



**KDIGO Controversies Conference on
Complement-Mediated Kidney Diseases: Atypical HUS and
C3 Glomerulopathy/Immunoglobulin-Associated MPGN**

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Breakout Group Questions

Breakout Group 1: Atypical HUS: Pathogenesis and Biomarkers

1. What are the preferred nomenclature and classification of TMAs?

- a. Should the primary versus secondary classification of TMA be dropped and replaced by a new schema? How should the NKF roadmap⁴ be incorporated/implemented in the preferred nomenclature?
- b. In the NKF roadmap nomenclature, which etiologies of TMA are dependent on the terminal complement pathway? Is the distinction between complement-mediated and complement-amplified helpful?
- c. In etiologies of TMA not dependent on complement, what are their underlying mechanisms?
- d. What are the knowledge gaps in the mechanisms of TMA that limit implementation of a comprehensive diagnostic schema?
- e. How do patients feel about a potential change in nomenclature?

2. What is minimum/optimal diagnostic workup required for TMAs?

- a. What are the minimum required diagnostic tests for the evaluation of etiologies of TMA?
- b. Resources permitting, what additional diagnostic tests should ideally be performed in the evaluation of TMA?
- c. What is the minimum evaluation required prior to kidney transplantation for both the recipient and donor, if applicable?

3. Do complement biomarkers help to diagnose complement-mediated TMA?

- a. Which complement components and regulators should be measured in TMA, when should they be measured in the disease course, and how should the results be interpreted?
- b. Which complement activation markers are useful in the diagnosis of TMA?
- c. Which complement autoantibodies cause TMA?
- d. What is the role of functional complement assays (including *ex vivo*) in the clinical evaluation of TMA?

4. What are the minimum/optimal techniques for genetic screening and gene variant classification of TMAs, and how do they inform management?

- a. What is the recommended panel of complement genes for analysis (including CNV and genetic rearrangement)?
- b. When identified, how should complement pathogenic variants be communicated to patients with atypical HUS?
- c. Which cobalamin pathway genes should be included in the evaluation of TMA, and what other genes have evidence for a role in TMA? Should

these genes be included in the genetic evaluation of TMA: *THBD*, *DGKE*, *EXOSC3*, *EXOSC5*, *TSEN2*, *STAT2*, *ZNFX1*, *TREX1*, etc.?

- d. How does detection of a pathogenic variant in a TMA-associated gene influence:
 - i. Kidney transplantation practice
 - ii. Familial screening
 - iii. Pre-implantation counselling
- e. Does the presence or absence of pathogenic genetic variants affect the clinical presentation of TMA?
- f. What knowledge gaps exist in our understanding of genetic contributors to TMA?

5. Does the kidney biopsy discriminate between underlying causes of TMA?

- a. How does kidney biopsy inform the etiology of TMA, and should biopsy be recommended in the routine evaluation of kidney injury when TMA is suspected?
- b. How can kidney biopsy assist in understanding the mechanisms of endothelial injury, including *in situ* complement activation and the role of the glycocalyx?
- c. What is the significance of renal-limited TMA versus TMA with systemic features?

Breakout Group 2: Atypical HUS: Management

1. Optimal complement inhibition in the acute phase:

- a. What is the optimal complement inhibition for the acute phase of atypical HUS?
- b. What defines an optimal complement inhibitor to be used during the acute phase of atypical HUS?
- c. Are plasma exchanges still required for the treatment of atypical HUS?
- d. What alternative treatment options can be used in settings where complement blockade is not available?

2. Long-term complement inhibition strategy:

- a. What is the optimal duration of treatment of atypical HUS?
- b. In which patients can complement inhibition be discontinued?
- c. What defines an optimal complement inhibitor to be used for the long-term treatment of atypical HUS?

3. How does kidney biopsy inform management?

4. Monitoring complement inhibition:

- a. When and how should we monitor complement inhibition in atypical HUS patients?
 - i. Should we use clinical parameters?
 - ii. Are there any biomarkers to assess complement activity? What are the research opportunities in validating diagnostic and monitoring techniques? What is the role of AI?

5. Management of complement inhibition in patients with atypical HUS undergoing kidney transplant:

- a. When should complement inhibition be used pre-emptively in patients undergoing kidney transplant following atypical HUS?
- b. How should these patients be screened for atypical HUS relapse post-kidney transplant, and when should complement inhibition be initiated if not started pre-emptively?
- c. Which complement inhibitor(s) should be used in this clinical scenario?
- d. In a transplanted patient with atypical HUS on complement inhibition, how and when should it be discontinued?

6. Management of anti-Factor H antibody-associated atypical HUS:

- a. How should one optimally manage anti-FH antibody-associated atypical HUS in the acute phase?
- b. How should one optimally manage anti-FH antibody-associated atypical HUS in the long-term?

7. Management of atypical HUS in pregnancy and post-partum:

- a. How should one optimally manage atypical HUS in pregnancy?
- b. How should one optimally manage atypical HUS in postpartum?

8. New perspectives:

- a. Address special scenarios: Is there a place for complement inhibition in other forms of HUS distinct from complement-mediated HUS? How should one optimally manage HUS in the setting of malignant hypertension?



- b. Is there a place for complement inhibitors distinct from C5 blockers in the management of atypical HUS?

9. Patient preferences:

- a. What are patient preferences regarding treatment regimen for atypical HUS (dosing frequency, route of administration, quality of life, etc.)? What are the unmet needs for patients? How can we best incorporate individual patient goals during treatment shared decision-making?

Breakout Group 3: C3G and Ig-MPGN: Pathogenesis and Biomarkers

1. Are C3G and Ig-MPGN distinct entities, and should they be treated differently?

- a. How distinct are C3G and Ig-MPGN in terms of pathogenesis?
- b. What secondary diseases or triggers (e.g., infections, hepatitis C, cryoglobulinemia) should be systematically evaluated in C3G/Ig-MPGN?
- c. Can clustering of clinical, histologic, genetic, and biomarker data define subgroups of C3G/Ig-MPGN with distinct pathogenesis, outcome or treatment response?
- d. How can we avoid overdiagnosing C3G/Ig-MPGN?

2. How does renal pathology impact diagnosis of C3G and Ig-MPGN?

- a. How distinct are C3G and Ig-MPGN in terms of pathology?
- b. Which histologic features (e.g., inflammatory cell infiltrates, crescents, extent of chronicity) best predict kidney outcomes in C3G/Ig-MPGN?
- c. Can standard immunofluorescence mask hidden Ig deposits or co-deposition of immunoglobulins in C3G, and how can this affect diagnosis?
- d. What is the role of the kidney biopsy in diagnosing post-transplant recurrence? Are protocol biopsies recommended, or should clinical manifestations drive biopsy decisions?

3. What minimal workup is needed in patients with C3G or Ig-MPGN?

- a. Should comprehensive genetic testing be performed in all cases? When identified, how should complement pathogenic variants and risk alleles be communicated to patients with C3G/Ig-MPGN?

- b. What is the frequency and clinical significance of complement autoantibodies in C3G and Ig-MPGN? Are standardized assays needed for their detection?
- c. How does monoclonal gammopathy (including MGUS and MGRS) contribute to C3G/Ig-MPGN pathogenesis? Which patients should be screened for an underlying clone?
- d. What is the role of plasma or urinary markers of complement activation in disease monitoring and prognostication?

4. Is personalized medical care possible based on complement profiling?

- a. Can complement pathway biomarkers guide selection of targeted therapies in C3G/Ig-MPGN?
- b. Can response to targeted therapies be predicted?
- c. Can biomarkers predict recurrence *prior* to kidney transplantation?
- d. In transplant recipients, what biomarkers predict recurrence of C3G/Ig-MPGN after kidney transplantation?

5. Patient preferences:

- a. How do patients feel about the current nomenclature in C3G and Ig-MPGN? What are the unmet needs in terms of the diagnosis of C3G/Ig-MPGN from patient perspectives?

Breakout Group 4: C3G and Ig-MPGN: Management

- 1. How does renal pathology impact the therapeutic approach to C3G and Ig-MPGN?**
 - a. How distinct are C3G and primary Ig-MPGN in terms of management?

- 2. What is the first-line treatment for C3G and primary Ig-MPGN?**
 - a. Is there still a place for immunosuppressive drugs in C3G and primary Ig-MPGN?
 - b. At what stage should proximal complement inhibitors be commenced? What is the added value of distinct complement inhibitors to conventional immunosuppression, based on available data?
 - c. Is the approach in children and adults the same?
 - d. Is the approach the same if there is an autoantibody or genetic mutation?
 - e. Does baseline histologic chronicity influence treatment decision and assessment of response?
 - f. What are the optimal treatment alternatives in settings where complement inhibition is not available?
 - g. Can proximal complement inhibition be used safely in patients with C3G/Ig-MPGN during pregnancy?

- 3. How should one monitor proximal complement inhibition in patients with C3G and primary Ig-MPGN?**
 - a. Can complement biomarkers be used to monitor disease course, activity, and treatment response in C3G/Ig-MPGN? If so, which biomarkers?

4. **Which infection prevention measures should be instigated in patients receiving proximal complement inhibition?**

5. **How should one define satisfactory response to treatment?**
 - a. What constitutes remission of C3G and primary Ig-MPGN?
 - b. What is the relevance of repeat biopsies in patients with C3G and Ig-MPGN receiving proximal complement inhibitors?
 - c. What is the respective place of different proximal complement inhibitors in the treatment of C3G and Ig-MPGN? (e.g., in the absence of remission should an alternative inhibitor be tried? Should additional immunosuppression be considered if not previously used? Is there a place for terminal complement inhibition?)
 - d. Is there a place for combined or sequential use of different complement inhibitors, including terminal complement inhibitors, in the treatment of some forms of C3G and Ig-MPGN?

6. **What is the optimal duration of treatment with proximal complement inhibitors in C3G and primary Ig-MPGN?**
 - a. Which parameters define a potential treatment discontinuation point?
 - b. Should eligibility for discontinuation be stratified by risk?
 - c. How should safety, including non-infectious aspects, be monitored in patients with C3G and primary Ig-MPGN on proximal complement inhibitors?
 - d. What monitoring is required following discontinuation of proximal complement inhibition?

- 7. What is the optimal use of proximal complement inhibitor therapy in patients receiving a kidney transplant with a native diagnosis of C3G/Ig-MPGN?**
 - a. When should pre-emptive proximal complement inhibitor therapy be considered?
 - b. How is relapse defined post-kidney transplant in patients with C3G/Ig-MPGN?
 - c. Which parameters (clinical or histological) should drive the decision to use proximal complement inhibition in this setting?
 - d. Once started, for how long should proximal complement inhibition be continued in patients with C3G/Ig-MPGN and a kidney transplant?

- 8. Patient preferences: What are patient expectations and unmet needs in the treatment of C3G/Ig-MPGN?**
 - a. What are patient preferences regarding treatment regimen for C3G and Ig-MPGN (dosing frequency, route of administration, quality of life, etc.)? What are the unmet needs for patients? How can we best incorporate individual patient goals during treatment shared decision-making?