# C3-glomerulopathy and MPGN

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Radboudumc

# Disclosures

- National study leader Otsuka sibeprenlimab
- Local PI danicopan trial Alexion
- Local PI avacopan trial Vifor
- Advisor: HiBio (Morphosys)

# Overview

- C3G versus “idiopathic” IC-MPGN
- C3G: causes
- C3G: evaluation
- C3G: treatment

# MPGN: history

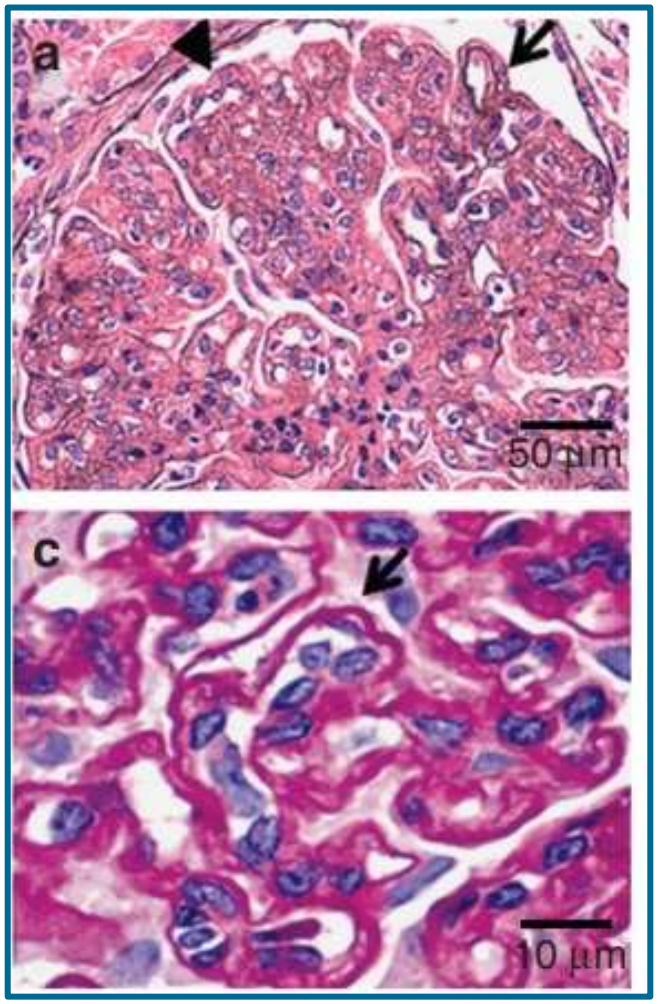
Membranoproliferative glomerulonephritis
(mesangiocapillary glomerulonephritis)

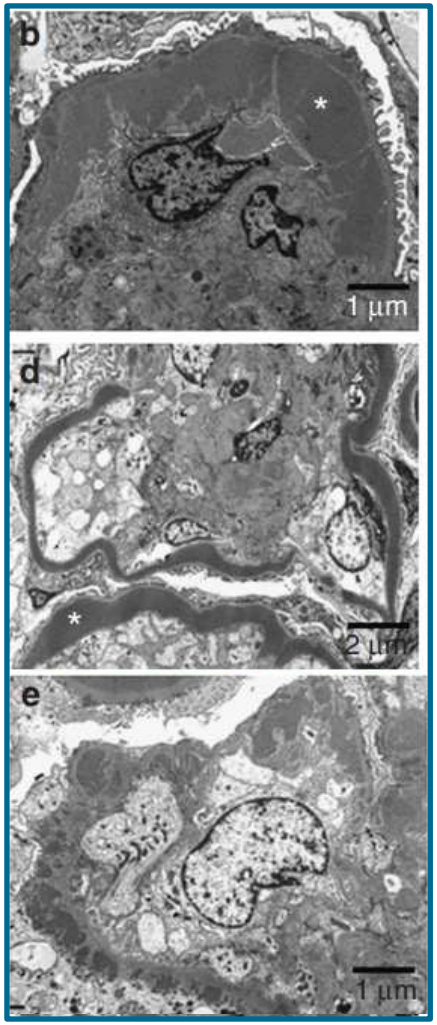
**Description of pattern of glomerular injury**

Thickening of capillary wall (double contours) and mesangial proliferation

EM:
Type I: subendothelial deposits
Type II: intramembranous dense (ribbon-like) deposits (DDD)
Type III: subendothelial, subepithelial (intramembranous) deposits

# MPGN: histology




TYPE I

TYPE II (DDD)

TYPE III

Hou H et al. A working definition of C3G by immunofluorescence Kidney International 2014;85:450-456

# MPGN: differences in IF patterns

**Immunofluorescence: variable**

- Negative (chronic TMA)
- Positive for IgG and C3 (C1q)
- Positive for C3 only

*Note: IF frozen more sensitive and reliable than IP paraffin*
*Note: Ig masked if transport media are used (→ pronase digestion)*

Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.217

# MPGN: differences in IF patterns

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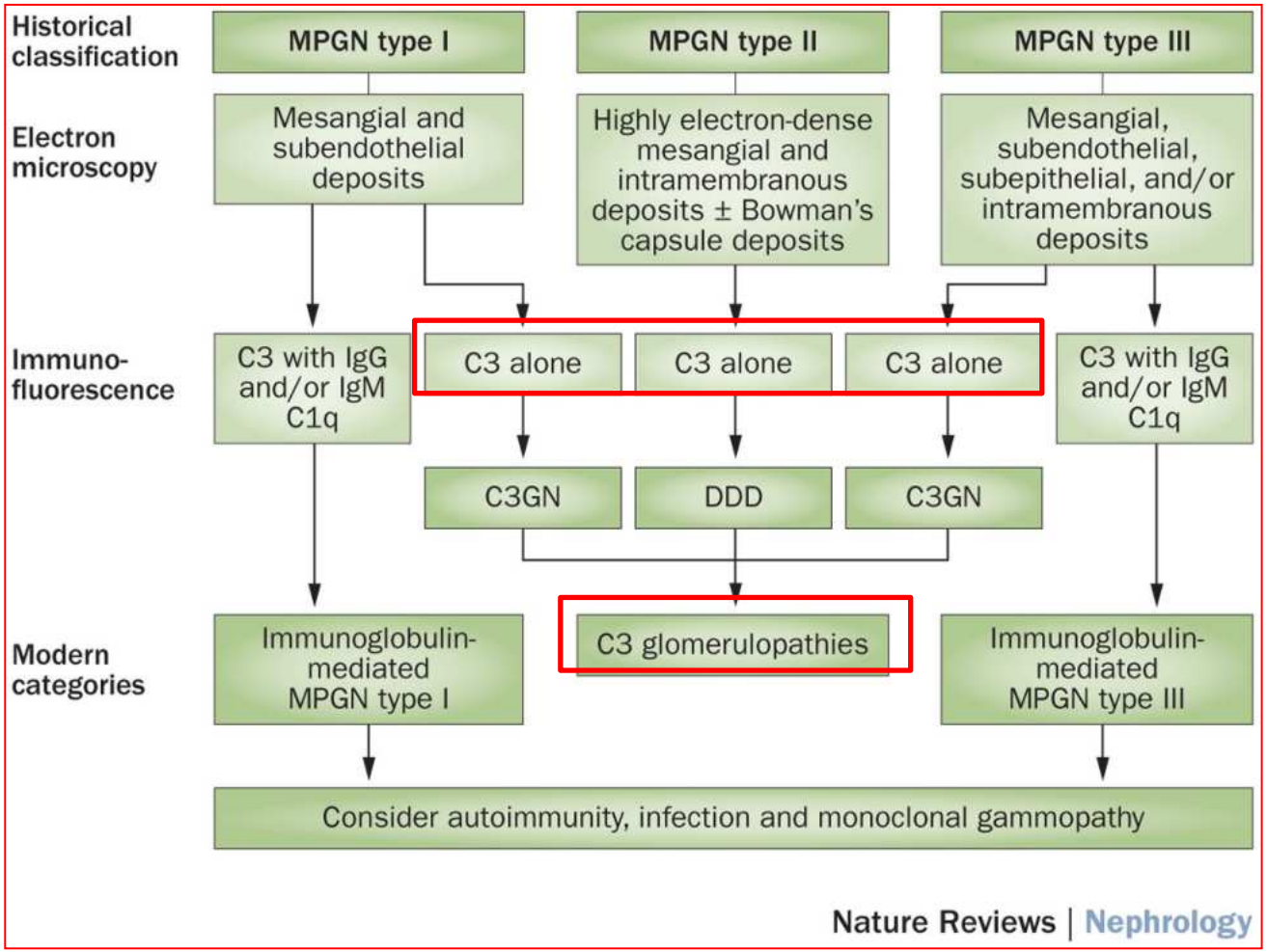
# The relationship between historical and modern classification of glomerulonephritis with membranoproliferative morphology




Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.217

# C3G definition: it is not that simple

Biopsy Bank Columbia University

Period 1999 – 2012

Biopsy with MPGN (N = 796)

Exclusion: N = 396 with systemic disease, HCV, cryoglobulins, M-protein
N = 58 inadequate biopsy material
N= 23 repeat biopsies

Included in study: n = 319 “primary”MPGN

- type I n=200
- Type II n= 42
- Type III n = 77

Biopsy reports: IF criteria (C3 alone; C3 > IgM; C3 > IgG by 2+; etc)

Hou H et al. A working definition of C3G by immunofluorescence Kidney International 2014;85:450-456

# C3G definition: it is not that simple

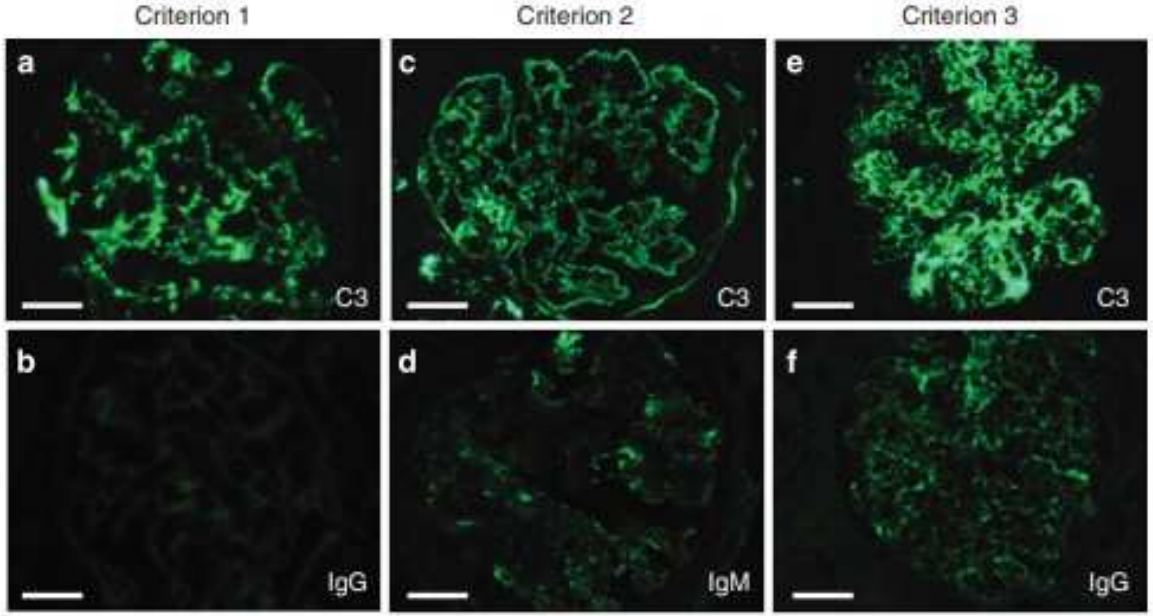



**Figure 2 | Illustrative examples of immunofluorescence (IF) staining meeting criteria 1–3.** IF microscopy findings (×400). (**a**, **b**) Criterion 1: C3G case with features of membranoproliferative glomerulonephritis (MPGN)1 showing 2–3 + mesangial and capillary wall staining for C3 (**a**), with negative immunoglobulin (Ig)G (**b**). (**c**, **d**) Criterion 2: dense deposit disease (DDD) case showing 2 + glomerular capillary wall and mesangial staining for C3 with mesangial ring forms (**c**), with trace (±) IgM (**d**). (**e**, **f**) Criterion 3: DDD case showing 3 + glomerular capillary wall and mesangial staining for C3 (**e**) with 1 + IgG (**f**). Bar = 100 μm.

*Kidney International* (2014) **85**, 450–456 455

Hou H et al. A working definition of C3G by immunofluorescence Kidney International 2014;85:450-456

# C3G: definition

**Table 1 | Primary membranoproliferative glomerulonephritis (MPGN) cases meeting criteria 1–3**

| Diagnosis | Number of primary cases | Criterion 1: C3 only (%) | Criterion 2: C3 dominant and up to 1 + IgM only (%) | Criterion 3: C3 dominant and ⩾2 orders of intensity greater than any combination of IgG, IgM, IgA, and C1q (%) | Criteria 1, 2, or 3 (%) |
|---|---|---|---|---|---|
| MPGN 1 | 200 | 16 (8%) | 13 (6.5%) | 32 (16%) | 61 (30.5%) |
| MPGN2/DDD | 42 | 21 (50%) | 9 (21.4%) | 7 (16.7%)[a] | 37 (88.1%) |
| MPGN 3 | 77 | 8 (10.4%) | 11 (14.3%) | 11(14.3%) | 30 (39%) |
| Total | 319 | 45 (14.1%) | 33 (10.3%) | 50 (15.7%) | 128 (40.1%) |

Abbreviations: DDD, dense deposit disease; Ig, immunoglobulin.

| diagnosis | cases | Criterium 1 | Criterium 2 | Criteria 3 | Combined |
|---|---|---|---|---|---|
| DDD | 42 | 50% | 21.4% | 16.7% | 88.1% |
| MPGN I | 200 | 8% | 6.5% | 16% | 30.5% |
| MPGN III | 77 | 10.4% | 14.3% | 14.3% | 39% |

DDD as " golden standard" for C3G → C3-only identified only 50% of cases! → Criterium 3

Many patients with MPGN do not have C3G! Although systemic disease etc were excluded!

Should we be lest strict?

Hou H et al. A working definition of C3G by immunofluorescence Kidney International 2014;85:450-456

# C3G: change in morphology during follow-up

**Table 3 | Primary membranoproliferative glomerulonephritis (MPGN) cases with serial biopsies**

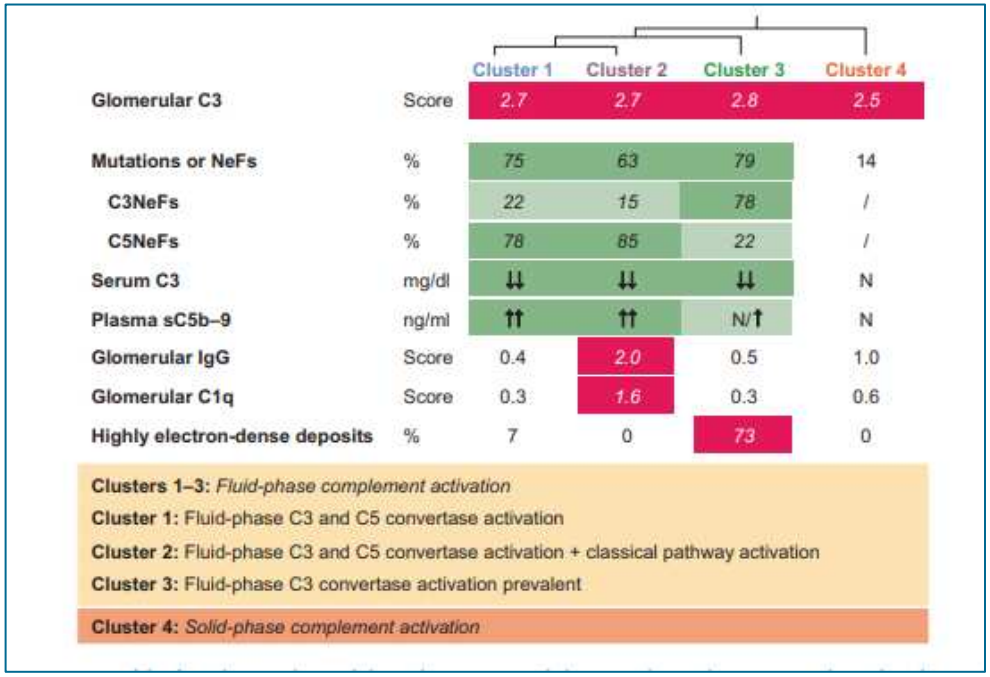
| | IF criterion of initial biopsy | | | | | |
|---|---|---|---|---|---|---|
| IF criterion of repeat biopsy | 1 | 2 | 3 | 4 | 5a | 5b |
| 1 | **4** | | 1 | | | |
| 2 | 2 | **6** | 1 | 1[a] | | |
| 3 | 1 | 1 | **3** | 1[a] | | |
| 4 | 1[b] | | | | | |
| 5a | 1[b] | | | | | |
| 5b | | | | | | |

Abbreviation: IF, immunofluorescence.
Thirteen of 23 patients (57%) had no change in immunofluorescence criteria (bolded).
[a]Two patients (8.7%) had an initial biopsy that failed to meet criteria 1–3 and a subsequent biopsy that did meet criteria.
[b]Two patients (8.7%) had an initial biopsy that did meet criteria 1–3 and a subsequent biopsy that did not.

2 patients with C3 only → IC-MPGN with only + C3>IgG or even codominant staining
2 patients with IC-MPGN → C3G

Hou H et al. A working definition of C3G by immunofluorescence Kidney International 2014;85:450-456

# C3G and "idiopathic" IC-MPGN: separate entities?



| | | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 |
|---|---|---|---|---|---|
| Glomerular C3 | Score | 2.7 | 2.7 | 2.8 | 2.5 |
| Mutations or NeFs | % | 75 | 63 | 79 | 14 |
| C3NeFs | % | 22 | 15 | 78 | / |
| C5NeFs | % | 78 | 85 | 22 | / |
| Serum C3 | mg/dl | ⇊ | ⇊ | ⇊ | N |
| Plasma sC5b–9 | ng/ml | ↑↑ | ↑↑ | N/↑ | N |
| Glomerular IgG | Score | 0.4 | 2.0 | 0.5 | 1.0 |
| Glomerular C1q | Score | 0.3 | 1.6 | 0.3 | 0.6 |
| Highly electron-dense deposits | % | 7 | 0 | 73 | 0 |

**Clusters 1–3:** *Fluid-phase complement activation*
**Cluster 1:** Fluid-phase C3 and C5 convertase activation
**Cluster 2:** Fluid-phase C3 and C5 convertase activation + classical pathway activation
**Cluster 3:** Fluid-phase C3 convertase activation prevalent
**Cluster 4:** *Solid-phase complement activation*

IC-MPGN may represent complement dysregulation in some patients?

Note: biopsy IC-MPGN → C3G
(3 out of 11 in Lomax-Browne CJASN 2022;17:994)
(2out of 23 in Hou J et al KI 2014;85:450-456; also in 2/23 the reverse C3G → IC-MPGN)

IC-MPGN without complement dysregulation: worse outcome
Separate entity?
Late stage C3G?

Age 29 yr (vs 14-17yr)
Kidney impairment 39% (vs 6-19%)
GS 17% (1-8%)

**Table 4.** Overlap between histologic groups and clusters

| Histologic Diagnosis | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Overall *P* Value[a] |
|---|---|---|---|---|---|
| C3GN | 42 | 2 | 4 | 20 | |
| DDD | 4 | 0 | 21 | 0 | |
| IC-MPGN | 16 | 30 | 8 | 26 | <0.001 |

[a]*P* value was calculated with the Fisher exact test.

# MPGN and C3G: pitfalls

**Box 1** | Causes of a membranoproliferative pattern

**With deposition of immunoglobulin and complement**

Autoimmune diseases including systemic lupus erythematosus

Infections

- Viral: hepatitis C and hepatitis B
- Bacterial: endocarditis, visceral abscess, infected atrio–ventricular shunt, leprosy
- Protozoa/other: malaria, schistosomiasis, mycoplasma

Cryoglobulinaemia

Proliferative glomerulonephritis with monoclonal IgG deposits

Fibrillary/immunotactoid glomerulonephritis

**With deposition of C3 alone**

C3 glomerulopathies

**Without significant immunoglobulin or complement**

Chronic thrombotic microangiopathy

- Atypical haemolytic uraemic syndrome/thrombotic thrombocytopaenic purpura
- Antiphospholipid syndrome
- Radiation nephritis
- Nephropathy associated with bone marrow transplantation
- Drug-associated thrombotic microangiopathy

Sickle-cell anaemia

Prothrombotic states

Transplant glomerulopathy

No underlying cause: IC-MPGN /Ig-MPGN
**may be complement mediated**

C3-dominant Glomerulopathies
**Not always MPGN pattern!**

| | |
|---|---|
| MPGN | 25-71% |
| Mesangialprol gn | 24-45% |
| Crescentic | 5-18% |
| Endocapillary prol | 12-19% |

Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.217

# C3G (and some IC-MPGN): causes

- Infections: Post-infectious GN cannot be differentiated from C3G
→ in patients with suspected PIGN with persistent hypocomplementemia and/or persistent kidney injury after 12 weeks → biopsy

- **Complement dysregulation:**
  - ❑ **Genetic: variants in CFH, CFI, C3, CFB, CFHR5**
  - ❑ **Acquired: nephritic factors, antibodies against CFH, CFB, C3**
  - ❑ **M-protein (MGRS)**

IC-MPGN without underlying disease: evaluate as C3G

# C3G: nephritic factors → complement activation

**Table 1** Antibodies activating the complement system in IC-MPGN and C3G

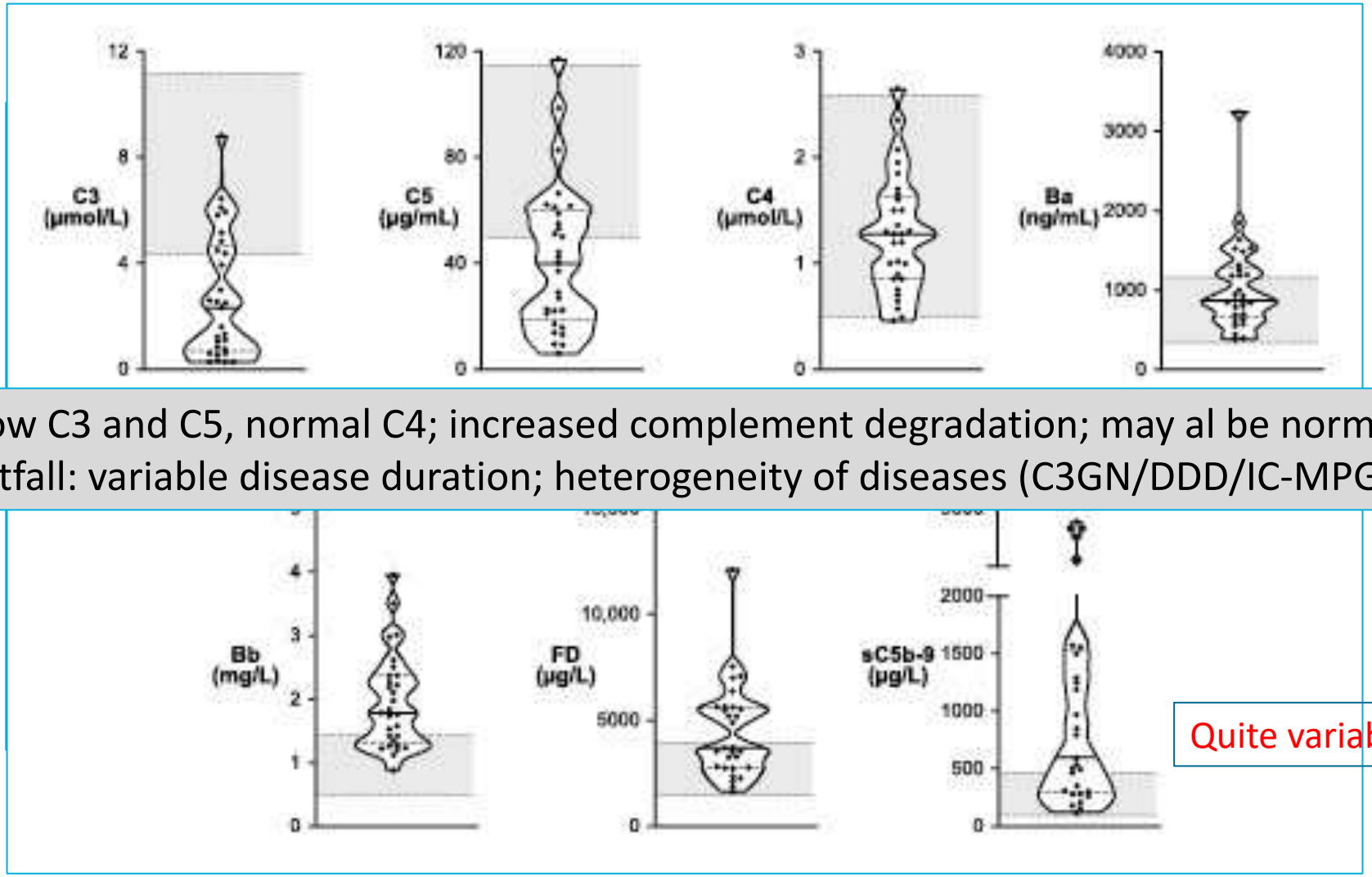
| Autoantibodies | Epitopes | Effect | Frequency | References |
|---|---|---|---|---|
| C3NeF | Different target neoepitopes on alternative pathway C3 convertase (C3bBb) | Stabilisation of C3bBb by preventing spontaneous decay and/or accelerated decay by FH, DAF or CR1 | 40–50% IC-MPGN<br>40–50% C3GN<br>70–80% DDD | [9, 13] |
| C5NeF | Different target neoepitopes on alternative pathway C5 convertase (C3bBbC3b) | Stabilisation of C3bBbC3b | 2 cases<br>22/39 C3GN<br>7/20 DDD | [24, 25] |
| C4NeF | Different epitopes on classical/lectin C3 convertase (C4bC2a) or/and C5 convertase (C4bC2aC3b) | Stabilisation of C4bC2a/C4bC2aC3b by preventing both spontaneous and the C4b-binding protein, CR1 or DAF-mediated decay | 1/13 C3G<br>5/168 C3G | [26, 27] |
| Anti-FB/C3b | Native FB and Bb fragment in the C3bBb complex | Stabilisation of C3bBb against decay; inhibition of C3bBbC3b activation | 1 DDD<br>3/32 DDD<br>5/23 IC-MPGN<br>4/23 IC-MPGN<br>1/118 C3G | [28–30] |
| Anti-factor H | Amino-terminal complement regulatory domain of FH | Unpaired fluid phase FH-mediated complement regulation | 1 IC-MPGN, 1 DDD<br>1/32 DDD<br>5 IC-MPGN<br>11 C3GN<br>1 DDD | [28, 32, 33] |

C3NeF most frequent; 50-80%

Pitfall: no standardized assays; no 100% association with clinical course

Noris M et al. Pediatric Nephrology 2019; 34: 1311-1323

# C3G: complement activation markers

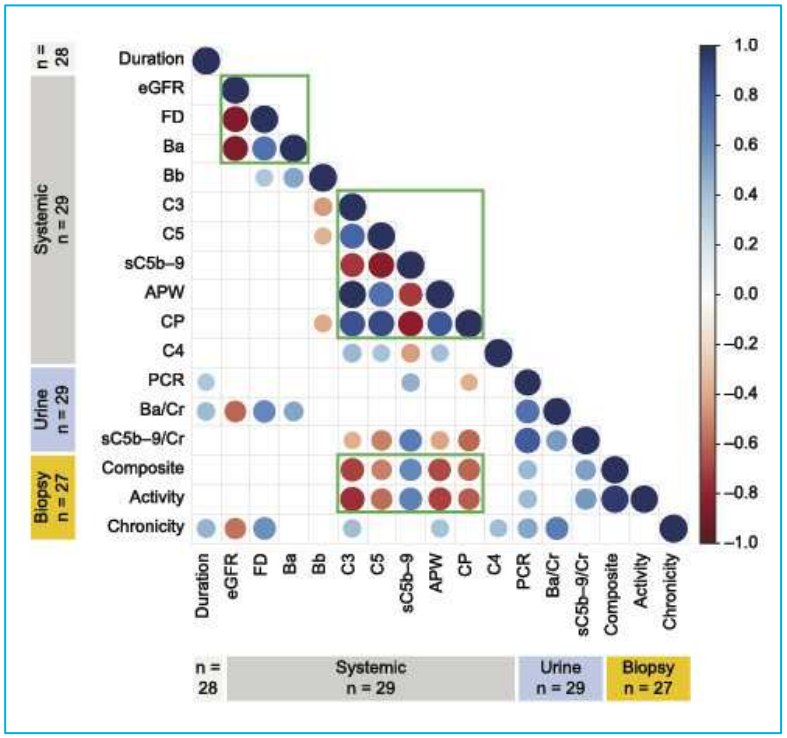


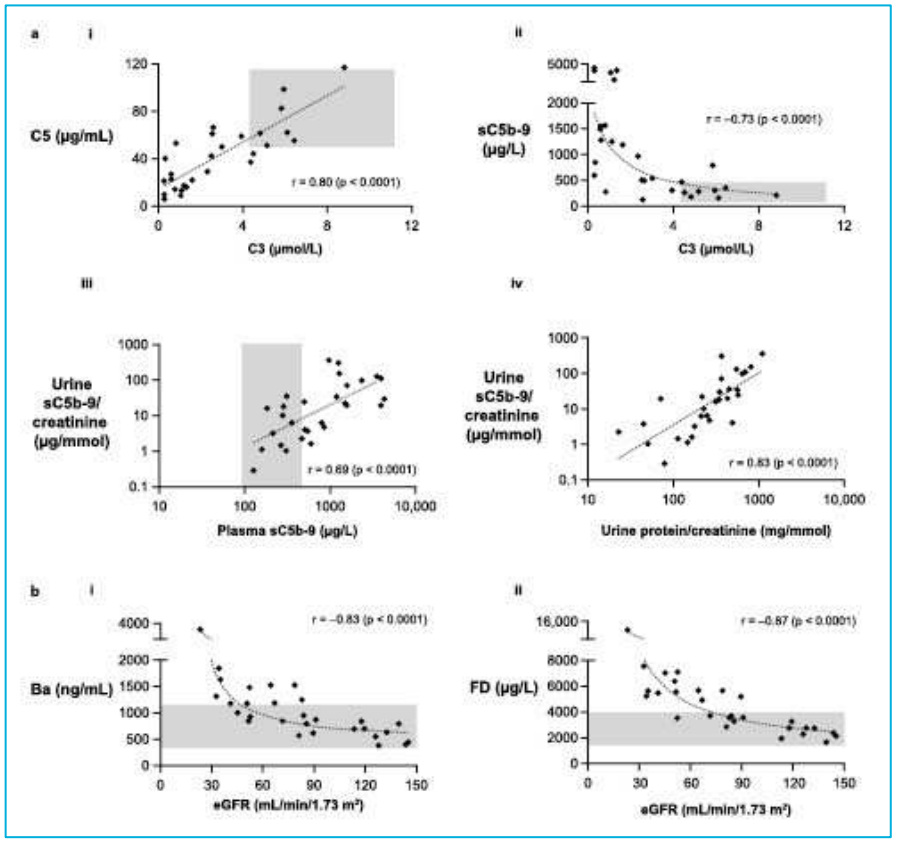

Low C3 and C5, normal C4; increased complement degradation; may al be normal!
Pitfall: variable disease duration; heterogeneity of diseases (C3GN/DDD/IC-MPGN)

Quite variable

Podos S et al. Baseline Clinical Characteristics and Complement Biomarkers of Patients with C3 Glomerulopathy Enrolled in Two Phase 2 Studies Investigating the Factor D Inhibitor Danicopan Am J Nephrol. 2023;53(10):675-686. doi:10.1159/000527166

# C3G: complement activation markers and eGFR

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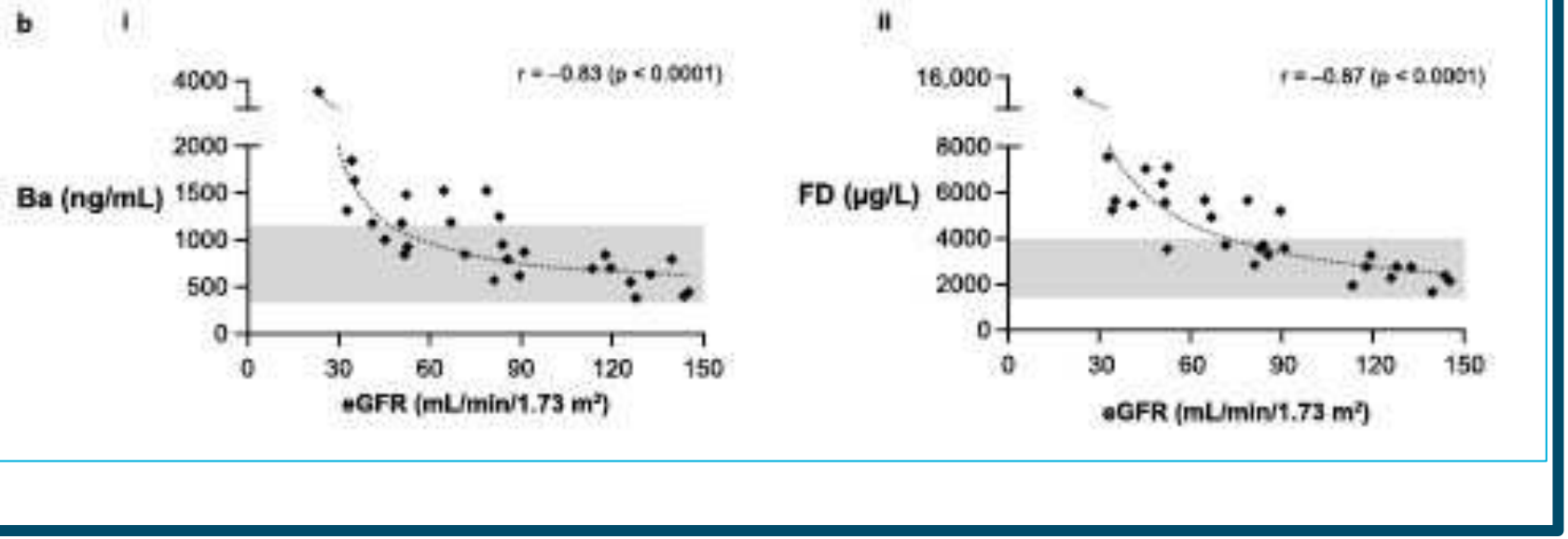
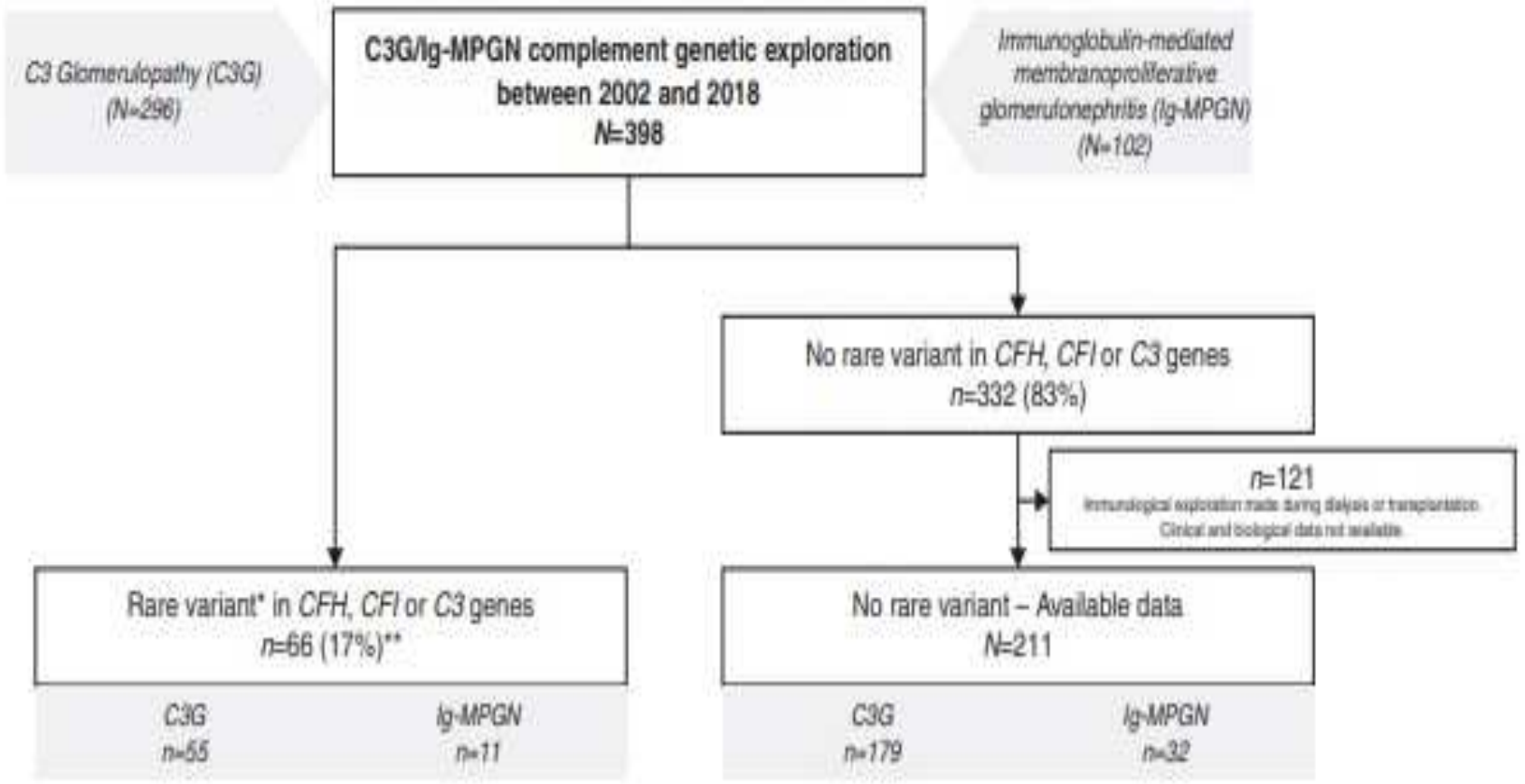
# C3G: complement activation markers and eGFR




Pitfall: CFD and Ba determined by eGFR

Podos S et al. Baseline Clinical Characteristics and Complement Biomarkers of Patients with C3 Glomerulopathy Enrolled in Two Phase 2 Studies Investigating the Factor D Inhibitor Danicopan Am J Nephrol. 2023;53(10):675-686. doi:10.1159/000527166

# C3G and IC-MPGN: complement variants




Meuleman et al C3G IgMPGN and complement rare variants CJASN 2023;18:1435-1445

# C3G and IC-MPGN: complement variants

**Table 1. Characteristics of patients referred to the Laboratory of Immunology of European Hospital Georges Pompidou between 2002 and 2018 with C3 glomerulopathy or immunoglobulin-mediated membranoproliferative GN proven on kidney biopsy**

| Characteristics of Patients | No. of Patients with Available Data | No Variant[a] N=211 | *CFH, CFI,* or *C3* Variants N=66 |
|---|---|---|---|
| **Clinical data at first clinical evaluation** | | | |
| Male sex | 277 | 112/211 (53) | 37/66 (56) |
| Age | 275 | 21 (12–38) | 31 (15–47) |
| Children | 275 | 86/210 (41) | 20/65 (31) |
| Proteinuria, g/d | 186 | 3.9 (2.0–7.7) | 2.9 (1.5–4.3) |
| Nephrotic syndrome | 233 | 95/175 (54) | 25/58 (43) |
| Ig-MPGN | 277 | 32/211 (15) | 11/66 (17) |
| **Treatment** | | | |
| No specific treatment | 235 | 47/173 (27) | 33/62 (53) |
| Plasma exchange | 235 | 1/173 (1) | 3/62 (5) |
| Immunosuppressive treatment | 235 | 125/173 (73) | 26/62 (42) |
| *Corticosteroid alone* | 235 | 41/173 (24) | 16/62 (26) |
| *Corticosteroid associated with other IS agent* | 235 | 84/173 (49) | 10/62 (16) |
| **Follow-up on native kidney** | | | |
| Follow-up | 222 | 65 (30–134) | 100 (60–180) |
| Kidney function at the last follow-up | | | |
| *eGFR >60 ml/min per 1.73 m²* | 222 | 72/156 (46) | 18/66 (27) |
| *eGFR <60 ml/min per 1.73 m²* | 222 | 29/156 (19) | 5/66 (8) |
| Kidney failure (dialysis or transplantation) | 222 | 55/156 (35) | 43/66 (65) |

With variants: older, lower eGFR, less often treated with IS; more ESRD

Meuleman et al C3G IgMPGN and complement rare variants CJASN 2023;18:1435-1445

# C3G and IC-MPGN: complement variants

**Table 3. Complement assays in C3 glomerulopathy/immunoglobulin-mediated membranoproliferative GN patients carrying rare variants in *CFH*, *CFI*, and *C3* genes or not**

| Characteristics of Patients | No. of Patients with Available Data | No Variant N=211 | *CFH*, *CFI*, or *C3* Variants N=66 |
|---|---|---|---|
| **Complement activation biomarkers** | | | |
| C3 level,[a] mg/L | 274 | 675 (310–954) | 677 (493–927) |
| Low C3 level | 274 | 102/208 (49) | 31/66 (47) |
| C4 level,[b] mg/L | 266 | 238 (178–296) | 252 (187–309) |
| Low C4 level | 266 | 4/200 (2) | 2/66 (3) |
| Soluble C5b-9,[c] ng/ml | 219 | 446 (282–798) | 437 (289–758) |
| High sC5b-9 | 219 | 123/174 (72) | 33/45 (73) |
| **Regulatory proteins** | | | |
| Factor H level (% of normal value) | 250 | 110 (90–126) | 101 (62–119) |
| Low factor H[d] | 250 | 2/184 (1) | 19/66 (29) |
| Factor I level (% of normal value) | 247 | 108 (97–124) | 107 (90–122) |
| Low factor I[d] | 247 | 1/181 (1) | 12/66 (18) |
| **Associated acquired abnormalities** | | | |
| Positive C3NeF | 267 | 98/201 (49) | 9/66 (13) |
| Anti-FH Ab | 245 | 24/179 (14) | 0/66 |

no difference in C3 or C5b-9

Without variants: more frequent C3Nef, anti-FH ab
With variants: more frequent reduced Factor H or Factor I levels

Meuleman et al C3G IgMPGN and complement rare variants CJASN 2023;18:1435-1445

# C3 glomerulopathy (non-MGRS): treatment

## no evidence from RCT, data suggest efficacy of MMF

Positive studies

Rabasco C et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney International 2015; 88: 1153-1160

Avasare RS et al. Mycophenolate mofetil in combination with steroids for treatment of C3 glomerulopathy. CJASN 2018; 13:406-413

But also many inconclusive/negative studies (uncontrolled, biased by indication etc)

Noris M ea NDT 2023; 0:1-13

# C3 glomerulopathy (non-MGRS): treatment MMF

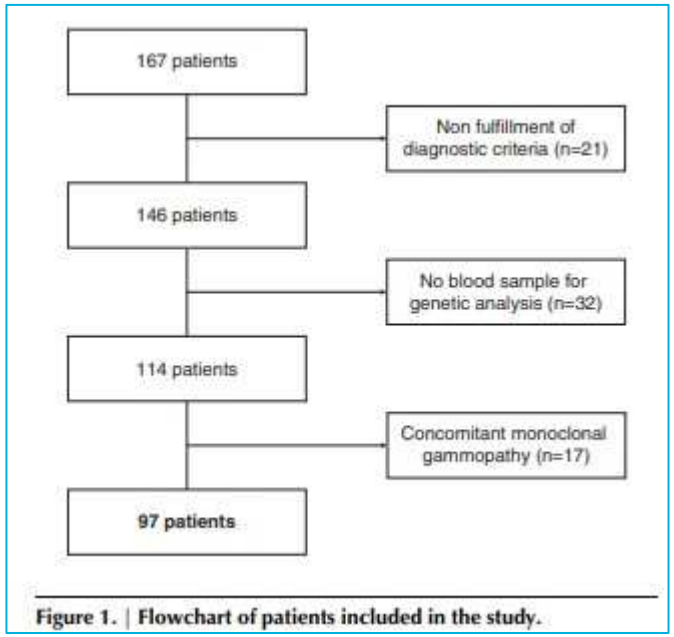



**Figure 1. | Flowchart of patients included in the study.**

**Table 1. Baseline clinical and histologic characteristics**

| Variable | Total, *n*=97 | C3 GN, *n*=81 | Dense Deposit Disease, *n*=16 |
|---|---|---|---|
| **Baseline** | | | |
| Age at diagnosis, yr | 32±21 | 34±21 | 22±15 |
| Adult/pediatric, % | 74/26 | 74/26 | 69/31 |
| Men, *n* (%) | 54 (56) | 49 (61) | 5 (31) |
| Antecedent infection, *n* (%) | 26 (27) | 21 (26) | 5 (31) |
| Clinical presentation, *n* (%) | | | |
| *Nephrotic syndrome* | 39 (40) | 32 (39) | 7 (44) |
| *Nephritic syndrome* | 29 (30) | 26 (32) | 3 (19) |
| *Asymptomatic urinary abnormalities* | 29 (30) | 23 (28) | 6 (38) |
| Serum creatinine, mg/dl | 1.5 [0.8–3] | 1.5 [0.8–3] | 1.1 [0.6–3.1] |
| eGFR at baseline, ml/min per 1.73 $m^2$ | 55 [20–120] | 53 [20–116] | 85 [26–134] |
| eGFR ranges, ml/min per 1.73 $m^2$, *n* (%) | | | |
| *≥60* | 41 (42) | 32 (40) | 9 (56) |
| *30–59* | 21 (22) | 18 (22) | 13 (19) |
| *<30* | 35 (36) | 31 (38) | 4 (25) |
| Albumin, g/dl | 3±0.8 | 3.1±0.8 | 3±0.8 |
| Proteinuria, g/24 h | 3 [1.6–6.8] | 3 [1.5–6.8] | 3.6 [1.8–7.9] |
| Serum C3, mg/dl[a] | 61±40 | 63±41 | 48±35 |
| Low serum C3, <75 mg/dl, *n* (%) | 66 (68) | 52 (64) | 14 (88) |
| Serum C4, mg/dl[b] | 24±9 | 25±9 | 23±9 |
| Serum C5b–9, mg/L[c] | 360 (170–828) | 294 (160–781) | 497 (329–1276) |
| Elevated serum C5b-9, >100 mg/L, *n* (%) | 82 (84) | 67 (82) | 15 (94) |
| **Histopathology** | | | |
| Light microscopy pattern, *n* (%) | | | |
| Membranoproliferative GN | 70 (73) | 55 (68) | 15 (94) |
| Diffuse endocapillary proliferative GN | 7 (7) | 7 (9) | 0 (0) |
| Mesangial proliferative GN | 15 | | |
| Diffuse sclerosing GN | 5 | | |
| Globally sclerotic glomeruli, % | 7 [ | | |
| Segmental sclerotic glomeruli, *n* (%) | 15 | | |
| Cellular or fibrocellular crescents, *n* (%) | 24 | | |
| Tubular atrophy/interstitial fibrosis, *n* % | | | |
| *Absence* | 36 | | |
| *Mild* | 32 | | |
| *Moderate* | 19 | | |
| *Severe* | 10 | | |
| Arterio- and arteriolosclerosis, *n* (%) | 24 | | |

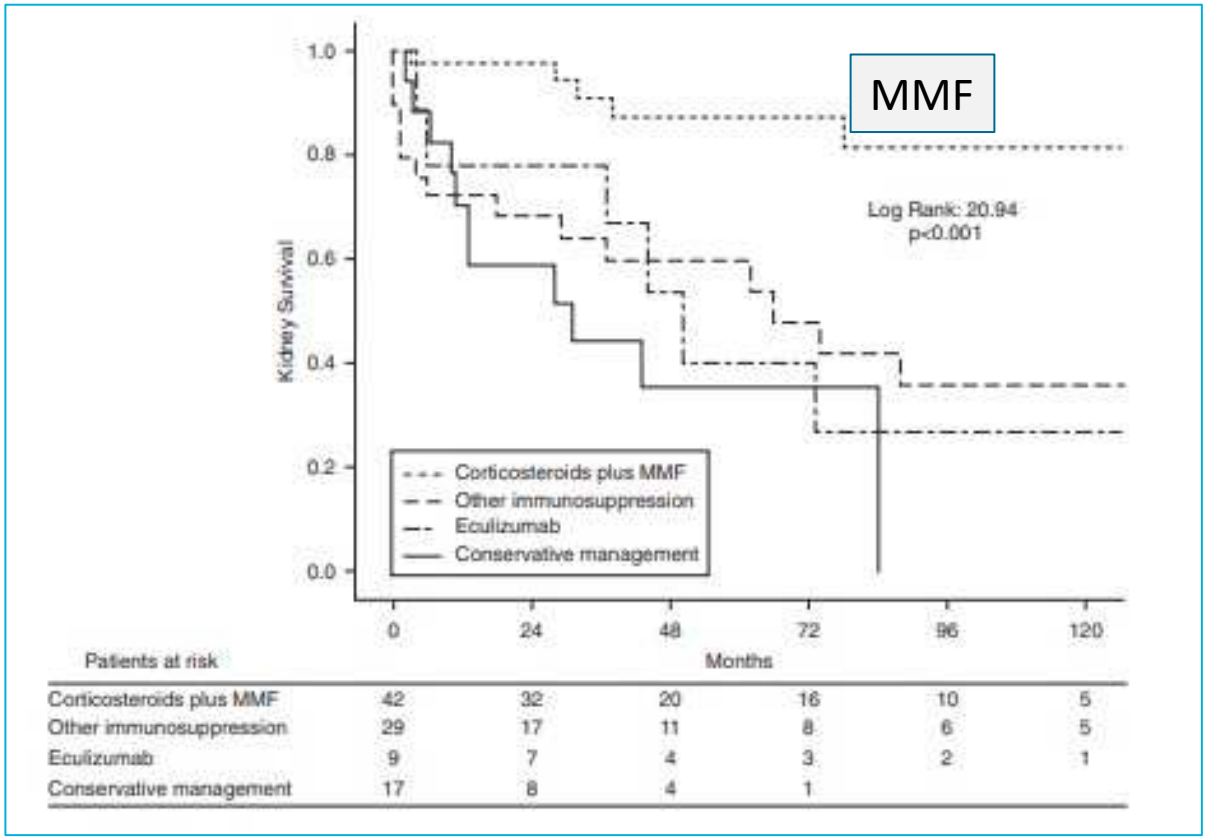
Continuous variables are presented as mean±SD, or median
[a]Reference values: 75–135.
[b]Reference values: 14–60.
[c]Reference values: <100.

Response rate:
Overall n=97: 46%
MMF n=42: 79%

Age: 32 (SD 21)
Screat 1.5 (0.8-3.0) mg/dl
Uprot: 3 (1.6-6.8) g/day
Low C3: 68%
MPGN: 70%

Caravaco-Fontan F et al. MMF in C3G. CJASN 2020;15:1287-1298

# C3 glomerulopathy (non-MGRS): treatment MMF

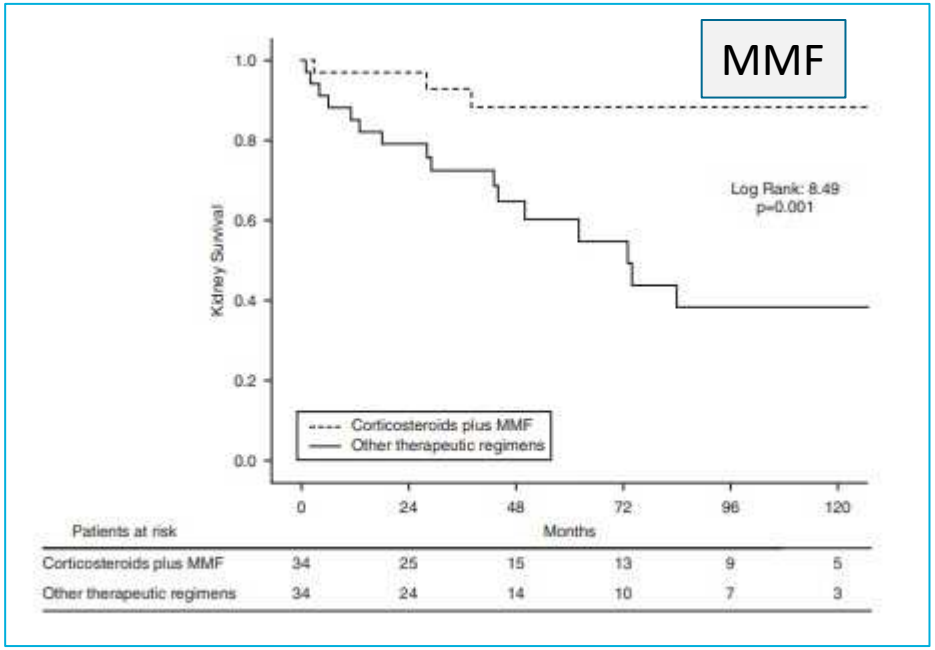



Overall

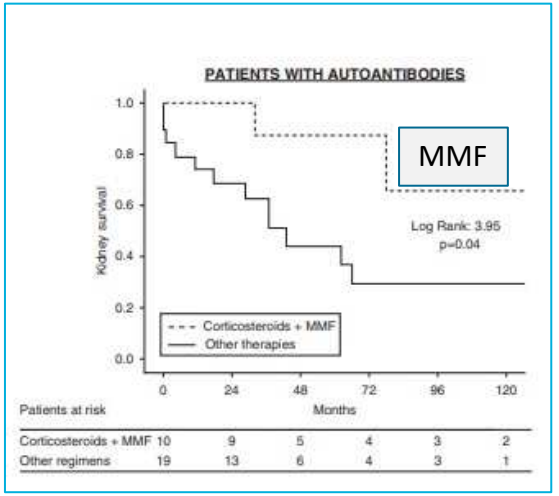
No adjustment

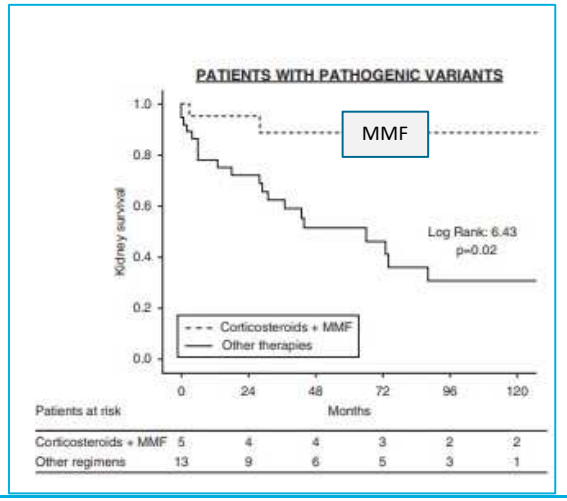
Caravaco-Fontan F et al. MMF in C3G. CJASN 2020;15:1287-1298

# C3 glomerulopathy (non-MGRS): treatment MMF




Comparison with propensity matched cohort




Caravaco-Fontan F et al. MMF in C3G. CJASN 2020;15:1287-1298

# C3 glomerulopathy: anticomplement therapy

Eculizumab in C3GN?  Retrospective case series of eculizumab treated patients 2010-2016 France+Québec

| | Children (n=13) | Adults (n=13) |
|---|---|---|
| Global response | 2 | 4 |
| Partial response | 5 | 1 |
| No response | 6 | 8 |

Overall response rate: children 54%, adults 38%

Le Quintrec M et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. AJKD 2018;72: 84-92

# C3 glomerulopathy: anticomplement therapy

## Eculizumab in C3GN: predictors of response?

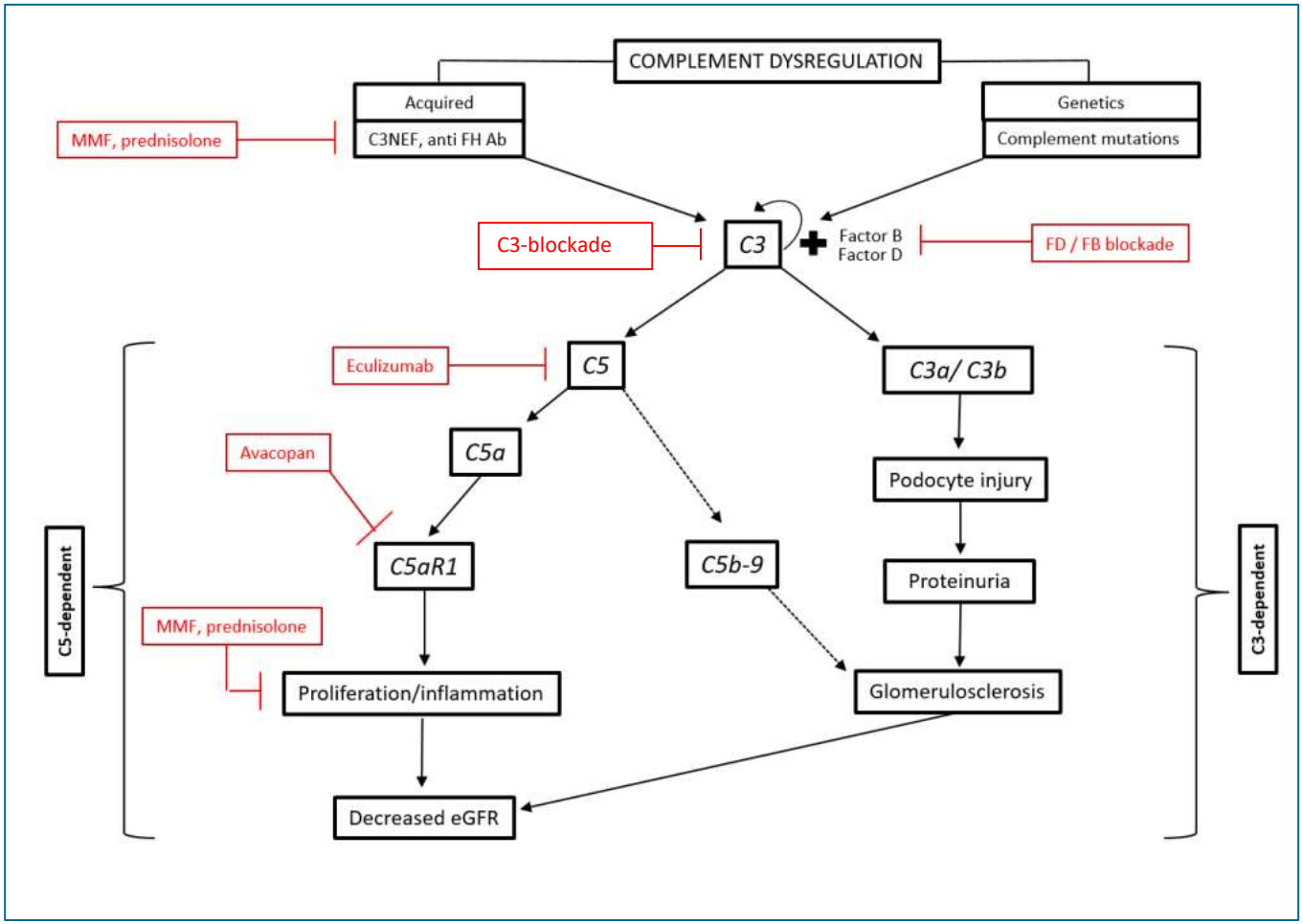
| | Global response (n=6) | Partial response (n=6) | No response (n=14) |
|---|---|---|---|
| Screat (mg/dl) | 4.8 (0.5-6) | 0.7 (0.6-1.1) | 1.2 (0.2-9.9) |
| UPCR (g/g) | 9.4 (0.24 – 12) | 3.9 (0.4-6.2) | 3.0 (1.3 -10) |
| RPGN | 5 (83%) | 0 (0%) | 2 (14%) |
| Crescents > 25% | 4 (66%) | 0 (0%) | 0 (0%) |
| Interstitial fibrosis > 25% | 3 (50%) | 1 (20%) | 1 (11%) |

C3, C3NeF, C5b-9: no predictive value

Eculizumab effective only in patients with RPGN

Le Quintrec M et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. AJKD 2018;72: 84-92

# Two pathways of kidney injury in C3G?



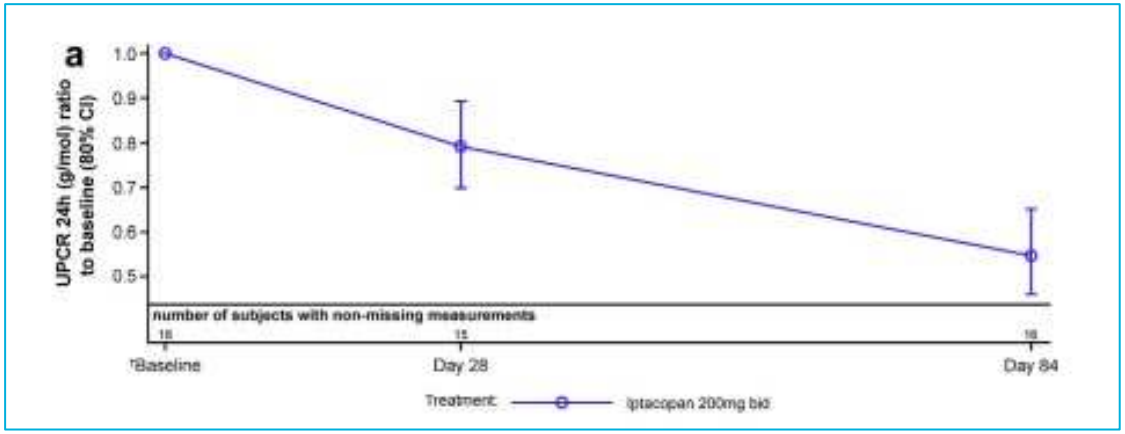

Smith et al. Nature Rev 2019
Duineveld et al. Ped Neph 2020

# C3 glomerulopathy (non-MGRS): what is new?

| Intervention | Target | Study n° | Phase | Condition | Age | Status | Results in C3G/Ig-MPGN |
|---|---|---|---|---|---|---|---|
| Danicopan | Factor D | NCT03369236, NCT03459443 | Phase 2 | C3G and Ig-MPGN | ≥ 18yrs | Terminated | Response not consistent due to suboptimal PK/PD |
| Vemircopan | Factor D | NCT04623710 | Phase 1 | HS, patients with renal dysfunction | ≥ 18yrs | Completed | NA |
| BCX9930 | Factor D | NCT05162066 | Phase 2 | C3G, IgAN, MN | ≥ 18yrs | Terminated | Renal toxicity at the highest dose |
| Iptacopan | Factor B | NCT03832114 | Phase 2 | C3G (A:native; B:tx) | ≥ 18yrs | Completed | A: 45% ↓proteinuria<br>B: ↓ C3 in glomeruli |
| | | NCT03955445 | Ext | C3G (A:native; B:tx) | ≥ 18yrs | Ongoing | A:53% met composite e.p.<br>B:stable eGFR, ↑ C3 levels |
| | | NCT04817618 | Phase 3 | C3G | 12 to 60 yrs | Recruiting | NA |
| | | NCT05755386 | Phase 3 | Ig-MPGN | 12 to 60 yrs | Recruiting | NA |
| Pegcetacoplan | C3 | NCT03453619 | Phase 2 | C3G, LN, IgAN, MN | ≥ 18yrs | Completed | ↑ C3, ↓sC5b-9 levels |
| | | NCT04572854 | Phase 2 | C3G /Ig-MPGN post-tx | ≥ 18yrs | Recruitment completed | NA |
| | | NCT05067127 | Phase 3 | C3G and Ig-MPGN | ≥ 12yrs | Ongoing | NA |
| ALXN2030 | C3 (siRNA) | NCT05501717 | Phase 1 | HS | ≥ 18yrs | Active, Not recruiting | NA |
| ARO-C3 | C3 (siRNA) | NCT05083364 | Phase 1/2a | HS, C3G | ≥ 18yrs | Recruiting | 88%↓ serum C3, 91% ↓ AH50 |
| Avacopan | C5aR1 | NCT03301467 | Phase 2 | C3G | ≥ 18yrs | Terminated | Less ↑in C3HI vs placebo |

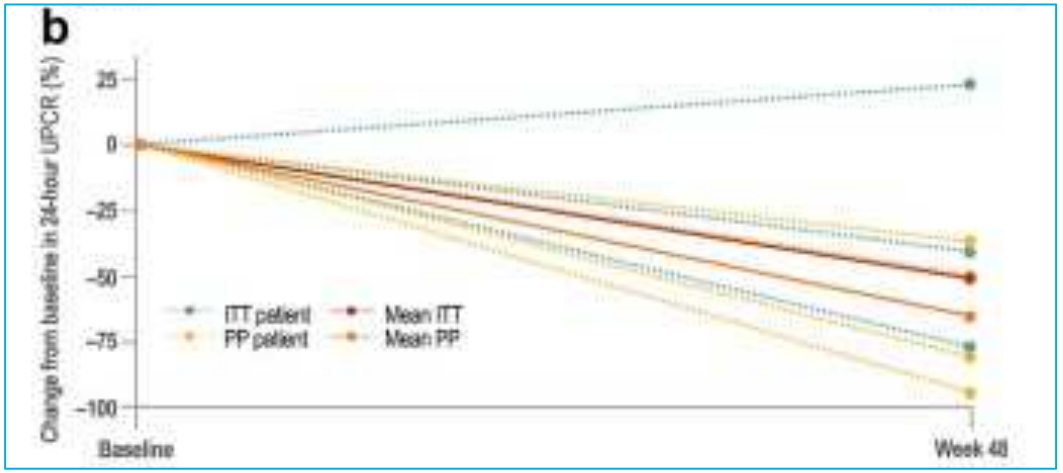
*Nephrol Dial Transplant*, gfad182, https://doi.org/10.1093/ndt/gfad182

# C3 glomerulopathy: complement-inhibitors




Iptacopan
N=16 native kidney

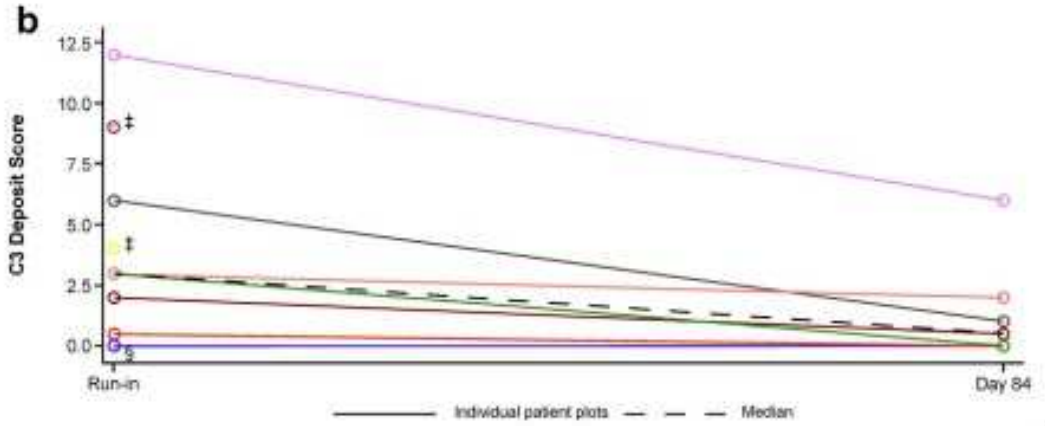
Wong E et al. Iptacopan in c3G. Kidney Int Reports 2023;8:2754-2764




pegcetacoplan
N=8 native kidney

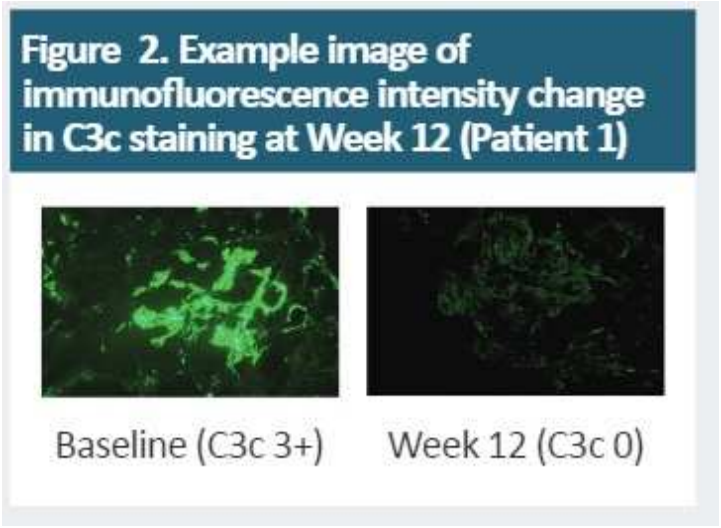
Dixon BP et al. Pegcetacoplan in C3G. Kidney Int Reports 2023;8:2284-2293

# C3 glomerulopathy: complement-inhibitors




Iptacopan
N=11 transplant recurrence

Wong E et al. Iptacopan in c3G. Kidney Int Reports 2023;8:2754-2764




pegcetacoplan
N=10 transplant recurrence

Bomback et al. ASN 2023 poster

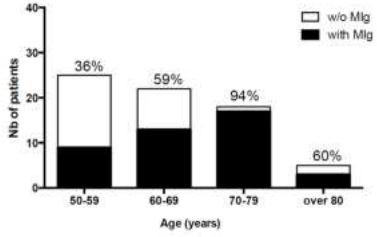
- 5 of 10 pegcetacoplan patients achieved a reduction of C3c staining by ≥2 OOM of intensity
- 4 of the 5 above pegcetacoplan patients completely cleared C3c staining and electron microscopy deposits at Week 12 (C3G, n=4)

# C3G: bimodal age distribution (dependent on M-protein)

| | With monoclonal Ig (n=36) | w/o monoclonal Ig (n=59) |
|---|---|---|
| Age (yrs) | 60 (20-85) | 28 (4-84) |
| Male/female | 25/11 | 28/31 |
| Screat (mg/dl) | 1.9 (0.8 – 14.7) | 1.3 (0.3-7.9) |
| Proteinuria (g/day) | 3 (0.2-15) | 1.7 (0.3-24.2) |
| MGRS/sMM/MM/CLL/CryoT1 | 26/2/5/2/1 | |
| Low C3 | 34% | 48% |
| Elevated C5b-9 | 83% | 86% |

Ravindran A et al. C3 glomerulopathy associated with monoclonal IgG is a distinct subtype. Kidney Int 2018;94:178-186

Figure 1: monoclonal gammopathy frequency in C3G patients according to age range.
Abbreviations: MIg, monoclonal immunoglobulin; w/o, without.




In patients with C3GN: always look for paraproteins, especially if > 50 years

Chauvet S et al. Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. Blood 2017;129:1437-1447

# Paraproteins and C3 Nephropathy

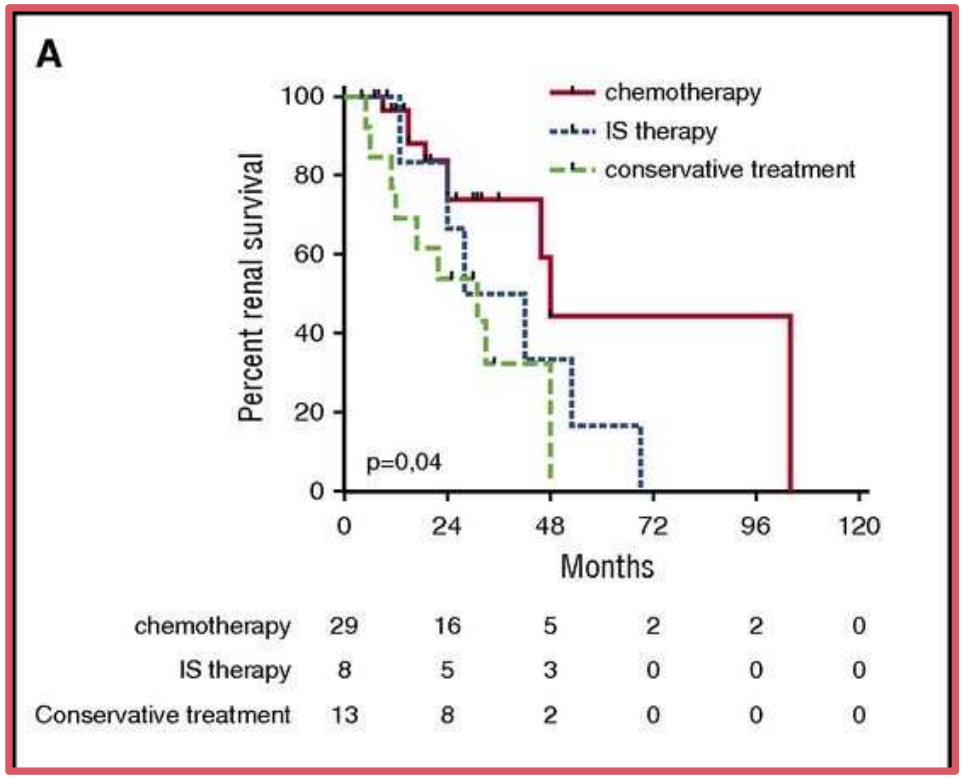
C3 glomerulonephritis: dominant C3 ( ≥ 2+ vs IgG)

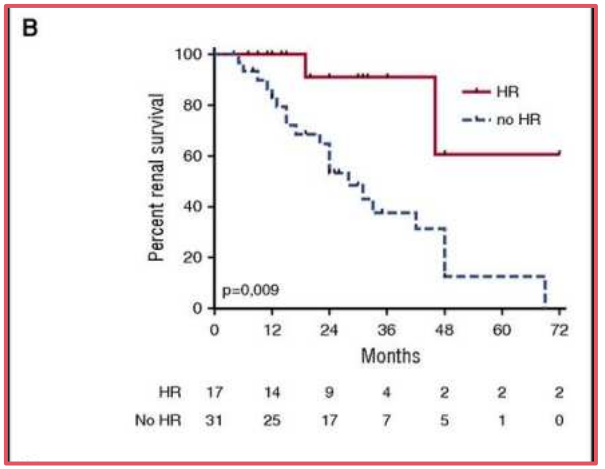
| Disorder | Symptoms | LM | IF | EM | Serum Urine |
|---|---|---|---|---|---|
| C3 glomerulopathy with monoclonal gammopathy | Variable Proteinuria Nephrosis Hematuria CKD | MPGN MesPGN Endo_GN | Granular C3 **No LC no Ig** | Intramembranous dense deposits (DDD) Subendothelial and mesangial deposits (C3GN) | sIEF 100% FLC 75-100% |

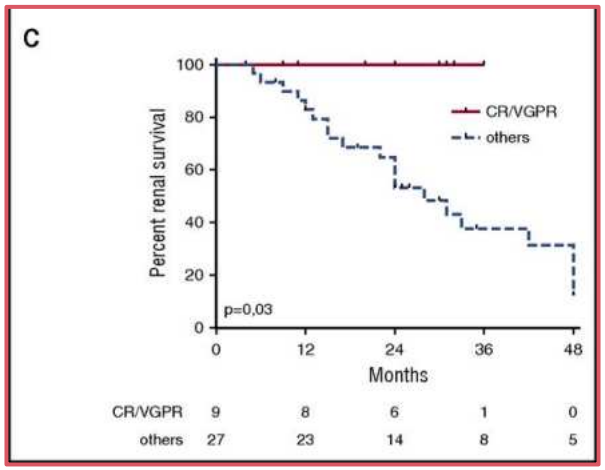
MPGN = membranoproliferative glomerulonephritis; MesPGN= mesangialproliferative glomerulonephritis; Endo-GN = endocapillary glomerulonephritis
LC = light chain; Ig = immunoglobulins

Frank Bridoux, et al Kidney International, Volume 87, Issue 4, 2015, 698–711

# C3 glomerulopathy (MGRS): efficacy of clone-directed therapy



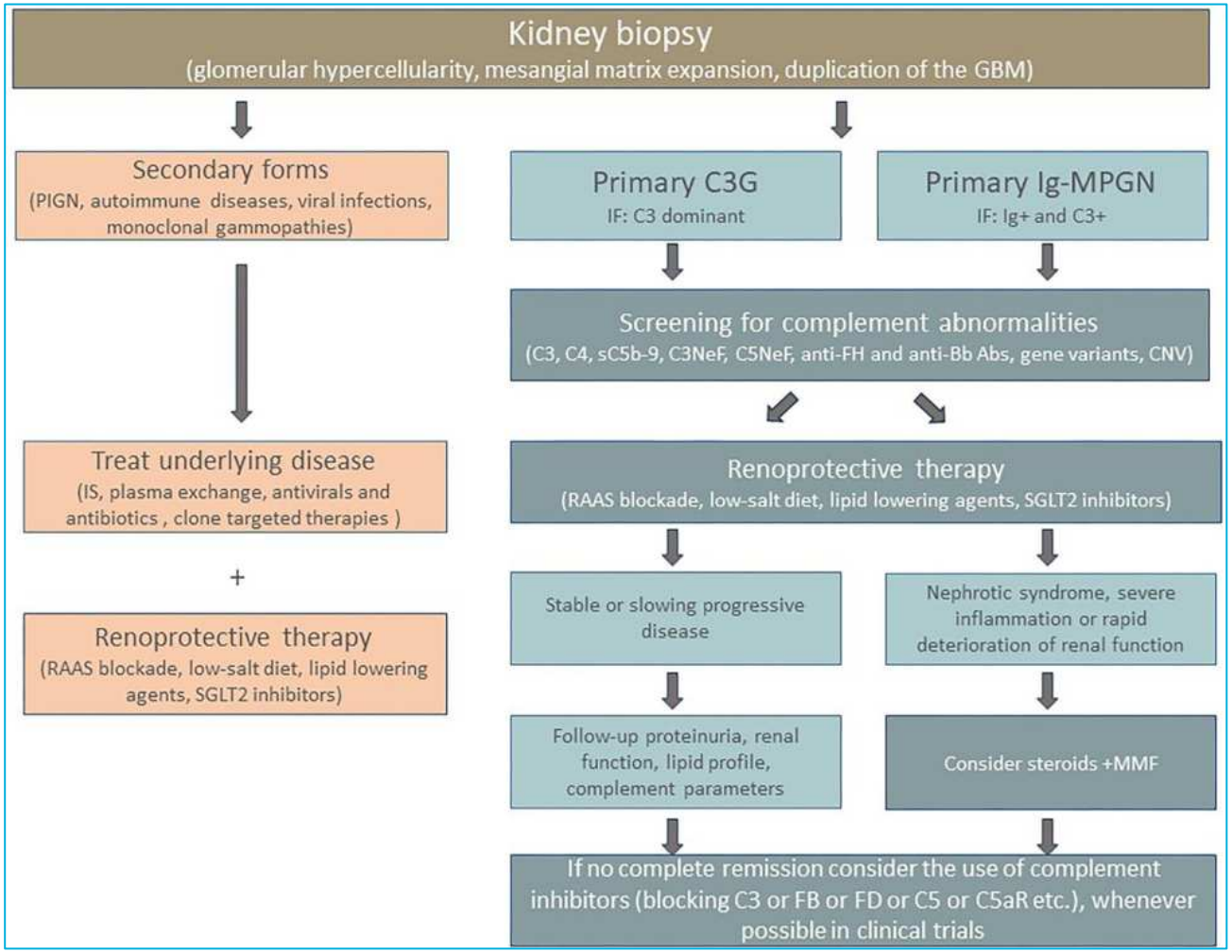




Clone directed therapy improves outcome; hematological rem. → renal remission

Chauvet S et al. Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. Blood 2017;129:1437-1447

**Figure 2:** Flow chart of diagnostic algorithm and currently available treatment algorithm in C3G and Ig-MPGN.




*Nephrol Dial Transplant*, gfad182, https://doi.org/10.1093/ndt/gfad182

# CONCLUSIONS I

C3G: entity caused by complement dysregulation:

young age: inherited or acquired

old age: M-protein

IC-MPGN: many patients should be managed as C3G

Post-infectious GN: may be a look-alike

<u>Evaluation/diagnosis:</u>

Good pathology!

Complement diagnostics (+ m-protein in older patients)

As yet: no accurate biomarkers

# CONCLUSIONS II

Management:

Maximal conservative therapy

Not all patients may need immunosuppressive or anticomplement therapy immediately

In progressive/severe cases: try MMF + prednisone
(or Cyclophosphamide in RPGN)

FUTURE: looks bright – novel anticomplement therapies

# Questions?