C3 Glomerulopathy

Epidemiology

C3 Glomerulopathy (C3G) is an ultra-rare disease with a prevalence of 1 in 1 million people per year diagnosed.

Presentation

Proteinuria / Microscopic hematuria

Alterations in GFR

Hypocomplementemia

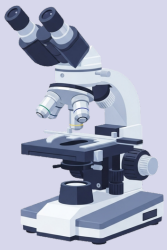
Retinal drusen

Not all of these may always be present.

Pathophysiology

- **Alternative pathway of complement mutations** (more common in children and more aggressive clinically)
- **Nephritogenic factors that activate C3 convertase C3bBb** (more common in adults)

Histology



Optic microscopy findings

Mesangial proliferative, membranoproliferative pattern, endocapillary proliferation with or without active crescents

Immunofluorescence findings

Dominant C3 deposition ≥2 orders of magnitude over other immune reactants

Electron microscopy findings

- C3GN: Amorphous mesangial ± subendothelial and/or subepithelial deposits
- DDD: Dense osmiophilic mesangial and intramembranous deposits

Treatment

Nephroprotection: RAASi (ACE inhibitors / ARBs), SGLT2i, MRAs

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

Corticosteroids & mycophenolate mofetil when anti-complement drugs are unavailable

Natural Course

- **Genetic causes lead to kidney failure in 90% of cases within 10 years of diagnosis**
- **When caused by nephritogenic factors, 50% of adults reach kidney failure within 10 years of diagnosis**

Histological recurrence as high as 90%

Allograft failure is high after recurrence (though this may change due to newly approved therapies)

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