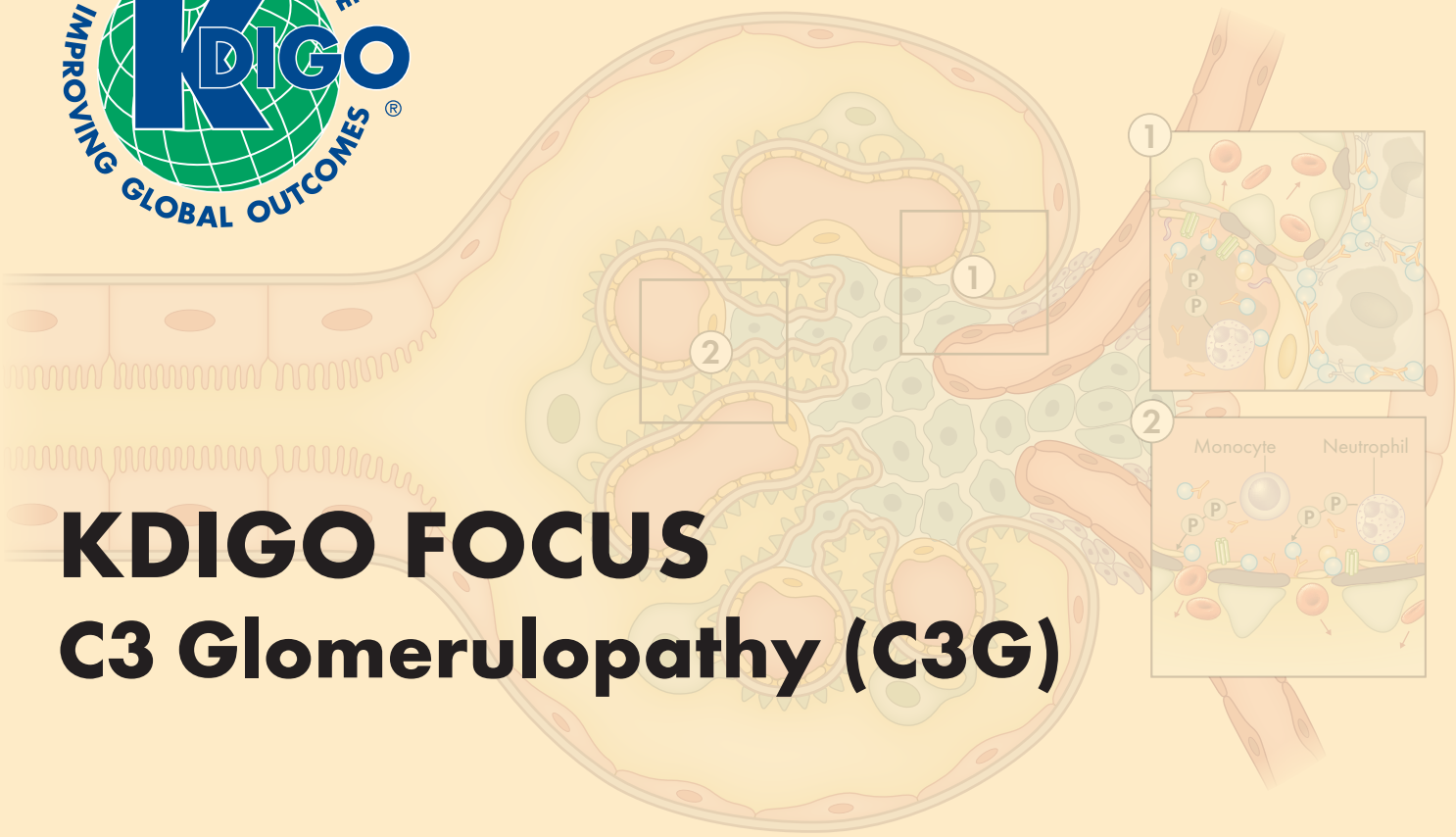


KDIGO FOCUS
C3 Glomerulopathy (C3G)

- **C3G (C3 glomerulopathy) is a histopathological diagnosis defined by the presence on kidney biopsy of a glomerulonephritis with sole or dominant glomerular C3 staining at least two orders of magnitude greater than any other immune reactant by immunofluorescence. Electron microscopy is used to resolve the two major subtypes – dense deposit disease and C3 glomerulonephritis.**
- **The annual incidence of C3G is 0.2–2 cases per million, with an overall prevalence of 0.05–1.4 per 10,000. The average age of diagnosis is 21 years.**
- **C3G conveys a poor prognosis, with approximately 30–50% of adults progressing to kidney failure within 10 years of diagnosis. Post-kidney transplant disease recurrence occurs nearly 90%, with allograft loss in approximately 50% of patients within 10 years.**
- **In a meeting of patients with C3G and their caregivers, more than half of the respondents stated that the disease affected their daily lives to a moderate or significant degree. Fatigue, edema and anxiety/depression are the three most common symptoms encountered. Although many respondents expressed a desire to participate in clinical trials, very few were actually enrolled.**
- **Current management strategies include supportive therapies with use of RASi to reduce proteinuria and immunosuppressives to mitigate kidney inflammation. However, there are emerging therapies, available or under investigation, that target key components of the complement cascade, thereby halting overactivation of the complement pathway. These new agents hold the promise of disease-specific treatments for C3G patients.**

Sources: Appel GB. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021; 100(4S):S1; Smith RJH., et al. *Nature Rev Neph.* 2019; 15: 129; Heiderscheit AK., et al. *Am J Med Genetics.* 2022; 190C: 344; Feldman DL., et al. *Voice of the Patient. Report of Externally Led Patient-Focused Drug Development Meeting on C3G,* 2018; Java A and Fuller L. *Kidney Med.* 2024; 7: 100928

SNAPSHOT OF C3G (C3 GLOMERULOPATHY)
MECHANISTIC TARGETS OF POTENTIAL NOVEL THERAPIES

C3G is an ultrarare entity that is defined by C3-dominant glomerulonephritis. Historically, membranoproliferative lesions (type I, II, and III) were classified based on the location of deposits but advances in our understanding of underlying disease mechanisms leading to the development of a membranoproliferative pattern of kidney injury have resulted in a new pathobiology-based classification. The new classification relies on immunofluorescence examination, with deposits defined as: primarily immunoglobulin (monoclonal); polyclonal immunoglobulin and complement; or predominantly complement-mediated as in the case for C3G.

Description

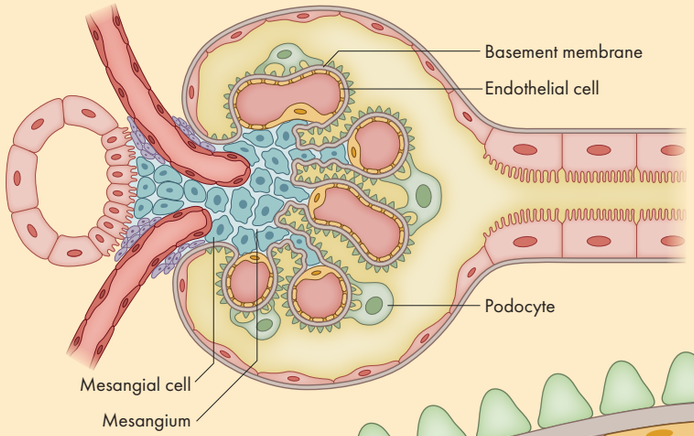
C3G is an ultrarare entity that is defined by C3-dominant glomerulonephritis, a proliferative histologic lesion with C3 deposition at least 2 orders of magnitude greater than any other immune reactant on immunofluorescence. C3G includes both dense deposit disease (DDD) and the newer designation of C3 glomerulonephritis (C3GN). Patients often exhibit signs of hematuria, proteinuria, or nephrotic syndrome but a kidney biopsy is required to diagnose C3G. IgG co-dominance is found in some patients, particularly children, and once secondary forms have been excluded, alternative pathway of complement dysregulation is also frequently found to drive these forms.

Management and Treatment

General supportive measures such as RAS blockade have been the therapeutic mainstays for C3G. According to the 2021 KDIGO guideline, for patients with moderate-to-severe disease, treatment can be initiated with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.

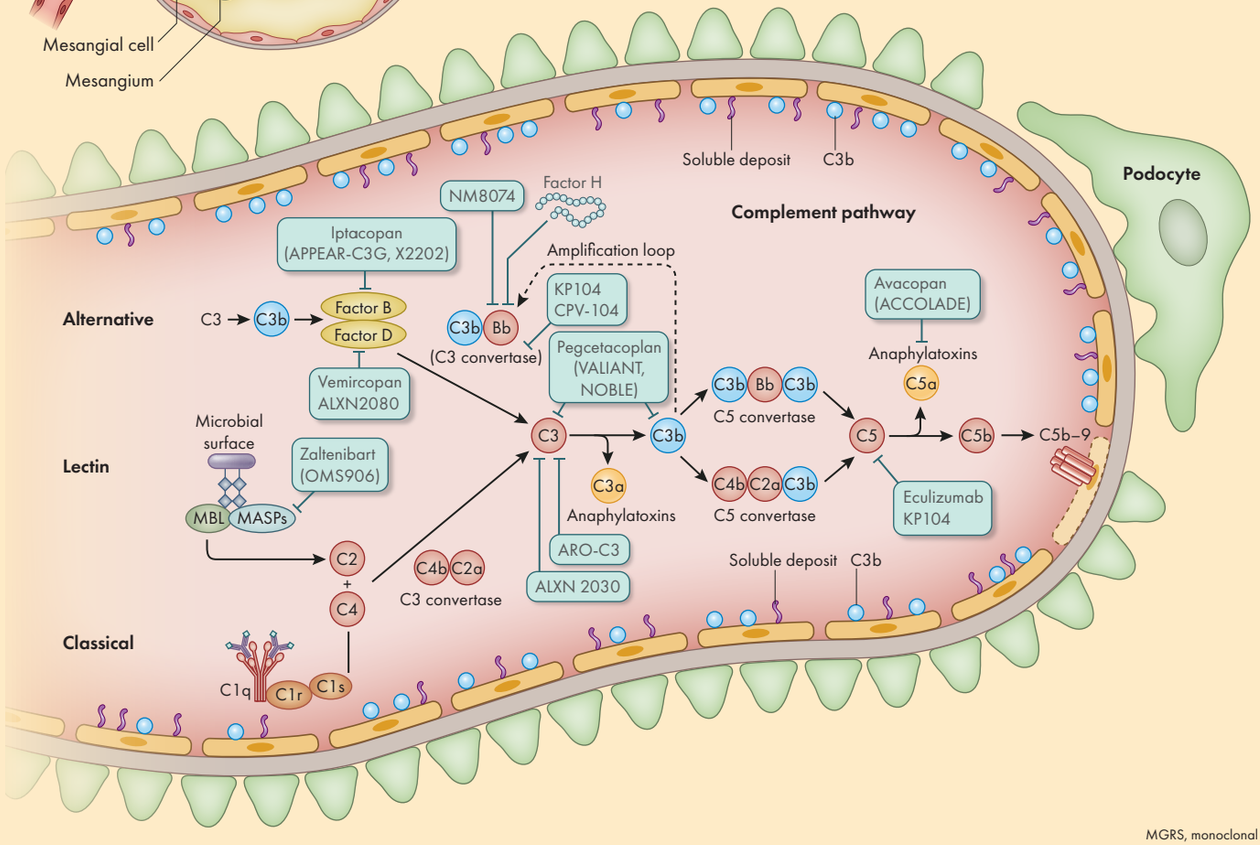
However, our enhanced understanding of the pathophysiology underlying C3G has allowed the development of a host of therapeutic agents targeting specific points in the complement cascade with great precision offering the potential for enhanced treatment efficacy.

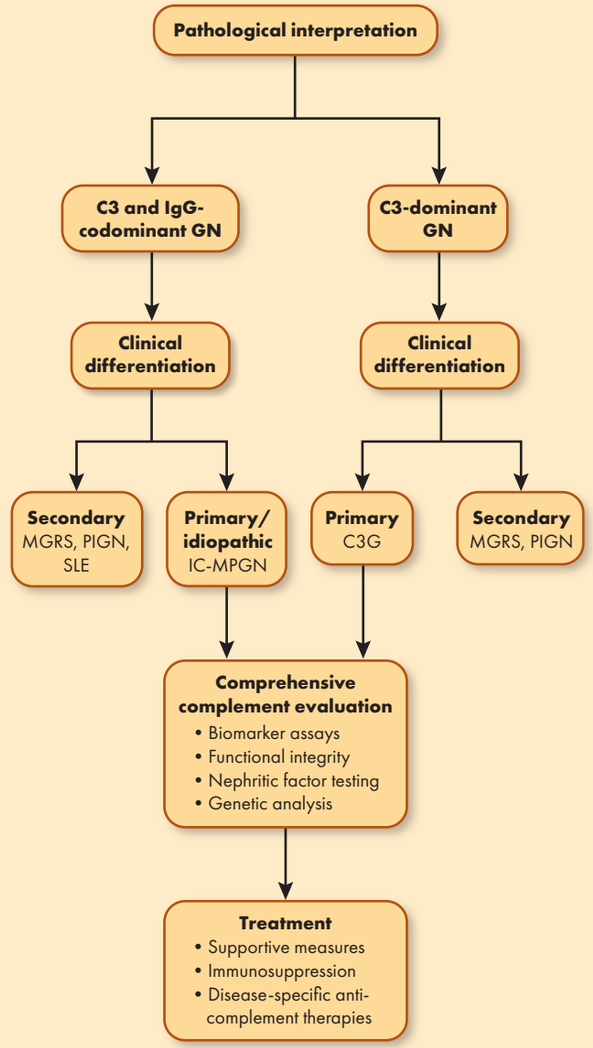
Patients who fail to respond to supportive treatments should be considered for upstream complement blockade with one of the new anti-complement therapies.



Pathophysiology

C3G arises from the overactivation of the alternative pathway of the complement cascade. The cornerstone of complement activity is the C3 convertase, C3bBb. Activity of this serine protease is controlled by a number of proteins including Factor H (FH) and Factor I (FI). When control is compromised, persistent C3 convertase activity leads to C3 fragment deposition, inflammation, and potential formation of the terminal complement complex (C5b–9). The consequence is glomerular damage.





Developed with educational funding provided by Novartis AG

C3G, C3 glomerulopathy; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis; MGRS, monoclonal gammopathy of renal significance; PIGN, post-infectious glomerulonephritis; SLE, systemic lupus erythematosus.