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

April 16–19, 2026
Rome, Italy

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by developing clinical practice guidelines and promoting their implementation. KDIGO also regularly hosts Controversies Conferences on a focused subject pertaining to kidney disease to review state-of-the-art evidence, set priorities for improving patient care and outcomes, and highlight priority areas for research.

BACKGROUND

In 2014, KDIGO convened a Controversies Conference on two prototypical complement-mediated kidney diseases: atypical hemolytic uremic syndrome (HUS) and C3 glomerulopathy (C3G). In that occasion, the transformative role of a terminal complement inhibitor, eculizumab, was recognized and its optimal use evaluated.[1] Since then, driven by this landmark success, literature has emerged which indicates a role of complement in the etiology of a broader range of kidney diseases. In parallel, many experimental therapies targeting complement have been investigated in a number of kidney diseases in addition to atypical HUS and C3G. To address the expanding role of complement in the pathophysiology, diagnosis, management and treatment of various glomerular diseases, nephropathies in the setting of diabetes, and other forms of HUS, KDIGO convened a second Controversies Conference in 2022 to

better understand the potential contribution of complement dysregulation in other kidney disease states.[2]

Since 2022, tremendous progress has been made in moving from bench research to clinical applications. The study of complement-mediated kidney diseases has been a perfect example of successful translational research, from the elucidation of the pathogenic mechanisms to the design of effective disease-specific treatments. Study of these rare diseases has also greatly contributed to the emergence of a new therapeutic class: complement inhibitors.

For atypical HUS, C5 blockade has become the cornerstone of treatment for this devastating disease.[3] Nevertheless, the optimal terminology for atypical HUS,[4] the cost-effectiveness C5 blockers and their accessibility worldwide, and their relevance in the management of other forms of thrombotic microangiopathy are still a matter of debate.[4, 5]

For C3 glomerulopathy (C3G) and immunoglobulin-associated membranoproliferative glomerulonephritis (Ig-MPGN), new treatment options targeting dysregulated activation of the alternative pathway C3 convertase—the primary disease driver—have become available.[6-8] The positive results of prospective randomized trials[9, 10] with these drugs have paved the way to their approvals but their long-term efficacy and safety remain to be confirmed by real-world data. Current unsettled issues in this field include the optimal duration of treatment, clinical relevance of complement biomarkers and autoantibodies, and drug accessibility.

Due to the pressing need to further define advances and resolve open issues in the diagnosis, definition and management of atypical HUS and C3G/Ig-MPGN, this Controversies Conference will once again focus on these diseases where complement dysregulation is the main driver of disease and our understanding concerning the utility of complement inhibitors are more advanced than in other nephropathies.

CONFERENCE OVERVIEW

The goal of this conference is to summarize our current understanding of the pathogenesis and pathology of complement-driven kidney diseases (atypical HUS, Ig-MPGN and C3G) and the available data on the therapeutic use of complement inhibitors in these clinical scenarios. It also seeks to identify key results, open questions and research gaps in the classification, diagnosis, prognostication and management of these disorders with the aim to bridge care gaps and improve patient outcomes for these extremely rare and complex conditions. Participants will include adult and pediatric nephrologists, pathologists, experts in complement biology and genetics, and patient and caregiver representatives.

Drs. Fadi Fakhouri (Centre Hospitalier Universitaire Vaudois et Université de Lausanne, Switzerland) and Marina Vivarelli (Bambino Gesù Children's Hospital IRCCS, Italy) will co-chair this Controversies Conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders who will critically review the literature and our current state of understanding in this area, and address the clinical issues outlined in the **Appendix: Scope of Coverage**. The conference output will result in a publication that will help guide KDIGO and others on the diagnosis and management of complement-mediated kidney diseases: atypical HUS, Ig-MPGN and C3G.

APPENDIX: SCOPE OF COVERAGE

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 roadmap[4] 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?

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