Expert Consensus on the Likelihood and Treatment of Inflammatory and Fibrotic Immunoglobulin A Nephropathy (IgAN)

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Background

- Immunoglobulin A nephropathy (IgAN) presents variably from asymptomatic hematuria to kidney failure.[1-3] Diagnosis requires a kidney biopsy, which may show inflammatory lesions, fibrosis/sclerosis, or both.
- Given there is no cure for IgAN, current therapies aim to slow disease progression. Renin-angiotensin-aldosterone system inhibitors (RAASi) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are commonly used as background therapy,[4-5] with additional options such as systemic corticosteroids, targeted-release budesonide, alternative pathway complement inhibitors, and endothelin receptor antagonists added for at-risk patients.[6-11]
- The "KDIGO 2025 Clinical Practice Guideline for the Management of IgAN and Immunoglobulin A Vasculitis" uses the broader term "IgA-containing immune complex-mediated glomerular injury,"[12] as inflammation and injury have essentially the same clinical implications.
- **The aim of this study was to develop expert-informed guidelines to define the high-inflammatory activity and low-inflammatory activity phenotypes of IgAN and assess preferred treatment options for each phenotype in the current treatment landscape.**

Methods

- The RAND/UCLA modified Delphi method, a validated approach, was used to achieve expert consensus.
- A panel of 11 clinicians (9 nephrologists, 2 medical kidney pathologists) reviewed clinical and histological parameters and rated 396 hypothetical patient scenarios.
- Scenarios varied by several clinical characteristics (**Table 1**).
- Panelists rated the likelihood of a patient having high-inflammatory activity (inflammatory) or low-inflammatory activity (fibrotic) IgAN and the appropriateness of various treatment options based on IgAN phenotype.
- Each scenario included ≥1 FDA-approved treatment class (**Figure 1**). Panelists rated scenarios on a 1-9 scale before and after an in-person meeting. Disagreement was defined as ≥2 ratings of 1-3 and ≥2 ratings of 7-9 within the same scenario.
- Consensus could be reached even if up to two panelists disagreed with the majority (e.g., consensus that a medication is suggested could occur when most panelists rated it as appropriate, while ≤2 rated it as inappropriate).

Table 1. Clinical characteristics

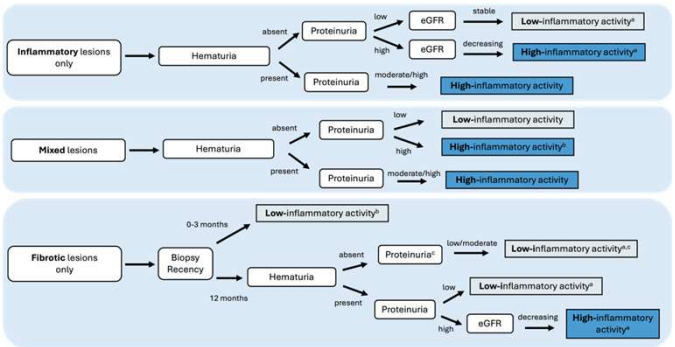
Clinical characteristics	Categories	Definitions
Current hematuria status	Absent	Negative hematuria on adequately concentrated urine sample [dipstick] or below ULN on microscopic exam
	Present	Positive dipstick or above ULN on microscopic exam, excluding extraglomerular causes of hematuria
Current degree of proteinuria	Low grade	<0.5g/24h
	Moderate grade	0.5-1.5g/24h
	High grade	>1.5g/24h
Current eGFR trajectory	Stable	0-10% decrease in last 6 months
	Declining	>10% decrease in last 6 months
Most recent kidney biopsy timing	More recent	Obtained at 0-3 months
	Less recent	Obtained ≥12 months
Histologic findings of most recent kidney biopsy (lesion type present)	Inflammatory	Inflammatory features only (e.g., E, C)
	Fibrotic	Fibrotic features only (e.g., S, T), excludes T2 lesions
	Mixed	Both inflammatory and fibrotic lesions

C: cellular/fibrocellular crescents; E: endocapillary hypercellularity; eGFR: estimated glomerular filtration rate; h: hour; ULN: upper limit of normal; S: segmental glomerulosclerosis; T: tubular atrophy/interstitial fibrosis.

Results

- Post-meeting, the panel agreed on 92% of scenarios, up from 66% during 1st round ratings.
- The group's recommendations for how to classify and treat high-inflammatory and low-inflammatory activity IgAN are summarized in **Figures 1-3.**
- High-inflammatory activity IgAN was characterized by hematuria, moderate- to high-grade proteinuria, and inflammatory histology, whereas low-inflammatory activity IgAN was marked by an absence of hematuria, low-grade proteinuria, relatively stable eGFR, and inactive, often fibrotic histology.
- Panelists more often suggested additional treatments beyond RAASi ± SGLT2is, alone or in combination, for high-inflammatory activity IgAN than for low-inflammatory activity IgAN.

Figure 1. IgAN by inflammatory phenotype



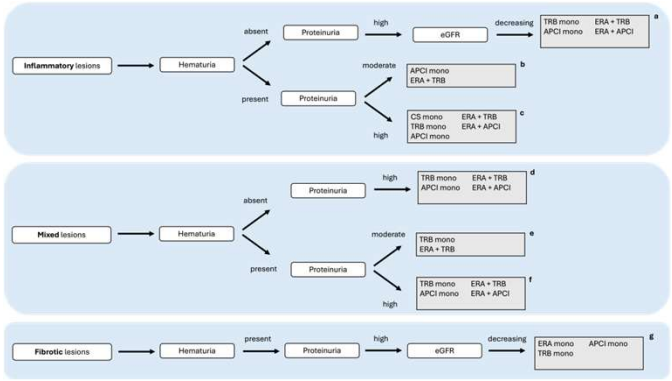
eGFR: estimated glomerular filtration rate

[a]Less recent biopsy only. [b]More recent biopsy only. If unspecified in the figure, refers to both more recent and less recent biopsies. [c]Panelists did not reach consensus on phenotype categorization for patients with high proteinuria.

Conclusion

- Our expert panel described distinct high- and low-inflammatory IgAN phenotypes and linked them to practical treatment pathways grounded in widely available biomarkers and histology.
- This structured framework offers clinicians a clear, evidence-informed strategy to navigate an increasingly complex therapeutic landscape and helps close a critical gap in IgAN management.

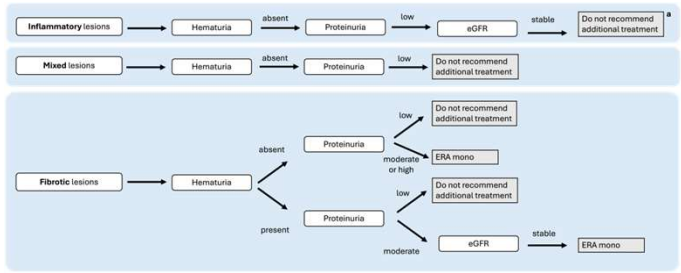
Figure 2. Treatment recommendations for the high-inflammatory activity phenotype



APCI: alternative pathway complement inhibitors, CS: systemic corticosteroids, eGFR: estimated glomerular filtration rate, ERA: endothelin receptor antagonists, mono: monotherapy, TRB: targeted-release budesonide.

[a]This scenario is only considered part of the high-inflammatory IgAN phenotype when the biopsy is less recent (≥12 months ago). Panelists did not consider more recent biopsies (0-3 months) with inflammatory lesions and absent hematuria because that was considered incongruent with real-world data. [b]If eGFR is decreasing, TRB monotherapy is also supported. [c]If eGFR is decreasing, TRB + APCI are also supported. [d]This scenario is only considered part of the high-inflammatory IgAN phenotype when the biopsy is more recent (0-3 months). All other scenarios are considered inflammatory regardless of biopsy timing (e.g., within the past 0-3 months or ≥12 months ago). [e]If eGFR is decreasing, IPCA monotherapy and ERA + IPCA are also supported; if eGFR is stable, ERA monotherapy is also supported. [f]If eGFR is decreasing, ERA + CS and TRB + IPCA are also supported; if eGFR is stable, ERA monotherapy is also supported. [g]This scenario is only considered part of the high-inflammatory IgAN phenotype when the biopsy is less recent (≥12 months ago).

Figure 3. Treatment recommendations for the low-inflammatory activity phenotype



eGFR: estimated glomerular filtration rate, ERA: endothelin receptor antagonist, mono: monotherapy.

[a]This scenario is only considered part of the fibrotic or low-inflammatory activity phenotype when the biopsy is less recent (≥12 months). All other scenarios are considered fibrotic or low-inflammatory activity regardless of biopsy timing (e.g., within the past 0-3 months or ≥12 months ago). In scenarios with no additional treatment recommendations, continued monitoring of patients is recommended.

References

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