



Global Action. Local Change.

KDIGO Controversies Conference on Complement-Mediated Kidney Diseases

November 19-21, 2015

Barcelona, Spain

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

BACKGROUND

The two prototypical complement-mediated kidney diseases are C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS). C3 glomerulopathy (C3G) defines a group of untreatable ultra-rare kidney diseases (incidence approx 1/million population) driven by uncontrolled activation of the complement cascade that leads to C3 deposition within the glomerulus.¹⁻⁶ Most frequently, dysregulation occurs at the level of the C3 convertase of the alternative pathway (AP) in the fluid phase and is driven by genetic and/or acquired defects. Broad inter-individual variability gives rise to two major subtypes of disease – dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) – that are characterized by findings on renal biopsy.⁷ Patient evaluation should include genetic testing and biomarker profiling of complement activity. Nearly half of the

patients diagnosed with C3G progress to end-stage renal disease (ESRD) within 10 years.^{8,9} Currently, there is no effective targeted treatment option for C3G and as a consequence a variety of supportive measures are used to delay progression to kidney failure.¹⁰ C3G remains an ideal disease in which to test new complement therapies as these become available. Trials must include a comprehensive evaluation of each patient at the genetic and biomarker level so that individual responses to therapy can be predicted and understood in light of the varying degree of complement dysregulation and underlying pathology.

Atypical hemolytic uremic syndrome (aHUS) is also an ultra-rare disease (incidence approx 0.5/million population).^{11,12} It is characterized by acute kidney injury, thrombocytopenia and microangiopathic hemolytic anemia, and renal histopathology shows thrombotic microangiopathy (TMA). There are other diseases which can present with a similar phenotype including Shiga toxin-producing E Coli associated hemolytic uremic syndrome (STEC HUS), thrombotic thrombocytopenic purpura (TTP) and other multisystem disorders. Criteria have been established to facilitate the diagnosis of aHUS. At least 50% of aHUS patients have an underlying inherited and/or acquired complement abnormality, which leads to dysregulated activity of the AP at the cell surface.¹³ There are, however, non-complement inherited abnormalities such as mutations in *DGKE*, which can result in an aHUS phenotype.¹⁴ Until recently, the prognosis for aHUS was poor with the majority of patients developing ESRD within two years of presentation.¹⁵

Likewise, kidney transplantation was associated with a poor outcome with a high rate of graft loss due to recurrent disease.^{16,17} The introduction of eculizumab, a humanized monoclonal antibody against C5, following open-label trials represents a step-change in the management of the disease. With early treatment it is now possible to reverse the renal TMA and prevent the development of ESRD.¹⁸ Likewise eculizumab can be used prophylactically to prevent recurrent disease post-transplant and treat recurrent disease in those individuals not given the drug prophylactically.¹⁹



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CONFERENCE OVERVIEW

The objective of this KDIGO conference is to gather a global panel of multi-disciplinary clinical and scientific expertise to identify key issues relevant to the optimal management of complement-mediated kidney diseases. The goal of this KDIGO conference is to define the renal pathology of C3G and aHUS; describe the clinical phenotype and evaluation of C3G and aHUS; characterize the genetic and acquired drivers of these two diseases; and determine best practice treatment and clinical trial strategies for C3G and aHUS. The conference also aims to summarize outstanding knowledge gaps and propose a research agenda to resolve standing controversial issues. It is hoped that the deliberations from this conference will inform clinicians of the evidence base for present treatment options and help pave the way for future studies in this area.

Drs. Tim Goodship (Newcastle University, United Kingdom) and Richard Smith (University of Iowa, USA) will co-chair this 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. Invited participants and speakers include worldwide leading experts and patient representatives who will address key clinical issues as outlined in the **Appendix: Scope of Coverage** below. The conference output will include publication of a position statement to help guide KDIGO and others on therapeutic management and future research in complement-mediated kidney diseases.

APPENDIX: SCOPE OF COVERAGE

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. DDD vs C3 GN: is the distinction clear-cut and how is it related to pathophysiology?
3. What is the relationship of post-infectious GN to C3 glomerulopathy?
4. How do pathological features in the biopsy relate to pathogenesis and clinical course?
5. 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 is the distinction of TMA associated with malignant hypertension as opposed to TMA due to other causes with secondary hypertension?
3. 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?

3. Genetic Drivers of Disease

1. Which criteria should be used to define variants as pathogenic/likely pathogenic (e.g., minor allele frequency (MAF) in general population, *in silico* prediction, functional insights, others)?
2. Disease penetrance: How do multiple genetic risk factors determine risk for disease?
3. How do pathogenic/likely pathogenic variants inform management and treatment response?
4. 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?
5. What does the clinician expect from a genetic test report?

6. How is diagnostic testing evolving?
7. 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?

5. Treatment Strategies

1. Nomenclature

What is the impact of nomenclature on treatment (i.e., value of assigning pathology- based definitions)?

- a. Complement mediated thrombotic microangiopathy versus aHUS?
- b. C3 Glomerulopathy – should we keep C3GN and DDD separate?

- c. What to do with the rest (aHUS) and how do they affect treatment protocols?
2. Status of the diagnostic criteria: how sure are we that we have the correct diagnosis?
 - Clinical diagnostic criteria
 - Pathology
 - Biomarkers
3. What are the science-directed treatment targets?
 - Regulators of complement
 - C3 and C5 convertases
 - Terminal complement complex
 - Anaphylotoxins
 - Monoclonal proteins
4. What treatments are available and what is the evidence for effectiveness and side effects?
 - Plasmatherapy
 - Anti-cellular Therapy
 - Eculizumab
 - Supportive cares (e.g., volume, blood pressure, etc)
5. What treatments are on the horizon and what treatments should we advocate for?
6. Safety considerations of treatments for complement mediated kidney disease:
 - Should combined therapies be prohibited?
7. Registry: What is their impact on treatment evidence?
 - Industry Based
 - Center Based – Opportunities for collaboration
8. What pressing research questions should be addressed to facilitate more clinical trials?

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