Global Action. Local Change.

KDIGO COMPLEMENT-MEDIATED KIDNEY DISEASES CONFERENCE
BREAKOUT GROUP QUESTIONS

1. Renal Pathology

C3 glomerulopathy

1. What are the criteria for diagnosis of C3 glomerulopathy? What is the role of ancillary immunohistology in diagnosis (including C4d, pronase unmasking, C5b-9 staining and electron microscopy)?

2. What is the significance of, and utility of detecting, different C3 breakdown products in glomeruli (e.g., C3b, iC3b, C3d)? Should more specific IF be required?

3. DDD vs C3 GN: is the distinction clear-cut and how is it related to pathophysiology?

4. What is the relationship of post-infectious GN to C3 glomerulopathy? Does PIGN evolve into C3G, and if so, what is the timeline?

5. How do pathological features in the biopsy relate to pathogenesis and clinical course?

6. How do pathological features in the biopsy guide therapy?

TMA

1. Nomenclature of TMA: is it a problem that TMA encompasses changes that are not 'thrombotic' (e.g., glomerular subendothelial expansion and myxoid arterial intimal thickening)?

2. What are the morphological differences between TMAs of different etiology?

3. What is the distinction of TMA associated with malignant hypertension as opposed to TMA due to other causes with secondary hypertension?

4. What are the morphological features of acute and chronic TMA lesions and is there an entity of chronic TMA due to complement abnormalities that leads to chronic renal impairment without acute episodes?

2. Clinical Phenotype & Assessment

1. How can the classification of aHUS and TMA be modified to reflect disease drivers and therefore a treatment pathway?

2. What is the evidence for ongoing "chronic" complement activation in aHUS and C3 glomerulopathy and can biomarkers be used to evaluate chronicity?

3. What are the significant extra-renal manifestations of TMA and can biomarkers be used to evaluate extra-renal disease?

4. What is the relative long-term disease risk based on genetic factors, autoimmune factors and biomarkers, and how does that risk compare with long-term eculizumab treatment in aHUS?

5. How are genetic variants of unknown significance best interpreted?

6. How should response to eculizumab therapy be monitored? If withdrawal is planned, how should withdrawal be followed?

7. How do acquired drivers of disease change in acute vs chronic aHUS and C3G?

3. Genetic Drivers of Disease

1. When should molecular diagnostics be done?

2. How is molecular diagnostics evolving?

3. Which criteria should be used to define variants as pathogenic/likely pathogenic vs VUS (e.g., minor allele frequency (MAF) in general population, *in silico* prediction, functional insights, others)?

4. Disease penetrance: How do multiple genetic risk factors determine risk for disease?

5. What are the benefits of molecular diagnostics?
    a. How does identification of pathogenic/likely pathogenic variants inform prognosis and treatment response?
    b. How do genetic profiles help in resolving complement-related overlapping phenotypes?
    c. Can complement blockade treatment be stopped safely and if so, in which patients and when?
    d. What are the indications and utility of molecular diagnostics in living-related kidney donor transplantation?

6. What does the failure to identify a genetic cause in aHUS and C3G patients mean?
    a. Comprehensive analysis of known candidate genes?
    b. Non-complement genes?
    c. Search for additional genes?
    d. Improved clinical diagnosis?

7. What does the clinician expect from a genetic test report?
    a. What information should be included and how should this information be reported?

8. Can we move towards more individualized management and treatment of aHUS and C3G patients based on genetic profiles?

4. Acquired Drivers of Disease

1. What are the clinically important acquired factors that should be screened for in patients with C3 glomerulopathy?

2. What are the clinically important acquired factors that should be screened for in patients with aHUS?

3. How should C3 nephritic factors be measured in the clinical laboratory? (Discussion needs to include relevance of quality controls, reliable quantitation, standardization of tests)

4. How should anti-factor H autoantibodies be measured and quantified? (Discussion needs to include relevance of quality controls, reliable quantitation, standardization of tests)

5. At what time and at which frequency should acquired factors be screened?

6. Should we include the screening of other biomarkers or genetic predisposition for acquired disease?

7. Can acquired drivers of disease be used to define subtypes of C3G?

5. Treatment Strategies

1. What is the optimal duration for eculizumab treatment in aHUS patients? What is the evidence that justifies life-long therapy especially in adults?

2. What is the evidence for optimal dose and dose interval for eculizumab and are there alternatives?

3. What is the optimal treatment for patients with aHUS due to anti-FH antibodies?

4. How do we stratify C3G patients for novel agents and clinical trials?

5. What should the current approach to treatment of C3G be?

6. Kidney transplantation in aHUS and C3G

    a. What is the best time frame for kidney transplantation after the onset of end-stage renal disease (ESRD) in aHUS or C3G patients treated with anti-cellular therapy and/or eculizumab?

   b. What is the risk of recurrence?

   c. What is the best strategy in order to prevent aHUS (C3G) recurrence after kidney transplantation: preventive vs. preemptive strategies?

   d. Should living kidney donors be used (preferentially?); living related?

7. How should eculizumab treatment be monitored: CH50, AP50, free eculizumab or total eculizumab, in vitro EC tests?

8. What is the optimal treatment for rapidly progressive or bad prognosis histology C3G?

9. What is the role for immunosuppression in the treatment of C3G?

10. What is the role of eculizumab in the treatment of C3G?

    a. In what subgroups might it be useful?