Key Takeaways for Clinicians in the Management of C3 Glomerulopathy

Diagnosis

C3G is diagnosed on 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.

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 are reported as direct consequence of complement activation.

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

Genetic analysis in C3G:
No clear benefit of genetic analysis except in kidney transplantation for possible donor evaluation

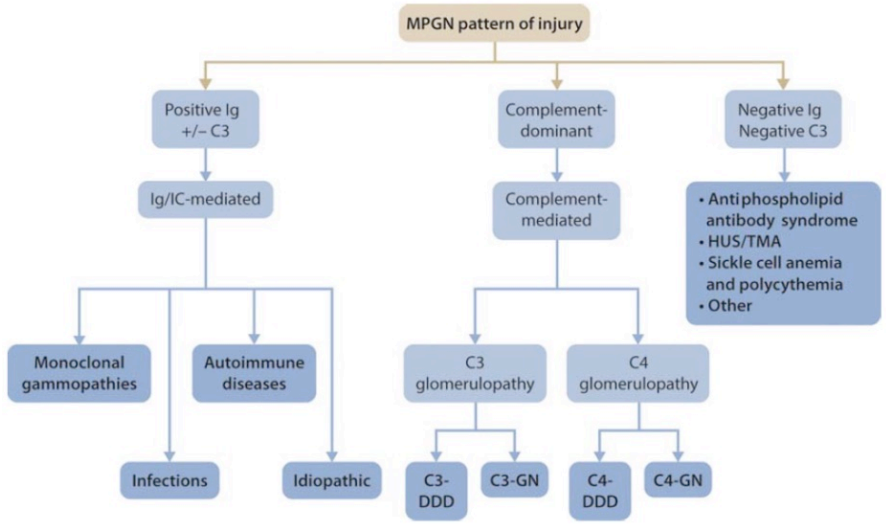
Treatment

All patients should have optimal blood pressure control with renin angiotensin aldosterone system inhibitors. Adequate lipid control should be achieved.

For patients with moderate disease:
Includes patients with 1) urine protein > 500 mg/ 24 hours despite supportive therapy, 2) moderate inflammation on biopsy, 3) Renal deterioration (increase in creatinine and/or proteinuria). Should be given prednisone and mycophenolate mofetil.

For patients with severe disease:
Includes patients with 1) urine protein > 2000 mg/ 24 hours despite supportive therapy and immunosuppression, 2) severe inflammation on biopsy, 3) Renal deterioration (increase in creatinine and/or proteinuria). For moderate-to-severe disease, such patients can be treated with MMF and glucocorticoids. If this fails, eculizumab should be considered. Non-responders should be considered for a clinical trial where available.

Kidney transplantation in C3G:
No specific data available. Carries high risk of histological recurrence (90%) with no known preventive strategies.



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)

Goodship, Timothy H J et al. "Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a KDIGO Controversies Conference." *Kidney intl* vol. 91,3 (2017): 539-551. doi:10.1016/j.kint.2016.10.005
KDIGO Glomerular Diseases Work Group. "KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases." *Kidney intl* vol. 100,4S (2021): S1-S276. doi:10.1016/j.kint.2021.05.021

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