KDIGO 2016 Controversies Conference

Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy

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OVERVIEW

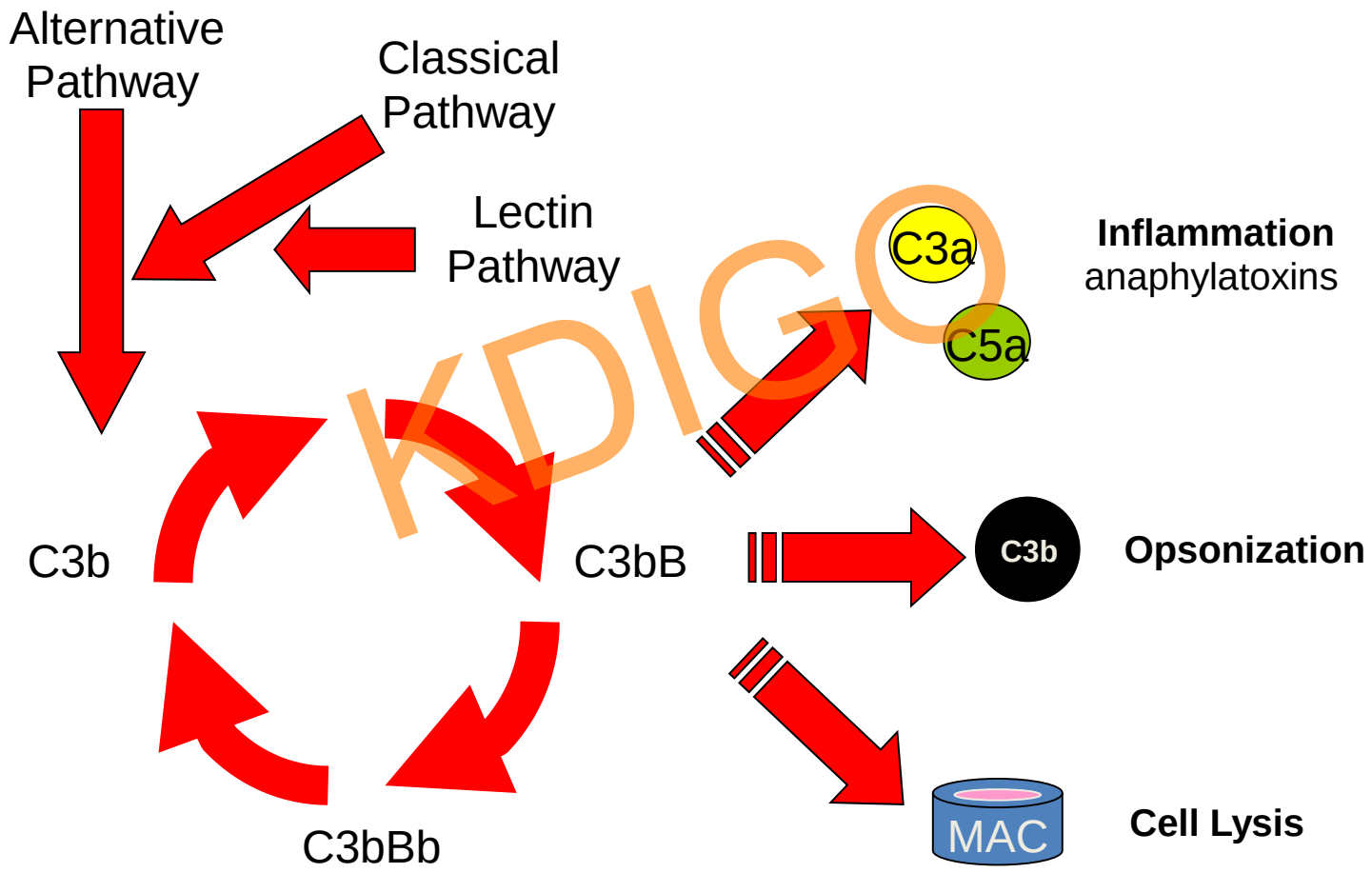
aHUS C3G CONTROVERSIES CONFERENCE

1. INTRODUCTION
2. RENAL PATHOLOGY
3. CLINICAL PHENOTYPE & ASSESSMENT
4. GENETIC & ACQUIRED DRIVES OF DISEASE
5. TREATMENT
6. RESEARCH RECOMMENDATIONS

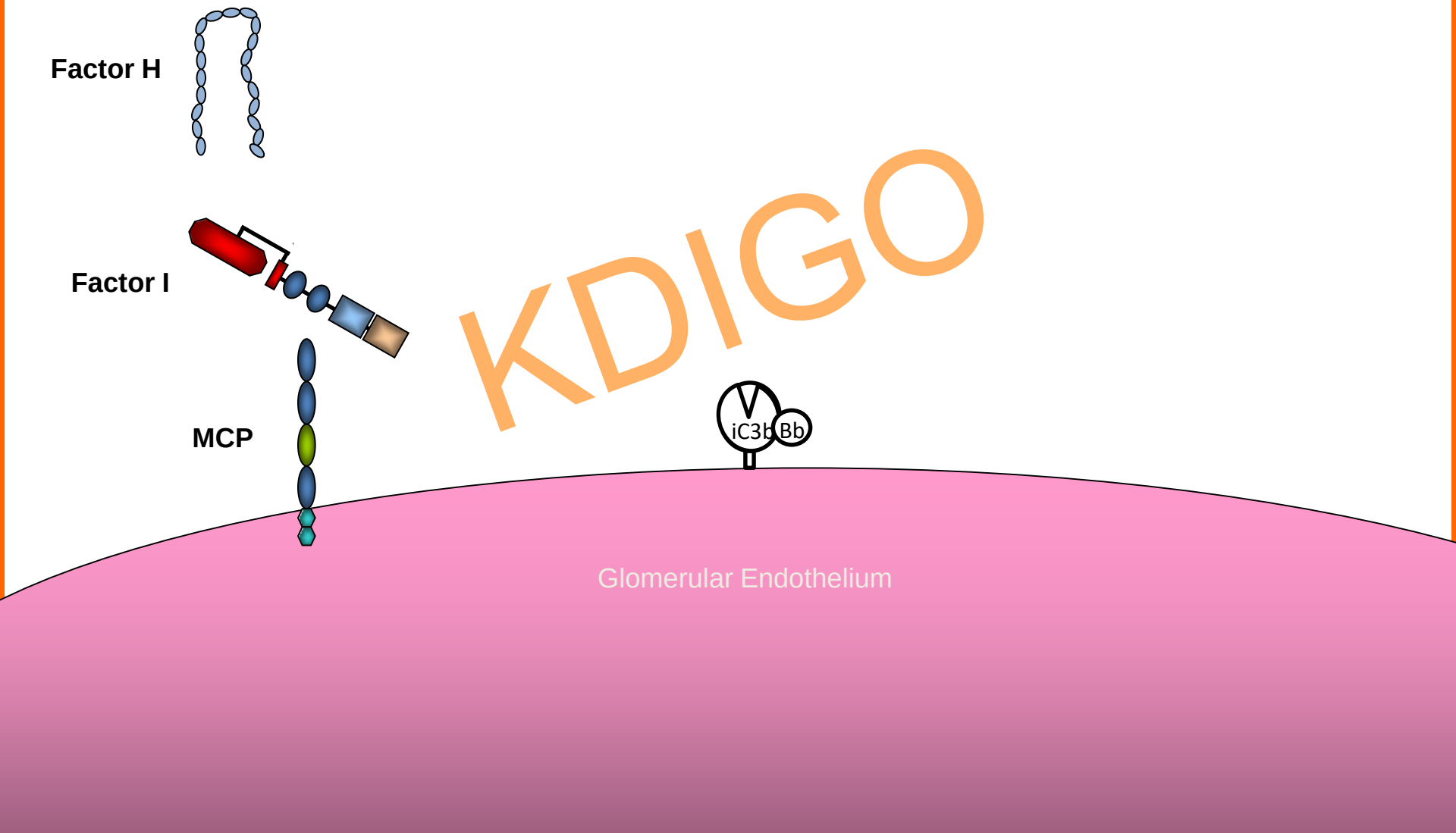
PART 1:

INTRODUCTION

Complement Activation



Complement Regulation



Atypical Hemolytic Uremic Syndrome (aHUS)

- Ultra-rare disease (UK- 0.42/million population/yr)
  - acute kidney injury
  - thrombocytopenia
  - microangiopathic hemolytic anemia.
- At least 50% of aHUS patients have an underlying inherited and/or acquired complement abnormality.
- Historically prognosis poor- most rapid ESRF
- Eculizumab, a humanized mAb against C5 changed natural history of disease

C3 Glomerulopathy (C3G)

- C3G ultra rare (1/million population/yr)
- C3G comprises a group of kidney diseases driven by uncontrolled activation of the complement cascade that leads to C3 deposition within the glomerulus.
- The dysregulation of C3 convertase is driven by genetic and/or acquired defects.
- A biopsy is required to make the diagnosis.
- Two major subtypes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN).

PART 2:

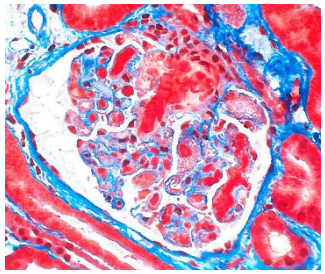
RENAL PATHOLOGY

aHUS Pathology

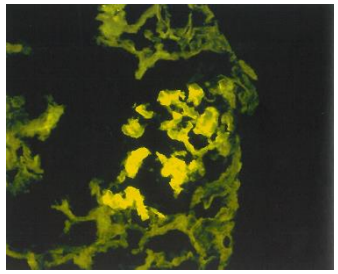
- aHUS is a thrombotic microangiopathy (TMA).
- Pathology -tissue response to endothelial injury.
- Overt thrombosis not always seen
  - **Suggested mircoangiopathy +/- thrombosis**
- In general, it is not possible to determine etiology from morphology.
- The presence of C5b-9 staining is not a reliable indicator of aHUS.

Morphological Features in Microangiopathy

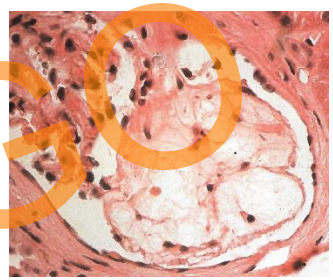
Active Lesions
Glomeruli • Thrombi • Endothelial swelling or denudation • Fragmented red blood cells • Subendothelial flocculent material by EM • Mesangiolysis • Microaneurysms
Arterioles • Thrombi • Endothelial swelling or denudation • Intramural fibrin • Fragmented red blood cells • Intimal swelling • Myocyte necrosis
Arteries • Thrombi • Myxoid intimal swelling • Intramural fibrin • Fragmented red blood cells



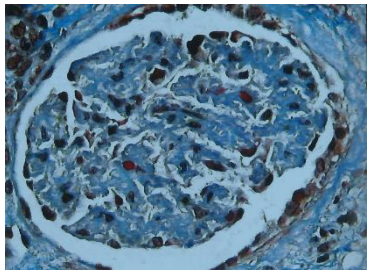
Thrombi



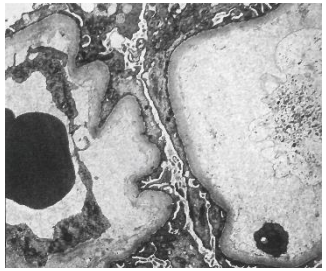
Fibrin



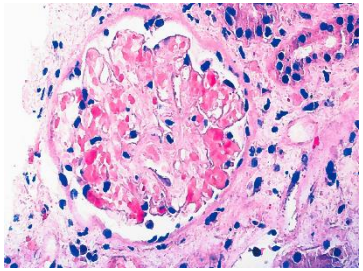
Mircoaneurysms



Bloodless / fragments



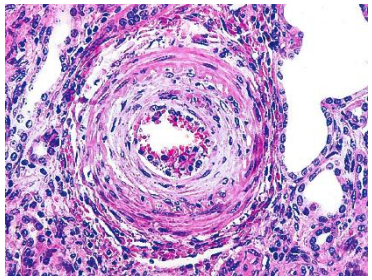
Flocculent material



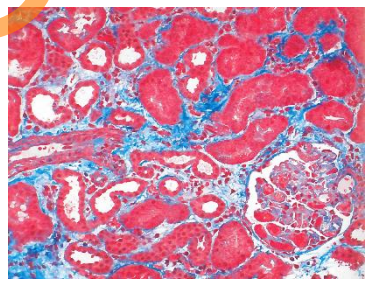
Mesangiolysis

Morphological Features in Microangiopathy

Chronic Lesions
Glomeruli • Double contours of peripheral capillary walls by LM, with variable mesangial interposition • New subendothelial basement membrane by EM • Widening of the subendothelial zone by EM
Arterioles • Hyaline deposits
Arteries • Fibrous intimal thickening with concentric lamination (onion skin)



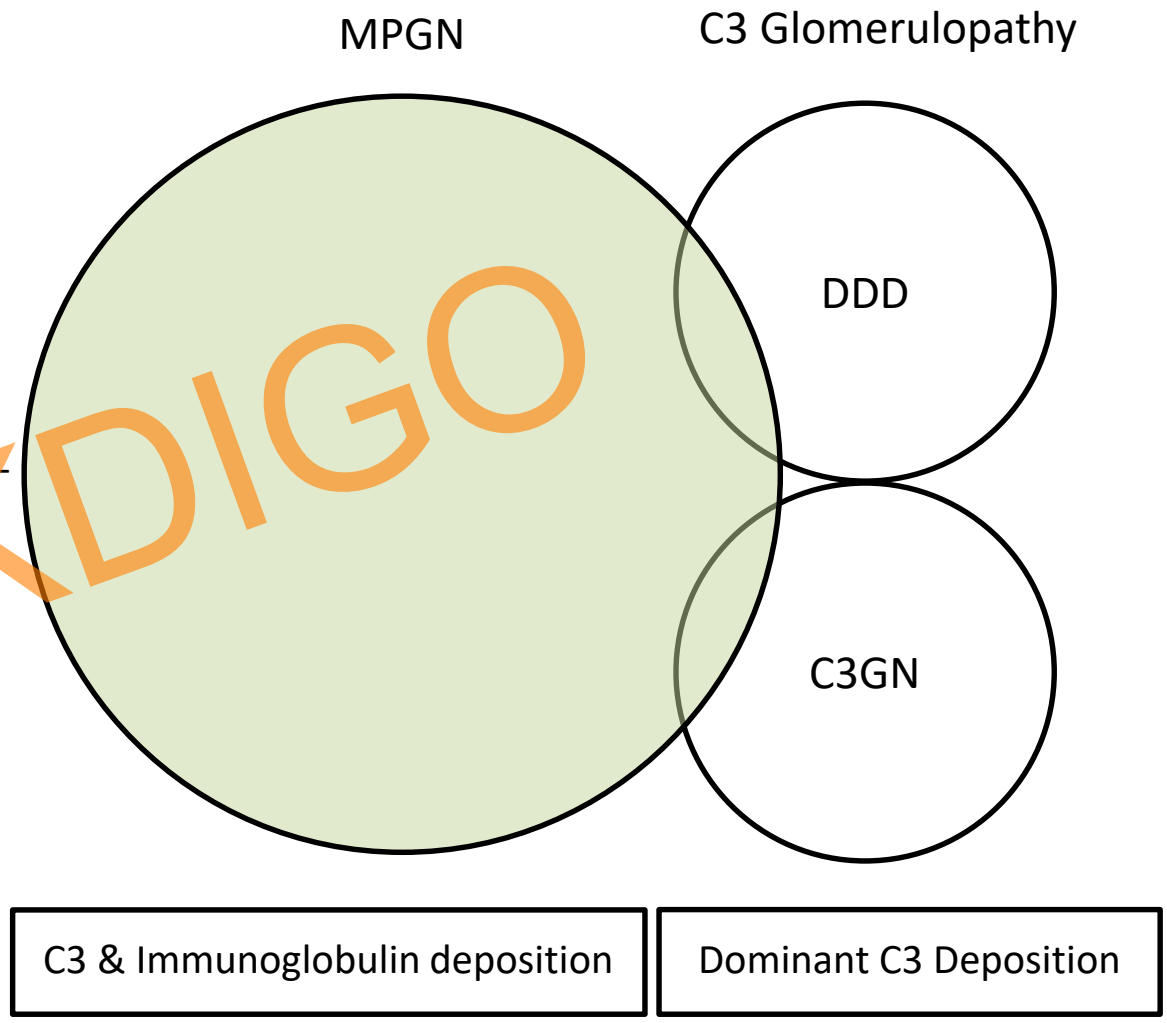
myointimal proliferation



Tubular atrophy

C3G PATHOLOGIES

- The C3G disease spectrum is caused by abnormal control of complement activation, deposition or degradation
- Light microscopy- diverse
- Predominant glomerular C3 fragment deposition on IF
  - (x2 greater than other immuno-reactants IgG, IgM, IgA C1q)
  - 90% DDD, less C3GN
- Electron microscopy (EM) is used to sub-classify C3G as DDD or C3GN.



Morphological Features of C3G

Light Microscopy

Active lesions

- Mesangial expansion with or without hypercellularity
- Endocapillary hypercellularity including monocytes and/or neutrophils
- Capillary wall thickening with double contours (the combination of capillary wall thickening and mesangial increase is referred to as a membranoproliferative pattern)
- Necrosis
- Cellular/fibrocellular crescents

Chronic lesions

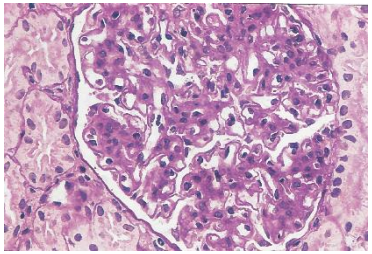
- Segmental or global glomerulosclerosis
- Fibrous crescents

Immunofluorescence Microscopy

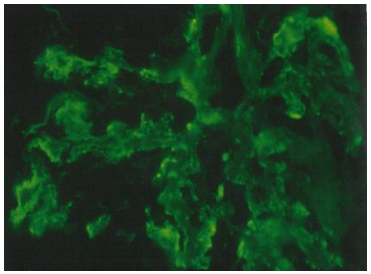
- Typically dominant C3 staining

Electron Microscopy

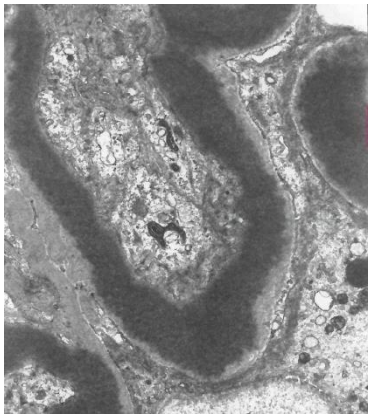
- DDD: Dense osmiophilic mesangial and intramembranous electron dense deposits
- C3GN: Amorphous mesangial with or without capillary wall deposits including subendothelial, intramembranous and subepithelial electron dense deposits
- Sub-epithelial 'humps' may be seen in both DDD and C3GN (not pathognomonic of post infectious GN)



DDD with MPGN pattern



Dominant C3 staining



Dense transformation BM

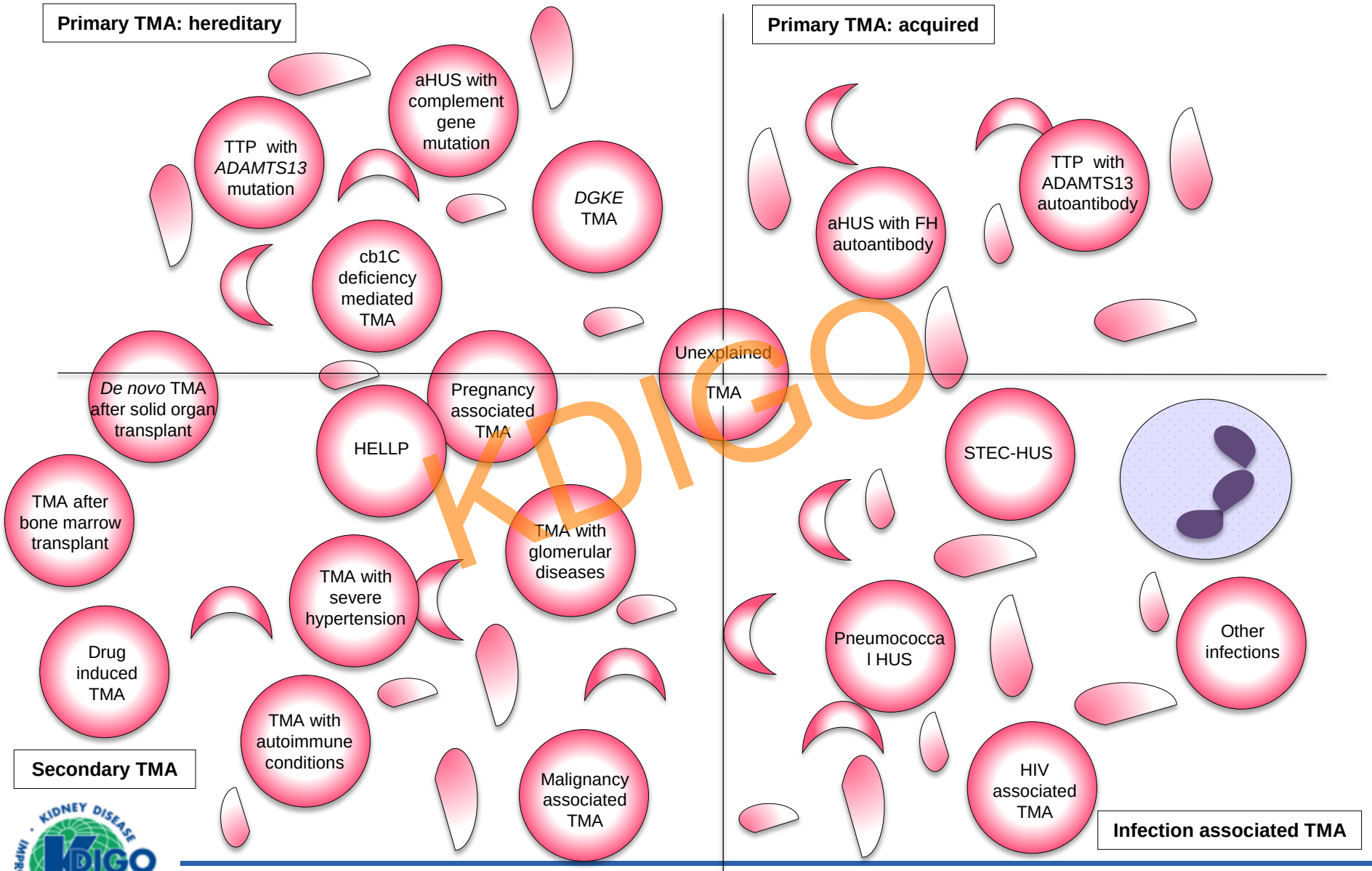
C3G Pathology: Controversies

- Correlations between renal biopsy appearances, etiology and clinical outcome are ill-defined.
- IF staining is subjective and semiquantitative.
  - Well-defined for dense deposit disease (DDD).
  - Not clear if characteristic for C3 glomerulonephritis (C3GN).
- Role of C4d staining in distinguishing C3G from IC MPGN requires further investigation
- Pronase digestion should be considered in all cases
  - Masked monotype Ig deposits

Part 3:

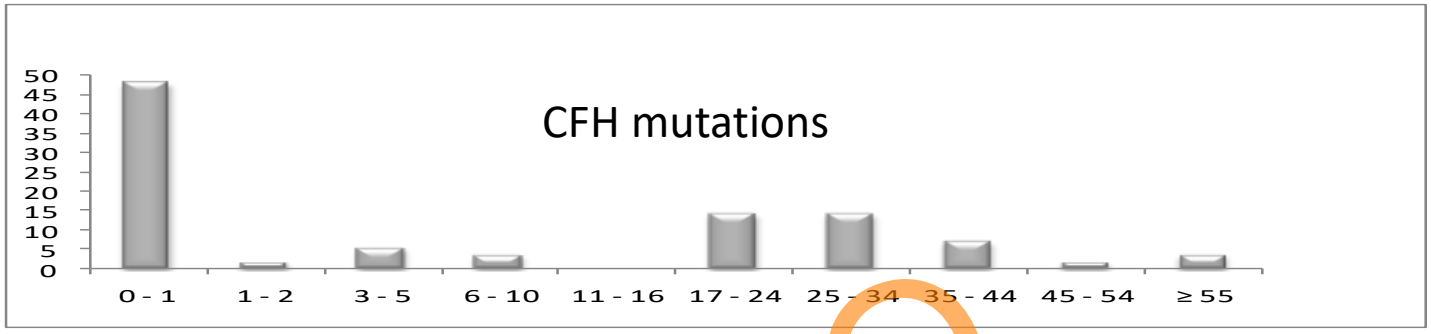
Clinical Phenotype and Assessment

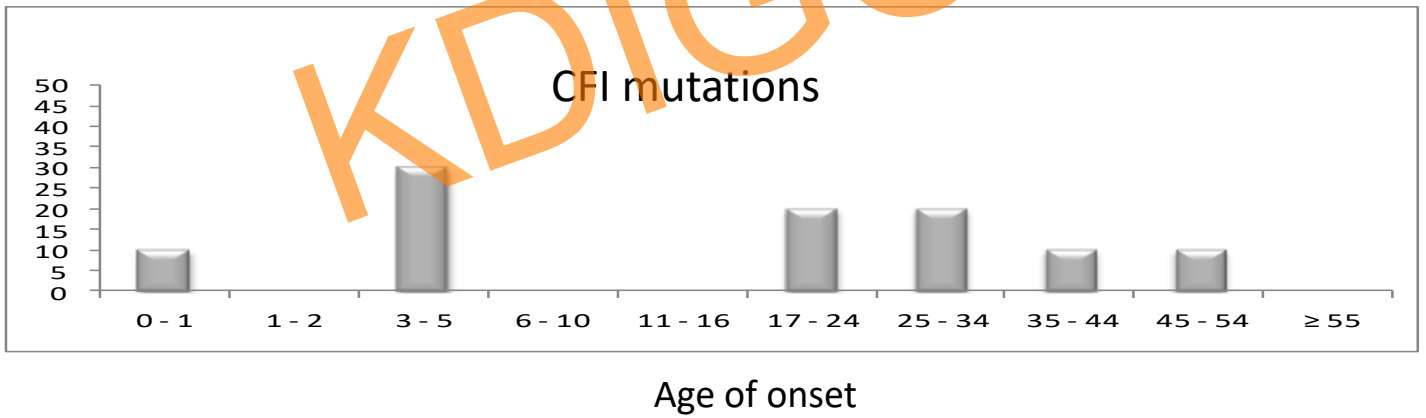
CLASSIFICATION OF THROMBOTIC MICROANGIOPATHIES



Kidney Disease: Improving Global Outcomes

PENETRANCE





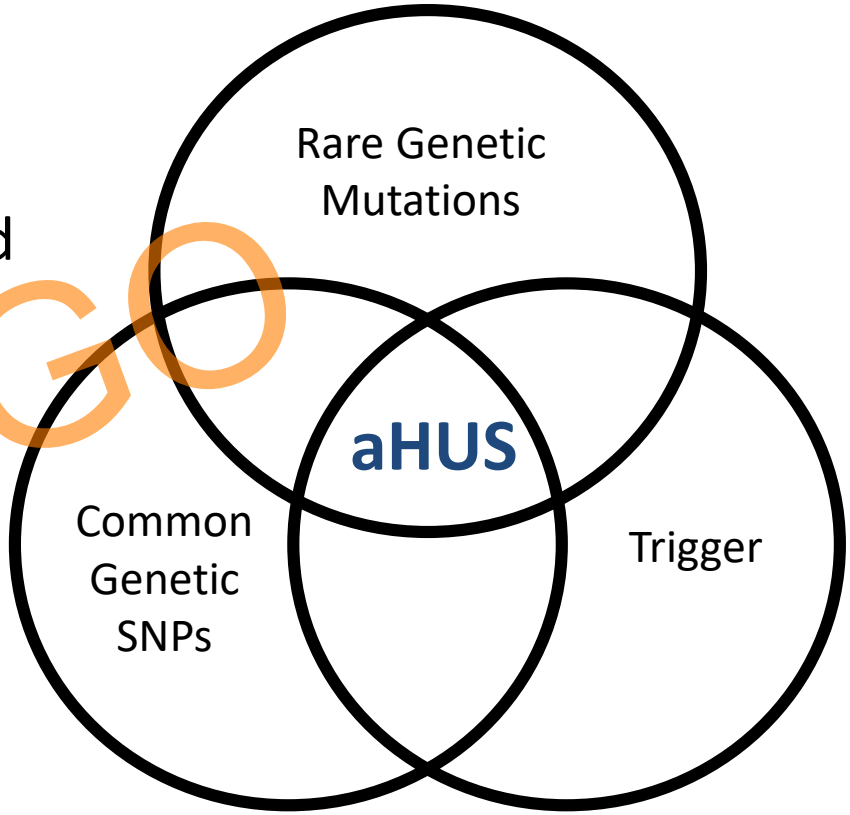
- Disease penetrance for an acute episode of aHUS in carriers of known pathogenic mutations increases with age.

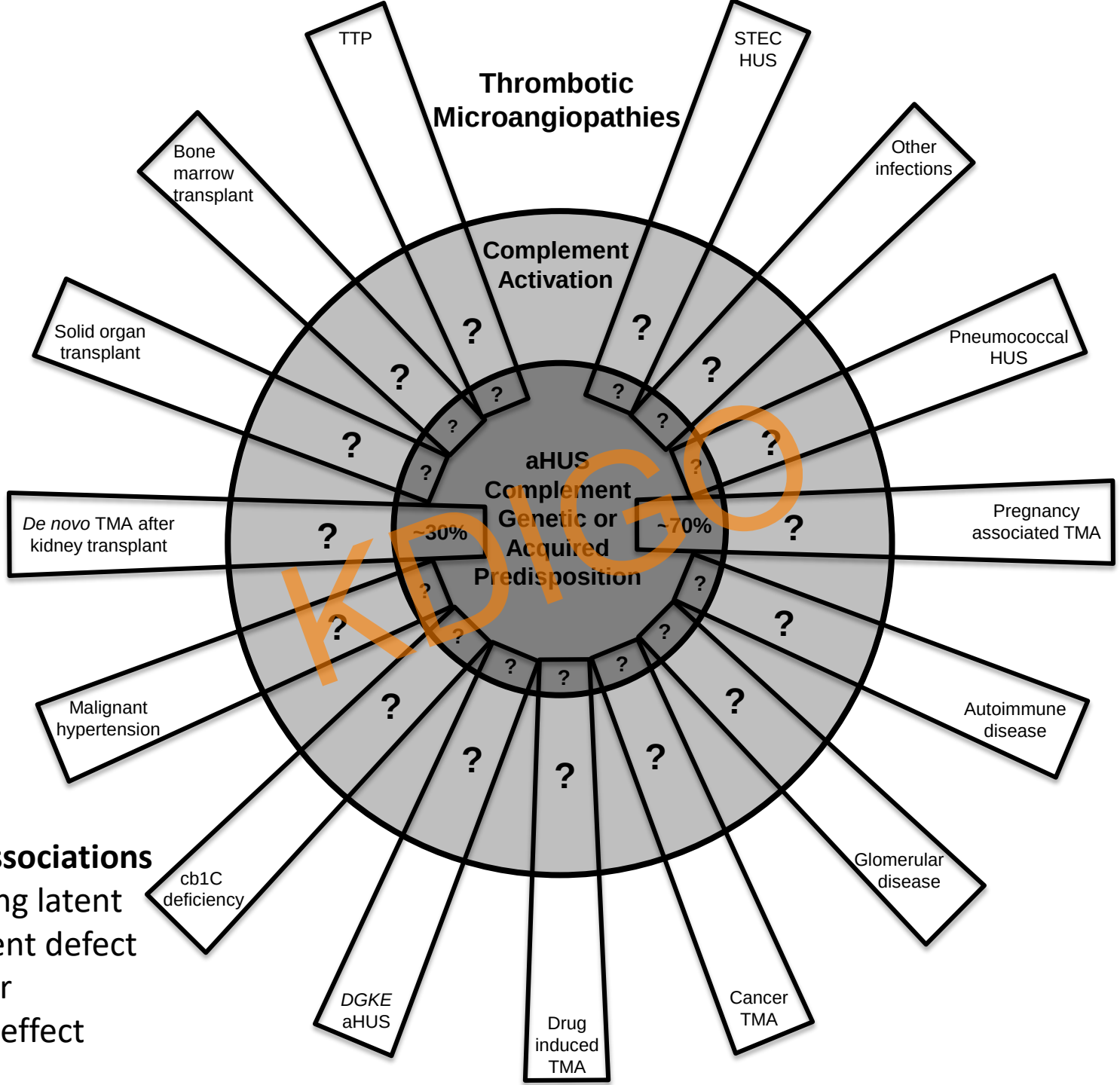
Noris CJASN 5:1844

aHUS

- Current classifications of aHUS reflect a better understanding of disease mechanisms, including the impact of genetic background and etiologic triggers.

- Triggers e.g. pregnancy, infections.





Multiple associations

Unmasking latent complement defect

Or

Direct effect

aHUS

- Eculizumab has changed the natural history of disease
  - Previously most rapidly progressed to ESRF
  - Prompt presentation usually leads to prompt resolution
  - Unclear what will happen on Ecu removal
- The time course and persistence of an aHUS episode are not well understood.
  - i.e. acute vs chronic disease
  - Some, but not all, patients may be at life-long risk for recurrent acute presentation.

C3G

- C3G generally follows a chronic, indolent course with persistent AP activation
- 10-year renal survival of approximately 50%.
- There are, however, cases of C3G that present as a rapidly progressive GN.

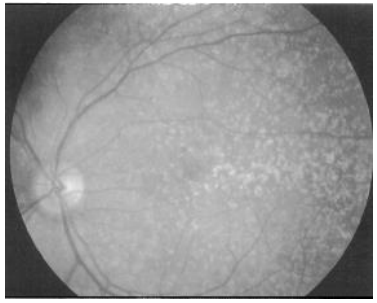
Extrarenal Manifestations

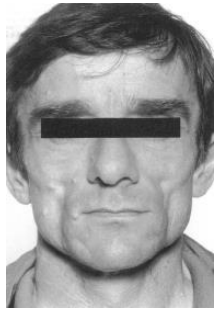
aHUS

- Extrarenal manifestations are reported in up to 20% of patients.
- It is unclear whether these manifestations are a direct consequence of complement activation, TMA, or other factors such as severe hypertension and uremia.

C3G

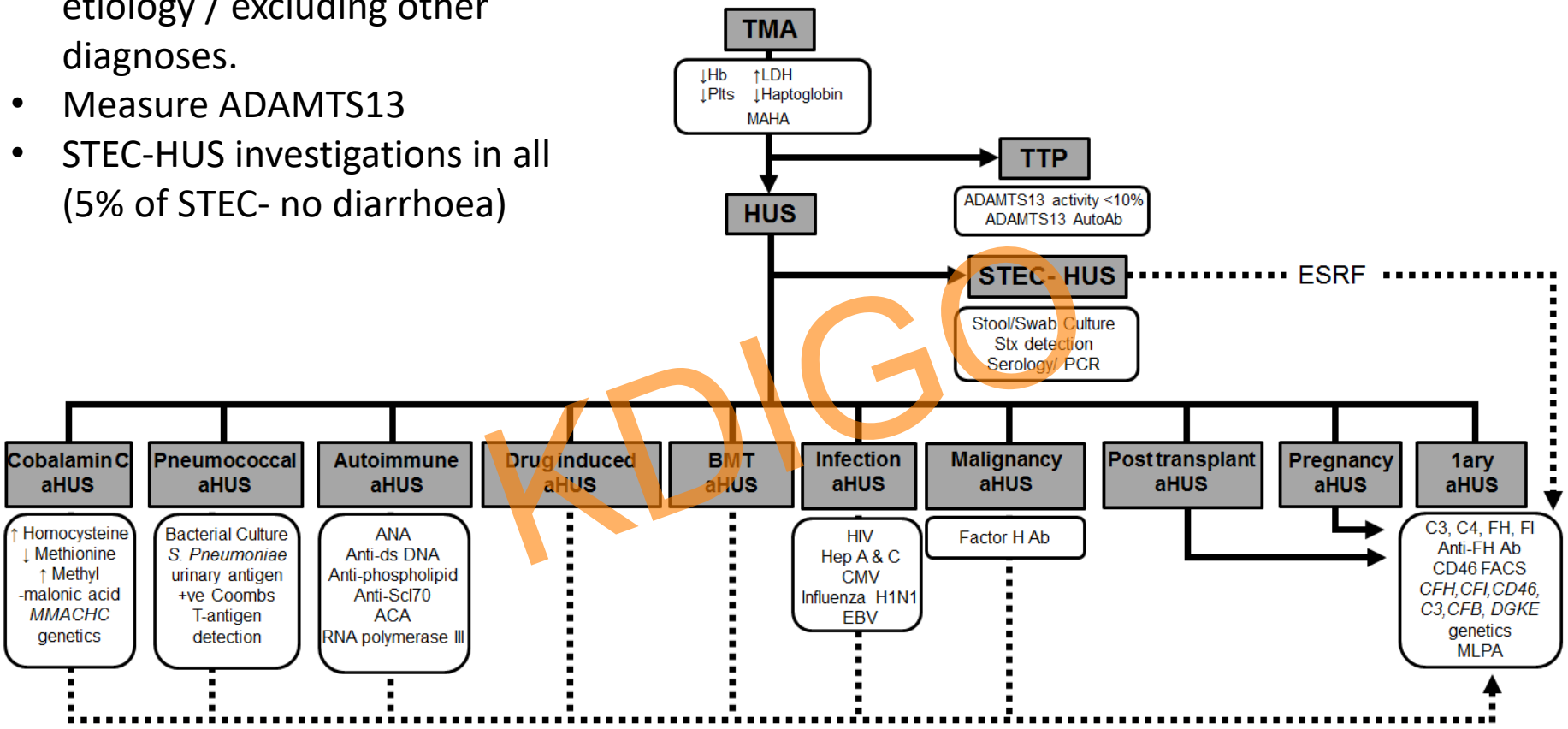
- Acquired partial lipodystrophy (APL) and retinal drusen are reported and appear to be direct consequences of complement activation.





LABORATORY ANALYSIS

- Determine underlying etiology / excluding other diagnoses.
- Measure ADAMTS13
- STEC-HUS investigations in all (5% of STEC- no diarrhoea)



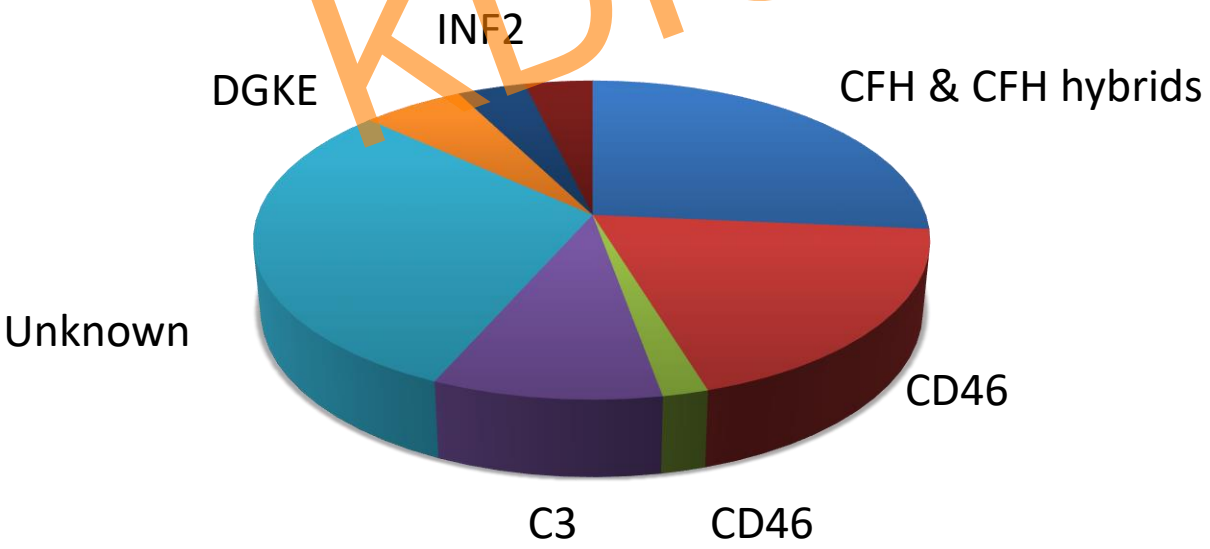
PART 4:

GENETIC AND ACQUIRED DRIVERS OF DISEASE

GENETIC DRIVERS OF DISEASE aHUS

aHUS

- Studies of hundreds of aHUS patients have provided an excellent understanding of genetic drivers of disease, leading to the development of individualized care.
- Genetic screening and molecular diagnostics, with expert interpretation of the results, should inform therapeutic decisions.



GENETIC DRIVERS OF DISEASE C3G

C3G

- Understanding of the genetics of C3G is not yet comparable to that of aHUS.

- There is no clear benefit to performing genetic analysis in all cases of C3G.

GENETIC TESTING

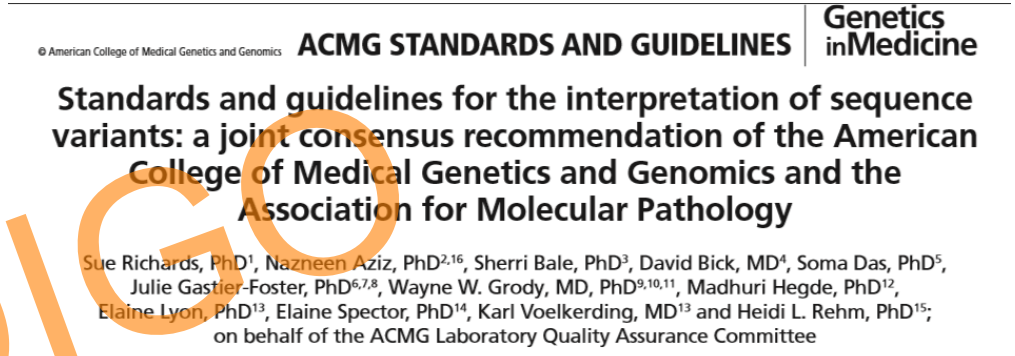
- In aHUS and C3G
  - Screen *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *THBD*, *CFHR1*, *CFHR5*, & *DGKE*.
- In aHUS,
  - Screen risk haplotypes *CFH-CFHR3* and MCP_{ggaac}
    - modify disease penetrance and severity.
- In both aHUS and C3G,
  - copy number variation analysis
  - hybrid genes and other complex genomic rearrangements in the *CFH/CFHRs* genomic region must be included in the genetic testing.

GENETIC TESTING

- In aHUS identification of pathogenic variant
  - Reinforces diagnosis & establishes cause of disease
  - Facilitates management & genetic counseling
- In aHUS genetic analysis is essential in living-related kidney donor transplantation.
  - Only consider if causative genetic factor identified & absent in donor
- In aHUS, genetic testing is recommended for patients in whom discontinuation of Eculizumab is being considered.
- In C3G less clear

UNDERSTANDING GENETIC VARIANTS

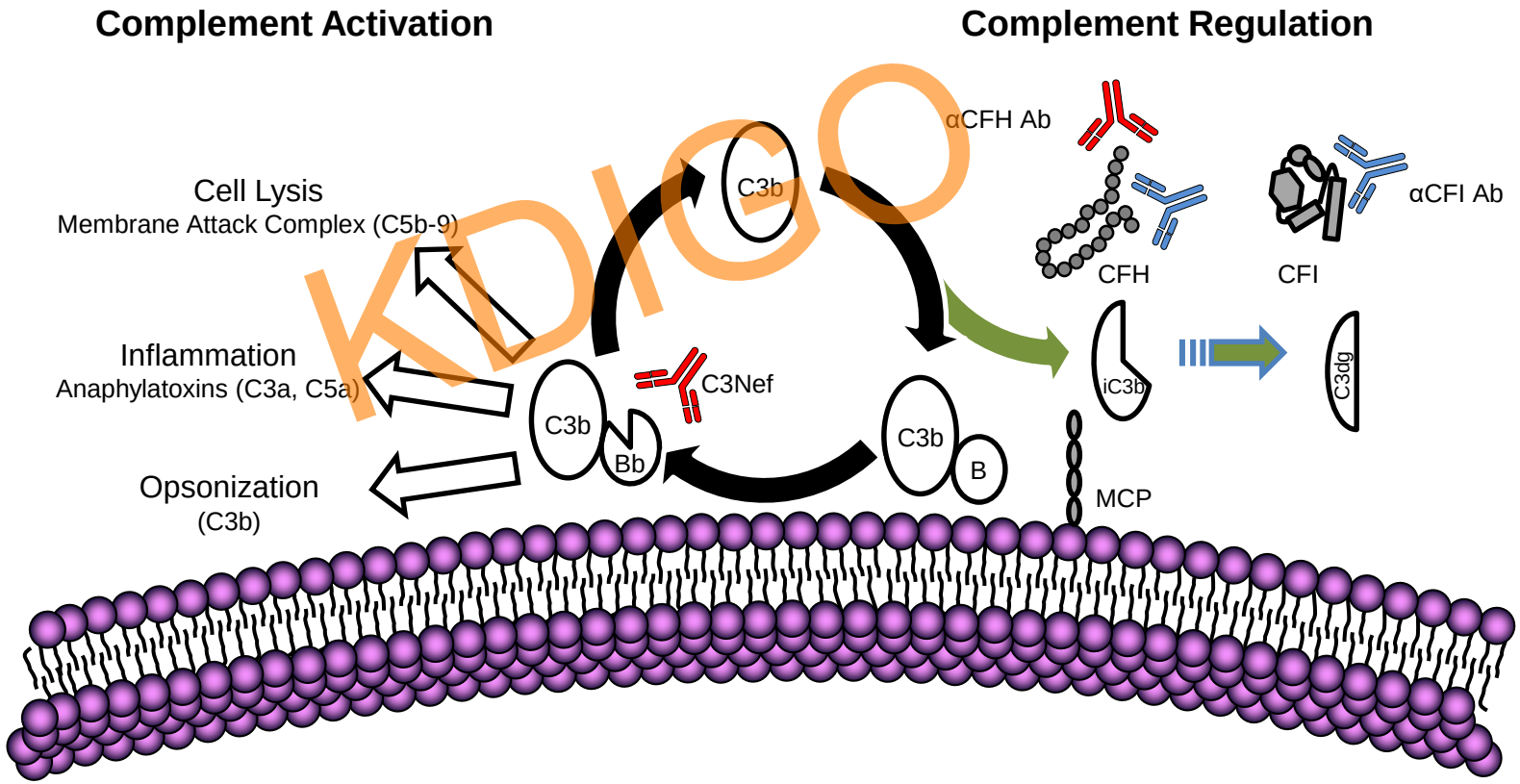
- Genetic variants should be classified as “benign,” “likely benign,” “variant of uncertain significance (VUS),” “likely pathogenic,” or “pathogenic,” following international guidelines.



- Genetic analysis should be interpreted by a laboratory with expertise in aHUS and C3G

Acquired Drivers of Disease

- In both aHUS and C3G, acquired drivers of disease are autoantibodies to complement proteins or protein complexes that impair normal function.



Acquired Drivers of Disease

- In aHUS, the best-studied acquired drivers are FH autoantibodies, which are usually seen in association with deletion of the *CFHR3* and *CFHR1* genes.
  - The deletion of *CFHR3* and *CFHR1* is a common copy number variation that can be identified on genetic testing.
  - The finding of FH autoantibodies should be confirmed in a second sample at least 4 weeks after the initial sample.

Acquired Drivers of Disease

- In C3G, the most common autoantibodies are to C3 convertase, a serine protease formed from C3b and Bb
  - These autoantibodies are called C3Nefs
  - They stabilize C3 convertase and prolong its half-life
- Other antibodies in C3G include FH autoantibodies and C4Nefs
- In older adults, serum free light chains (FLC) should be assayed.
  - Serum FLC assays have contributed to major improvements in care for patients with monoclonal gammopathy.
  - Serum FLC assays can be used as a first-line test in screening pathways for a light chain clone in older adults with kidney disease

PART 5:

TREATMENT STRATEGIES

TREATMENT: aHUS

- All patients with a clinical diagnosis of primary aHUS are eligible for treatment with eculizumab.
  - The dosing schedule as per Eculizumab registration trials

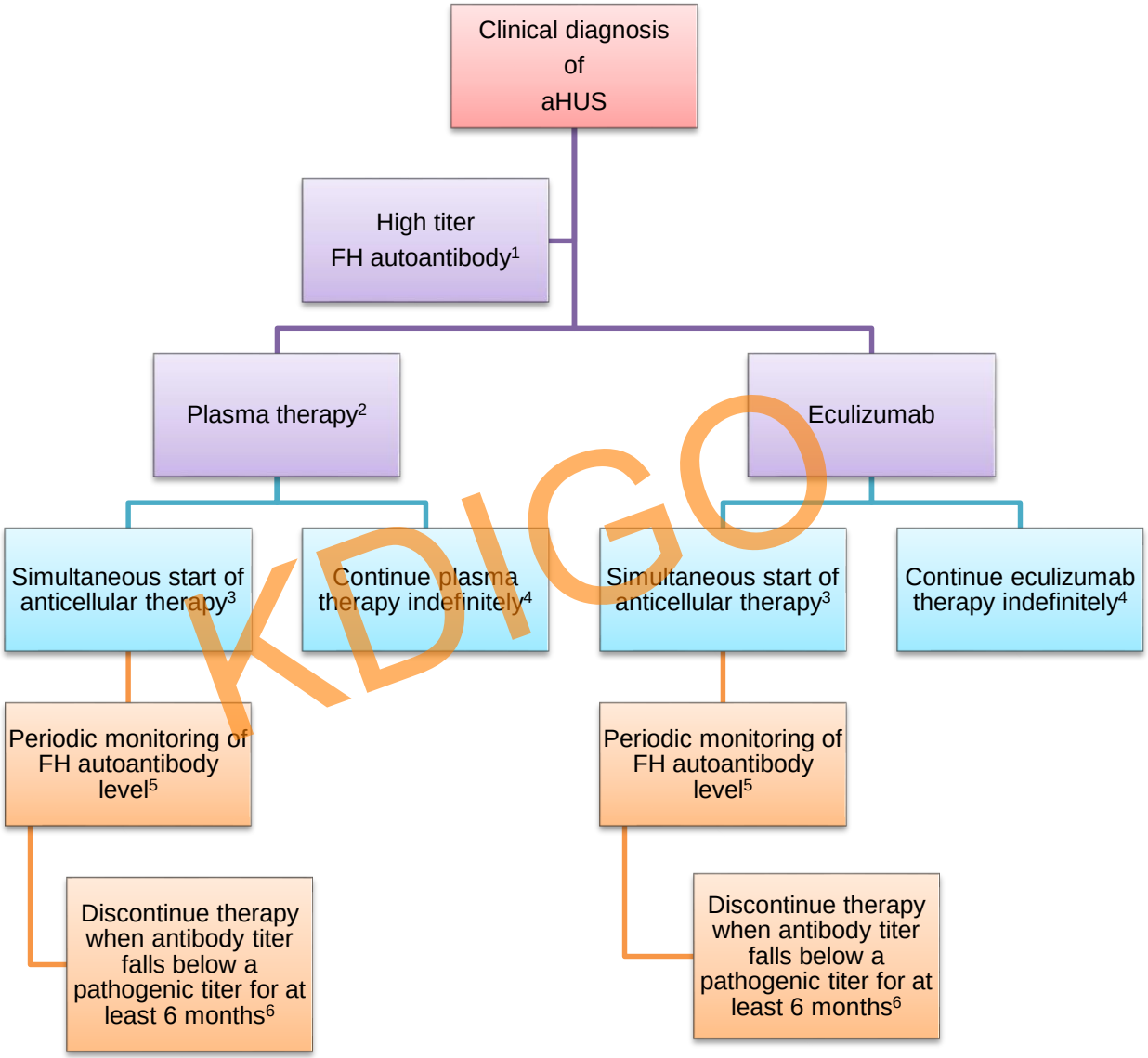
- Treatment duration is controversial as there is no evidence to support life-long therapy in all aHUS patients.
  - Two options for long-term dosing have been considered:
    - The minimal dose required to achieve complement blockade
    - A discontinuation dosing schedule.
  - Dose reduction or discontinuation require ongoing monitoring

TREATMENT: aHUS

- If access to eculizumab is unavailable, plasma therapy can be used.
- The use of plasma exchange when eculizumab is available may be associated with some improvement but delaying use of eculizumab may lead to a suboptimal therapeutic outcome.
- Eculizumab increases the risk of meningococcal infection.
  - Patients should receive vaccination against meningococcus (including Type B); however, vaccination should not delay the start of eculizumab therapy.
  - Antibiotic prophylaxis is mandated during the first 2 weeks.

TREATMENT: aHUS: TRANSPLANT

- Kidney transplantation should be delayed for at least 6 months after the start of dialysis as limited renal recovery is possible several months after starting eculizumab.
- Living-related kidney donation carries a risk for recurrence in the recipient and a risk of de novo disease in the donor should the donor carry an at-risk genetic variant.
- Liver transplant remains an option in patients with liver-derived complement protein abnormalities, in particular for renal transplant recipients with uncontrolled disease activity despite eculizumab therapy.


Clinical diagnosis of aHUS
High titer FH autoantibody[1]
Plasma therapy[2]
Eculizumab
Simultaneous start of anticellular therapy[3]
Continue plasma therapy indefinitely[4]
Simultaneous start of anticellular therapy[3]
Continue eculizumab therapy indefinitely[4]
Periodic monitoring of FH autoantibody level[5]
Periodic monitoring of FH autoantibody level[5]
Discontinue therapy when antibody titer falls below a pathogenic titer for at least 6 months[6]
Discontinue therapy when antibody titer falls below a pathogenic titer for at least 6 months[6]

TREATMENT: C3G: ALL PATIENTS

All Patients	• Optimal blood pressure control (suggested blood pressure below the 90% in children and ≤120/80 in adults) • Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers • Optimal nutrition for both normal growth in children, healthy weight in adults • Lipid control
Moderate Disease	**Description** • Urine protein over 500 mg/24 hours despite supportive therapy ***OR*** • Moderate inflammation on renal biopsy ***OR*** • Recent increase in serum creatinine suggesting risk for progressive disease **Recommendation** • Prednisone • Mycophenolate mofetil
Severe Disease	**Description** • Urine protein over 2000 mg/24 hours despite immunosuppression and supportive therapy ***OR*** • Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy ***OR*** • Increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy **Recommendation** • Methylprednisolone pulse dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease • Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

TREATMENT: C3G

- A retrospective study supports the effectiveness of mycophenolate mofetil in C3GN patients.
- No specific recommendation can be made for plasma therapy or rituximab (an anti-CD20 antibody).
- Since the pathogenesis of C3G is due to dysregulation and hyperactivity of the alternative pathway of complement, eculizumab has been tried in a limited number of patients with varied results.

TREATMENT: C3G: TRANSPLANT

- No specific data are available to inform decisions surrounding transplantation in C3G.
- Recommendations reflect expert opinion and limited case reports.
- C3G recurs in allografts at a high rate, leading to graft loss in ~50% of patients.

Research Recommendations: Summary

- aHUS
  - A comparative study of biopsies from patients with well-documented malignant hypertension and patients with well-documented alternative complement pathway disease
  - A longitudinal study of patients with features of chronic microangiopathy on biopsy but without a history of acute presentation
- C3G
  - A multicenter study analyzing biopsies to define the relationship of morphology to etiology, clinical course and response to therapy
  - Comprehensive genetic testing to fill the knowledge gap in establishing robust phenotype-genotype correlations

Research Recommendations: Summary

- Clinical studies – aHUS
  - Define how complement biomarkers correlate with current or impending aHUS relapse and/or renal involvement
  - Identify risk factors for relapse upon cessation of anti-complement therapy
  - Identify alternative anti-complement therapeutics
- Clinical studies – C3G
  - Assess the value of proximal (at the level of the AP) anti-complement therapy
    - Development and trial novel complement inhibitors
  - Determine value of complement biomarkers to inform clinical outcome in C3G patients and stratify them into targeted treatment groups

CONCLUSIONS

- While there are knowledge gaps in both aHUS and C3G, the evidence base for the management of patients with C3G lags behind that of aHUS; addressing this disparity should be a priority.

- Although these two diseases are presented as distinct entities, there is substantial overlap in their pathogenesis and clinical presentation.

Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

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