C3 Glomerulopathy

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C3G is Rare Kidney Diseases

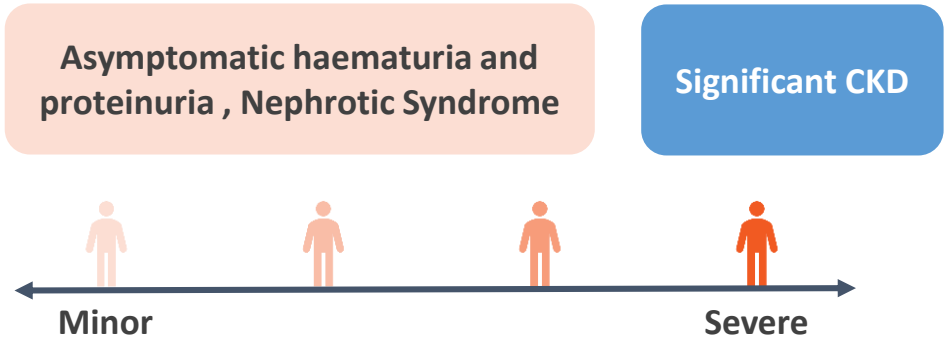
The **incidence** of C3G is estimated to be **1-3 cases per million per year**[1,2]

The estimated **prevalence** of C3G in US/Europe is **14-140 cases per million**[1,3]

1. Smith et al Nat Rev Nephrol 2019. 2. Caravaca-Fontan et al Nephron 2020. 3. 0.5 for IC-MPGN + 0.8 for C3G

The Clinical Presentation and Progression of C3G is Heterogenous

Presentation at diagnosis varies widely in severity[1,2]



Prognosis

Will progress to **ESRD** within 10 years, requiring **dialysis** or **transplantation**[3]

Other symptoms at presentation[1–4]

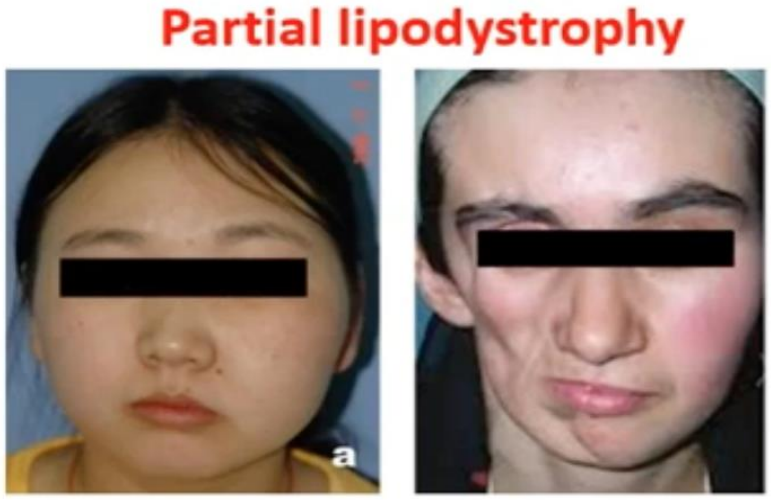
- Low serum C3 (**>50% of patients**)
- Retinal drusen
- Partial lipodystrophy

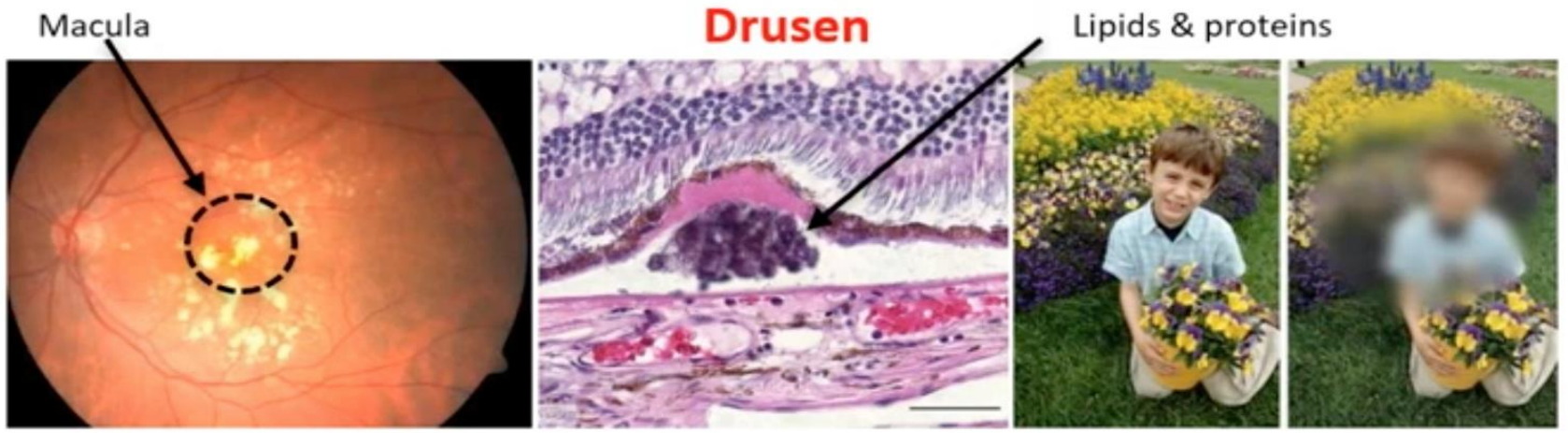
Renal transplantation:
High risk of recurrence (>80%) with poor allograft survival (50%)[1,4]

C3, complement 3; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; ESRD, end-stage renal disease; IC-MPGN, immune complex membranoproliferative glomerulonephritis.

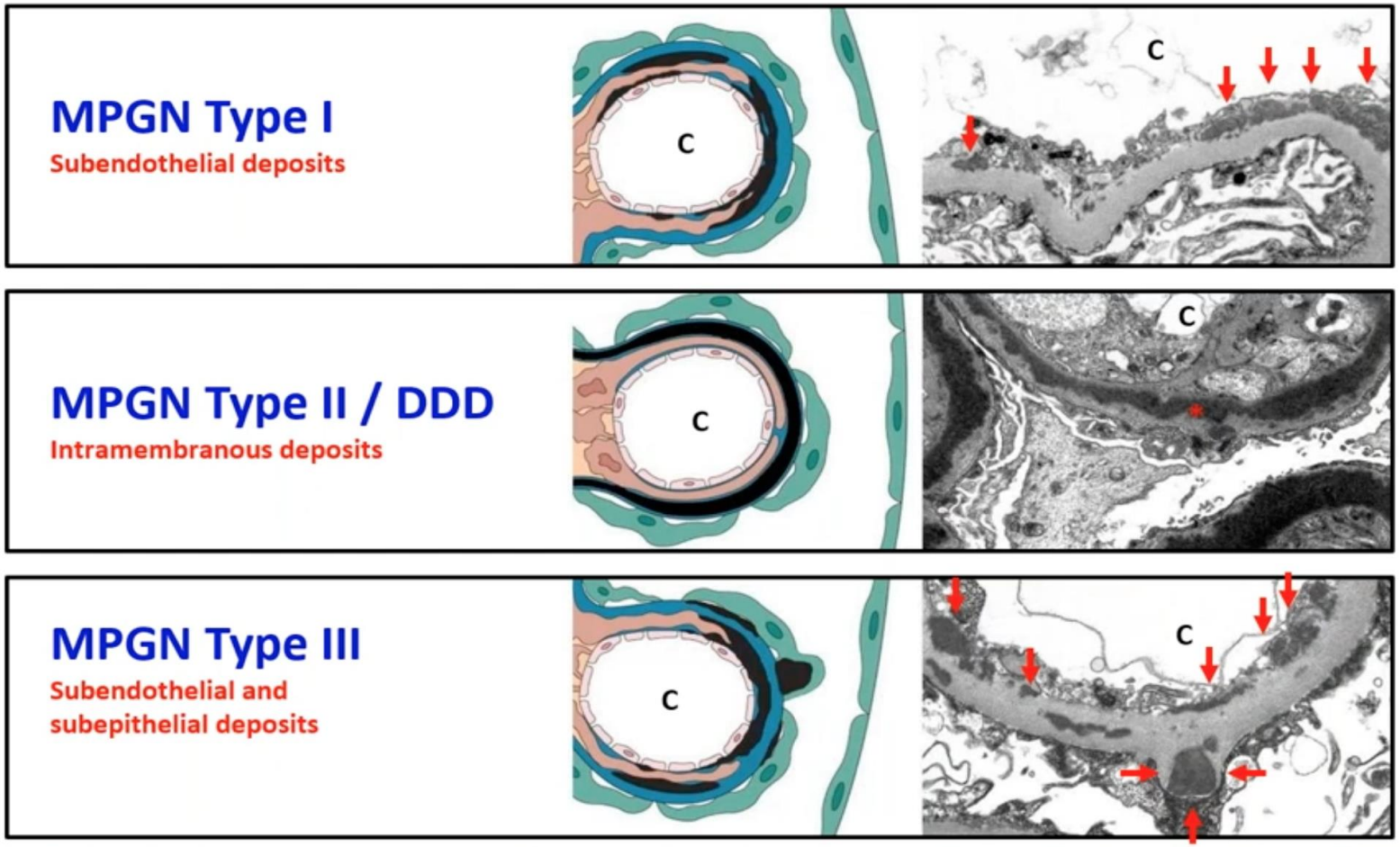
1. Servais A, *et al*. *Kidney Int* 2012;82:454–64; 2. Bomback AS, *et al*. *Kidney Int* 2018;93:977–85; 3. Smith RJH, *et al*. *Nat Rev Nephrol* 2019;15:129–43; 4. Caravaca-Fontan F, *et al*. *Nephron* 2020;144:272–80.

Phenotype :





Historical Perspective -MPGN : Old Classification



Low density deposits

High density deposits

Low density deposits

In 2007….A new disease Entity

ORIGINAL ARTICLE

Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome

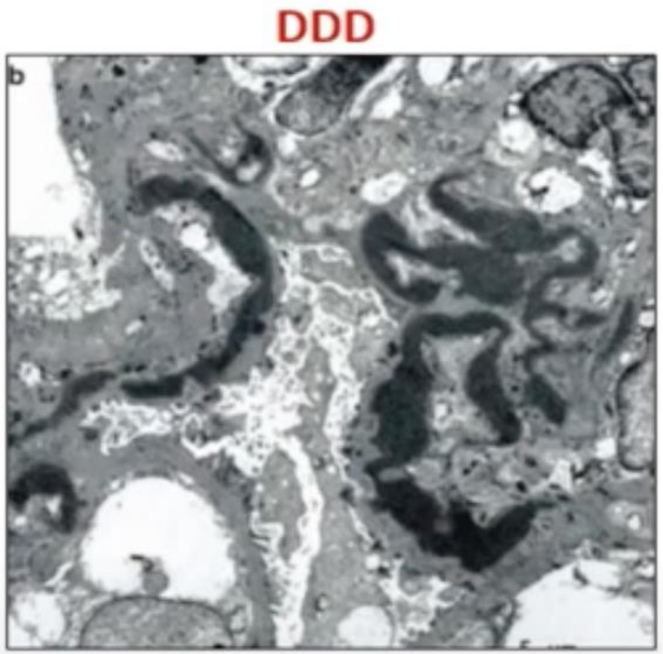
Aude Servais, Véronique Frémeaux-Bacchi, Moglie Lequintrec, Rémi Salomon, Jacques Blouin, Bertrand Knebelmann, Jean-Pierre Grünfeld, Philippe Lesavre, Laure-Hélène Noël, Fadi Fakhouri

J Med Genet 2007;**44**:193–199. doi: 10.1136/jmg.2006.045328

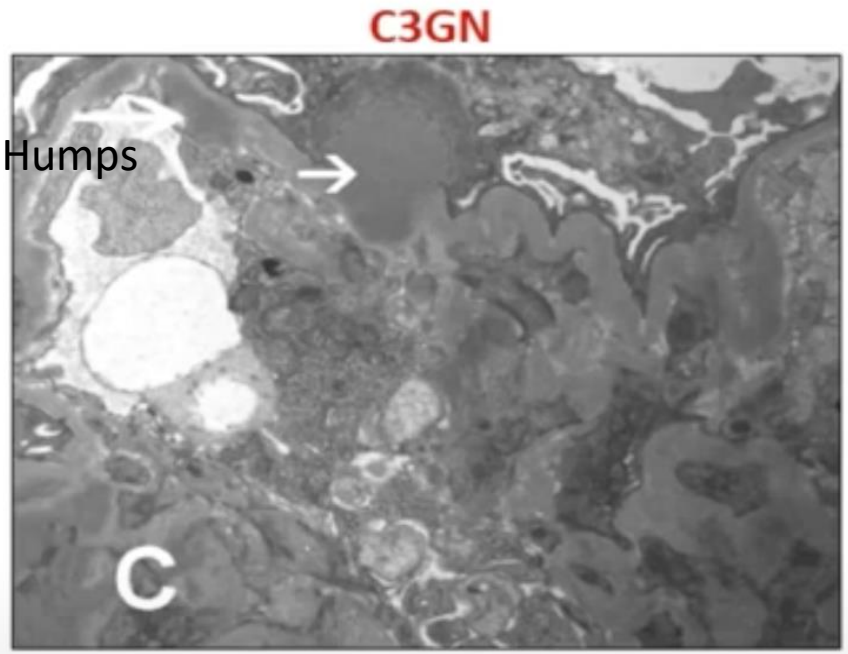
19 patients with unusual proliferative glomerulonephritis and:

- **evidence of complement dysregulation**
- **isolated C3 deposits**
- **no dense intramembranous deposits**

Two diseases with C3 Deposits – DDD and C3GN – Now classified as C3 Glomerulopathy (C3G)



Walker PD et al, Modern Pathol 2007

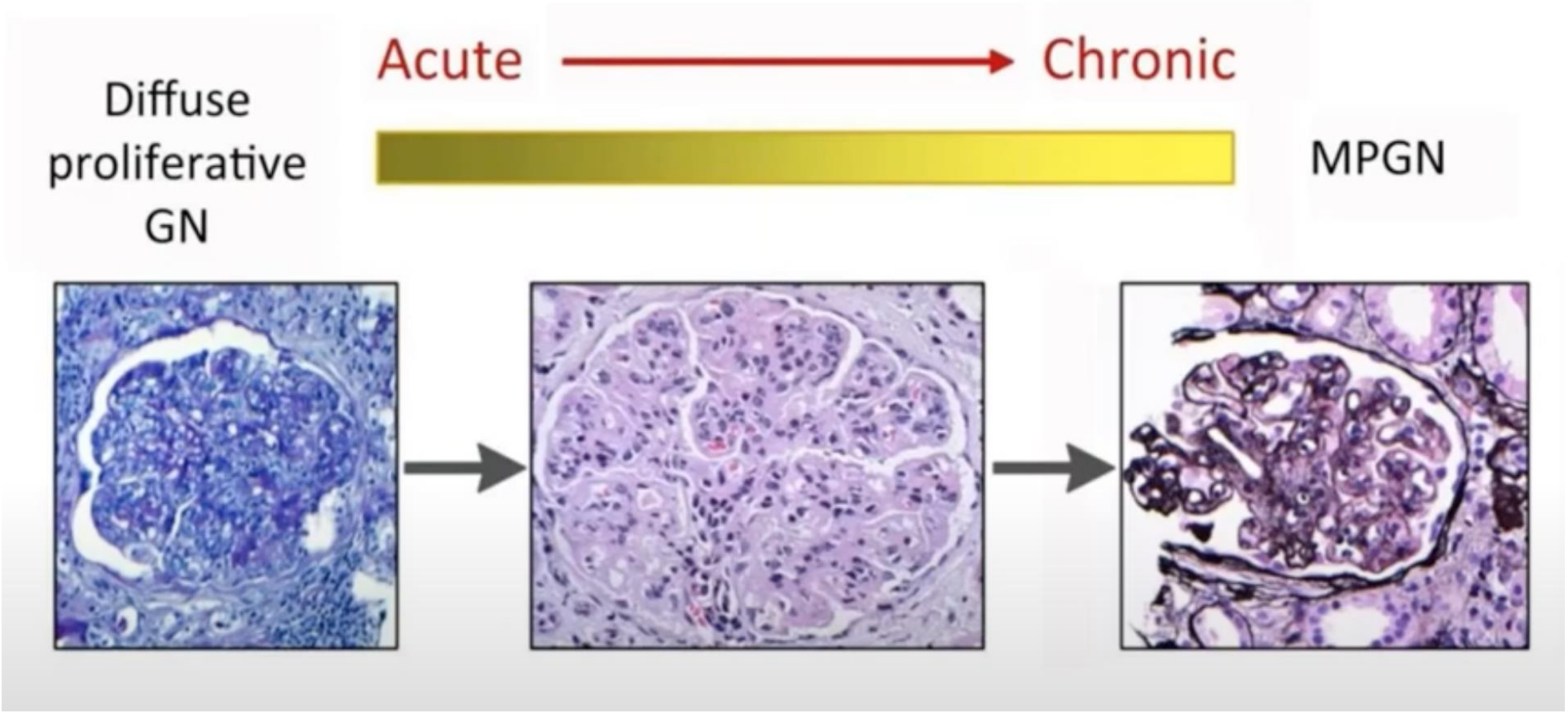


Sethi S et al, Clin J Am Soc Nephrol 2011

Subepithelial Humps also seen in Acute Post Infectious GN

Distinction between DDD and C3GN requires Electron Microscopy

Mesangial Proliferative and MPGN may represent a continuum of the same disease



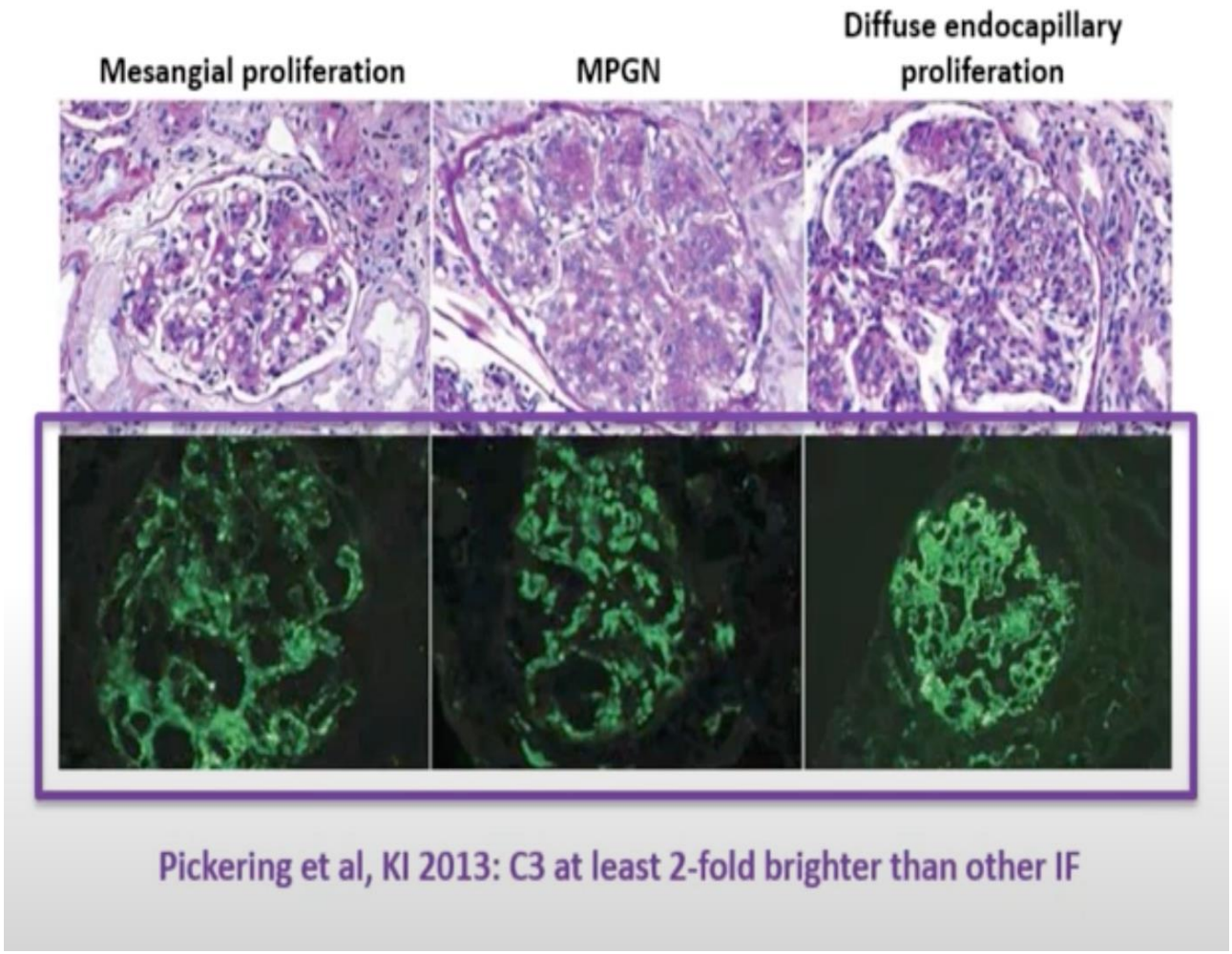
Deposition of Immunoglobulin and Complement along glomerular capillary walls ,leads to **inflammation and proliferative changes**

Healing/Resolving leads to remodeling of capillary walls

The MPGN lesion , is thus characterized by Inflammation and Healing

Sethi S, Fervenza FC: Semin Nephrol 2011

C3G in Kidney Biopsy – Light Microscopy and IF



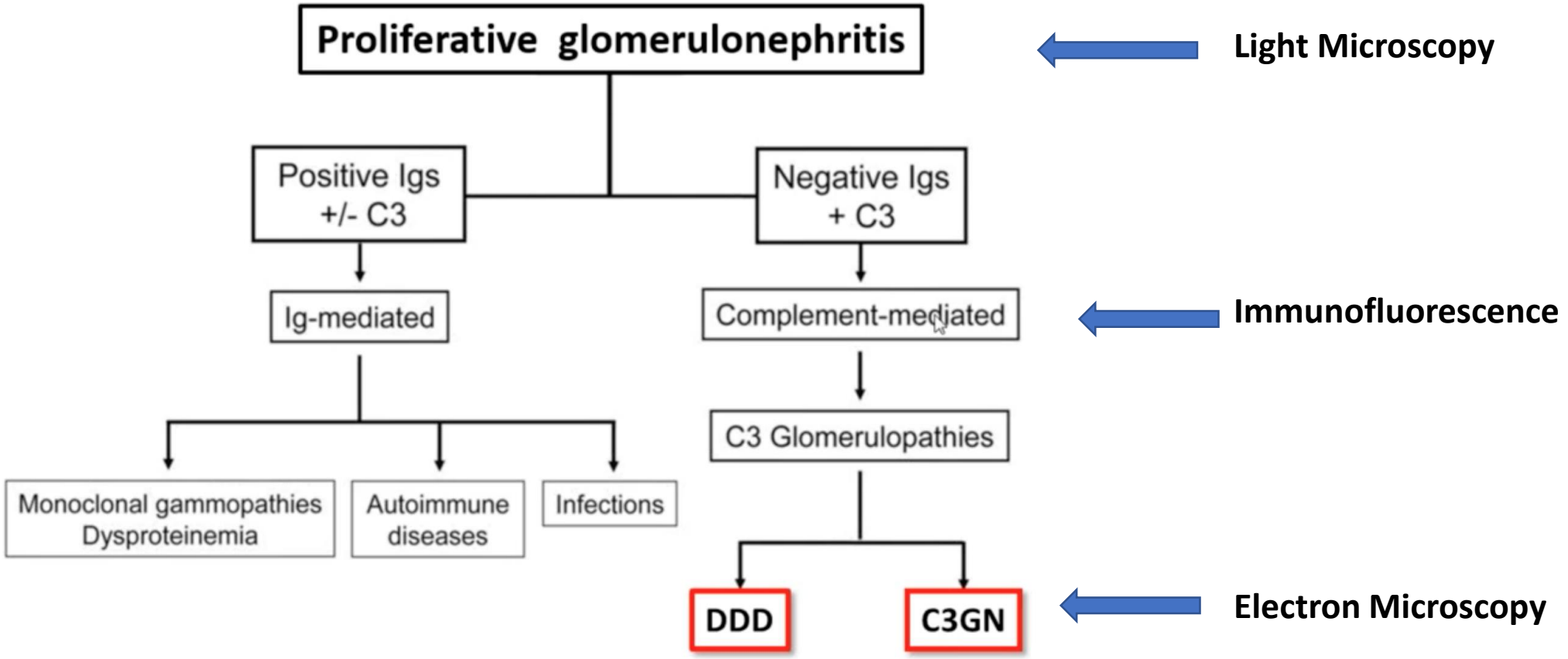
LM :
Inflammation Phase : **Endocapillary and Mesangial Proliferation**

Healing Phase: Mesangial expansion with matrix , thickened capillary walls and double contour formation : **Membrano-portion of MPGN**

IF : Immunoglobulins and C3 deposition

EM: mesangial and subendothelial capillary wall deposits and new BM formation : DOUBLE CONTOURS

2012: A New classification for MPGN : IC- MPGN vs C3 GN



Sethi S and Fervenza FC, Semin Nephrol 2011
Sethi S and Fervenza FC, NEJM 2012

MPGN is currently classified based on immunofluorescence analysis of kidney biopsies

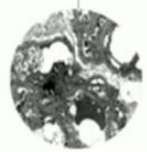
C3G and **IC-MPGN** are a group of complement-driven **renal diseases**[1,2]

Up to **17%** of patients shift from IC-MPGN to C3G when a kidney is repeated[2-4]

MPGN[1–4]

C3 Glomerulopathies (C3G)
No or few immunoglobulins
C3 dominant*

Dense Deposit Disease (DDD)



C3 Glomerulonephritis (C3GN)

C3/Ig Deposits (IC-MPGN)
Ig positive
Not C3 dominant*

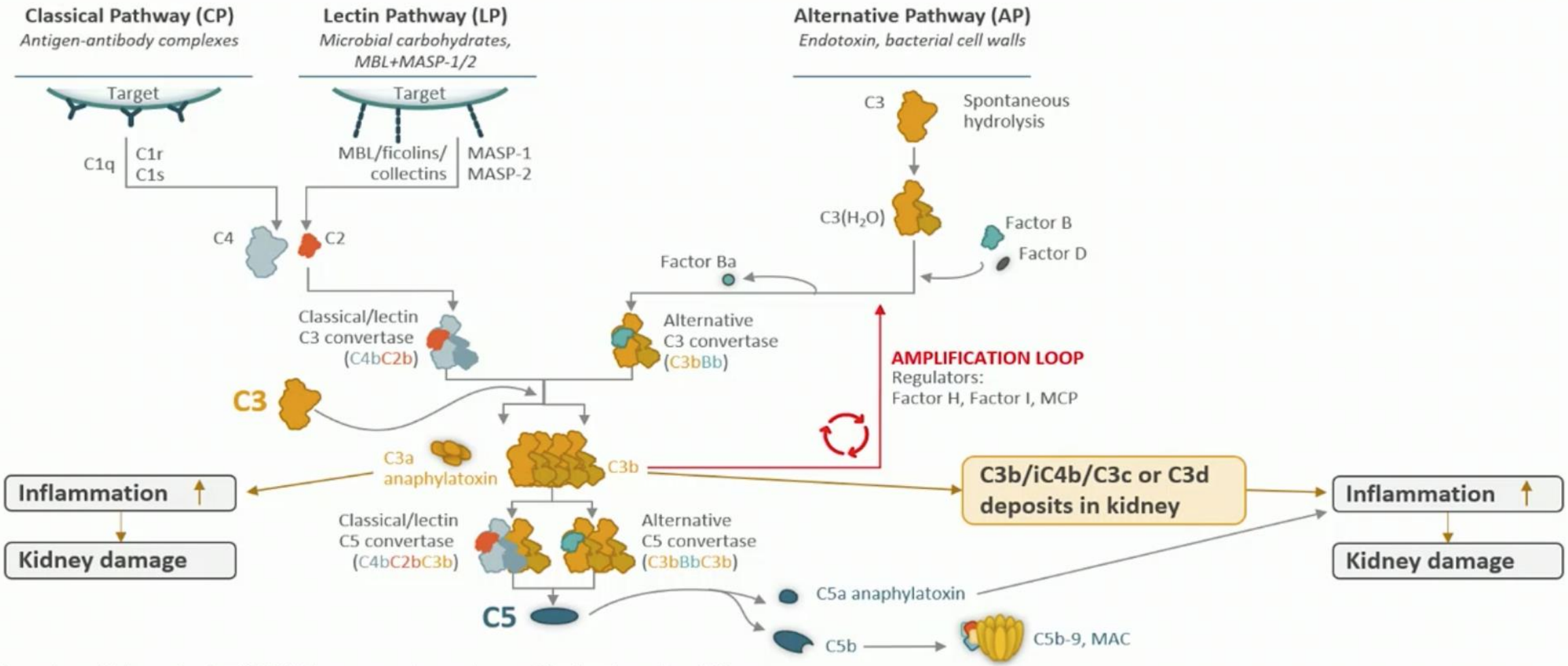
- Infectious diseases
- Autoimmune diseases
- Monoclonal gammopathies, dysproteinemia
- No underlying condition, primary IC-MPGN

*C3 dominant: C3 at least two orders of magnitude stronger than any other common immune reactant.
C3G, complement 3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis.

1. Medjeral-Thomas NR, *et al. Clin J Am Soc Nephrol* 2014;9:46–53; 2. Pickering MC, *et al. Kidn Int* 2013;84:1079–89; 3. Hou J, *et al. Kidn Int* 2014;85:450–56; 4. Kerns E, *et al. Ped Nephr* 2013;28:2227–31.

Images courtesy of the Arkana Photo Reference Library. https://www.arkanalabs.com/resources/physician-resources/. Accessed June, 2023.

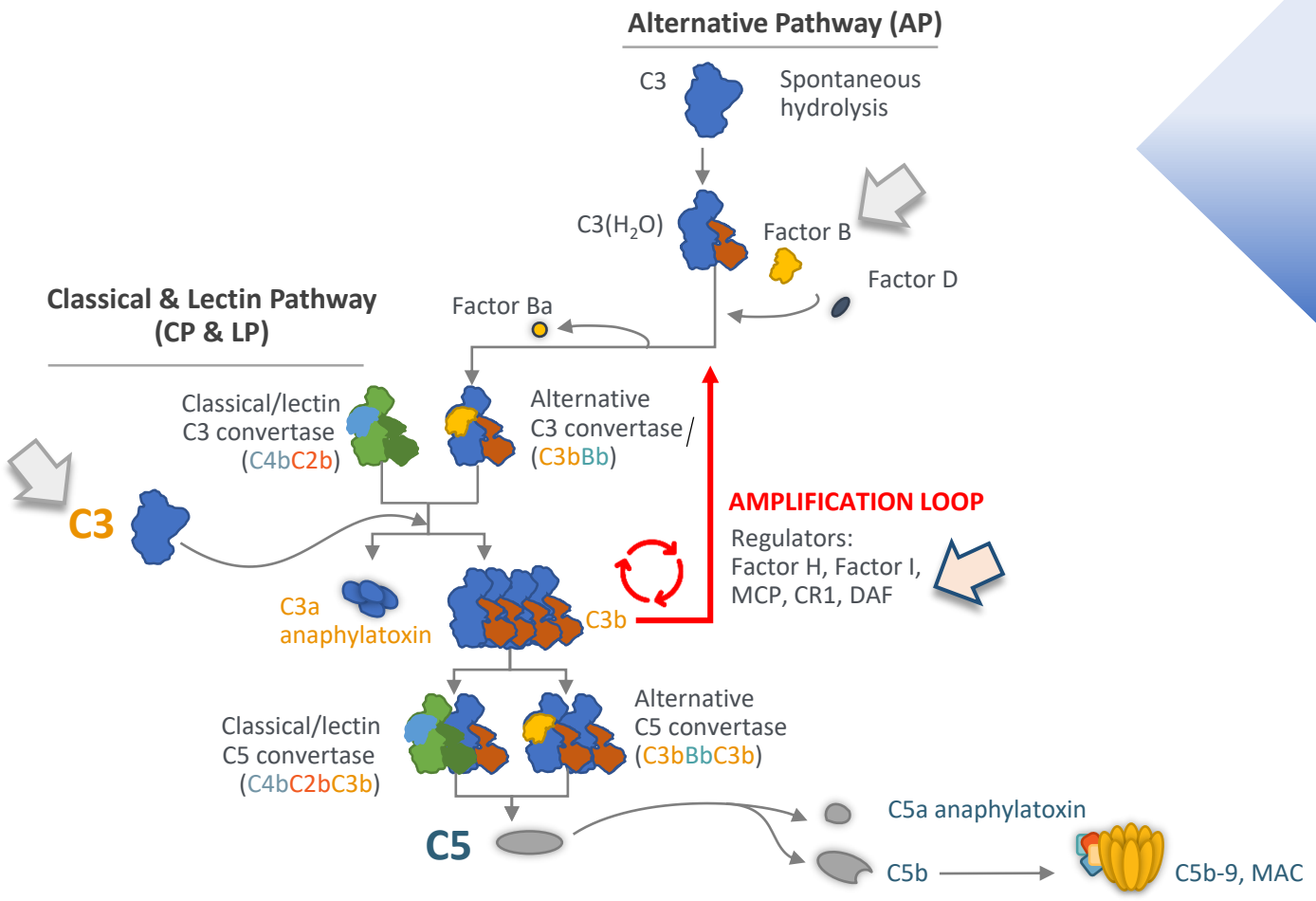
Overview of complement activation in C3G & IC-MPGN[1–7]



C3G, complement 3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; MAC, membrane attack complex; MASP-1/2, mannan-binding lectin serine protease-1/2; MBL, mannose-binding lectin; MCP, membrane cofactor protein.

1. Patriquin C, *et al. Transfus Med Rev* 2019;33:256–65; 2. Merle NS, *et al. Front Immunol* 2015;6:262; 3. Dunkelberger JR & Song WC, *Cell Res* 2010;20:34–50; 4. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 5. Zipfel PF, *et al. Front Immunol* 2019;10:2166; 6. Businesswire, 2022. Available at: https://www.businesswire.com/news/home/20220729005194/en/FDA-Grants-Orphan-Drug-Designation-to-Omeros%E2%80%99-MASP-3-Inhibitor-OMS906-for-Treatment-of-Paroxysmal-Nocturnal-Hemoglobinuria. Accessed June 2023; 7. Meuleman MS, *et al. Semin Immunol* 2022;60:101634.

Genetic abnormalities can lead to C3G/IC-MPGN[1–3]



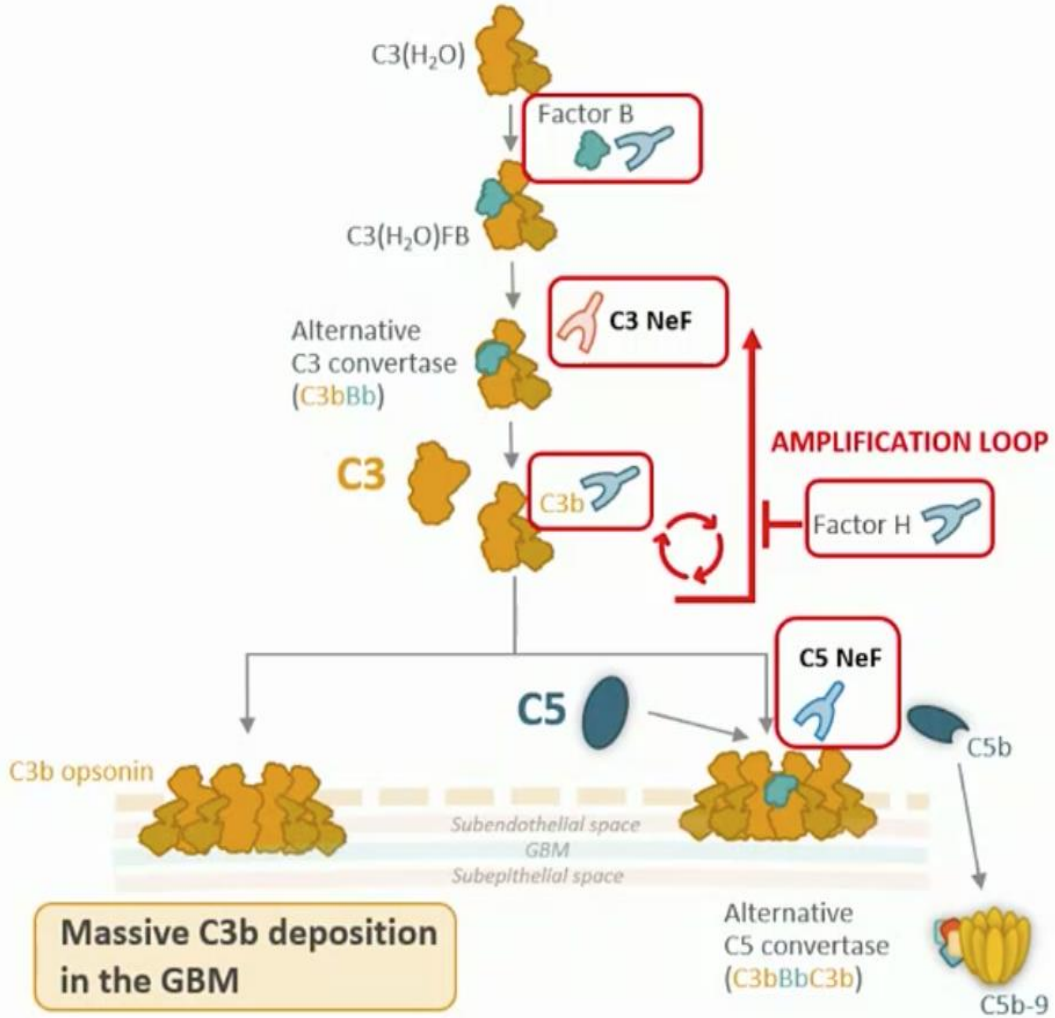
In C3G and primary IC-MPGN, abnormalities in **complement-related genes** have been identified in **up to 25% of** cases[1,4]

Type of mutation	Mutated gene identified[1,2,5,6]
Gain of function in complement activators	C3, Properdine CFB, Factor D CFHR5dup, CFHR1dup CFHR-2/5, 3/1 ,5/2
Loss of function in complement regulators	CFH CFI MCP, DAF

C3G, complement 3 glomerulopathy; CR1, complement receptor 1; DAF, decay-accelerating factor; IC-MPGN, immune complex membranoproliferative glomerulonephritis; MAC, membrane attack complex; MCP, membrane cofactor protein.

1. Smith RJH, et *al. Nat Rev Nephrol.* 2019;15:129–43. 2. Zipfel PF, *et al. Front Immunol* 2019;10:2166. 3. Meuleman MS, *et al. Semin Immunol.* 2022;60:101634. 4. Iatropoulos P, *et al. J Am Soc Nephrol.* 2018;29:283–94.
5. Caravaca-Fontán F, *et al. Nephron.* 2020;144:272–80. 6. Pickering MC, *et al. Kidney Int.* 2013;84:1079–89.

Immunological drivers are observed at varying frequencies both in patients with IC-MPGN and in those with C3G



Nephritic factors (NeFs) are autoantibodies that stabilise the convertase complexes

C3 & C5 NeFs bind to the assembled C3 and C5 convertase complexes and prevent spontaneous and FH-mediated decay, respectively[1-3]

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Dysregulation of the complement cascade in C3 glomerulopathy

Table 4 | **Acquired drivers of C3 glomerulopathy**

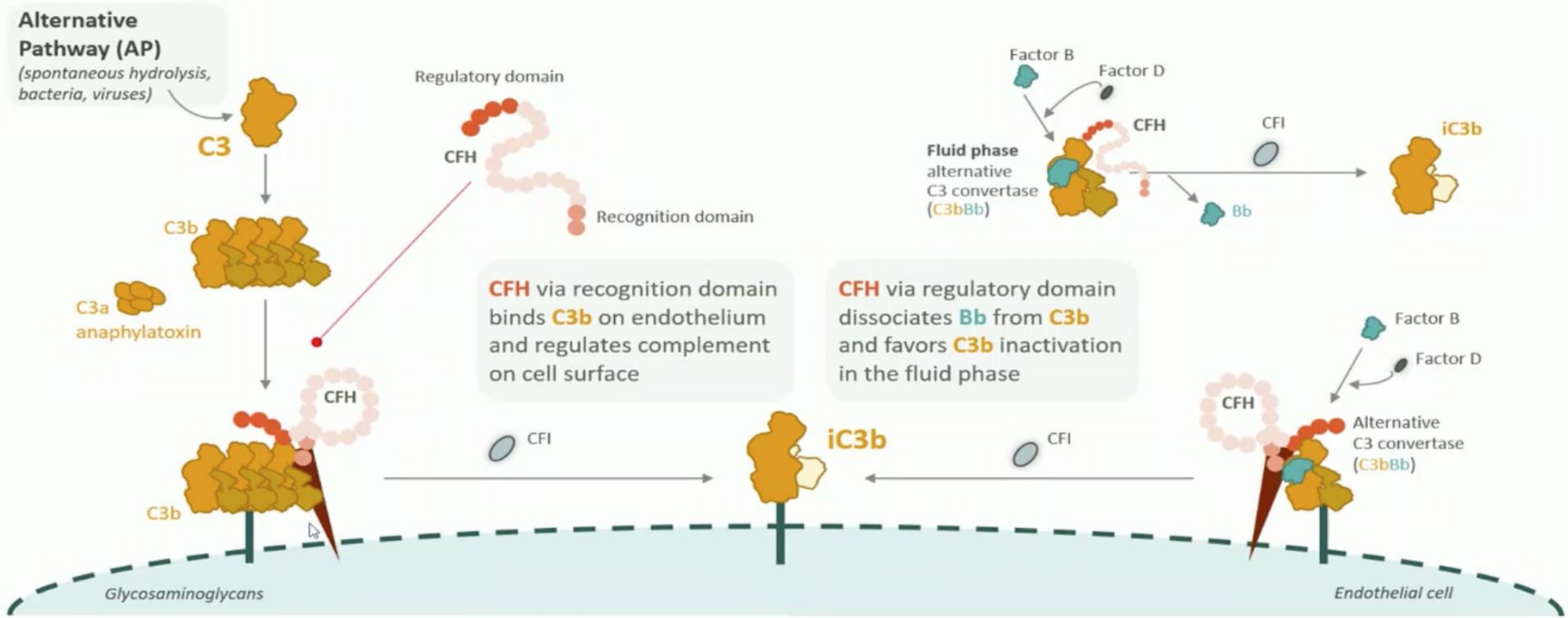
Driver	Frequency in affected patients (%)	Function	Knowledge gaps
C3 nephritic factors	50–80	Dysregulation of C3 convertase (C3bBb)	• Diagnostic assays need standardization • In vitro function of antibodies is well characterized; however, well-documented in vivo data supporting cause-and-effect relationships to disease are needed • Not known whether antibody characteristics change over the disease course • Unclear why antibody removal methods (plasma exchange or B cell-targeted agents) are generally not effective • Defining the mechanism underlying complement dysregulation is often very difficult
C4 nephritic factors	2.4	Dysregulation of C3 and C5 convertases of the classical and lectin pathways (C4b2a and C4b2aC3b)	
C5 nephritic factors	50	Dysregulation of C5 convertase (C3bBbC3b)	
Factor H autoantibodies	~1.0	Affects factor I cofactor activity; not associated with *CFHR3* or *CFHR1* gene deletion	
Factor B autoantibodies	~2.5	Recognizes the Bb fragment; binds C3 convertase; increases release of C3a and Bb; does not enhance C5 convertase activity	
C3b autoantibodies	1.5	Recognizes C3b and C3c; stabilizes C3 convertase; reduces binding to complement receptor type 1; increases activity of C5 convertase	
Monoclonal immunoglobulins	Sporadic cases of multiple myeloma or MGRS	Intact antibody and/or light-chain fragments interfere with alternative pathway regulation	

Smith et al Nat Rev Nephl 2019

C3G, complement 3 glomerulopathy; FB, factor B; FH, factor H; GBM, glomerular basement membrane; IC-MPGN, immune complex membranoproliferative glomerulonephritis; NeF, nephritic factor.

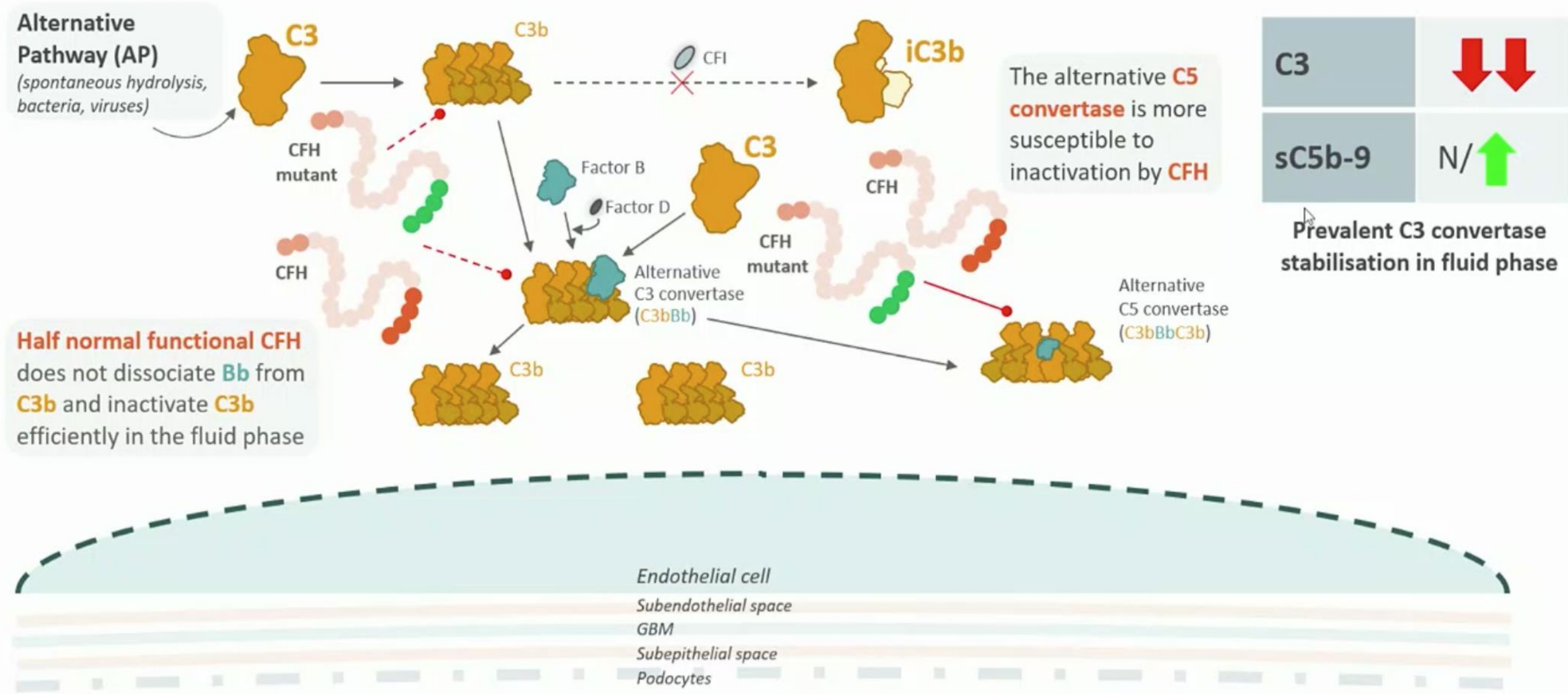
1. Daha MR, *et al. Immunology* 1981;43:33–38; 2. Marinozzi MC, *et al. Kidn Int* 2017;92:1232–41; 3. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43.

The role of Factor H as a regulator of the alternative pathway



CFH, complement factor H; CFI, complement factor I.
Noris M & Remuzzi G. *Semin Nephrol* 2013;33:479–92.

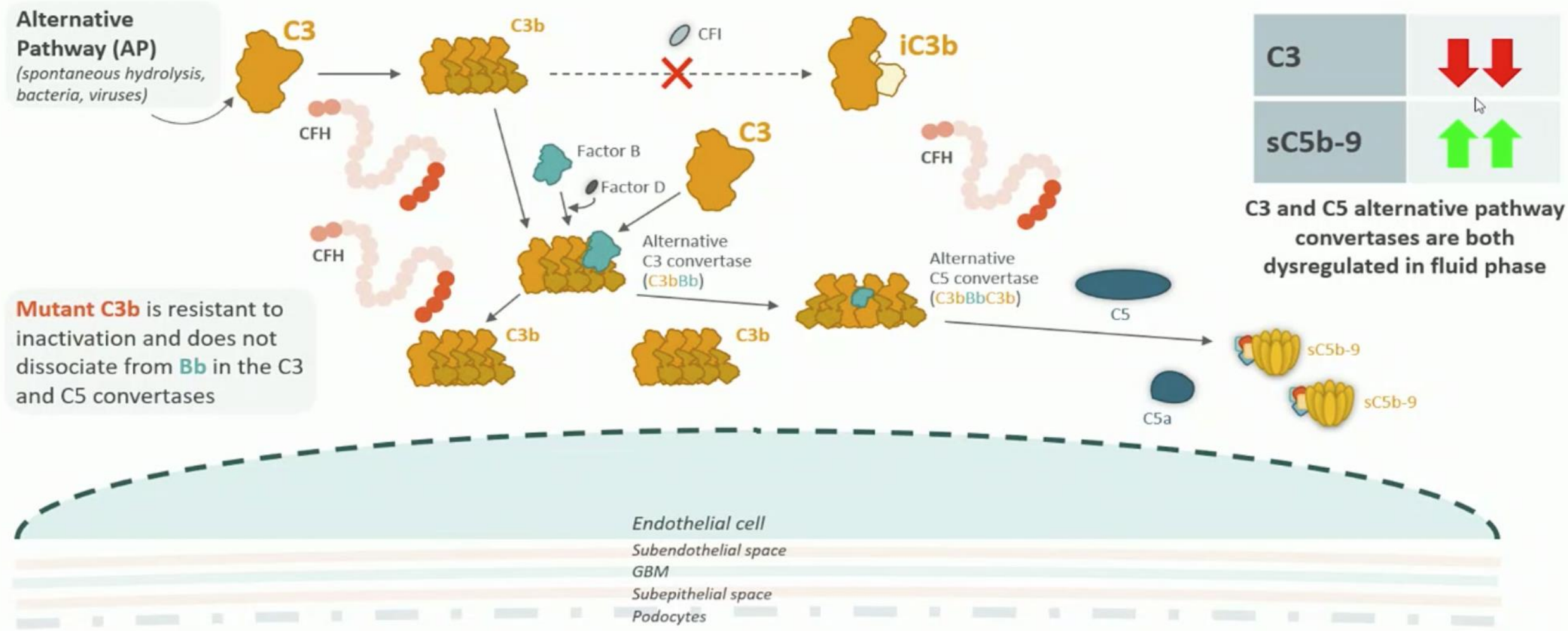
Heterozygous loss of function variants in complement Factor H



CFH, complement factor H; CFI, complement factor I; GBM, Glomerular basement membrane.

Noris M & Remuzzi G, *Am J Kidney Dis* 2015;66:359–75.

Heterozygous $C3_{923\Delta DG}$ gain-of-function variant



C3	↓↓
sC5b-9	↑↑

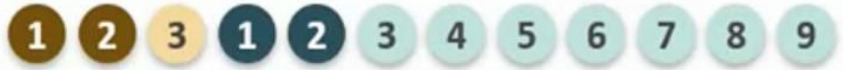
C3 and C5 alternative pathway convertases are both dysregulated in fluid phase

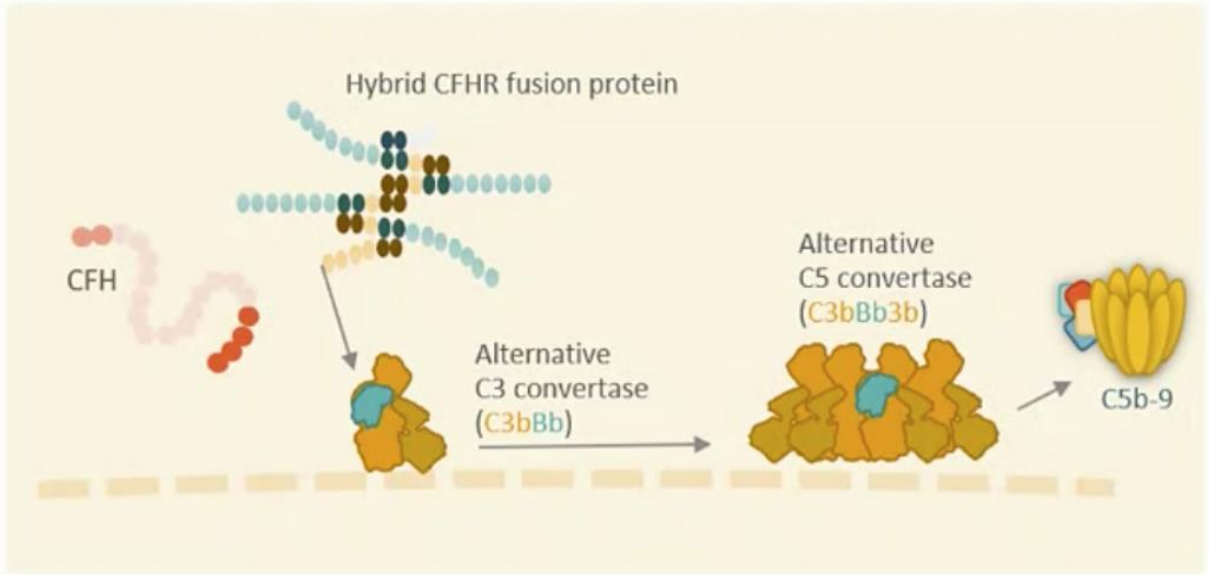
CFH, complement factor H; CFI, complement factor I; GBM, Glomerular basement membrane.
Martínez-Barricarte R, *et al. J Clin Invest* 2010;120:3702–12.

Factor H-related proteins: role in C3G & IC-MPGN

Factor H-related proteins (CFHRs 1–5) are glycoproteins **related in structure to Factor H**.
Hybrid fusion proteins have been found with different domain rearrangement in patients with C3G/IC-MPGN[1,2]

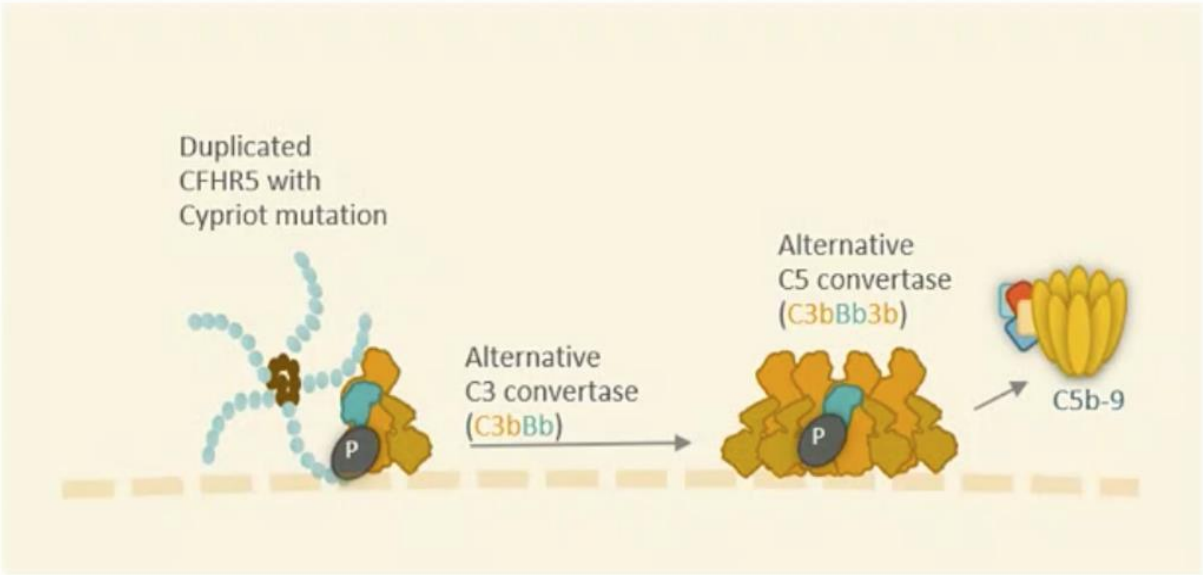
The CFHR1-5 hybrid gene





Patients exhibited permanently **low C3 levels** and **elevated plasma sC5b-9 levels**[1,3]

The "Cypriot ancestry C3G" CFHR5 duplication

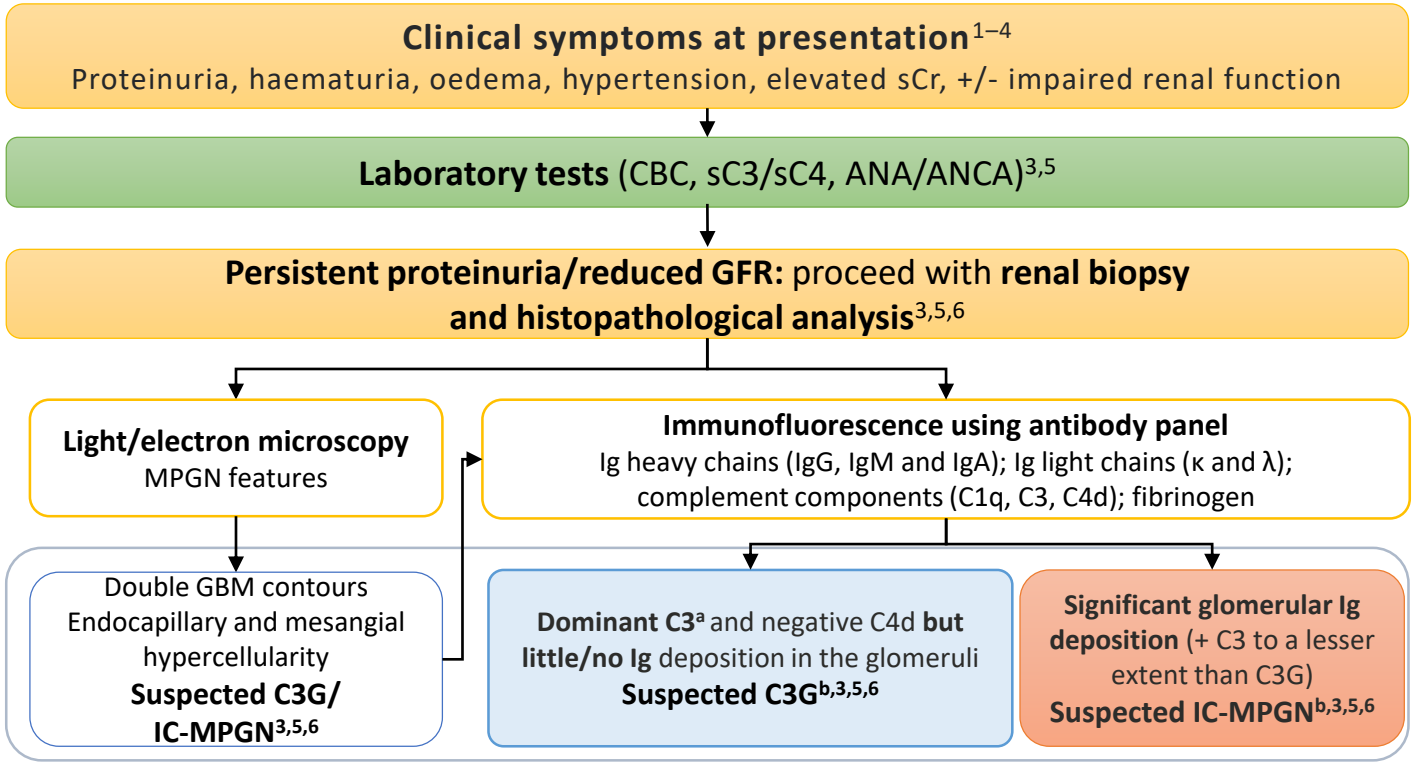


Patients have **normal C3 and sC5b-9 levels:** deregulation of complement mostly local in the glomeruli[2,3]

C3G, complement 3 glomerulopathy; CFH, complement factor H; CFHR, complement factor H-related proteins; IC-MPGN, immune complex membranoproliferative glomerulonephritis.

1. Goicoechea de Jorge E, *et al. PNAS* 2013:110;4685–90; 2. Chen Q, *et al. J Am Soc Nephrol* 2016:27;1413–25; 3. Piras R, *et al. Front Genet* 2021;12:670727.

Putting it all Together : Differential diagnosis of C3G/Primary IC-MPGN



PIGN, MGRS and secondary forms of IC-MPGN should be ruled out[5]

[a]Glomerular C3 staining intensity ≥2 orders of magnitude more than any other immune reactant.
[b]Negative C3 or Ig findings suggest alternative causes of MPGN including antiphospholipid antibody syndrome, HUS/TTP, sickle cell anemia and polycythemia, dysfibrinogenemia or POEMS syndrome.
ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; C1q, complement component 1q; C3, complement 3; C3G, complement 3 glomerulopathy; CBC, complete blood count; GBM, glomerular basement membrane; GFR, glomerular filtration rate; HUS, hemolytic-uremic syndrome; IC-MPGN, immune complex membranoproliferative glomerulonephritis; Ig, immunoglobulin; MGRS, monoclonal gammopathy of renal significance; MPGN, membranoproliferative glomerulonephritis; PIGN, post infectious glomerulonephritis; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; sC3, serum C3; sC4, serum C4; sCr, serum creatinine; TTP, thrombotic thrombocytopenic purpura.
1. National Kidney Foundation. Accessed 4 October 2023. https://www.kidney.org/atoz/content/complement-3-glomerulopathy-c3g; 2. Meuleman M-S, *et al. Semin Immunol* 2022;60:1016–34; 3. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 4. Iatropoulos P, *et al. J Am Soc Nephrol* 2018;29:283–94; 5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–276; 6. Zipfel PF, *et al. Front Immunol* 2019;10:2166.

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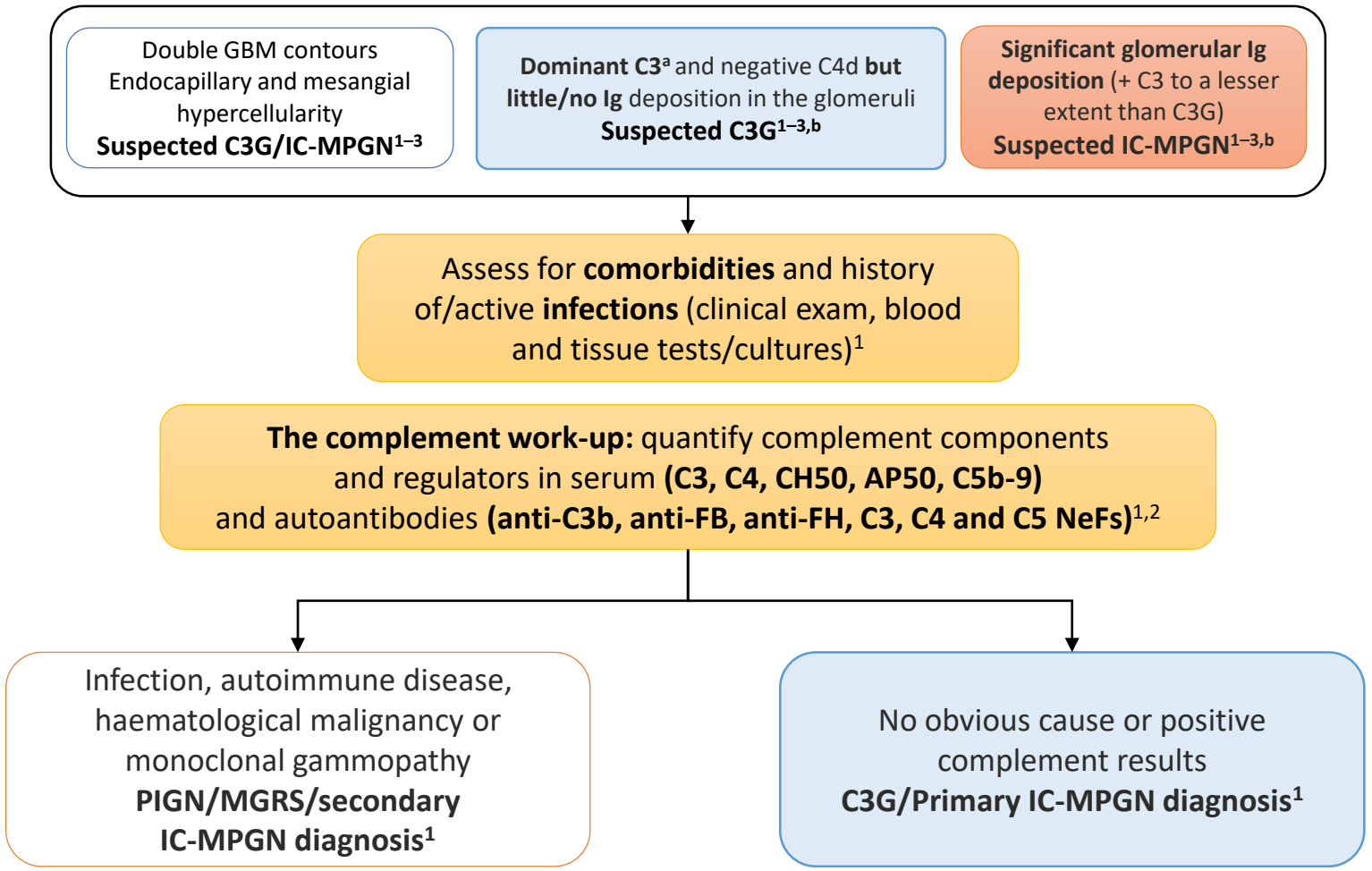

[a]Glomerular C3 staining intensity ≥2 orders of magnitude more than any other immune reactant.
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C3, complement 3; C3G, complement 3 glomerulopathy; C4, complement 4; CH50, 50% classical hemolytic complement pathway activity; FB, factor B; FH, factor H; GBM, glomerular basement membrane; HUS, hemolytic-uremic syndrome; IC-MPGN, immune complex membranoproliferative glomerulonephritis; Ig, immunoglobulin; MGRS, monoclonal gammopathy of renal significance; MPGN, membranoproliferative glomerulonephritis; NeFs, nephrotic factors; PIGN, post infectious glomerulonephritis; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TTP, thrombotic thrombocytopenic purpura.
1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–276; 2. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 3. Zipfel PF, *et al. Front Immunol* 2019;10:2166.

Prognosis and Treatment

Risk factors of poor long-term outcome in C3G

Multivariate analysis of the association of long-term renal outcome with clinical, laboratory and genetic features.

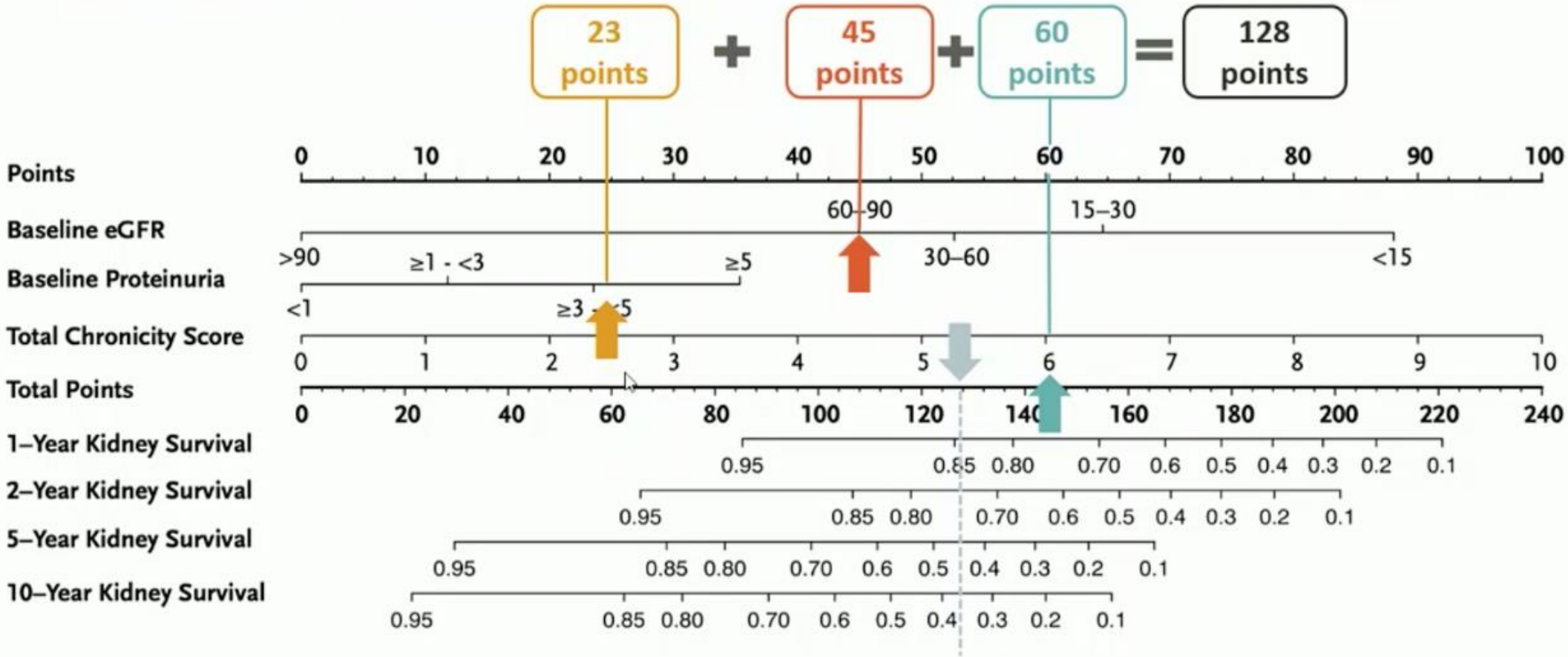
	All patients		
	HR	HR 95%CI	*p*
Absence of mutations or C3NeFs	7.1	1.9–26.3	0.004
Sclerotic glomeruli (% of glomeruli)	69.3	3.1–1553	0.008
Crescents (% of glomeruli)	39.7	3.3–481	0.004
Nephrotic syndrome at onset	10.9	2.5–47	0.002

HR: hazard ratio calculated by Multivariate Cox proportional-Hazards analysis. CI: confidence Interval.nc: not calculable. Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m2 in children together with albuminemia $\leq$3 g/dL. Intensified immunosuppression was also included in multivariate Cox Regression analysis but was not significantly associated with progress to ESRD (HR = 3.9, 95%CI 0.65–23.9, p = 0.138).

Iatropoulos et al, Mol Immunol 2016

C3G: how to estimate kidney prognosis at baseline

Nomogram for the prediction of kidney failure at 1, 2, 5 and 10 years



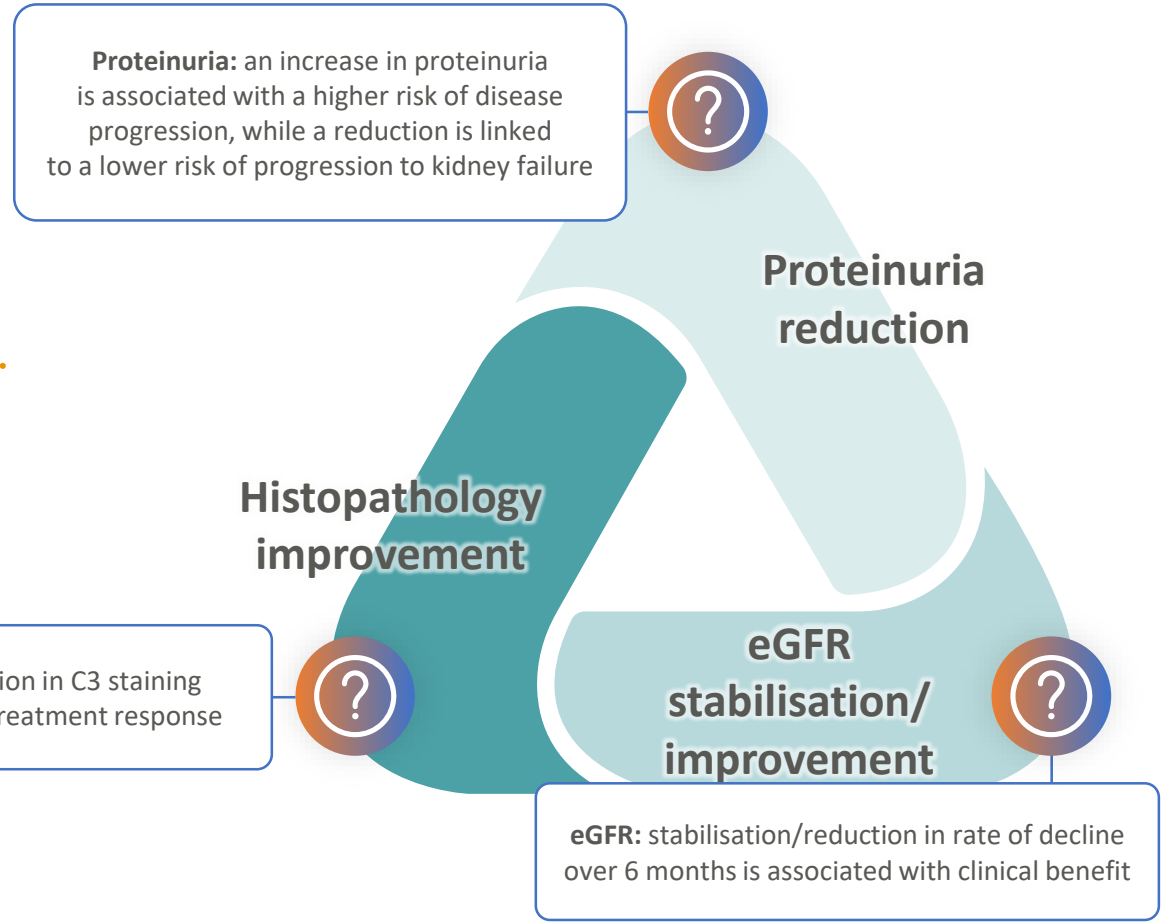
eGFR, estimated glomerular filtration rate.

Caravaca-Fontán F, *et al. Clin Kidney J* 2022;15:1737–46.

Experts have identified the **importance of measuring treatment effect** via **three clinical endpoints**

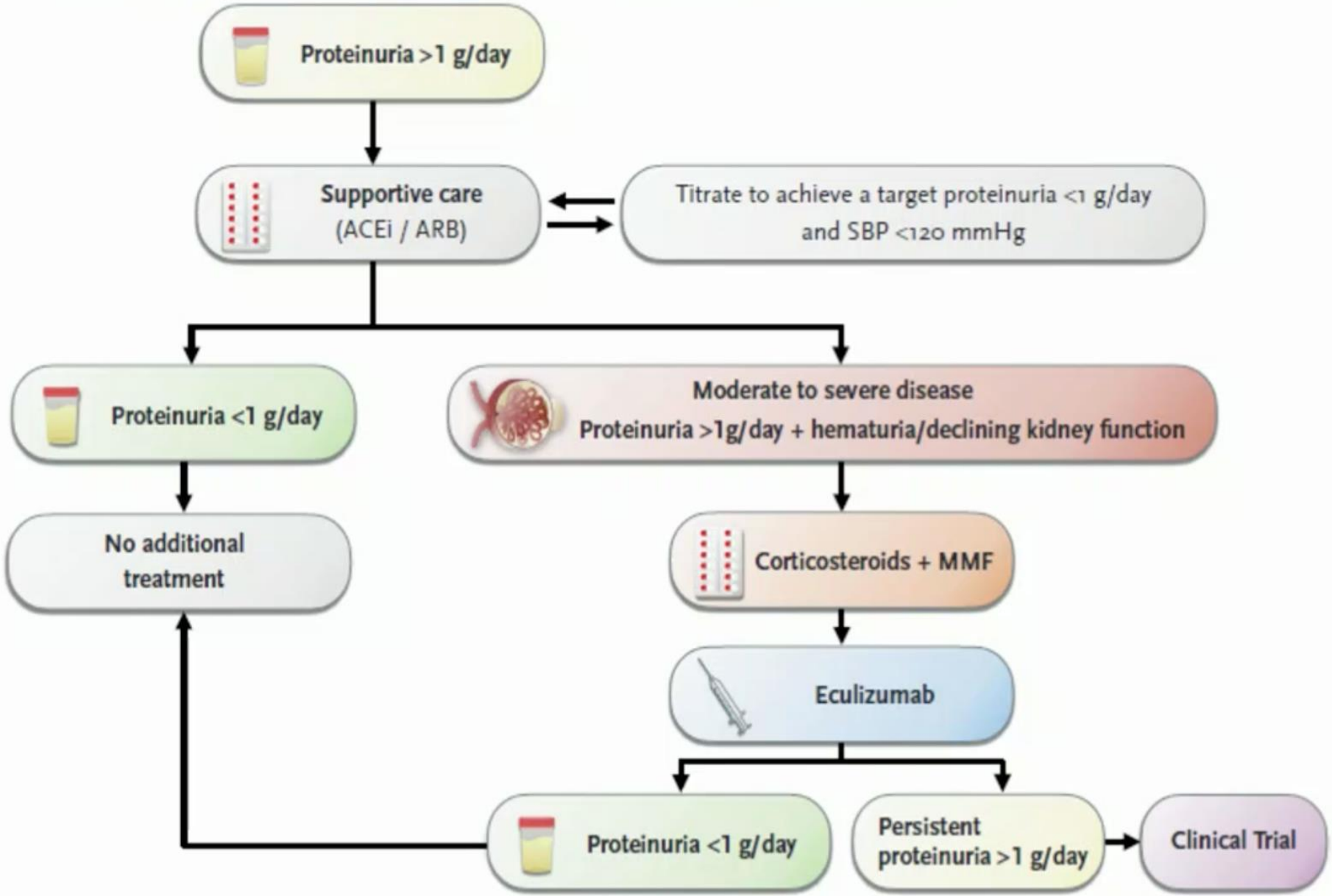
The **Kidney Health Initiative** (KHI) convened a panel of experts to reach a consensus on clinical endpoints in C3G

Experts concluded that a **favourable treatment effect on three endpoints** (histopathology improvement, proteinuria reduction, eGFR stabilisation) **provides convincing evidence of effic** targeting the complement pa

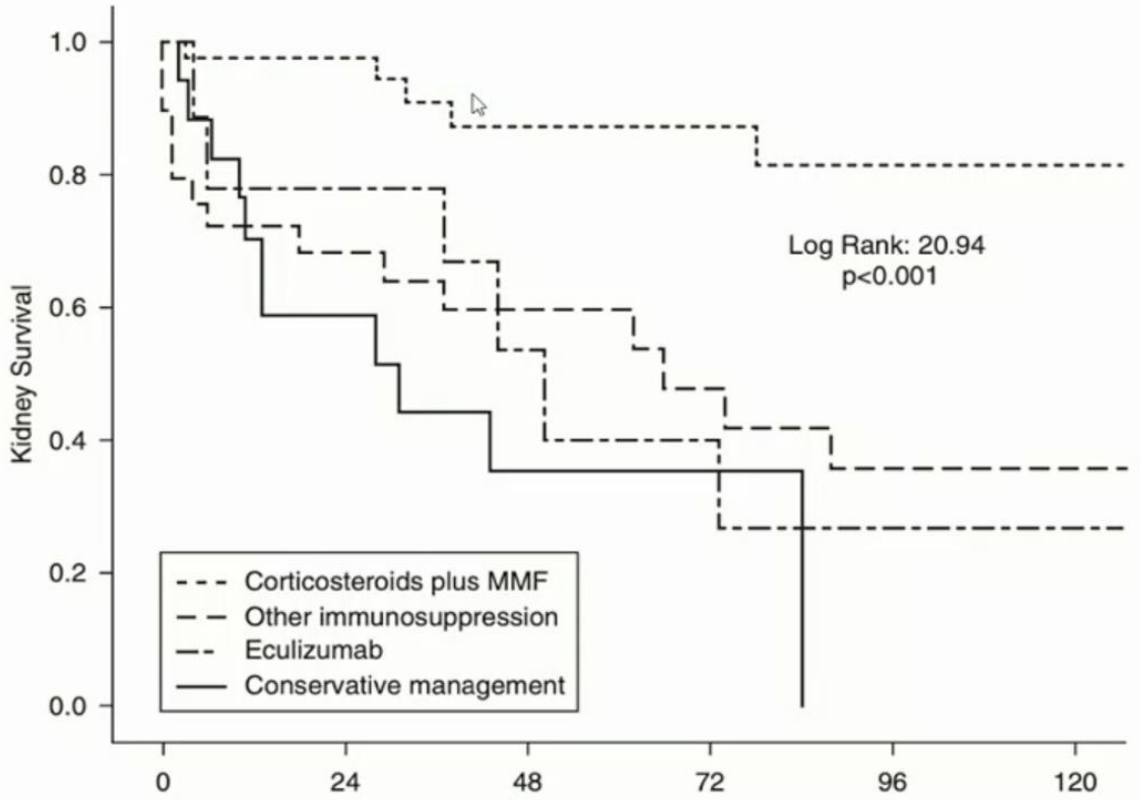


C3c, complement 3c; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate.
Nester C, *et al. Clin J Am Soc Nephrol* 2024;19:1201–8.

Management of C3G (based on KDIGO guidelines)



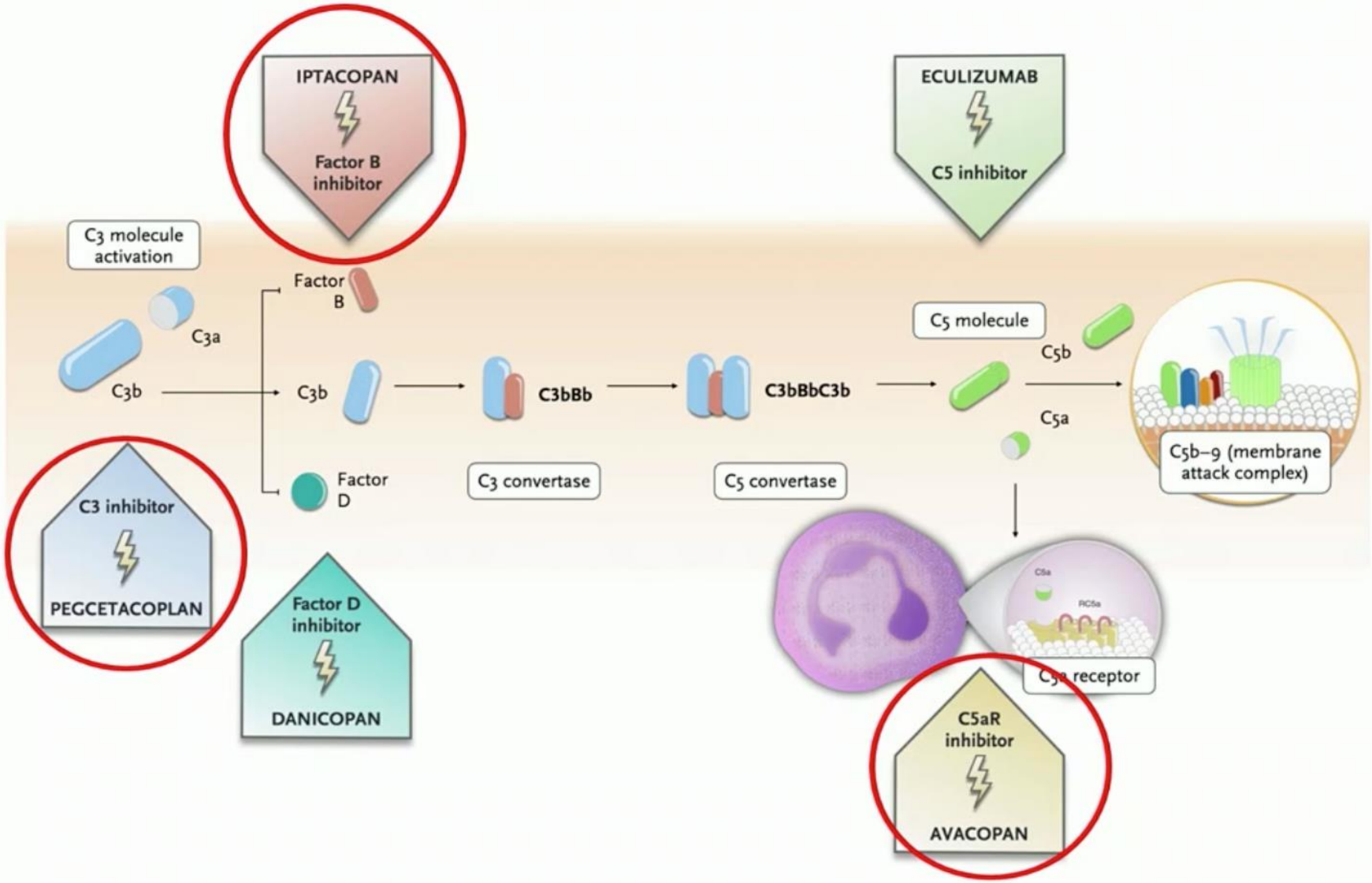
C3G : Response to Immunosuppressive Therapy



Patients at risk						
Corticosteroids plus MMF	42	32	20	16	10	5
Other immunosuppression	29	17	11	8	6	5
Eculizumab	9	7	4	3	2	1
Conservative management	17	8	4	1		

Caravaca- Fontatn et al CJASN 2020

Landscape of complement inhibitors in C3 Glomerulopathy

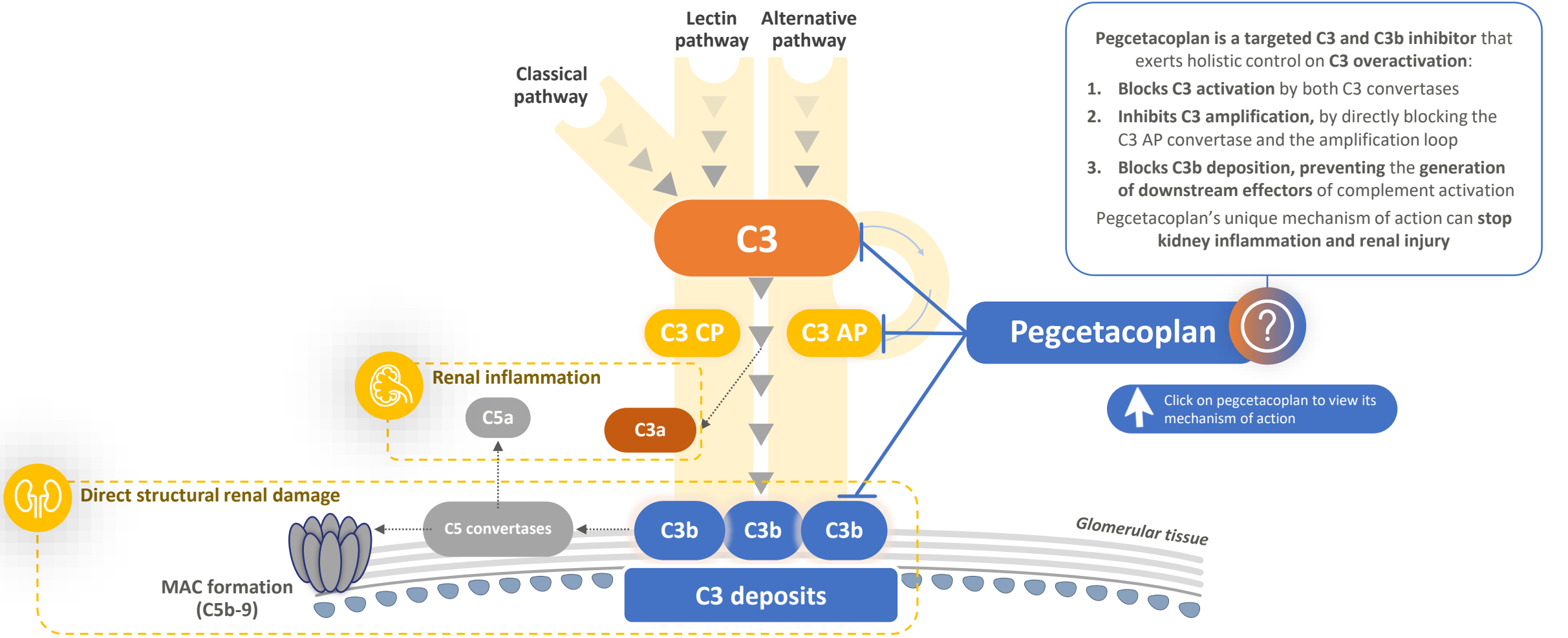


Encouraging preliminary results with some Complement Blockers:

Iptacopan
Pegcetacoplan
Avacopan

- ***Important proteinuria reduction***
- ***eGFR stabilization***
- ***Good safety profile***

Pegcetacoplan is a targeted C3/C3b inhibitor designed to control C3 overactivation[1–7]



Pegcetacoplan is being assessed in several clinical trials[1–7]

Phase 1

Phase 1 Single Ascending Dose (SAD)

To investigate the safety, tolerability, PK and PD of **escalating single doses** of **SC** pegcetacoplan in **healthy volunteers**

Phase 1 Multiple Ascending Dose (MAD)

To investigate the safety, tolerability, PK and PD of **escalating multiple doses** of **SC** pegcetacoplan in **healthy volunteers**

Phase 1 Single Ascending Dose (SAD) for IV administration

To investigate the safety, PK and PD of **escalating single doses** of **IV** pegcetacoplan in **healthy volunteers**

Phase 2

Phase 2 DISCOVERY

To investigate the safety and biological activity of **SC** pegcetacoplan in patients with complement-mediated glomerulopathies (IgAN, LN, PMN and **C3G**)

Phase 2 NOBLE

To investigate the safety and efficacy of SC pegcetacoplan in the treatment of post-transplant recurrence of C3G or primary IC-MPGN

Phase 3

Phase 3 VALIANT

To investigate the efficacy of **SC** pegcetacoplan in **adult** and **adolescent** patients with **C3G** or primary **IC-MPGN**, including those with **post-transplant recurrence,** in comparison with placebo on the basis of a **reduction in proteinuria**

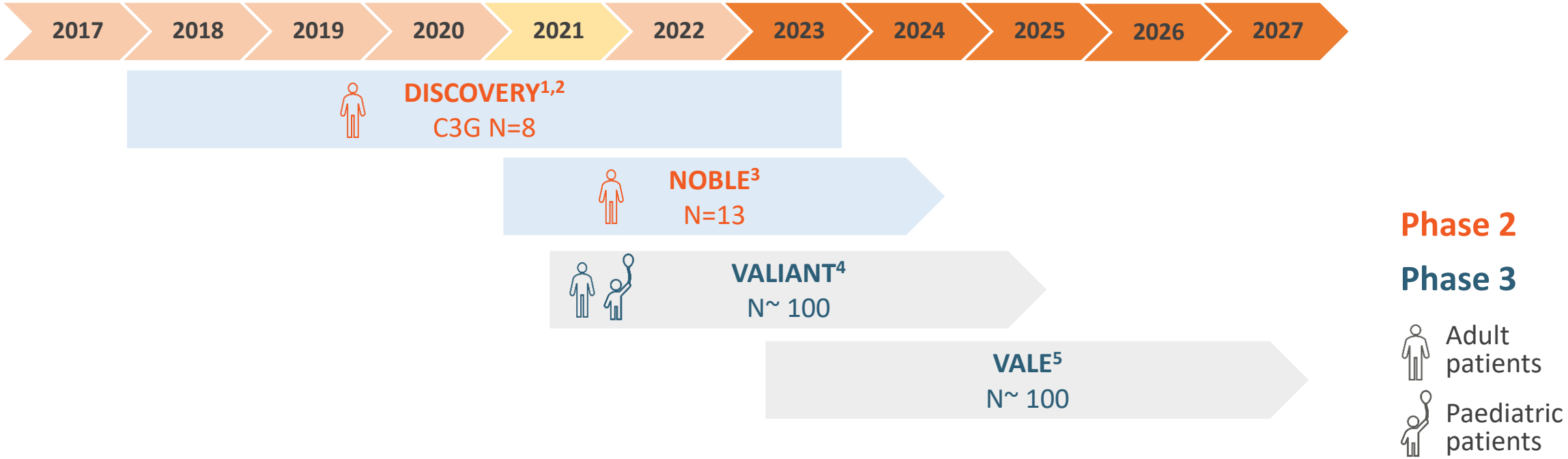
Phase 3 Extension Study VALE (314 Study)

To investigate the long-term safety and efficacy of pegcetacoplan treatment in **SC** pegcetacoplan in **adult and adolescent** patients with **C3G** or primary **IC-MPGN,** including those with **post-transplant recurrence** that previously participated in a pegcetacoplan trial

C3G, complement 3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; IgAN, immunoglobulin A nephropathy; IV, intravenous; LN, lupus nephritis; MAD, multiple ascending dose; PD, pharmacodynamic; PK, pharmacokinetic; PMN, primary membranous nephropathy; SAD, single ascending dose; SC, subcutaneous.
Full references in Notes.

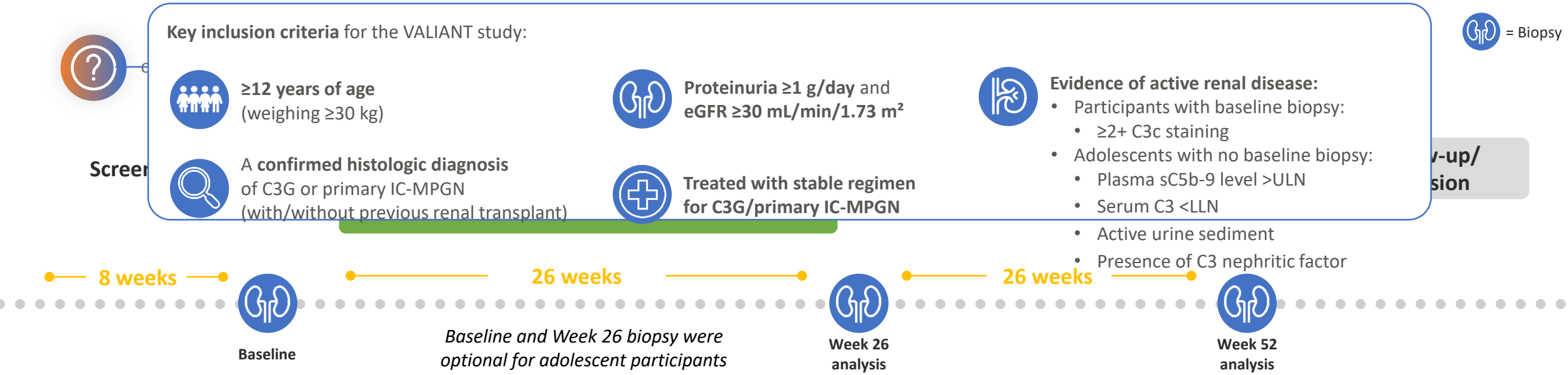
Ongoing study

Pegcetacoplan in C3G/primary IC-MPGN: **Clinical study programme**



C3G, complement 3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis.
1. Clinicaltrials.gov identifier: NCT03453619; 2. Dixon B, et al. *Kidney Int Rep* 2023 Epub August 24 doi: https://doi.org/10.1016/j.ekir.2023.08.033; 3. Clinicaltrials.gov identifier: NCT04572854;
4. Clinicaltrials.gov identifier: NCT04572854; 5. Clinicaltrials.gov identifier: NCT05067127.

VALIANT Phase 3 study design: ≥12 years old, native/recurrent C3G or primary IC-MPGN[1,2]



Study endpoints:

Primary Endpoint | Log-transformed ratio of uPCR at 26 weeks vs baseline

Key Secondary Endpoints

- Composite renal endpoint
  Stable/improved eGFR (≤15% reduction in eGFR) and ≥50% reduction in uPCR vs baseline
- ≥50% reduction in uPCR vs baseline
- C3G histologic index
- C3c staining
- eGFR

C3/3c, complement 3/3c; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN; immune complex-mediated membranoproliferative glomerulonephritis; LLN, lower limit of normal; R, randomised; SC, subcutaneous; sC5b-9, soluble C5b-9; SOC, standard-of-care; ULN, upper limit of normal; uPCR, urine protein-to-creatinine ratio. [a]All adults and adolescents weighing ≥50 kg self administered 1080 mg/20 mL. Adolescent patients weighing 30–34 kg received 540 mg/10 mL for the first 2 doses, then 648 mg/12 mL. Adolescent patients weighing 35–49 kg received 648 mg/12 mL for the first dose, then 810 mg/15 mL. bStable, optimized antiproteinuric regimens:

1. Dixon BP, *et al.* American Society of Nephrology Kidney Week 2023 (Poster 048); 2. Nester CM, *et al.* Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

VALIANT **key eligibility criteria**

Inclusion criteria

- Age ≥18 years; where approved, adolescents (aged 12-17 years) weighing at least 30 kg may also be enrolled.
- Primary diagnosis of C3G or primary IC-MPGN (w/wo previous renal transplant).
- Evidence of **active renal disease**, based on one or more:
  - In participants **with biopsy**: at least 2+ C3c staining on the baseline renal biopsy.
  - In adolescents **not providing a baseline renal biopsy**: at least one of the following:
    - sC5b-9 level above the ULN during screening
    - sC3 below the LLN during screening
    - Presence of an active urine sediment during screening
    - Presence of C3 nephritic factor within 6 months of screening, based on central laboratory results or medical history.
- **≤50% global glomerulosclerosis or interstitial fibrosis**
- ≥ 1 g/day of proteinuria and a uPCR ≥ 1000 mg/g in at least 2 first-morning spot urine samples collected during screening.
- **eGFR ≥30 mL/min/1.73 m2**
- Stable regimen for C3G/IC-MPGN treatment
- Vaccinated against following diseases within the previous 5 years or agree to receive vaccinations during screening:
  - *Neisseria meningitidis* type A, C, W, Y, and B
  - *Haemophilus influenzae* type B

Exclusion criteria

- Previous exposure to pegcetacoplan
- C3G/IC-MPGN secondary to another condition
- Current or prior diagnosis of (HIV), (HBV), or (HCV) infection or positive serology during screening that is indicative of infection with any of these viruses
- Body weight greater than 100 kg at screening
- Hypersensitivity to pegcetacoplan or to any of the excipients.
- History of meningococcal disease.
- Malignancy, except for the following:
  - Cured basal or squamous cell skin cancer
  - Curatively treated in situ disease
  - Malignancy-free and off treatment for ≥5 years
- Severe infection within 14 days prior to the first dose of pegcetacoplan
- An absolute neutrophil count <1000 cells/mm3 at screening
- Use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan within 5 half-lives of that product prior to the screening period.

C3 glomerulopathy; eGFR, estimated glomerular filtration rate; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IC-MPGN, immune complex membranoproliferative glomerulonephritis; LLN, lower limit of normal; ULN, upper limit of normal; uPCR, urine protein creatinine ratio.
ClinicalTrials.gov identifier NCT05067127.

VALIANT baseline demographics: broad patient population

Characteristic[†]	Pegcetacoplan (N=63)	Placebo (N=61)
Age	28.2 (17.1)	23.6 (14.3)
Adolescents (12–17 years)/adults (≥18 years), n (%)	28 (44.4)/35 (55.6)	27 (44.3)/34 (55.7)
Age of adolescents/adults, mean (SD), years	14.6 (1.7)/39.1 (15.9)	14.8 (1.7)/30.6 (15.9)
Sex, female, n (%)	37 (58.7)	33 (54.1)
Race, white, n (%)	45 (71.4)	46 (75.4)
Baseline 24 hr uPCR, mean (SD), g/g	3.95 (2.89)	3.29 (2.36)
Baseline triplicate first-morning spot uPCR, mean (SD), g/g	3.12 (2.41)	2.54 (2.01)
Baseline eGFR, mean (SD), mL/min/1.73 m^2	78.5 (34.1)	87.2 (37.2)
Underlying disease based on screening biopsy, n (%)		
C3G	51 (81.0)	45 (73.8)
C3GN	45 (71.4)	41 (67.2)
DDD	4 (6.3)	4 (6.6)
Undetermined	2 (3.2)	0 (0.0)
Primary IC-MPGN	12 (19.0)	16 (26.2)
Time since diagnosis, mean (SD), years	3.6 (3.5)	3.8 (3.6)
Post-transplant recurrent disease, n (%)	5 (7.9)	4 (6.6)

[†]Intention-to-treat population (all randomised patients).
C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; hr, hour; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; SD, standard deviation; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

VALIANT study: data support pegcetacoplan's effect on disease pathology and the clinical effect of resolving C3 deposits

The **VALIANT study** includes the following patient subgroups:

C3 C3G | C3 Primary IC-MPGN | Adults | Adolescents | Native kidneys | Transplanted kidneys

Click here for study population information

Week 26

1 Histopathology improvement:

71%

of pegcetacoplan-treated patients **had no C3 deposits* after treatment**

2 Proteinuria reduction:

68%

relative reduction in proteinuria

between pegcetacoplan-treated vs placebo-treated patients

Consistent across subgroups of disease type, age and transplant status

51%

of treated patients achieved **<1 g/g in proteinuria**

3 eGFR stabilisation:

+6.3 mL/min/1.73 m²

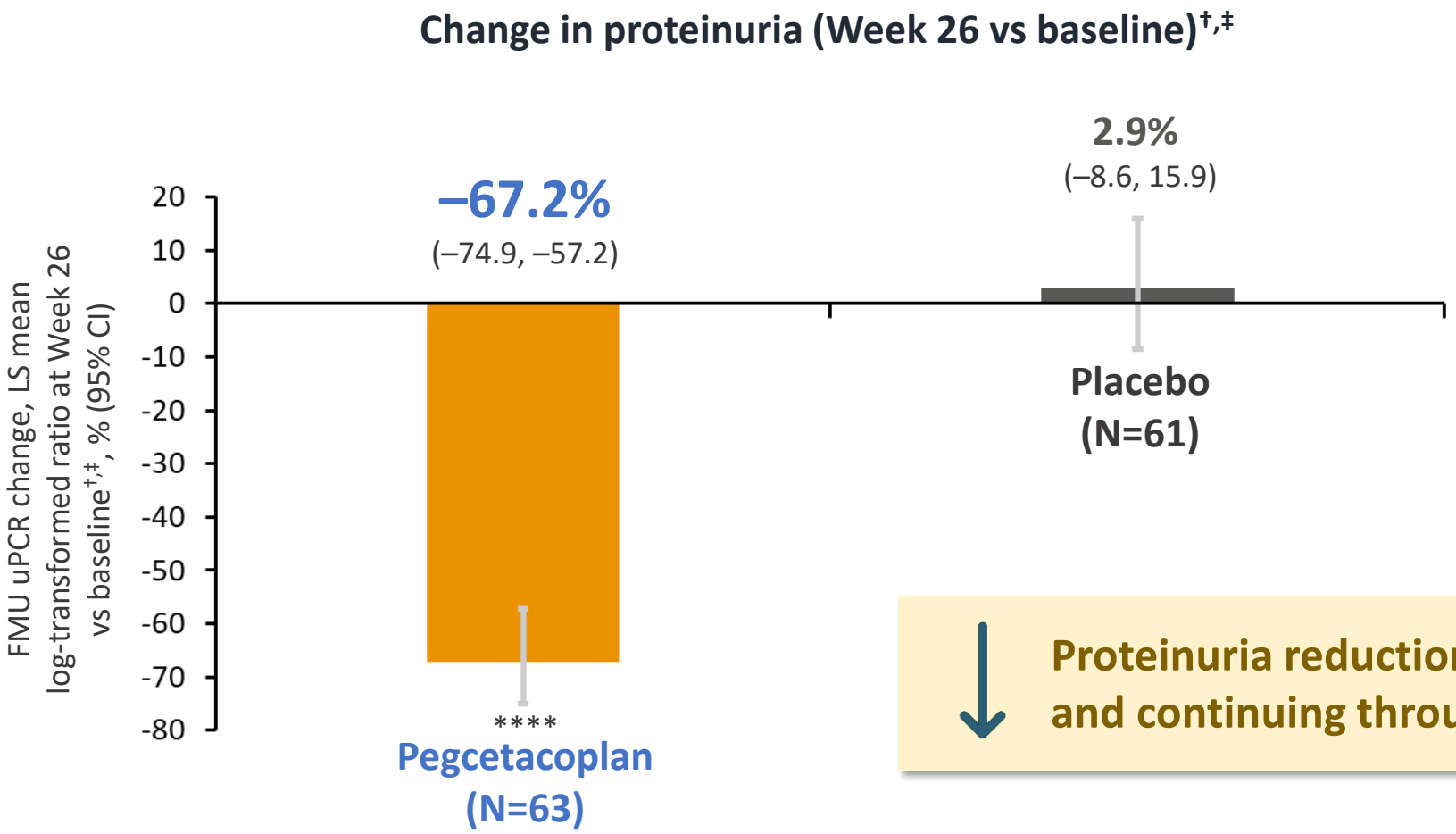
difference in eGFR

for pegcetacoplan-treated vs placebo-treated patients

Patients treated with pegcetacoplan were significantly more likely to achieve eGFR stabilisation vs placebo

*All patients had ≥2-OOM in staining intensity at baseline.
C3, complement 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; OOM, order of magnitude.
Reference available in slide notes.

Highly statistically and clinically significant proteinuria reduction of 68.1% with pegcetacoplan vs placebo



Primary endpoint

Relative reduction‡ (95% CI) in pegcetacoplan vs placebo

68.1%

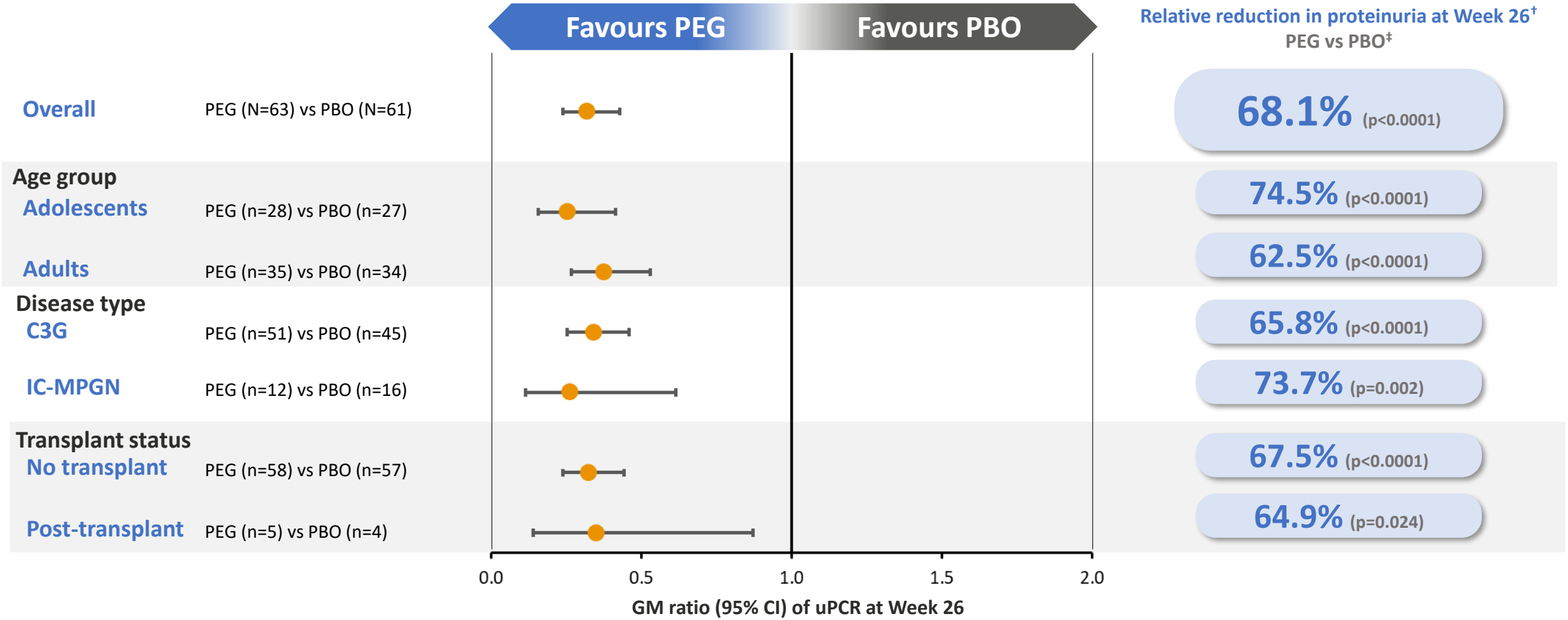
(57.3, 76.2)

p<0.0001

Proteinuria reduction observed as early as Week 4 and continuing through Week 26

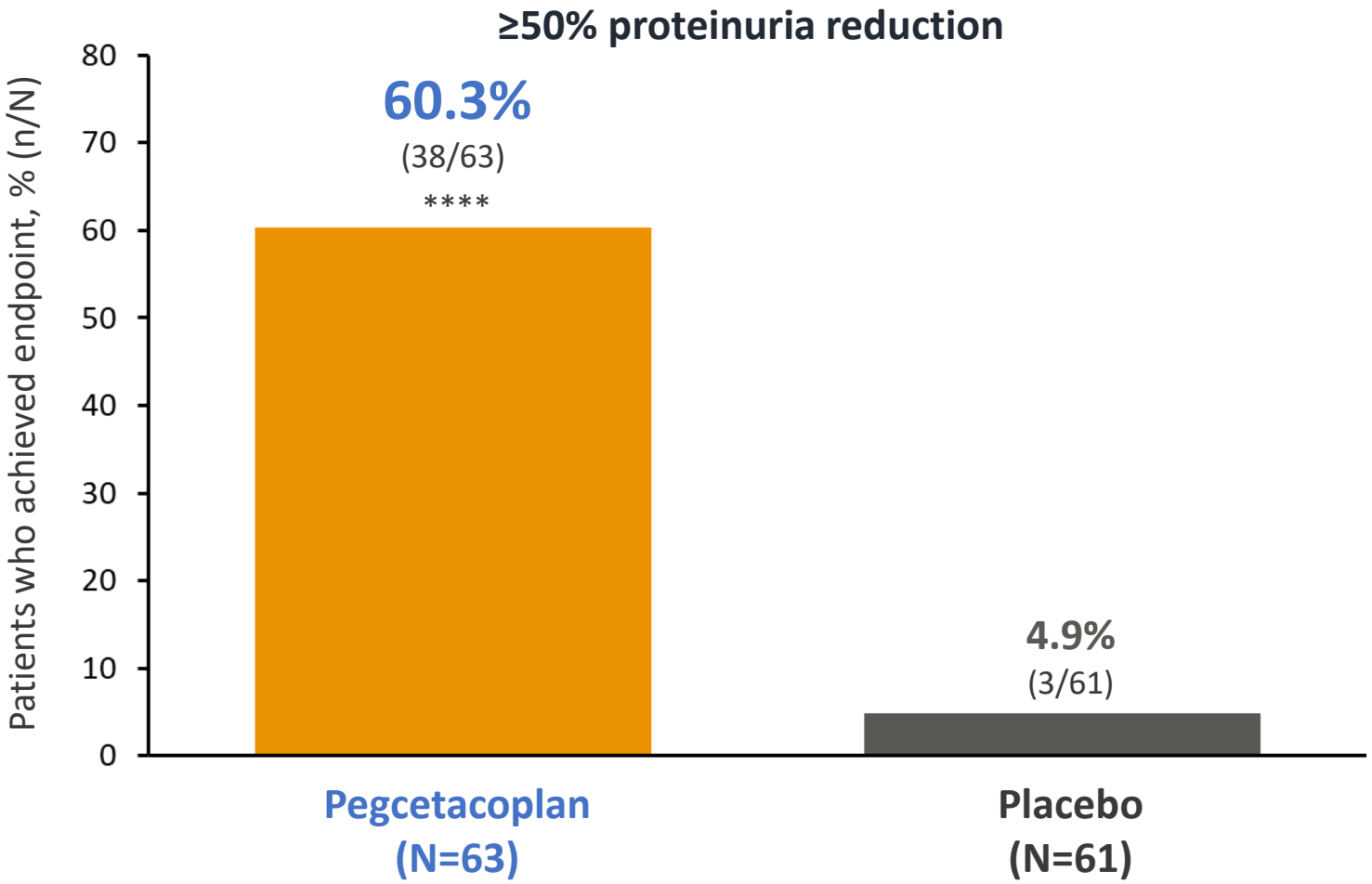
****p≤0.0001. Intention-to-treat population (all randomised patients).
†Using an equal-weighted average from FMU over Weeks 24, 25 and 26. ‡Percentages calculated by converting the ratio of geometric means to percentages.
CI, confidence interval; FMU, first-morning spot urine; LS, least squares; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Consistent, clinically meaningful proteinuria reductions with pegcetacoplan vs placebo were observed across broad patient subgroups



Intention-to-treat population (all randomised patients).
†Using an equal-weighted average over Weeks 24, 25, and 26 compared with baseline. ‡Percentages calculated by converting the ratio of geometric means to percentages.
C3G, complement 3 glomerulopathy; CI, confidence interval; GM, geometric mean; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; PBO, placebo; PEG, pegcetacoplan; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Significantly more patients achieved ≥50% proteinuria reduction with pegcetacoplan vs placebo



Key secondary endpoint

Odds ratio
pegcetacoplan vs placebo

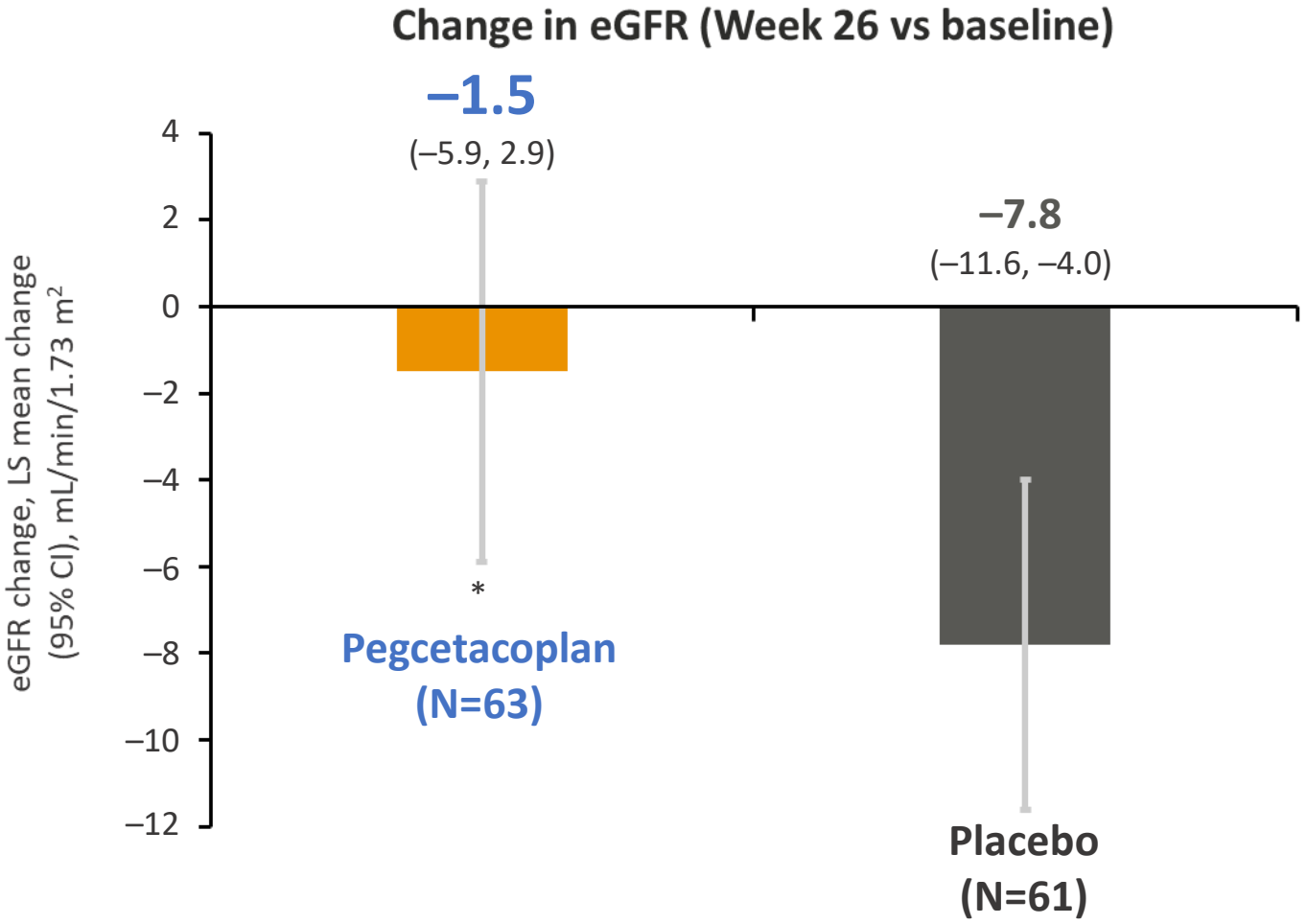
31x

higher odds of achieving ≥50% proteinuria reduction

p<0.0001

****p≤0.0001. Intention-to-treat population (all randomised patients). 2-sided p values.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Pegcetacoplan **significantly stabilised eGFR** compared with placebo



Key secondary endpoint

Difference in pegcetacoplan vs placebo

+6.3 mL/min/1.73 m²

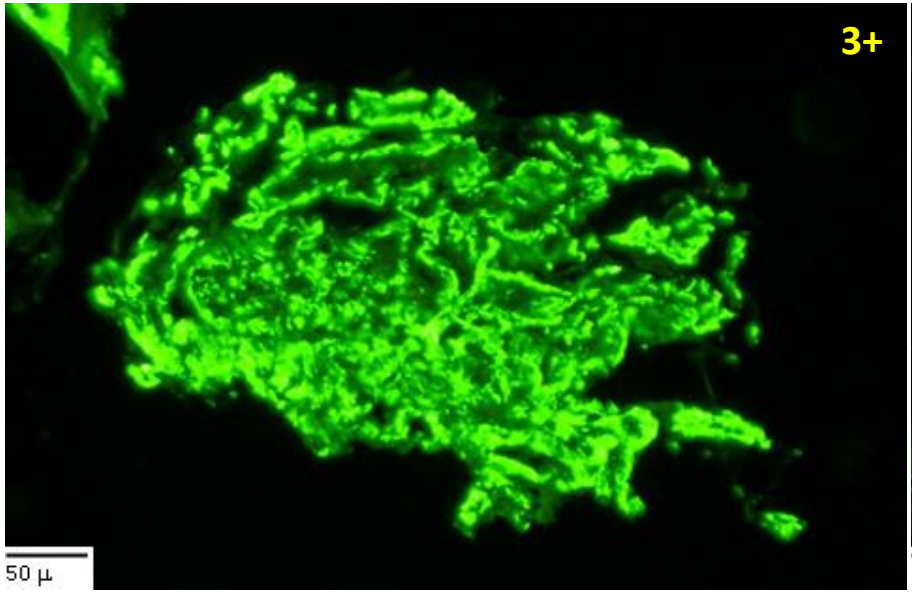
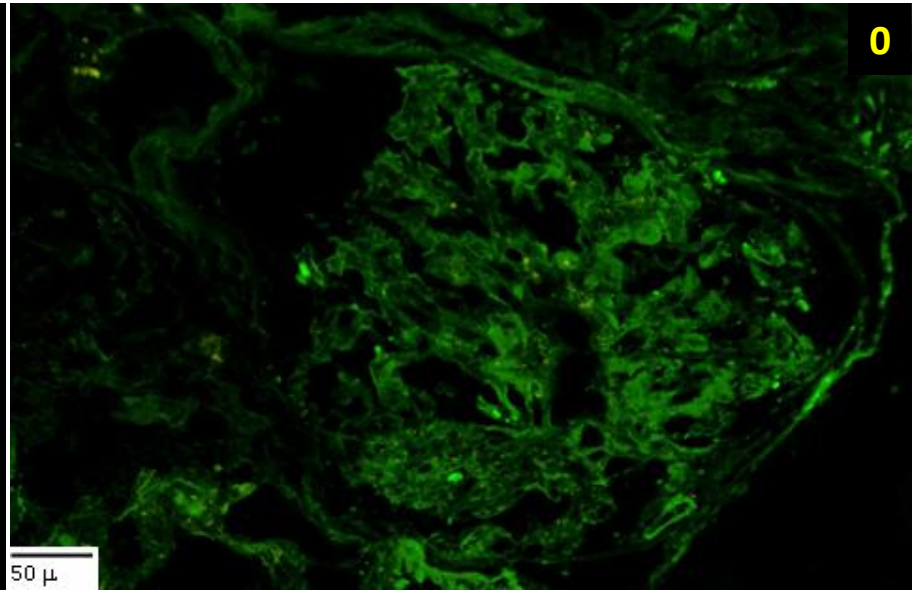
P=0.03

nominal†

*p≤0.05. Intention-to-treat population (all randomised patients). †Statistical testing stopped after first endpoint to not reach significance between treatment arms (i.e., change in activity score of C3G histologic index score at Week 26 vs baseline).
CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Pegcetacoplan treatment stopped C3 deposition as seen by C3 staining in renal biopsy

Renal biopsies from a pegcetacoplan-treated C3G native kidney patient:

Baseline	Week 26
	

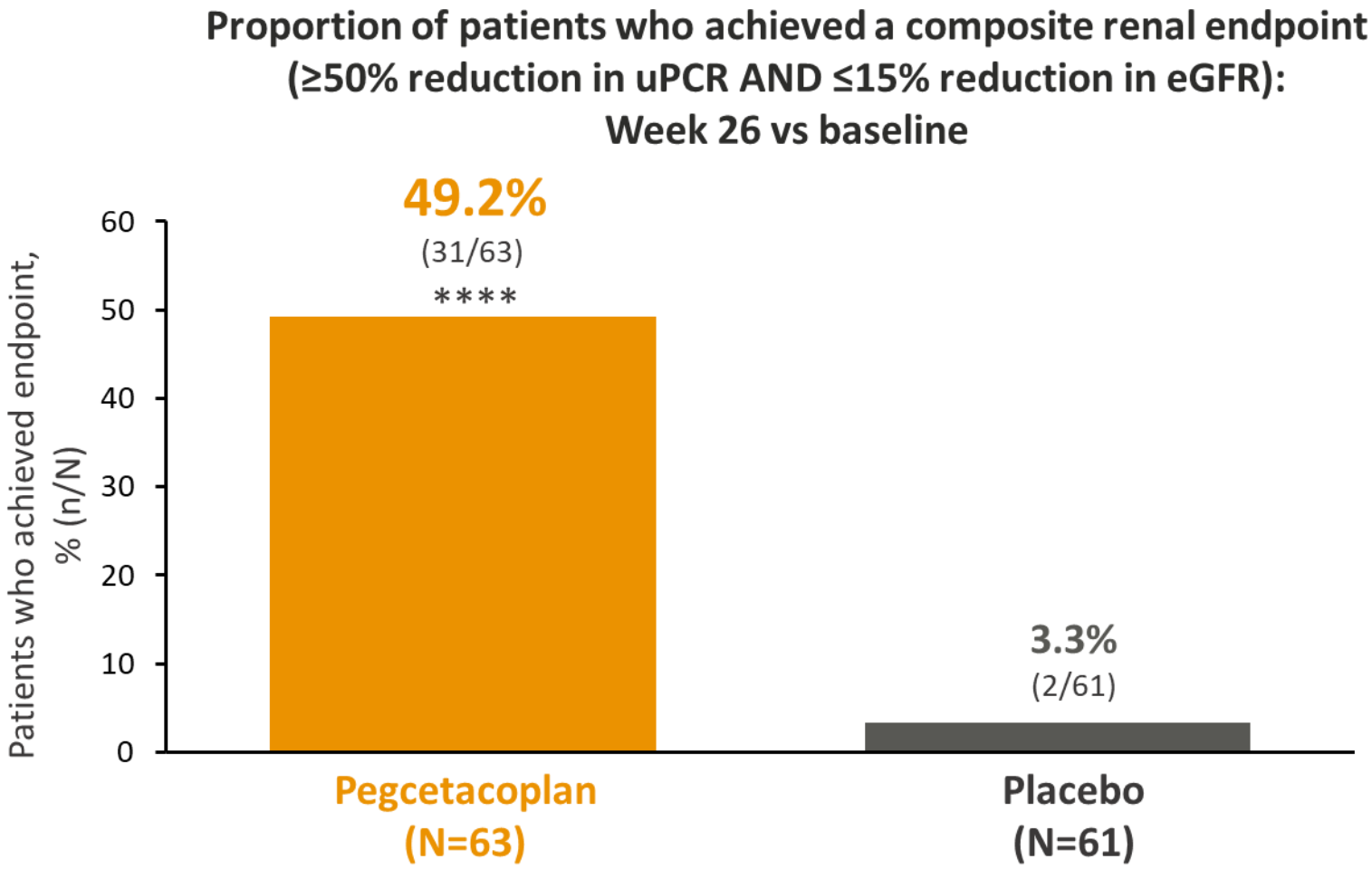
71.4% (25/35) of pegcetacoplan-treated patients achieved 0 intensity staining

Key secondary endpoint	
Proportion with reduced C3c renal biopsy staining[†]	
Pegcetacoplan	74.3% (26/35)
Placebo	11.8 (4/34)

27x higher odds of achieving ≥2 OOM reduction
(6.5, 115.9); nominal[‡]
p<0.0001

[†]Difference defined as ≥2 OOM at Week 26 vs baseline; in all adults. Baseline renal biopsies were not required for adolescent participants.
[‡]Statistical testing stopped after first endpoint to not reach significance between treatment arms (i.e., change in activity score of C3G histological index score at Week 26 vs baseline).
C3c, complement 3c; C3G, complement 3 glomerulopathy; OOM, orders of magnitude.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Pegcetacoplan treatment resulted in **significantly more patients achieving the positive composite renal endpoint**



****p≤0.0001. Intention-to-treat population (all randomised patients). 2-sided p values.
eGFR, estimated glomerular filtration rate; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al.* Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Key secondary endpoint

Odds ratio
pegcetacoplan vs placebo

27x

higher odds of achieving composite renal endpoint vs placebo

p<0.0001

Pegcetacoplan was well tolerated:

TEAE frequency and severity were similar between treatment arms

Patients, n (%)	Pegcetacoplan (N=63)	Placebo (N=61)
TEAEs	53 (84.1)	57 (93.4)
Treatment-related TEAEs	25 (39.7)	26 (42.6)
Severe TEAEs	3 (4.8)	4 (6.6)
Serious TEAEs	6 (9.5)	6 (9.8)
Serious infections		
COVID-19 pneumonia	1 (1.6)	0 (0.0)
Influenza	1 (1.6)	**0 (0.0)**
Pneumonia	1 (1.6)	**0 (0.0)**
Viral infection	**0 (0.0)**	1 (1.6)
TEAEs leading to treatment discontinuation	1 (1.6)	1 (1.6)
Deaths (COVID-19 pneumonia, unrelated to pegcetacoplan)	1 (1.6)	**0 (0.0)**

No encapsulated *N. meningitidis*
cases among the four reported serious infections (pegcetacoplan, n=3; placebo, n=1)

Consistent with >2,000 patient-years of pegcetacoplan exposure†

Safety population (all randomized and treated patients). TEAEs defined as any new AE that began, or any preexisting condition that worsened in severity, after the first dose of study drug and ≤56 days beyond the last dose of study drug.
†Includes exposure in clinical trials and post marketing across multiple indications.
AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent AE.
Nester CM, et al. Presented at American Society of Nephrology Kidney Week 2023 (Oct 31-Nov 5).

Pegcetacoplan treatment may preserve kidney function with favourable safety profile in patients ≥12 years old with native or recurrent C3G or primary IC-MPGN

1

Histopathology improvement

>70% of pegcetacoplan-treated patients

achieved **zero intensity staining of C3c**

2

Proteinuria reduction

68% reduction in proteinuria

pegcetacoplan vs placebo

- Consistent **across subgroups** based on age, disease type and transplant status
- **50.8%** of pegcetacoplan-treated patients **achieved <1 g/g** at Week 26

3

eGFR stabilisation/improvement

Significant stabilisation of eGFR, +6.3 mL/min/1.73 m²

pegcetacoplan vs placebo

4

Pegcetacoplan has been **well tolerated** with **no encapsulated meningitis** reported…

consistent with previous trials and with more than **2000 patient-years of pegcetacoplan exposure**

C3c, complement 3c; eGFR, estimated glomerular filtration rate.

Nester CM, *et al.* Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Case 1:

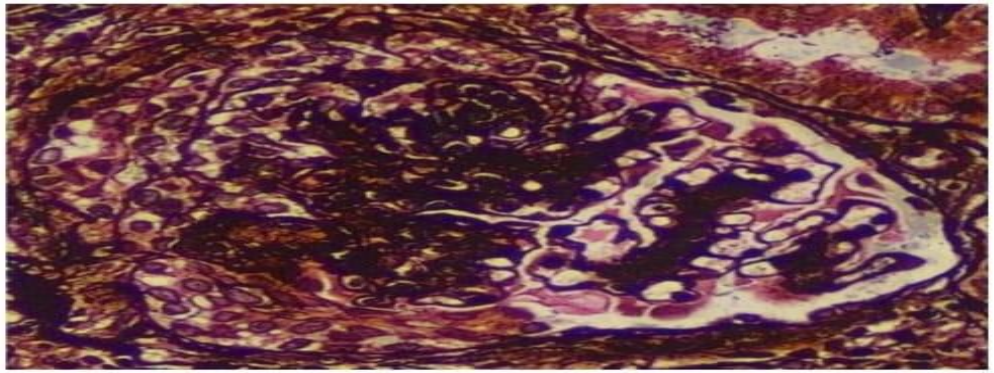
A 28 years old male patient, previously healthy

Not known to have chronic medical illness

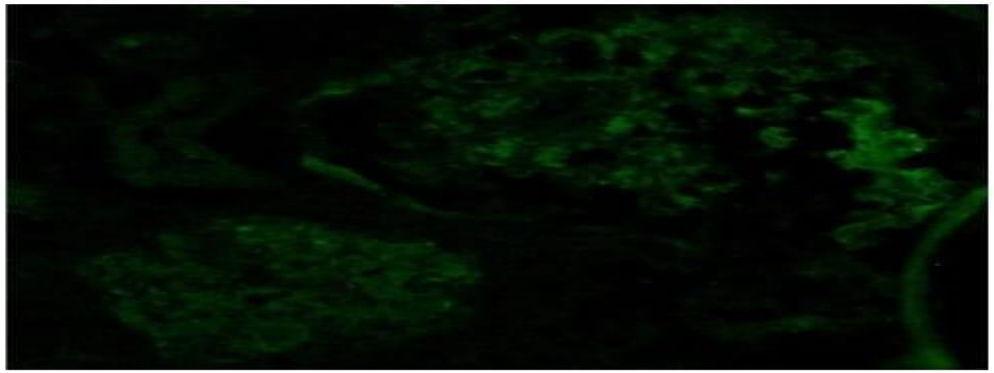
No family h/o renal disease

Work as driver , not smokers

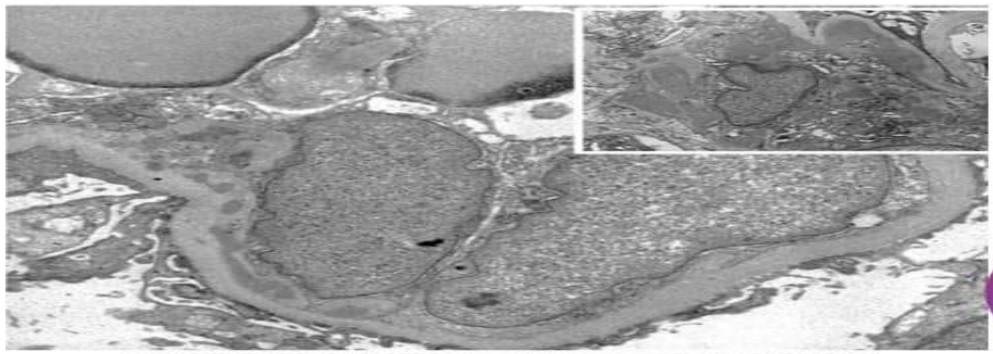
no history of NSAIDS or herbal medication



Glomerulus

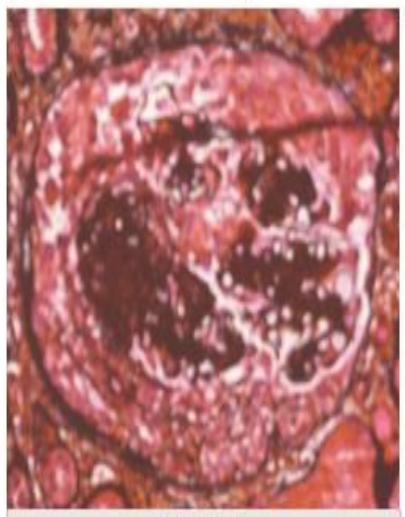


C3

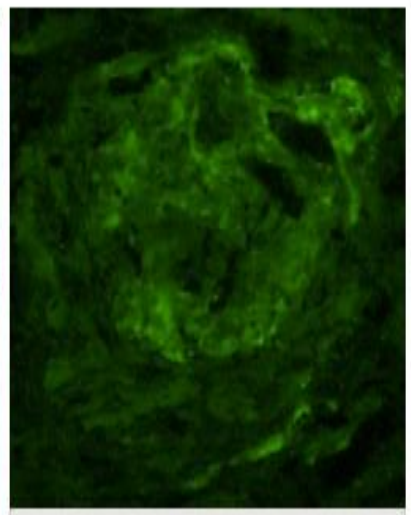


Subendothelial deposits. INSET: Mesangial deposits

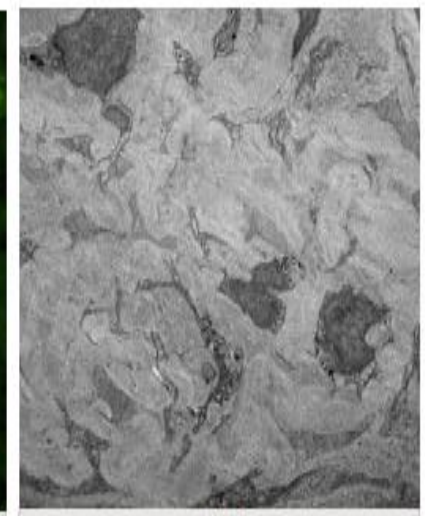
Images:



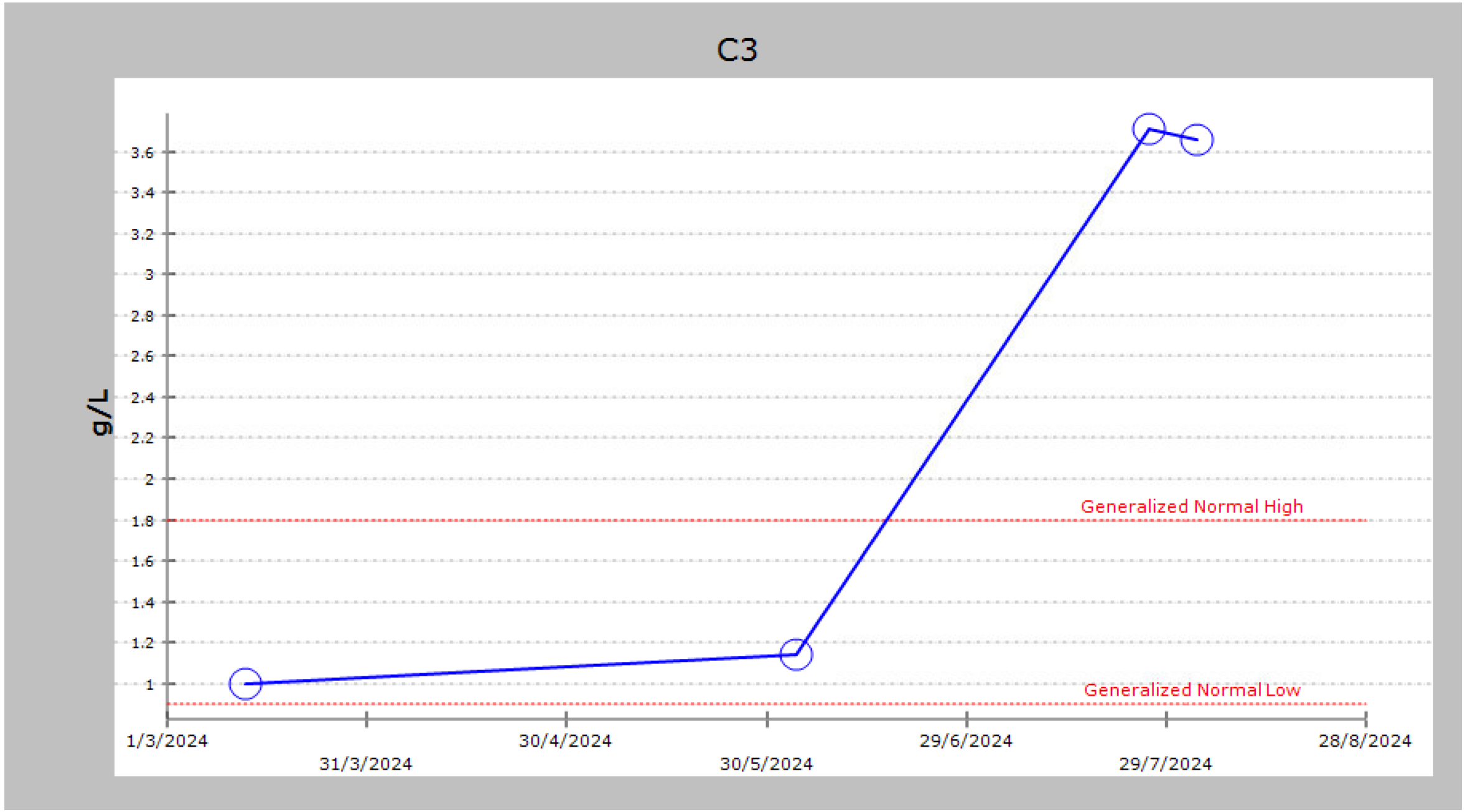
Crescent

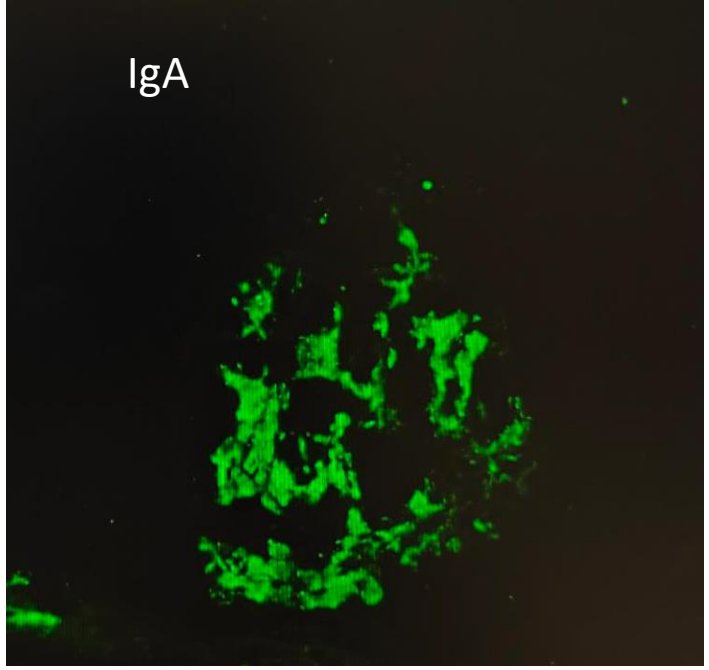


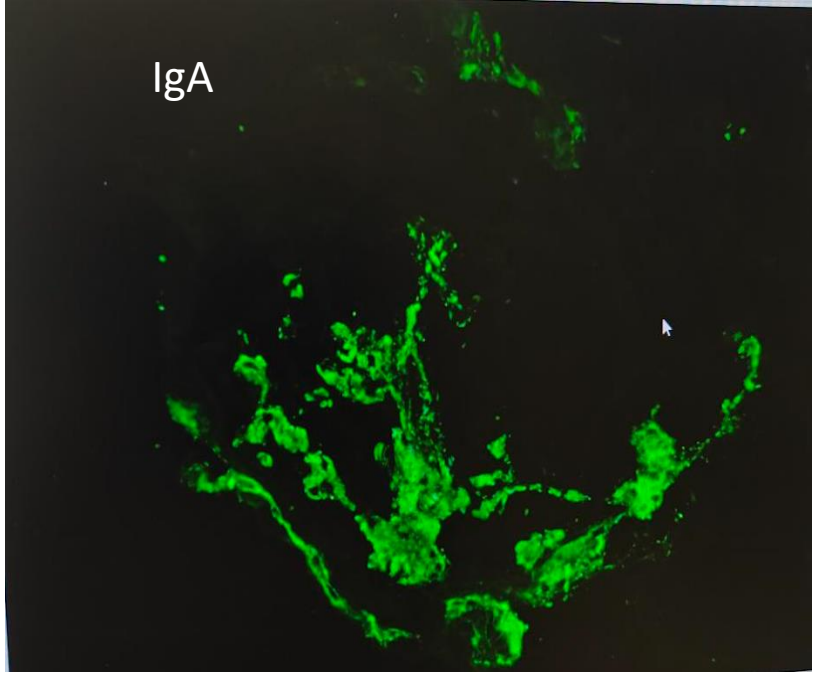
C3

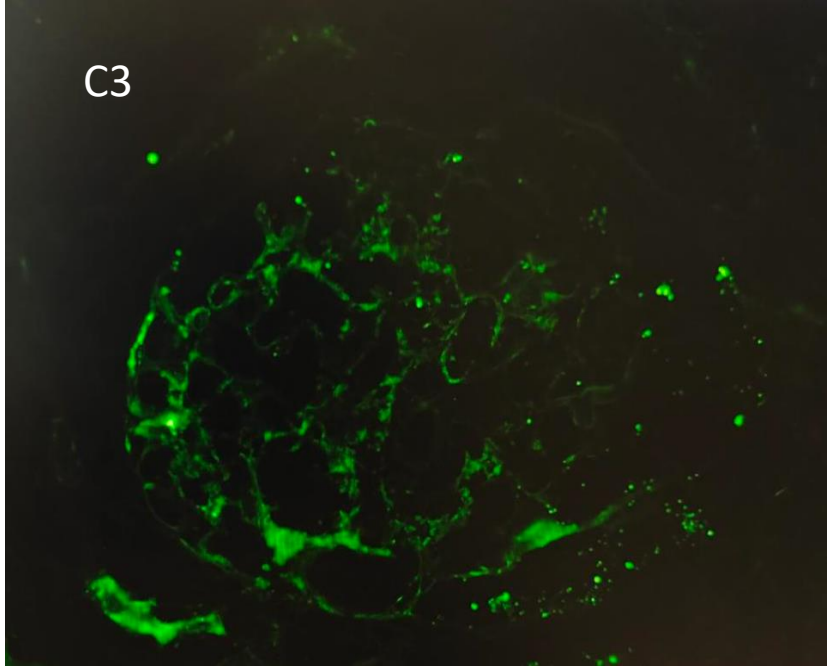


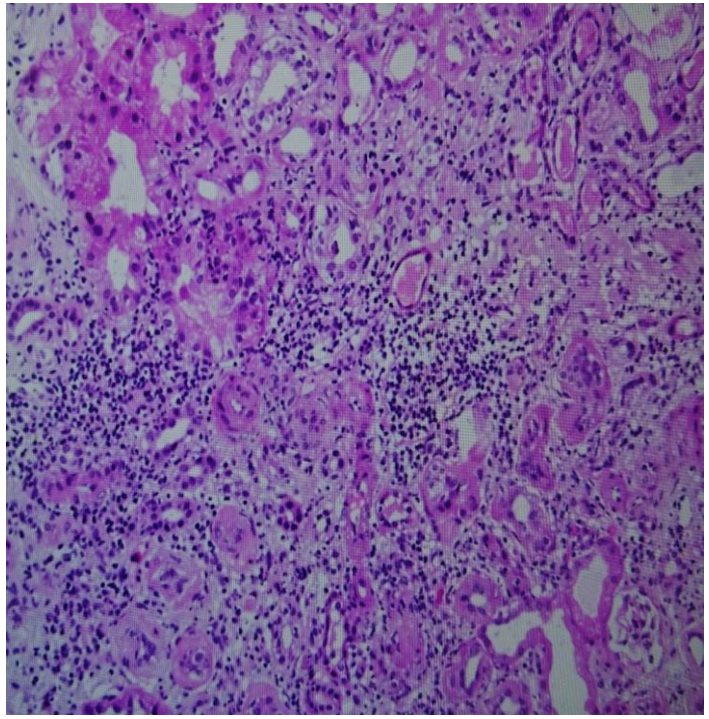
EM

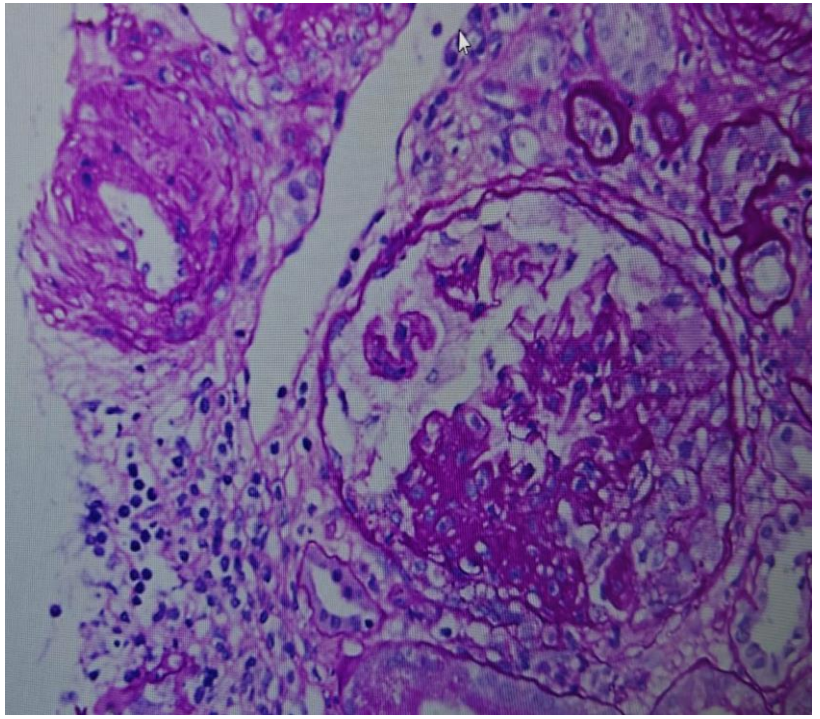

C3
g/L
3.6
3.4
3.2
3
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
Generalized Normal High
Generalized Normal Low
1/3/2024
31/3/2024
30/4/2024
30/5/2024
29/6/2024
29/7/2024
28/8/2024

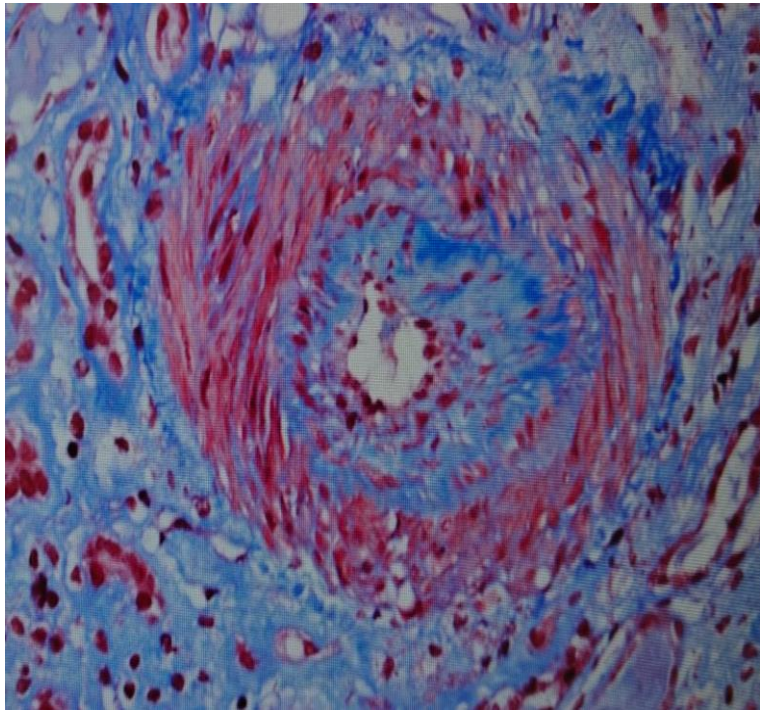

IgA


IgA


C3







CASE 2:

- 20 year old Male presented with sudden onset of Nephrotic Syndrome

- **HPI:**
- Works as a Policeman , No Pmhx , No family Hx , Not on any Herbal or Allopathic Medications
- No recent infections
- But may have had a facial rash

- **Labs :**
- Creatinine : **134 umol/l**
- S. Albumin : 19 g/l
- Lipid Profile : Abnormal
- Urinalysis : **RBC++, Protein ++**
- uPCR : **7 g/g**

- **Immunology :**
- **ANA + (1:160) , Histone +**
- dsDNA -, SPEP/UPEP - , All other Immunological markers negative

Kidney Biopsy:

Light microscopic study

Renal tissue submitted for light microscopy consists of cortex and medulla and contains 5 glomeruli, none of which is globally sclerosed. There is accentuation of glomerular sizes with increase lobulation. There is mesangial expansion. There is global endocapillary proliferation in 5 glomeruli. Neutrophil polymorphs are seen in 5 glomeruli. Segmental Wire loop is seen in 3 glomeruli. No fibrinoid necrosis in the examined material. There are 2 cellular crescents. John's methenamine silver stain and PAS show segmental double contour appearance in peripheral capillary loops. There is focal acute tubular injury. Intratubular casts are noticed. There is isometric vacuolation of few proximal convoluted tubules. Some tubules show intraluminal neutrophil polymorphs. There is patchy moderate interstitial mixed inflammatory cells infiltration consisting of lymphocytes mainly with plasma cells. There is mild interstitial edema. There is focal mild interstitial fibrosis constituting 10% of cortical tissue core. Sampled blood vessels are unremarkable.

Immunofluorescent study

Renal tissue submitted for immunofluorescent study contains 6 glomeruli, none of which is globally sclerosed. The glomeruli show granular immunoreactivity to IgG (3+), IgA (1+), IgM (1+), C3 (3+), c1q (3+), kappa light chain (2+), Lambda light chain (3+), along the glomerular capillary loops as well as in the mesangium. The glomeruli show no immunoreactivity to fibrinogen and albumin. Tubular protein reabsorption droplets are immunoreactive for IgA.

Electron Microscopic study

Survey sections of renal tissue submitted for electron microscopic examination show 2 glomeruli none of which is globally sclerosed. The glomerular basement membrane (GBM) thickness ranges 0.413-1.133um with a mean thickness of 0.772um±0.224 (Normal= 0.360 ± 0.076um). There were subendothelial and mesangial electron dense deposits in the examined material. Few small subepithelial deposits are seen in one capillary loop. No evidence of subepithelial humps in the examined material. The podocytes are swollen and the podocytes foot processes are diffusely effaced with an overall involvement of approximately >90% of the capillary surface. The mesangium is expanded because of the increase in mesangial matrix and immune complex deposition.

Comment

The electron microscopic features confirms immune complex deposition and are mainly subendothelial and mesangial compatible with the immunofluorescent and light microscopic features.

Kidney Biopsy:

Comment

The biopsy shows diffuse global endocapillary proliferation with increased lobulation, segmental duplication of GBM and full house immunofluorescent staining pattern consistent with diffuse proliferative glomerulonephritis with membranoproliferative pattern of glomerular injury. The strongly positive IF staining for C1q (3+), IgG (3+) and C3 (3+) is consistent with an immune complex process with activation of classic complement pathway. The differential diagnosis may include MPGN-immune complex type, lupus nephritis and post infectious proliferative glomerulonephritis, hence, thorough investigation are recommended to confirm the diagnosis.
Electron microscopy is requested and final conclusion will be reported in an addendum,

The biopsy also shows few neutrophil polymorphs within few tubules, hence, urine microscopic examination and culture are recommended to confirm or exclude UTI/ pyelonephritis, please.

Dx:

Lupus Nephritis with MPGN pattern of Injury

Possible C2 Deficient Lupus Nephritis (ANA+, dsDNA-)

SUMMARY OF MAIN FINDINGS						
RESULT: VARIANT OF UNCERTAIN SIGNIFICANCE						
CHROMOSOME POSITION	TYPE	ZYGOSITY	CYTOBAND	LENGTH	CODING GENES COVERED	PATHOGENICITY
chr1:196767129-196853138	Deletion	Heterozygous	1q31.3	86009 bp	CFHR1, CFHR3, ENSG00000289697	VARIANT OF UNCERTAIN SIGNIFICANCE [Quality Score =57]

RESULTS

C3 Nephritic factor of the alternative pathway (C3 Nef)

	Result	*Units*	*Reference range*
C3 Antigen #	202	mg/L	880-1650
C3 nephritic factor *(blood)(haemolysis)*	Positive		

Result Interpretation:

The screening for nephritic factor C3 is positive. The result should be compared to the clinical context and monitored in 10 to 12 weeks

aHUS Complement Panel, S and P

AHUS Interpretation SDL

Laboratory findings consistent with a-HUS/C3 GN and dysregulation of the alternative pathway. The abnormal pattern suggestive of a-HUS includes normal C4 and absentAH50. Consider genetic testing for Complement abnormalities and autoantibodies for Factor H if clinically indicated.

Is Eculizumab or Ravulizumab taken? SDL

No

Complement, Total, S SDL

3 U/mL (Low)

Reference Value 30–75

Alternative Complement Path Func, S 1 SDL

<10 %of norm (Low)

Reference Value ≥46

Complement C3, S SDL

20 mg/dL (Low)

Reference Value 75–175

Complement C4, S SDL

34 mg/dL

Reference Value 14–40

Factor B Complement Antigen, S 1 SDL

19.0 mg/dL

Reference Value 15.2–42.3

Factor H Complement Antigen, S 1 SDL

19.6 mg/dL

Reference Value 18.5–40.8

C4d Complement, P 1 SDL

1.9 mcg/mL

Reference Value <9.9

CBb Complement, P 2 SDL

0.7 mcg/mL

Reference Value <1.7

SC5b-9 Complement, P 1 SDL

>1200 ng/mL (High)

Reference Value <251

Received: 27 Nov 2023 07:38

Reported: 30 Nov 2023 17:56

- **Final Diagnosis :** IC- MPGN with Activation of Alternate Pathway
- **Etiology :** C3NEF with possible underlying VUS CFHR1/CFHR3
- **Trigger :** Unclear
- **Treatment :** Strong Consideration for Anti-Complement Therapy

Thank You

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