Key Takeaways for Clinicians in the Management of C3 Glomerulopathy

C3G is suspected in patients with proteinuria and microhematuria, with or without hypocomplementemia.

Diagnosis is based on a kidney biopsy with a membranoproliferative pattern of injury on light microscopy and C3 deposition at least 2 orders of magnitude greater than any other immune reactant on immunofluorescence

Diagnosis

Differential diagnosis of C3G:
Infection related glomerulonephritis and post-infectious glomerulonephritis should be ruled out. In patients ≥ 50 years of age at presentation, evaluate for presence of monoclonal protein

Clinical phenotype of C3G:
Usually follows a chronic indolent course with persistent alternative complement pathway activation

Extra-renal manifestations of C3G:
Acquired partial lipodystrophy and retinal drusen when present, are reported as direct consequence of complement activation.

Laboratory Investigations for C3G:
Serum levels of complement proteins should be measured in all patients. Low C3 is seen in up to 75% cases of C3G. C3 nephritogenic factors, Factor H autoantibodies and free light chains should be assayed

Genetic analysis in C3G:
Should be performed if available for a precise diagnosis. Particularly useful for kidney transplantation for possible living donor evaluation

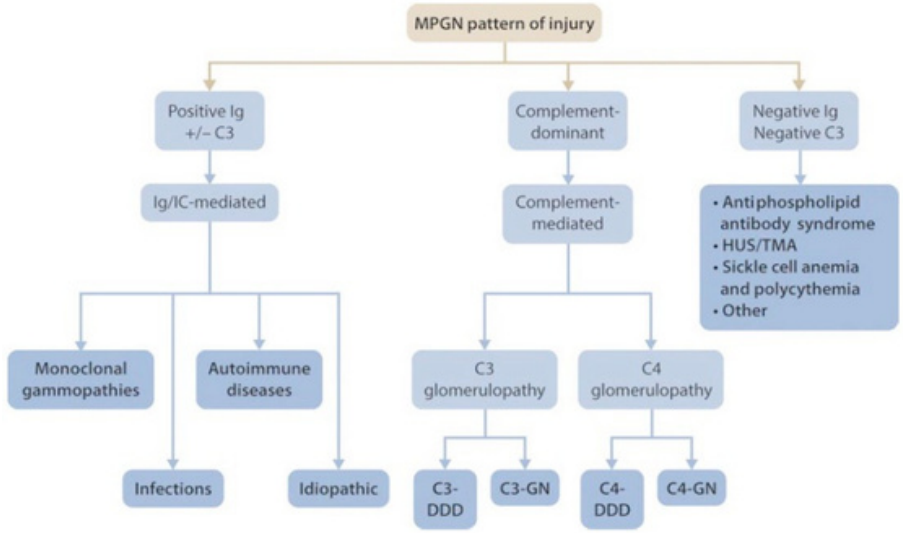
All individuals should follow non-pharmacological nephroprotective measures, including smoking cessation, blood pressure control, weight control, regular physical activity, healthy diet, and avoidance of harmful substances.

Treatment

For nephroprotection:
RAASi (ACE inhibitors / ARBs), SGLT2i, MRAs

Anti-complement drugs:
To date, the approved therapies are: Iptacopan (Factor B inhibitor), Pegcetacoplan (C3 inhibitor)

If anti-complement drugs are unavailable:
Corticosteroids & mycophenolate mofetil



Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders†	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

References

- Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017;91(3):539-551. doi:10.1016/j.kint.2016.10.005
- Kavanagh D, Alladin-Karan A, Alexander S, et al. Outcomes from the International Society of Nephrology forum on complement therapeutics in C3 glomerulopathy and IgA nephropathy. Kidney Int. 2026;110(5):1126-1140. doi:10.1016/j.kint.2026.08.007
- Kavanagh D, Ardissino G, Brocklebank V, et al. Outcomes from the International Society of Nephrology Hemolytic Uremic Syndromes International Forum. Kidney Int. 2024;106(6):1038-1050. doi:10.1016/j.kint.2024.09.012
- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

For funding and support information, visit: https://www.theisn.org/initiatives/toolkits/complement- mediated-kidney-disease-toolkit/#Support