4</td>
<td>Consider switching to an alternative first-line regimen when there is persistent disease activity (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)</td>
</tr>
</tbody>
</table>
| 5 | Consider the following in patients refractory to first-line treatment regimens:  
   - Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or  
   - Addition of rituximab or other biologic therapies  
   - Extended course of i.v. pulse cyclophosphamide |
ANCA VASCULITIS
ANCA Vasculitides

Diagnosis of AAV

Disease assessment

Induction of remission

No organ-threatening involvement

Consider mycophenolate mofetil

Cyclophosphamide + glucocorticoids

Rituximab + glucocorticoids

Vital organ/life-threatening Serum creatinine 5.7 mg/dl (>500 μmol/l)

Consider plasmapheresis

Disease control 'on drug' remission

Maintenance

Switch to azathioprine Taper glucocorticoids

Continue rituximab Taper glucocorticoids

Taper azathioprine

Stop rituximab

'Off drug' remission
**Viral Infection-related GN – Human Immunodeficiency Virus (HIV) – Prognosis**

Practice Point 7.2.3.2.1: The factors contributing to the long-term outcome of HIV infection associated with GN are numerous and include persistence of viral replication, response to antiviral treatment, genetic predisposition to glomerular injury (e.g., APOL1 risk alleles), coinfection with other viruses, and development of immune complex disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.

<table>
<thead>
<tr>
<th>Host genetic susceptibility</th>
<th>Socio-demographics</th>
<th>Exposures and comorbid non-infectious conditions and their treatment</th>
<th>HIV-related factors</th>
<th>Coinfections</th>
<th>Underlying CKD etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOL1 G1 and G2 risk variants</td>
<td>Age</td>
<td>Diabetes, Obesity</td>
<td>HIV viremia</td>
<td>Hepatitis B or C virus</td>
<td>HIVAN</td>
</tr>
<tr>
<td>Sickle cell trait?</td>
<td>Race/ethnicity</td>
<td>Hypertension</td>
<td>CD4+ cell count</td>
<td>Tuberculosis</td>
<td>FSGS-UC</td>
</tr>
<tr>
<td>ABCC14 variants?</td>
<td>Illicit drug use</td>
<td>Cardiovascular disease</td>
<td>Composition and timing of ART initiation</td>
<td>Syphilis</td>
<td>Immune complex disease</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>Recurrent/severe acute kidney injury</td>
<td>Malignancy</td>
<td></td>
<td>Parasitic infections</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Traditional/ herbal medicines</td>
<td></td>
<td></td>
<td>Arteriosclerosis</td>
</tr>
</tbody>
</table>

[Diagram showing various factors affecting prognosis with arrows pointing to different causes of CKD etiology]
Recommendation 7.2.3.3.1: We recommend that antiretroviral therapy be initiated in all patients with HIV and CKD, especially biopsy-proven HIV-associated nephropathy (HIVAN), regardless of CD4 count, adjusted to the degree of kidney function (1C).

Practice Point 7.2.3.3.1: A decision for the use of glucocorticoids as an adjunct therapy for HIVAN must be made on a case-by-case basis, as the risks and benefits long-term are uncertain.
Nephropathies due to Infections – Schistosomal Nephropathy - Diagnosis

Practice Point 7.3.1.1.1: Test for appropriate endemic coinfections (Salmonella, HBV, HCV, HIV), as targeted treatment may alter the aggressiveness of an underlying GN or the sequela of schistosomiasis.

Practice Point 7.3.1.1.2: Obtain a kidney biopsy in patients suspected of having schistosomal GN in the presence of a viral coinfection (HCV, HBV, HIV).

<table>
<thead>
<tr>
<th>AFRAN classification</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>I Mesangial proliferative</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>II Proliferative exudative</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>III Membranoproliferative</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>IV Focal segmental glomerulosclerosis</td>
<td>Schistosoma mansoni</td>
</tr>
<tr>
<td>V Amyloidosis</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>VI Cryoglobulinemia</td>
<td>Schistosoma mansoni  Hepatitis C</td>
</tr>
</tbody>
</table>
**Nephropathies due to Infections – Schistosomal Nephropathy – Treatment**

Practice Point 7.3.1.2.1: Treat patients with schistosomal infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. There are no indications for use of immunosuppressive agents in schistosomal nephropathy.

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Praziquantel</th>
<th>Ospamniquine</th>
</tr>
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<tbody>
<tr>
<td>Adult</td>
<td>20 mg/kg, 3 times a day, for 1 day</td>
<td>15 mg/kg, single dose</td>
</tr>
<tr>
<td>Pediatric &gt;1 year old</td>
<td>20 mg/kg, 2–3 times a day, for 1 day</td>
<td>20 mg/kg, single dose</td>
</tr>
</tbody>
</table>
“Then, gentlemen, it is the consensus of this meeting that we say nothing, do nothing, and hope it all blows over before our next meeting.”
GUIDELINE UPDATES

• Focused updating of specific chapters will be conducted based on new evidence

• The process will entail:
  • Conduct systematic searches for the topics of interest from 2020 to current date
  • Screen search results to identify new studies eligible for inclusion based on the inclusion criteria for the 2021 Update
  • Perform meta-analyses, where appropriate
  • WG will evaluate the change implications to the guideline recommendations and practice points based (wording, grading, need for additional statements) based on this new evidence review
  • Guideline text will be revised accordingly and presented to the full Work Group for consensus
Challenges in Diagnosis and Management of Glomerular Disease in Resource-Limited Settings

- Delayed presentation
- Diagnostic w/u not available
- Treatment not available
- High cost of care
“Good news.
Your cholesterol has stayed the same,
but the research findings have changed.”