CONTROVERSIES CONFERENCE ON GLOMERULAR DISEASE

MPGN AND C3G

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Disclosure of Interests

I have no disclosures relevant to today's presentation. The following includes a list of recent affiliations:

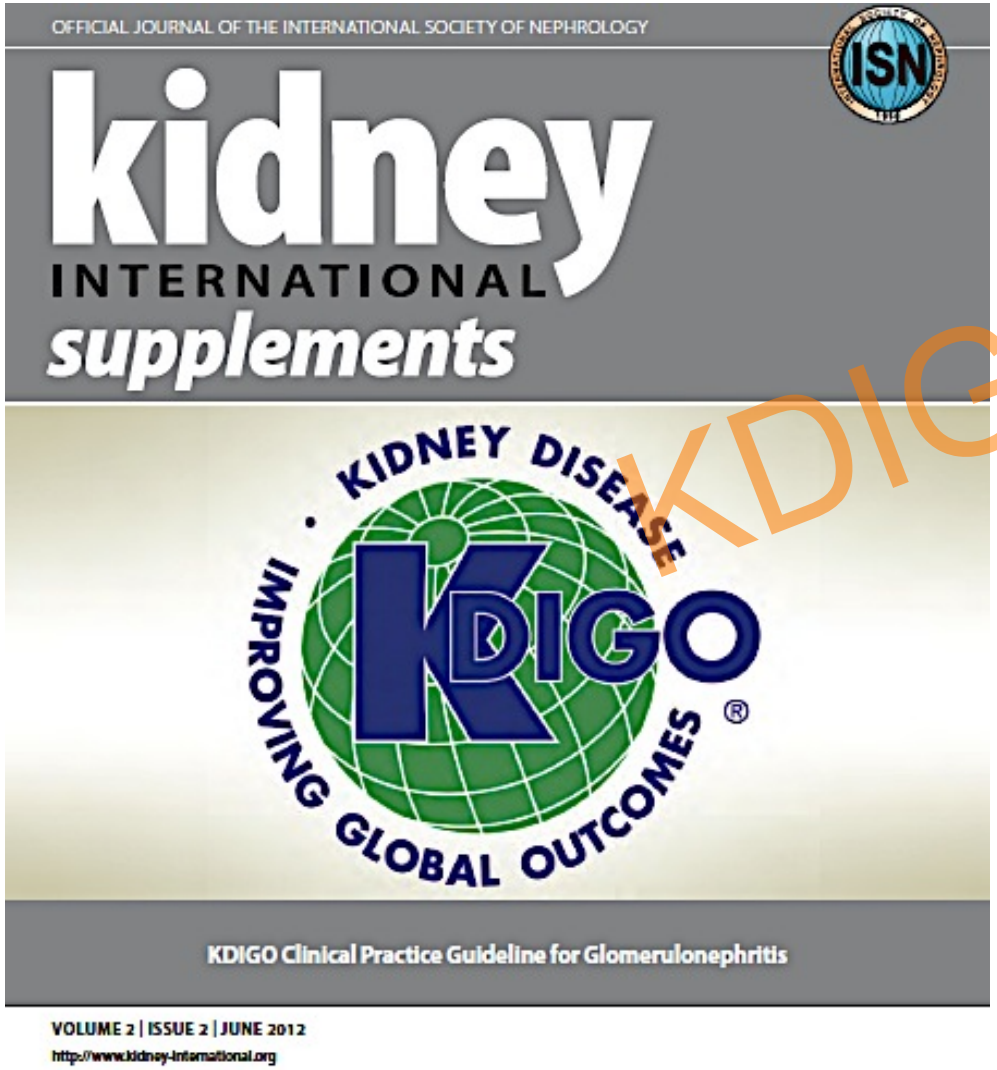
Affiliation / Financial Interest	Organization
2016 – Consultant	Achillion Pharmaceuticals

My conflicts are managed by a University of Iowa mandatory conflict plan. Both prior and current relationships are on record at the University of Iowa's Conflict in Research Office: https://coi.research.uiowa.edu/

Objectives

- Summarize the state of the literature pertaining to topic
- Identify new and important questions or controversies related to diagnosis and management of these diseases
- Explain why these topics are controversial
- Evaluate the data supporting opinions related to these questions/controversies
- Discuss what types of studies would help to move the field forward with regards to these questions

Historical Perspective



Chapter 8 - Idiopathic Membranoproliferative Glomerulonephritis

- "Light microscopic pattern of injury"
- "Further classified based on the extent and location of deposits" (I, II, and III)
- "Heterogeneity of cause"
- "Truly idiopathic MPGN is now a very uncommon condition"
- "Those in which C3 is exclusively deposited are known as C3GN".
- "Treatment is highly dependent on proper identification of underlying cause."

Etiologic Perspective

- Biopsy diagnoses - defined primarily by the character/ location of deposits
  - MPGN: Pattern of injury with multiple causes.

versus

  - C3G: Abnormal complement role (with no way to rule out „normal“ complement activity)

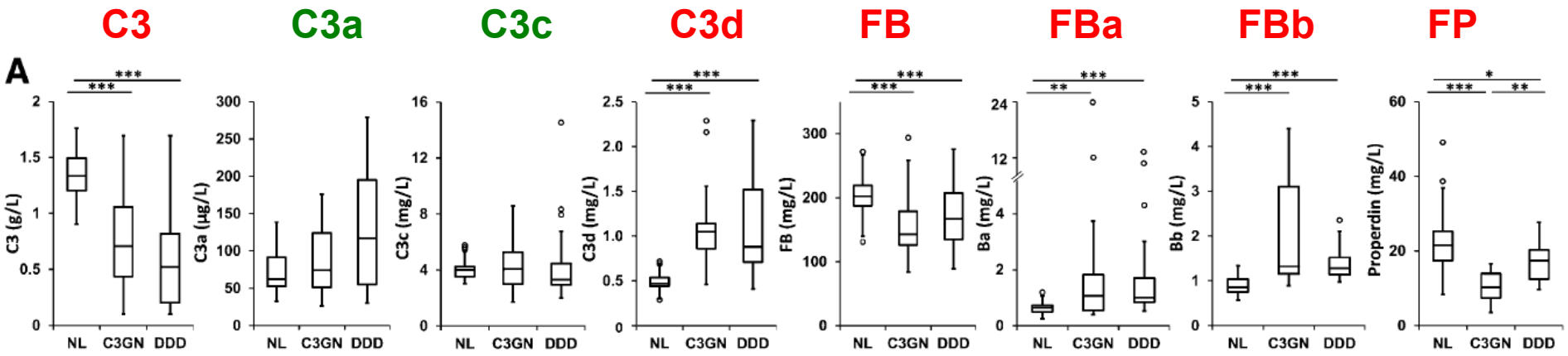
Definition of C3 Glomerulopathy

C3 glomerulopathy: consensus report

Matthew C. Pickering[1], Vivette D. D'Agati[2], Carla M. Nester[3,4], Richard J. Smith[3,4], Mark Haas[5], Gerald B. Appel[6], Charles E. Alpers[7], Ingeborg M. Bajema[8], Camille Bedrosian[9], Michael Braun[10], Mittie Doyle[9], Fadi Fakhouri[11], Fernando C. Fervenza[12], Agnes B. Fogo[13], Véronique Frémeaux-Bacchi[14], Daniel P. Gale[15], Elena Goicoechea de Jorge[1], Gene Griffin[9], Claire L. Harris[16], V. Michael Holers[17], Sally Johnson[18], Peter J. Lavin[19], Nicholas Medjeral-Thomas[1], B. Paul Morgan[16], Cynthia C. Nast[5], Laure-Hélène Noel[20], D. Keith Peters[21], Santiago Rodríguez de Córdoba[22], Aude Servais[23], Sanjeev Sethi[24], Wen-Chao Song[25], Paul Tamburini[9], Joshua M. Thurman[17], Michael Zavros[26] and H. Terence Cook[1]

"……. designates a disease process due to abnormal control of complement activation, deposition, or degradation and characterized by predominant glomerular C3 fragment deposition……."

Kidney Int. 2014 Feb;85(2):450-6.

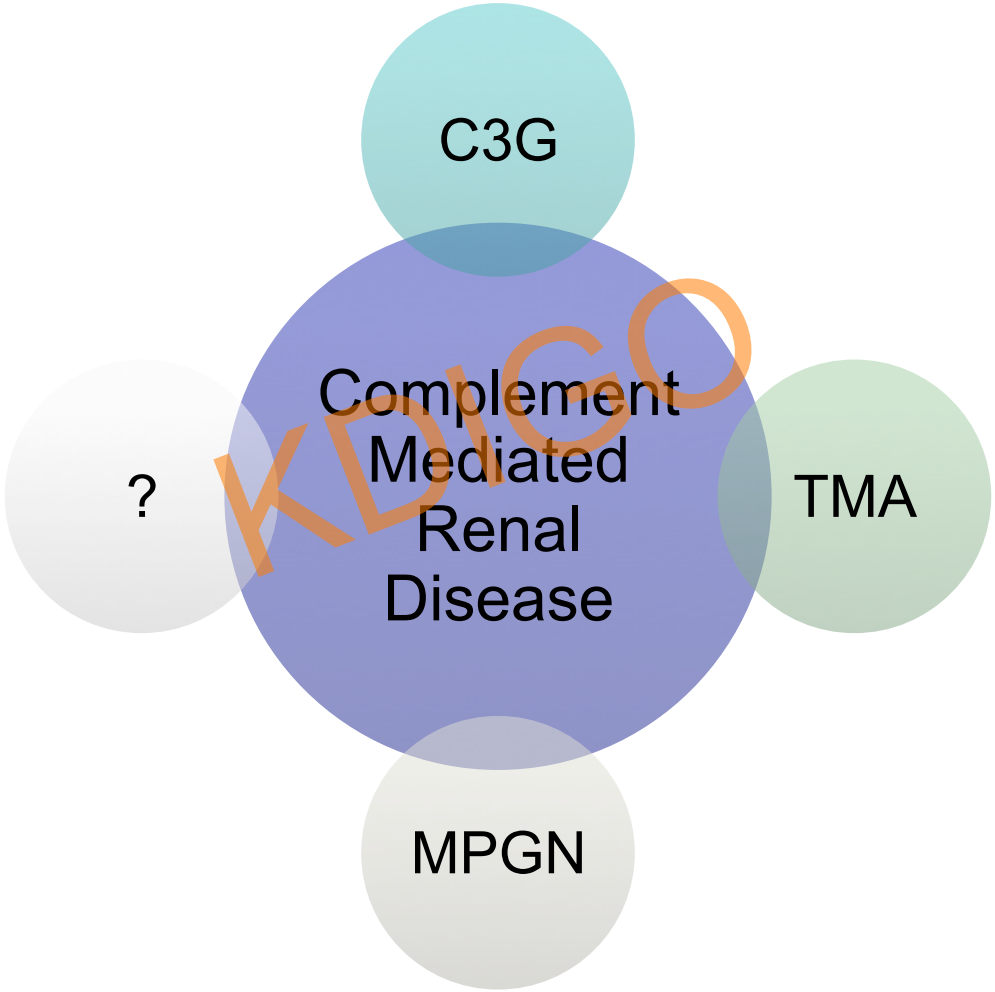


Role of Biomarkers

- Target Identifiers?
- Outcomes Signals?

Clin J Am Soc Nephrol. 2014 Nov 7;9(11):1876-82.

Complement and the Kidney



MPGN and C3G: Spectrum?

	MPGN	DDD	C3GN

Kidney International (2012) 82, 454–464;

Background: KDIGO Guidelines

8.1: Evaluation of MPGN

8.1.1: Evaluate patients with the histological (light microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (Not Graded)

Table 20 | Underlying conditions associated with a membranoproliferative pattern of GN

Chronic infections (especially hepatitis C)
Autoimmune diseases (especially LN)
Monoclonal gammopathies (especially light-chain deposition disease and monoclonal IgG disease)
Complement dysregulation (especially complement factor H deficiency)
Chronic and healed thrombotic microangiopathies

2012 Controversies Conference

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

OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

Kidney International (2017) 91, 539–551;

Complement Investigations

Tests recommended for all patients
Measurement of serum C3 and C4
Measurement of C3 Nephritic Factor
Measurement of serum factor H
Serum paraprotein ecalutation
Screening for *CFHR5* mutaton
Tests that should be considred on a case-by-case basis as they require expert interpretation and/or clinical validation
Measurement of serum factor B
Measurement of serum C5
Measurement of markers of C3 Activation
C3d, C3c, C3adesArg
Measurement of C5 activation
Soluble C5b-9
Measurement of FH autoantibodies
Measurement of FB autoantibodies
Mutation Screening of complement regulatory genes/activation genes
CFH, CFI, CD46/C3, CFB
Assessment of Copy Number cariants across the *CFH-CFHR* locus

The Challenge

Devising diagnostic and treatment approaches when heterogeneity prevails

Background: KDIGO Guidelines

8.2: Treatment of idiopathic MPGN
8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (2D)

Background

Table 2. Treatment failure

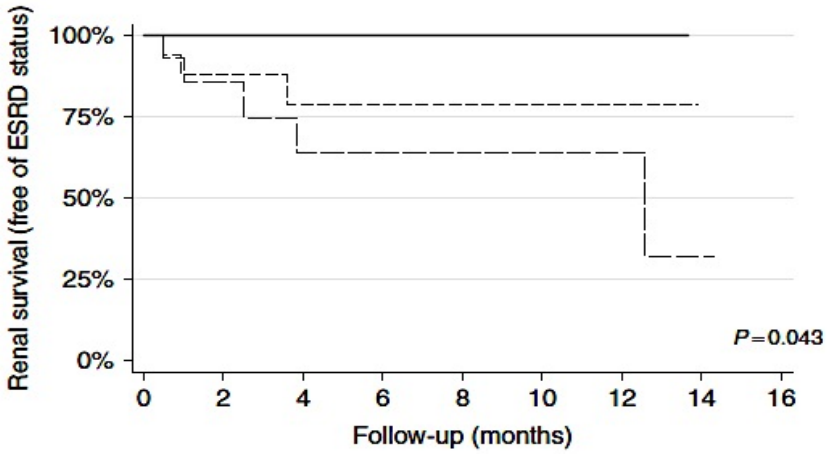
	Prednisone		Lactose		Fisher's exact	
					one-tailed	two-tailed
All patients ($n = 80$)	16/44	36.4%	18/33	54.5%	0.087	0.164
Status known						
Including 3 status unknown	19/47	40.4%	–	–	0.154	0.258
Types I, III ($n = 59$)	9/31	29.0%	15/26	57.7%	0.028	0.035
Status known						
Including 3 status unknown	11/33	33.3%	–	–	0.054	0.071
Type II ($n = 14$)	5/ 9	55.6%	3/ 5	60.0%	0.657	1.0
Status known						
Type unknown ($n = 7$)	2/ 4	50.0%	0/ 2	0%	0.400	0.467
Status known						
Including 1 status unknown	3/ 5	60.0%	–	–	0.286	0.429

RCTs of well characterized patients are needed.

Pediatr Nephrol (1992) 6: 123-130

Table 5. Kidney International (2017) 91, 539–551;

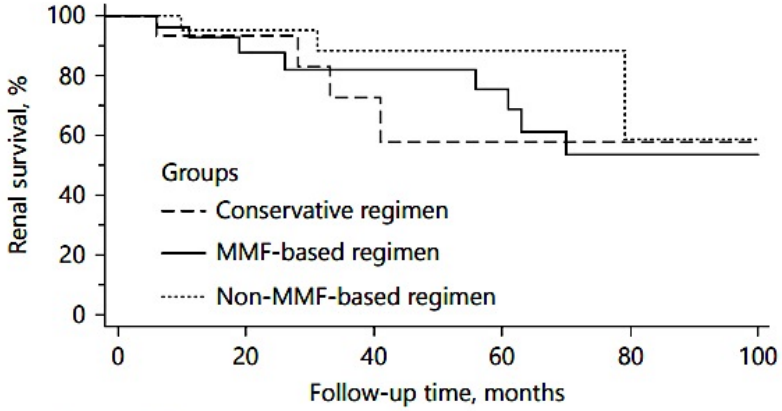
All Patients	• Optimal blood pressure control (Suggested: BP below the 90% in children and ≤ 120/80 in adults) ○ Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers, • Optimal nutrition for both normal growth in children, healthy weight in adults • Lipid control
Moderate Disease	**Description** • Urine protein over 500mg/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 500mg/24 hours despite supportive therapy • Or Moderate inflammation on renal biopsy • Or recent increase in serum creatinine suggesting risk for progressive disease **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.



MMF-IST ----- Other-IST
No IST

Patients at risk according to months of follow-up

Group of treatment	0	2	4	6	8	10	12	14	16
MMF-IST	22	15	10	5	4	4	2	1	1
Other-IST	18	13	10	6	4	2	2	1	1
No IST	20	14	11	7	6	6	5	4	3



Number at risk

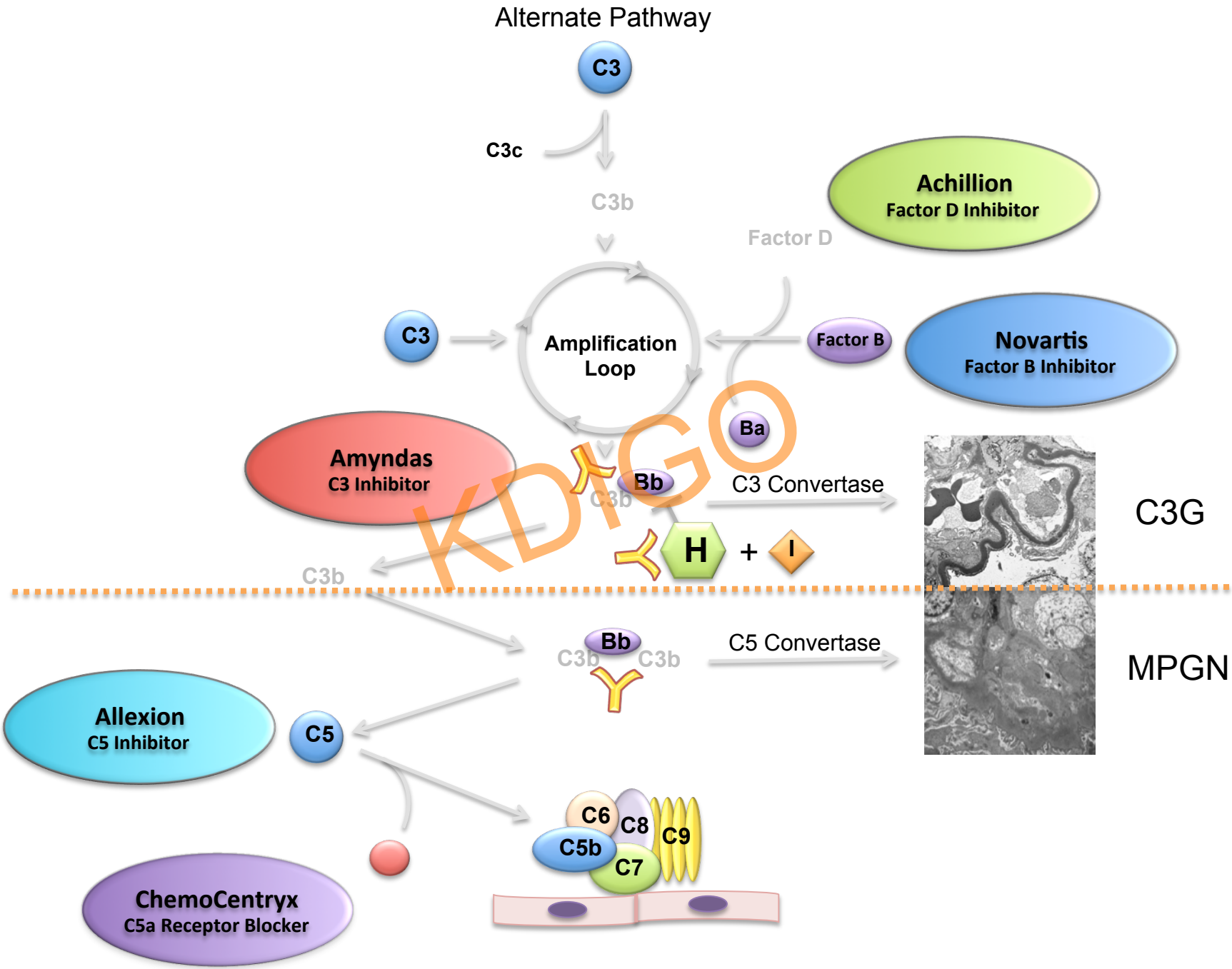
Group: conservative regimen						
16	12	5	4	3	2	
Group: MMF-based regimen						
27	18	15	11	4	4	
Group: non-MMF-based regimen						
a 23	14	9	5	2	1	

	No Immune Suppression	MMF	Other IST
Complete Remission	2/20 (40%)	6/22 (32%)	5/18 (56%
Partial Remission	3/20 (60%	13/22 (68%)	4/18 (44%)
ESRD	10/20 (35%	0/22 (0%)	3/18 (16%)

Kidney International (2015) 88, 1153–1160;

Am J Nephrol 2017;46:96-107

1	☐	Active, not recruiting	Eculizumab in Primary **MPGN**	**Membranoproliferative Glomerulonephritis**	Drug: Eculizumab
2	☐	Recruiting	A Proof-of-Mechanism Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients With C3G or IC-**MPGN**	C3 Glomerulonephritis Dense Deposit Disease **Membranoproliferative Glomerulonephritis**, Type II (and 2 more...)	Drug: ACH-0144471
3	☐	Not yet recruiting	Effect of Rituximab in Treatment of**Membranoproliferative Glomerulonephritis**	**Membranoproliferative Glomerulonephritis**	Drug: Rituximab Drug: Cyclosporin
4	☐	Recruiting	Daratumumab in Treatment of PGNMID and C3 GN	**Membranoproliferative Glomerulonephritis**	Drug: Daratumumab
5	☐	Completed	Pilot Study of Rituximab for**Membranoproliferative Glomerulonephritis**	Glomerulonephritis, Membranoproliferative	Drug: Rituximab
6	☐	Unknown †	Eculizumab Therapy for Dense Deposit Disease and C3 Nephropathy	Dense Deposit Disease **Membranoproliferative Glomerulonephritis**	Drug: Eculizumab
8	☐	Recruiting	Controlled Trial Evaluating Avacopan in C3 Glomerulopathy	C3 Glomerulopathy (C3G)	Drug: Avacopan Drug: Avacopan Matching Placebo


Alternate Pathway
C3
C3c
C3b
Factor D
Achillion
Factor D Inhibitor
C3
Amplification Loop
Factor B
Novartis
Factor B Inhibitor
Ba
Amyndas
C3 Inhibitor
Bb
C3b
C3 Convertase
H
+
I
C3G
C3b
Bb
C3b
C3b
C5 Convertase
MPGN
Allexion
C5 Inhibitor
C5
C6
C8
C9
C5b
C7
ChemoCentryx
C5a Receptor Blocker
KDIGO

Controversy

- Do we understand enough of the natural history of disease, or the variability in the phenotype?
- Do the differences in pathology signifiy an important phenotypic characteristic?
- Is complement „primary“/critical to the etiology of each of the dieases in the spectrum?
- Can the diagnosis (or activity) of either be secured with „biomarkers“?
    - What about genetics?
- Must we define disease more precisely in order to treat effectively?

Controversy

- Can we recommend a clinically/therapeutically important workup?
- What is “Idiopathic” MPGN?
- Is it time for us to say ICGN?