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## **KDIGO Controversies Conference on the Role of Complement in Kidney Disease**

### **Breakout Group Discussion Questions**

#### **Breakout Group 1: Diabetic Nephropathy and Nephrotic Syndrome**

##### **Diabetic Nephropathy: Pathogenesis**

1. What is the evidence (from genetic associations, biomarker data, and animal models) that complement is activated in diabetic nephropathy?
2. Is complement activation causally related to disease development in diabetic nephropathy or is it a result of glomerular injury?
3. Do any co-morbid conditions increase complement activity in this disease?

##### **Diabetic Nephropathy: Complement Biomarkers**

4. Should complement-related biomarkers be part of the work-up for diabetic nephropathy? If yes, which? What is the prognostic value of these biomarkers? How do urinary complement biomarkers compare to blood biomarkers?

##### **Diabetic Nephropathy: Treatment**

5. Is there a role for therapeutic complement inhibition in diabetic nephropathy?



6. Who should be considered for complement inhibitor therapy? Should it be disease stage specific? Do we have biomarkers of response to treatment?

**FSGS: Pathogenesis**

7. What is the evidence (from genetic associations, biomarker data and animal models) that complement is activated in FSGS?
8. Is complement activation causally related to disease development in FSGS or is it a result of glomerular injury?
9. Which forms of FSGS are more likely to be causally driven by complement activation?
10. Do any co-morbid conditions increase complement activity in this disease?

**FSGS: Complement Biomarkers**

11. Should complement-related biomarkers be part of the work-up for FSGS? If yes, which?
12. What is the prognostic value of these biomarkers? How do urinary complement biomarkers compare to blood biomarkers?

**FSGS: Treatment**

13. Is there a role for therapeutic complement inhibition in FSGS? In what forms of FSGS is complement inhibition most likely to be beneficial?
14. Who should be considered for complement inhibitor therapy? Should it be disease stage specific? Do we have biomarkers of response to treatment?



**Breakout Group 2: Lupus, Anti-Phospholipid Syndrome (APS), and ANCA-Associated Vasculitis (AAV)**

**Thrombosis Associated with APS**

1. Is increased complement activity involved in the pathogenesis of both venous and arterial thrombosis?
2. Is it helpful to measure complement-related biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) in APS?
3. What insights can be gained from complement C5 inhibition in catastrophic APS?
4. Would modifying complement activity interfere with the mechanism of action of currently used anti-thrombotic agents?
5. What are the risks of complement inhibition in APS?
6. How would complement inhibition be tested in APS?

**Lupus Nephritis**

7. What is the contribution of complement activity to kidney injury in relation to the other effector mechanisms active in lupus nephritis? Is complement activation a driver of kidney injury or a consequence of immunoglobulin deposition in the kidney?
8. Is complement activity a driver of non-renal lupus lesions?
9. What is the place for anti-complement protein antibodies in lupus nephritis (e.g., anti-C1q antibodies); are they useful biomarkers with relevance for diagnosis and prognosis?
10. What is the relevance of the link between complement deficiencies and lupus (the “systemic lupus erythematosus [SLE] paradox”)?



11. Is it useful to measure complement activation biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) and where (e.g. plasma, urine, kidney biopsy)? Could novel approaches (transcriptomics, multiplex imaging) provide more information?
12. What insights can be gained from complement C5 inhibition in lupus nephritis?
13. Would modifying complement interfere with the mechanism of action of currently used treatments in lupus nephritis?
14. What are the risks of complement inhibition in lupus?
15. How would complement inhibition be tested in lupus nephritis?

#### **ANCA-Associated Vasculitis (AAV)**

16. What have we learned from use of avacopan in AAV?
17. Is it useful to measure complement activation biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) and where (e.g. plasma, urine, kidney biopsy)?
18. Is there a role for targeting other parts of the complement system (e.g. C3) in AAV?

#### **Breakout Group 3: IC-MPGN, C3G, and Postinfectious Glomerulonephritis (PIGN)**

##### **Diagnosis**

1. IC-MPGN, C3G, PIGN which histological criteria should be used to distinguish one from the others?



2. How do we explain repeat biopsies changing from IC-MPGN to C3G and vice versa?
3. Are there new histopathological approaches emerging to help differential diagnosis?

### **Serological Testing**

4. Which is (are) the best assay(s) for NeFs?
5. How can we organize a standardization of NeF testing?
6. NeFs are a very heterogenous group of antibodies (C3NeF, C5NeF, C4NeF). What is the impact of each on disease pathogenesis, disease classification and clinical outcome of IC-MPGN, C3G, PIGN?
7. What is the prevalence of anti-factor H, anti-factor B, and anti-C3b antibodies in IC-MPGN, C3G, and PIGN, and what is the utility of assays for each in clinical practice and in monitoring response to therapy?
8. How important are measurements of functional complement activity (eg AP50, CH50), and serum C4, C3 and their degradation products in assessment of patients with these disorders? Do they reveal pathway activity or predict histological, clinical or post-transplant findings/progress?
9. Can serological tests inform or revise a histological diagnosis?
10. Are there other emerging serologic markers?

### **Genetic Testing**

11. What are the indications for genetic or genomic testing in patients with IC-MPGN, C3G, PIGN? Should asymptomatic family members be screened for the presence of kidney disease (urinalysis, blood pressure, serum creatinine)?



12. How should complement gene variants of undetermined significance in patients with C3G be interpreted in the clinical setting? Is there a role for identifying non-monogenic (i.e. common) genetic risk factors for C3G in clinical practice?
13. Which genes should be included in comprehensive genetic testing by clinical laboratories for the work-up of C3G and IC-MPGN? What is the role of genetic testing in the clinical management of these diseases, including in the setting of renal transplantation and in the choice of living related donors?

#### **Treatment of C3G, IC-MPGN, PIGN**

14. Which is the current best approach to treatment of C3G and IC-MPGN? When should complement inhibition be considered?
15. Should C3G and IC-MPGN be considered equivalent with respect to complement inhibiting therapies?
16. Which endpoints of response to treatment should be employed?
17. Which biomarkers, both serological, urinary and on the kidney biopsy, may be helpful in monitoring effectiveness of complement inhibition in C3G and IC-MPGN?
18. Do we have enough information to tailor the choice of complement inhibitor based on the serological, genetic and biomarker work-up of patients with C3G and IC-MPGN?
19. Is there a role for complement inhibition in PIGN?



### **Monoclonal Gammopathies**

20. Which patients presenting with C3G/MPGN should be tested for a monoclonal gammopathy? Which tests should be performed to identify/exclude a monoclonal gammopathy in these patients?
21. Is C3G-monoclonal gammopathy of renal significance (MGRS) an indication for treatments targeting a hematological clonal abnormality?
22. Is there a role for complement inhibition in this condition?

### **Breakout Group 4: IgA Nephropathy (IgAN), Immunoglobulin A–Associated Vasculitis (IgAV) With Nephritis, and Membranous Nephropathy (MN)**

#### **IgAN and IgAV With Nephritis: Disease Pathogenesis**

1. What is the evidence (from preclinical models and human and genetic studies) that complement activation plays a role in kidney injury in IgAN/IgAV with nephritis?
  - a. What is the role of the alternative pathway?
  - b. What is the role of the lectin pathway?
2. For each disease and each pathway, is complement-mediated injury a primary driver of disease or a generic downstream consequence of glomerular immunoglobulin deposition?
3. In what way, if any, does the role of complement activity differ between IgAN and IgAV with nephritis?



#### **IgAN and IgAV With Nephritis: Biomarkers**

4. Are there data to support the use of complement-associated biomarkers to inform prognosis, treatment selection, or monitoring of response to treatment in IgAN/IgAV, including circulating biomarkers, urinary biomarkers and kidney biopsy immunofluorescence stains (C3, C4, C1q, others) as well as novel biomarkers?

#### **IgAN and IgAV With Nephritis: Treatment**

5. What is the evidence that complement inhibition in IgAN/IgAV is safe and efficacious, and when should a complement inhibitor be used—for induction, maintenance of remission, or lifelong? What is the evidence to indicate which pathway should be targeted?

#### **MN: Disease Pathogenesis**

6. What is the evidence (from preclinical models and human and genetic studies) that complement activation plays a role in kidney injury in membranous nephropathy?
  - a. What is the role of the alternative pathway?
  - b. What is the role of the lectin pathway?
7. In different forms of MN, is complement-mediated injury a primary driver of disease or a generic downstream consequence of glomerular immunoglobulin deposition? Is there a difference in the role of complement depending on the antigen involved (i.e. PLA2R vs other identified antigens vs no identified antigen)? Is there a role for complement in secondary forms of membranous nephropathy?





**MN: Biomarkers**

8. Are there data to support the use of complement-associated biomarkers to inform prognosis, treatment selection, or monitoring of response to treatment in MN, including circulating biomarkers, urinary biomarkers and kidney biopsy immunofluorescence stains (C3, C4, C1q, others) as well as novel biomarkers?

**MN: Treatment**

9. What is the evidence that complement inhibition in MN is safe and efficacious? When should a complement inhibitor be used—for induction, maintenance of remission, or lifelong? What is the evidence to indicate which pathway should be targeted?

**Breakout Group 5: Complement-Mediated Forms of HUS**

**Terminology & Pathogenesis**

1. What is the definition and the spectrum of complement-mediated forms of HUS? Is the current terminology “atypical HUS” accurate, or does it need updating? If updating is needed, what is a preferable alternative? Is the term “complement-mediated forms of HUS” useful and adequate?
2. Which complement pathways—and to what extent—are involved in complement-mediated HUS? Are pathways other than complement involved in the pathogenesis of complement-mediated HUS?
3. Is it possible to distinguish complement activation/dysregulation in different forms of HUS as transient versus permanent? Can this distinction be helpful in classification and management of HUS?



4. Does the renal microenvironment contribute to the pathogenesis of renal involvement in complement-mediated forms of HUS?

### **Genetics & Biomarkers**

5. What biomarkers and/or tests are helpful to diagnose and monitor complement-mediated forms of HUS?
6. How should the results of complement genetics (common and rare variants, copy number variation, etc...) and tests for acquired autoantibodies (i.e. anti factor H autoantibodies) be reported and interpreted in index cases and healthy carriers?
7. How do genetic results and test for acquired autoantibodies (i.e. anti-factor H autoantibodies) impact on the management of complement-mediated HUS, including in the setting of renal transplantation and in the choice of living related donors?

### **Management & Therapeutics**

8. What is the optimal use of current therapies and what are the emerging therapies for complement-mediated HUS?
9. When and how should complement inhibition be discontinued in complement-mediated HUS?
10. Is there a role for complement inhibition in STEC-HUS?
11. Is there a role for complement inhibition in other forms of HUS (i.e. HUS post-bone marrow transplant, pregnancy-associated HUS, etc.)?