Articles
Challenges in the Diagnosis and Management:
https://www.kireports.org/article/S2468-0249(24)01945-4/fulltext
Outcome of Patients Transplanted:
https://www.kireports.org/article/S2468-0249(24)01966-1/fulltext

🔔Tweetorial Alert 🔔

1/
Hey #NephTwitter!
Welcome to a 🆕 #tweetorial #xtorial brought to you by @KIReports.

2/
Our author is Melvin @MChanMD (pediatric nephrologist)
Our topic: Understanding the latest updates in 2024 about diagnosing and managing patients with immune-complex glomerulonephritis and complement 3 glomerulonephritis

#MedTwitter #nephtwitter @ISNkidneycare #XTwitter

3/
There are no conflicts of interest. Please also check out #KIReportsCommunity educational #blogposts at https://www.kireportscommunity.org/. FOLLOW US at @KIReports for more expert #MedEd in #kidneydisease. #FOAMed @MedTweetorials

4a/ Make sure to check out this amazing review article by @Ghobby on this topic.
👉https://www.kireportscommunity.org/post/unlocking-the-role-of-complement-the-evolution-of-c3g-and-immune-complex-mpgn-classification

4b/ @Ghobby's review article and this #Tweetorial is based on these recent publications:
🔪https://www.kireports.org/article/S2468-0249(24)01945-4/fulltext

5a/ Historical Context
💡Membranoproliferative disease (MPGN) was diagnosed based on location of glomerular disease prior to 2010.
💡Such classification was not optimal as it was not based on disease pathogenesis and multiple disease processes fell under type 1 and type 2.

5b/ Historical Context
💡Afterwards, a new system was developed to account for pathologic composition, reclassifying them as complement 3 glomerulopathy (C3G) or immune-complex MPGN (IC-MPGN).

5c/ Historical Context
💡C3G is defined by C3 IF staining of >= 2 orders of intensity stronger than other Ig deposits, whereas ICGN is defined by Ig and complement proteins.
💡Dense deposit disease (DDD) is a sub-category of C3G and has highly electron-dense deposits in the BM.
👇

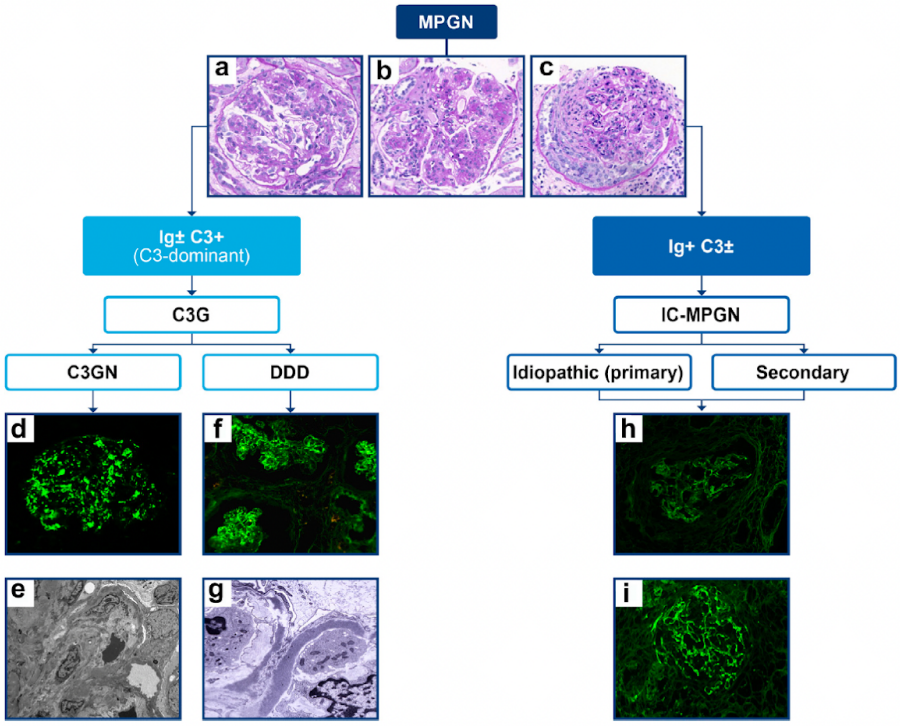
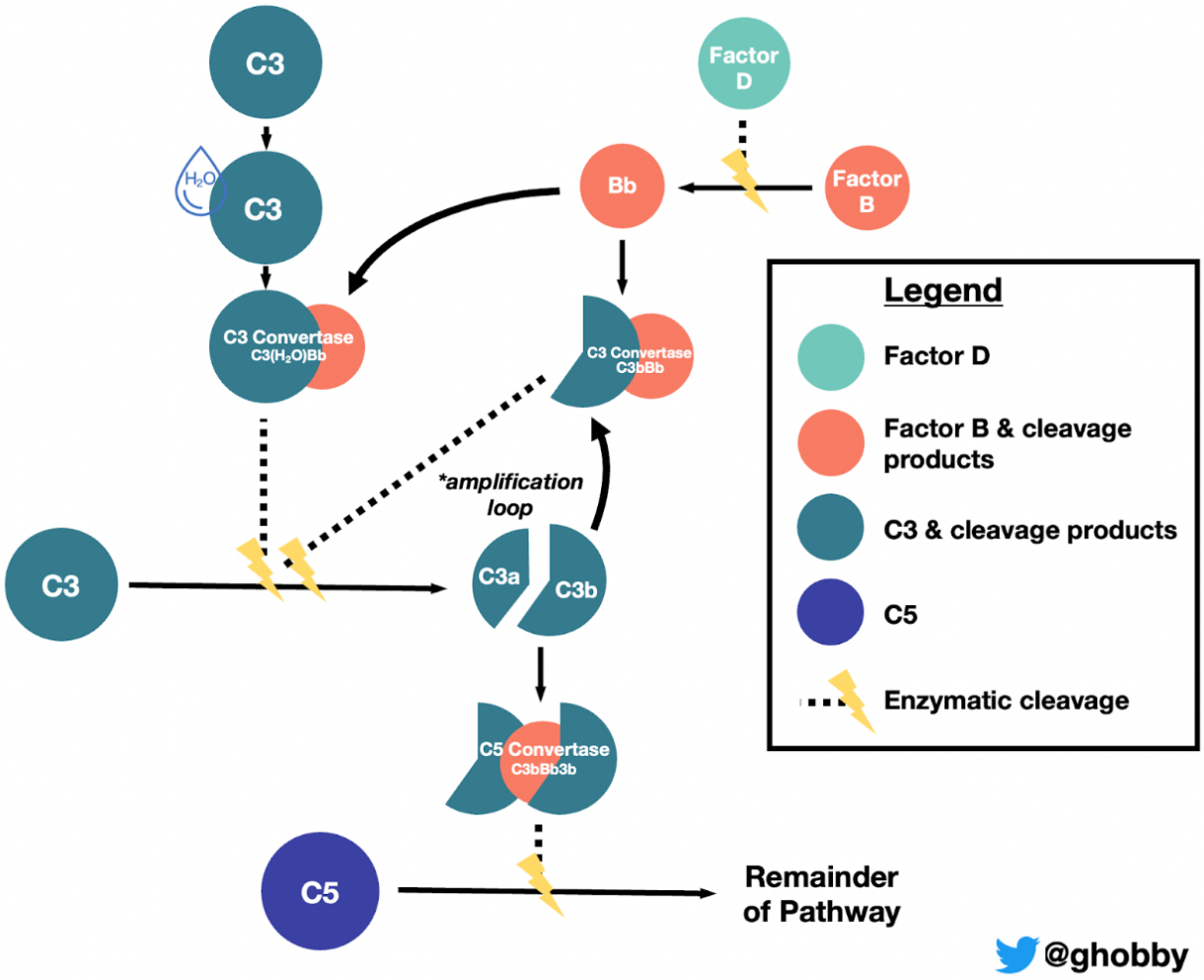


Figure 1. Pathobiology-based classification of membranoproliferative lesions.[3,11] The current classification of MPGN relies on IF examination of glomerular deposits that are defined as either C3-dominant (C3G) or Ig-dominant (IC-MPGN).[3,11] Other unrelated disorders may present with an MPGN pattern of injury in the absence of C3 and Ig deposits, such as chronic thrombotic microangiopathy, aHUS, and chronic transplant glomerulopathy (not shown).[1,3] (a) Mesangioproliferative injury; (b) classical membranoproliferative injury with lobular proliferation and double contours in basement membranes; (c) crescentic injury; (d) C3GN with intense granular deposits of C3 in mesangial regions and segmental deposits along the capillary walls; (e) C3GN with electron-dense deposits in subendothelial, intramembranous, and mesangial regions viewed by EM; (f) DDD with mesangial and capillary staining for C3; (g) DDD with ribbon-like deposits along the basement membrane lamina densa; (h) IC-MPGN with IgG staining; and (i) IC-MPGN with C3 staining. aHUS, atypical hemolytic uremic syndrome; C, complement; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; EM, electron microscopy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IF, immunofluorescence; MPGN, membranoproliferative glomerulonephritis. Images reprinted from Kovala *et al.*,[12] Li *et al.*,[13] Ponticelli *et al.*,[14] and Hanna *et al.*[15] without modification under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

6/ C3G Intro

- Due to overactivation of the alternative pathway
- Progression to kidney failure is anywhere from 30-35% in 10 years.
- Treatment involves a combination of mycophenolate, steroids, and supportive care. Anti-C5a treatment is considered for treatment failures.



7/ C3G Genetic Causes

📣Around ⅓ of cases are attributable to genetic abnormalities in the alternative pathway.

📣Impact of genetic abnormalities on outcomes is unknown.

📣Common genes include C3, CFB, CFH, CFHR, CFI, MCP (CD46), and THBD, as seen 👇with associated frequencies.

Table 1. Frequency of genetic and acquired abnormalities in complement proteins in patients with IC-MPGN and C3G from published cohort studies

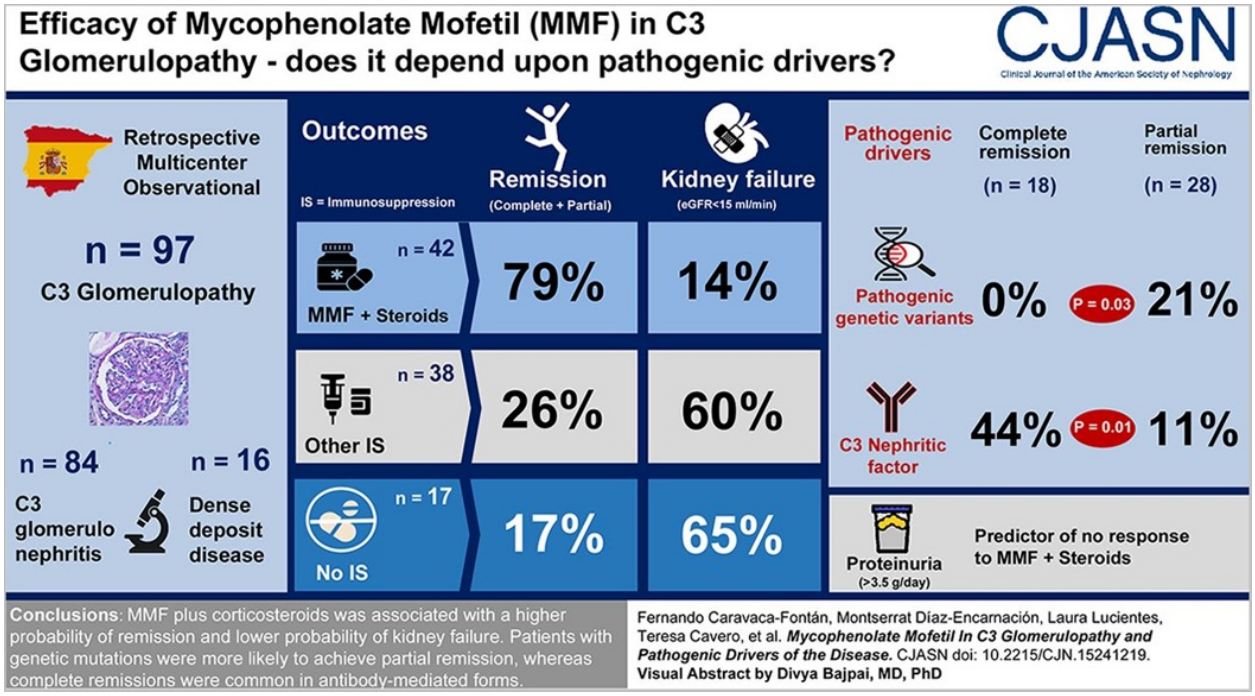
Complement protein(s)	Reference	C3G, *n/N* (%)	C3GN, *n/N* (%)	DDD, *n/N* (%)	IC-MPGN, *n/N* (%)
Complement factor gene variant or mutation					
C3	Bomback *et al.*[19]		2/42 (4.8)	0/9 (0)	
	Ravindran *et al.*[21]	6/62 (9.7)			
	Ravindran *et al.*[20]		6/61 (9.8)		
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	2/44 (4.5)[a]
	Iatropoulos *et al.*[7]		6/50 (12.0)	0/21 (0)	6/64 (9.4)[a]
	Iatropoulos *et al.*[8]		9/68 (13.2)	0/25 (0)	5/80 (6.3)[a]
CFB	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	1/62 (1.6)			
	Garam *et al.*[39]		1/37 (2.7)	0/11 (0)	0/44 (0)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	0/21 (0)	3/64 (4.7)[a]
	Iatropoulos *et al.*[8]		0/68 (0)	0/25 (0)	3/80 (3.8)[a]
CFH	Servais *et al.*[6]		9/56 (16.1)	5/29 (17.2)	
	Bomback *et al.*[19]		8/42 (19.0)	3/9 (33.3)	
	Ravindran *et al.*[21]	10/62 (16.1)			
	Ravindran *et al.*[20]		8/61 (13.1)	2/9 (22.2)	
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	1/44 (2.3)[a]
	Iatropoulos *et al.*[7]		3/50 (6.0)	1/21 (4.8)	1/64 (1.6)[a]
	Iatropoulos *et al.*[8]		5/68 (7.4)	2/25 (8.0)	3/80 (3.8)[a]
CFHR5	Bomback *et al.*[19]		1/42 (2.4)	0/9 (0)	
	Ravindran *et al.*[21]	4/62 (6.5)			
	Ravindran *et al.*[20]		4/61 (6.6)		
CFI	Servais *et al.*[6]		4/56 (7.1)	2/29 (6.9)	
	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	2/62 (3.2)			
	Ravindran *et al.*[20]		2/61 (3.3)		
	Garam *et al.*[39]		1/37 (2.7)	1/11 (9.1)	0/44 (0)[a]
	Iatropoulos *et al.*[7]		1/50 (2.0)	1/21 (4.8)	0/64 (0)[a]
	Iatropoulos *et al.*[8]		3/68 (4.4)	1/25 (4.0)	0/80 (0)[a]
MCP	Servais *et al.*[6]		2/56 (3.6)	0/29 (0)	
	Bomback *et al.*[19]		1/42 (2.4)	0/9 (0)	
	Ravindran *et al.*[21]	0/21 (0)[b]			
	Garam *et al.*[39]		4/37 (10.8)	0/11 (0)	4/44 (9.1)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	0/21 (0)	1/64 (1.6)[a]
	Iatropoulos *et al.*[8]		0/68 (0)	0/25 (0)	1/80 (1.3)[a]
THBD	Garam *et al.*[39]		2/37 (5.4)	0/11 (0)	2/44 (4.5)[a]
	Iatropoulos *et al.*[7]		0/50 (0)	1/21 (4.8)	0/64 (0)[a]
	Iatropoulos *et al.*[8]		1/68 (1.5)	1/25 (4.0)	0/80 (0)[a]
Complement-associated autoantibody					
C3NeF	Servais *et al.*[6]		24/53 (45.3)	19/22 (86.4)	
	Bomback *et al.*[19]		13/42 (31.0)	1/9 (11.1)	
	Ravindran *et al.*[21]	25/61 (41.0)			
	Ravindran *et al.*[20]	30/69 (43.5)	27/59 (45.8)	3/10 (30.0)	
	Garam *et al.*[39]			5/11 (45.5)	11/44 (25.0)[c]
	Garam *et al.*[38]		7/40 (17.5)	5/12 (41.6)	15/67 (22.4)[a]
	Iatropoulos *et al.*[7]	NA/NA (54)	NA/NA (44)	NA/NA (78)	NA/NA (44)[c]
	Iatropoulos *et al.*[8]		24/62 (38.7)	18/23 (78.3)	31/77 (40.3)[c]
	Kovala *et al.*[12]	2/11 (18.2)			0/22 (0)[c]
C4NeF	Garam *et al.*[38]		7/40 (17.5)	1/12 (8.3)	9/67 (13.4)[c]
C5NeF	Ravindran *et al.*[20]		1/59 (1.7)		
Factor B	Bomback *et al.*[19]		0/42 (0)	0/9 (0)	
	Ravindran *et al.*[21]	5/60 (8.3)			
	Ravindran *et al.*[20]		5/59 (8.5)		
	Garam *et al.*[38]		3/37 (8.1)	2/12 (16.7)	2/67 (3.0)[a]
	Kovala *et al.*[12]	2/13 (15.4)			1/17 (5.9)[c]
Factor H	Bomback *et al.*[19]		3/42 (7.1)	1/9 (11.1)	
	Ravindran *et al.*[21]	3/60 (5.0)			
	Ravindran *et al.*[20]		2/59 (3.4)	1/8 (12.5)	
	Kovala *et al.*[12]	1/13 (7.7)			1/18 (5.6)[c]

C, complement; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H related 5; CFI, complement factor I; DDD, dense deposit disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MCP, membrane cofactor protein; NA, not available; NeF, nephritic factor; THBD, thrombomodulin.
[a]Patients with idiopathic IC-MPGN only (patients with secondary IC-MPGN were excluded from the study).
[b]Patients with C3G and monoclonal Ig only.
[c]Includes patients with primary and secondary IC-MPGN.

8/ C3G Nephritic Factors

📣Detection of autoantibodies has been documented in 50% of cases, with C3NeF being the most common. Nephritic factors are more common in children than adults.

📣C3NeF positivity seems to predict better patient outcomes and treatment response, as depicted by @divyaa24.

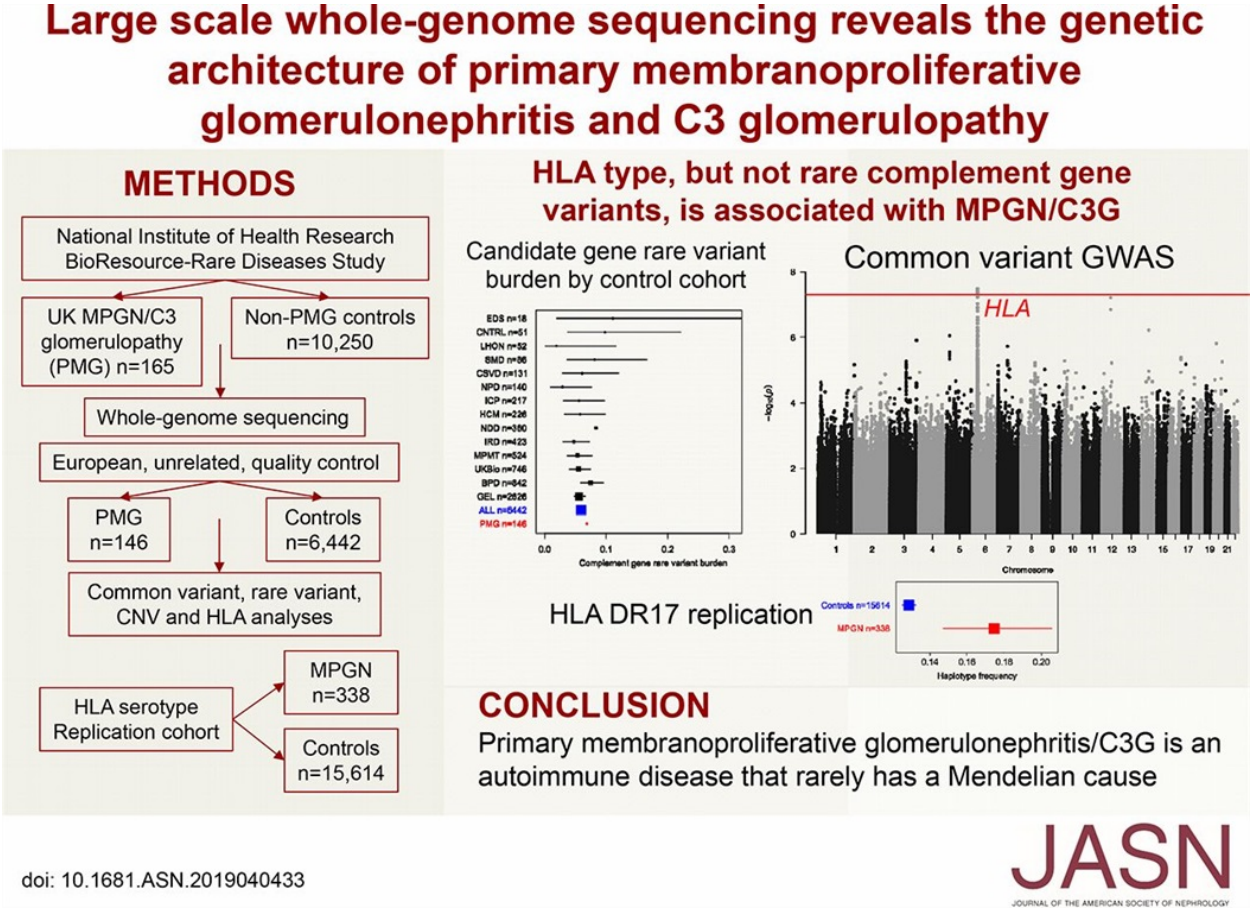


https://journals.lww.com/cjasn/pages/articleviewer.aspx?year=2020&issue=09000&article=00013&type=Fulltext

9/ C3G with MGUS
📌Common >= 50 years old.
📌Likely from monoclonal Ig leading to overactivation of the alternative pathway by activating C3 convertase or acting as an autoantibody.
📌Results are inconclusive with B-cell therapy or standard treatment.

👉https://www.kireportscommunity.org/post/monoclonal-gammopathy-of-renal-significance-unmasked-mgrs-a-pointed-review

10/ C3G with No Identified Cause
📌No identified causes have been reported in 35-85% of cases.
📌Whole exome sequencing has not shown rare variants.
📌Levine et al show that there may be increased prevalence of HLA-DQ2, B8, and DR17 in C3G patients.



https://journals.lww.com/jasn/fulltext/2020/02000/large_scale_whole_genome_sequencing_reveals_the.14.aspx

11a/ DDD

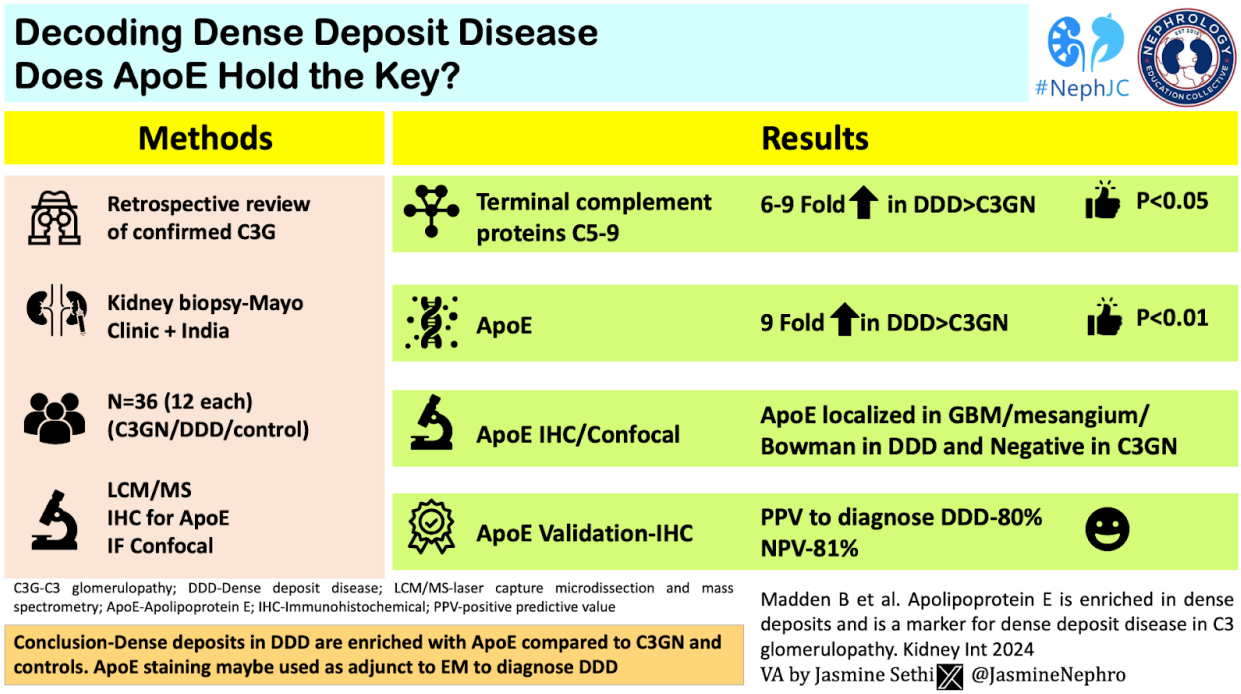
🫘DDD typically affects pediatric patients, whereas C3G generally affects adults.
🫘85% of cases are from autoantibodies.
🫘Patients with DDD have worse prognosis than those with C3G, as it is more rapid.
🫘Treatment is similar to C3G.

https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2023.1289812/full

11b/ DDD

🫘DDD is likely under-diagnosed due to the subjectivity of characterizing a deposit as “highly dense.”
🫘A recent paper by @SethiRenalPath suggests these deposits are enriched with apolipoprotein E. Do these results suggest pathogenesis or tx ❓

https://www.kidney-international.org/article/S0085-2538(24)00169-8/fulltext

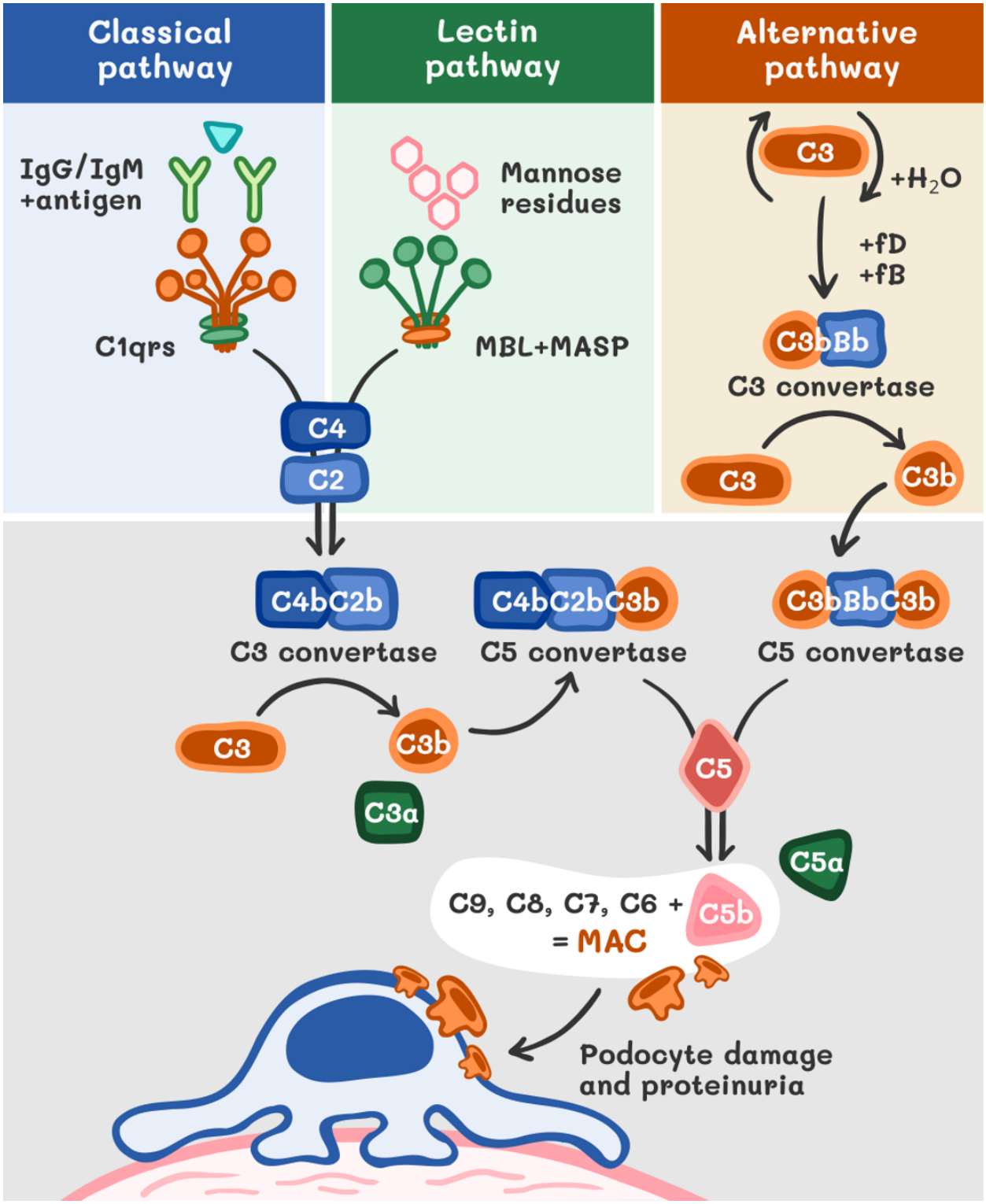


12/ Primary Immune-Complex MPGN (IC-MPGN)

⚡ Due to overactivation of the classical pathway.

⚡ The table on slide 7 shows some common genetic and autoantibodies associated with IC-MPGN.

⚡ Treatment is similar to C3G. Few studies look at the benefits of selective complement inhibition.



13/ Secondary IC-MPGN

⚡ Common causes include autoimmune disease, infectious causes, and hematologic malignancies.

⚡ Treat the underlying cause.

⚡Antiviral medication with and without immunosuppression +/- plasma exchange may be needed with rapidly progressive GN.

14/ IC-MPGN/C3G Spectrum?
🔄Both processes may represent a spectrum.
🔄20% of cases exhibited a shift from one to another on repeat biopsy.
🔄Such cases may be caused by an infectious cause that activate multiple complement pathways.

https://link.springer.com/article/10.1007/s00467-021-05088-7

15a/ Key Learning Points
🔑There is much overlap in C3G, DDD, & ICGN.
🔑Causes include genetic, autoantibodies, & other secondary causes. The vast majority don't have an identifiable cause.
🔑DDD may be differentiated from C3G based on the presence of apolipoprotein E.

15b/ Key Learning Points
🔑Data is lacking on the efficacy of selective complement inhibitors on clinical outcomes.

16/ Now let's see if you have learned something!

Can ICGN be diagnosed in a C3G patient undergoing a repeat biopsy?
1. Yes
2. No
3. I don't know.

17/ The answer is Yes. We hope this #tweetorial has "complemented" your knowledge on C3G and ICGN. Please share this #tweetorial with your followers and friends! Thanks to @MChanMD for authoring & @Brian_Rifkin @sophia @nephroseeker for great feedback! #FOAMed #nephtwitter @ISNkidneycare @KIReports

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