

THE IMMUNE SYSTEM IS ONE OF THE MOST SOPHISTICATED BIOLOGICAL SYSTEMS KNOWN. IT IS ALSO, WHEN IT GOES WRONG, ONE OF THE MOST DESTRUCTIVE.

In C3 glomerulopathy, the immune system's complement cascade — a rapid-fire sequence of protein activation designed to identify and destroy pathogens — becomes dysregulated. It loses its off switch. The alternative pathway of complement activation, normally self-limiting and tightly controlled, runs without restraint. And in the absence of the regulatory mechanisms that should be governing it, it deposits one of its core proteins — complement component C3 — relentlessly into the glomeruli of the kidney.

The glomeruli were not the target. There is no pathogen to destroy. But the cascade does not know that. It continues, and the deposits accumulate, and the filtration architecture of the kidney is progressively disrupted, and the kidney function declines — typically in the patient's teens or twenties or thirties, over years, toward dialysis.

This is C3 glomerulopathy. It affects 1-3 people per million per year. It is one of the hardest glomerular diseases to treat. And until very recently, the treatment approach was essentially borrowed from other, better-understood kidney diseases and applied here with limited success.

In 2024, for the first time, there is specific, targeted, complement-pathway therapy with clinical trial evidence in C3G. The treatment era for this disease has arrived.

This post covers the complete picture — the biology, the two subtypes, the new drugs, and what every C3G patient should be asking their nephrologist right now.

PART 1 — THE COMPLEMENT SYSTEM: THE BIOLOGICAL CONTEXT

To understand C3G, you need to understand the complement system — one of the most ancient components of innate immunity, present in all vertebrates, and a cornerstone of the human immune response.

WHAT THE COMPLEMENT SYSTEM IS:

The complement system is a cascade of over 50 proteins circulating in the blood in inactive forms. When activated, these proteins amplify each other sequentially — like a chain of dominoes — producing a rapid and powerful immune response that kills pathogens, marks them for destruction by phagocytes, and recruits additional immune cells to the site of infection.

THE THREE ACTIVATION PATHWAYS:

The complement system can be activated by three distinct pathways:

CLASSICAL PATHWAY:

Activated by antibody-antigen complexes (IgG or IgM bound to a pathogen). The most regulated pathway — requires a specific immune recognition event to begin.

LECTIN PATHWAY:

Activated by lectins (proteins that recognize specific carbohydrate patterns on pathogen surfaces). Also well-regulated — requires specific pattern recognition.

ALTERNATIVE PATHWAY:

The oldest and least regulated pathway. Activated spontaneously — C3 undergoes low-level spontaneous hydrolysis constantly ("C3 tick-over"), which generates C3b that can bind to any nearby surface. Normally, regulatory proteins (particularly factor H) rapidly inactivate this C3b on self-tissues, preventing the cascade from amplifying. On pathogen surfaces, factor H cannot bind (pathogens lack the surface markers that recruit factor H), so the cascade proceeds to destruction.

THE REGULATION THAT FAILS IN C3G:

In C3 glomerulopathy, the alternative pathway is dysregulated — the regulatory mechanisms that should control C3 tick-over and prevent amplification on self-tissues fail. The result: unchecked alternative pathway activation that deposits C3 and its downstream products in the glomeruli.

The specific causes of dysregulation include:

- Mutations in factor H or factor I (complement regulatory proteins) — loss-of-function mutations reduce the ability to control alternative pathway activation
- Mutations in C3, factor B, or factor D — gain-of-function mutations that increase complement activation
- Anti-factor H autoantibodies — the immune system produces antibodies that block factor H function
- C3 nephritic factor (C3NeF) — an autoantibody that stabilizes the alternative pathway convertase (C3bBb), preventing its normal decay and allowing sustained C3 cleavage



C3G is defined by the finding on kidney biopsy of predominant C3 complement deposition in the glomeruli, with absent or minimal immunoglobulin staining — indicating the complement pathway rather than immune complex deposition as the primary driver.

Two subtypes are recognized, distinguished by electron microscopy findings:

C3 GLOMERULONEPHRITIS (C3GN):

- More common subtype
- Electron microscopy: mesangial, subendothelial, and subepithelial deposits of varying density and location — no single defining pattern
- Clinical presentation: typically hematuria and proteinuria; hypertension; variable rate of progression
- Complement profile: reduced C3, low C3 nephritic factor in many patients; factor H mutations or anti-factor H antibodies in a subset

DENSE DEPOSIT DISEASE (DDD):

- Less common, more aggressive subtype
- Electron microscopy: the defining characteristic — a continuous, dense, osmiophilic ribbon-like material transforming the lamina densa of the glomerular basement membrane; visually distinctive and diagnostic
- Clinical presentation: more severe proteinuria; more rapid eGFR decline; more likely to progress to ESKD
- Associated finding: partial lipodystrophy (loss of subcutaneous fat, particularly from the upper body) in approximately 25% of DDD patients — a unique extrarenal manifestation driven by complement activation in adipose tissue
- C3 nephritic factor is more commonly positive in DDD than C3GN; factor H mutations less common

THE DIAGNOSTIC WORKUP:

When C3G is suspected (predominant C3 on biopsy with hematuria and proteinuria in a young patient), the complement evaluation should include:

- Serum C3 and C4 levels — C3 typically low (consumed); C4 typically normal (distinguishes from classical pathway activation which depletes both C3 and C4)

- C3 nephritic factor (C3NeF) — the most common acquired cause; positive in approximately 50% of C3GN and 80% of DDD
- Genetic panel: factor H (CFH), factor I (CFI), C3, factor B (CFB), factor D (CFD), CFHR1-5 mutations — increasingly performed at specialist centers
- Anti-factor H antibody titer — particularly important as this identifies a potentially treatable acquired cause (immunosuppression can reduce anti-factor H antibodies)
- Factor H level and function
- Factor B and factor D levels

WHY THE WORKUP MATTERS:

Identifying the specific complement defect guides treatment. A patient with anti-factor H antibodies has an acquired, potentially immunosuppression-responsive cause. A patient with a genetic factor H mutation may benefit from plasma therapy (providing exogenous factor H). A patient with C3NeF requires targeted complement inhibition. The workup is not academic — it is the map for personalized therapy.

PART 3 — THE PROGNOSIS: WHY NEW TREATMENTS MATTER SO URGENTLY

The natural history of C3G is sobering:

- Approximately 50% of patients reach ESKD within 10 years — one of the highest rates of any primary glomerular disease
- DDD has a worse prognosis than C3GN: approximately 50% ESKD by 5-8 years in many series
- Transplantation is possible but recurrence is common — C3G recurs in the transplanted kidney in approximately 50-70% of cases, because the underlying complement dysregulation persists regardless of the transplanted organ
- Recurrence in the transplanted kidney occurs more rapidly in DDD than C3GN and can lead to graft failure

The high ESKD rate, the young age at diagnosis (typically teens to thirties), and the high post-transplant recurrence rate make C3G a disease where specific, effective treatment is urgently needed — and where the absence of specific treatment has been, until recently, the defining clinical reality.

PART 4 — THE TREATMENT LANDSCAPE: BEFORE AND AFTER 2024

BEFORE 2024 — THE NON-SPECIFIC ERA:

Eculizumab (anti-C5 monoclonal antibody):

Eculizumab — which blocks the terminal complement pathway (C5 cleavage) and is highly effective in paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS) — showed inconsistent results in C3G. Multiple case series and small trials showed responses ranging from significant benefit to no benefit. The inconsistency is now partially understood: blocking C5 does not block the upstream C3 deposition that characterizes C3G; patients with active C3 deposition may not respond to a downstream C5 inhibitor.

Mycophenolate mofetil (MMF):

Multiple retrospective series and one prospective pilot study (Rabasco et al., CJASN 2015) suggested MMF reduced proteinuria and stabilized eGFR in C3GN — particularly in patients with crescentic or proliferative histology. MMF is not a complement-targeted therapy; it reduces generalized immune activation and may reduce C3NeF production. Evidence remains limited; MMF is used empirically in many centers while awaiting specific complement therapy.

Hydroxychloroquine:

Increasing use in C3G based on case series showing proteinuria reduction; mechanism unclear but may reduce C3NeF production or modify complement activation; awaiting randomized trial evidence.

Plasma therapy:

- Fresh frozen plasma (FFP) or plasma exchange: provides exogenous factor H in patients with factor H mutations or anti-factor H antibodies; can temporarily reduce complement activity; used in acute presentations and as a bridge to other therapy; not a sustainable long-term treatment

★ THE 2024 TREATMENT REVOLUTION — SPECIFIC COMPLEMENT INHIBITORS IN C3G:

IPTACOPAN (FABHALTA — NOVARTIS):

The most important development in C3G treatment in 2024.

What it is: iptacopan is an oral, once-daily factor B inhibitor. Factor B is an essential component of the alternative pathway C3 convertase (C3bBb) — the amplification enzyme that drives the runaway C3 activation in C3G. By blocking factor B, iptacopan prevents the formation of the alternative pathway convertase and stops the cascade at the amplification step.

FDA approval history:

- December 2023: iptacopan approved by FDA for paroxysmal nocturnal haemoglobinuria (PNH)
- 2024: Phase III C3G data published — the APPEAR-C3G trial

THE APPEAR-C3G TRIAL (2024):

A randomised, double-blind, placebo-controlled Phase III trial in patients with C3G and significant proteinuria (urine protein-to-creatinine ratio above 1.5g/g).

Key results at 6 months:

- Proteinuria reduction: iptacopan reduced urine protein-to-creatinine ratio by approximately 35% from baseline vs placebo (statistically significant)
- eGFR: eGFR stabilised in the iptacopan group vs continued decline in placebo
- C3 levels: serum C3 rose toward normal in the iptacopan group, confirming target engagement — the complement cascade was being blocked
- Histology: a histological sub-study showed reduction in C3 deposits in kidney biopsy in the iptacopan group at 6 months
- Safety: well-tolerated; increased risk of encapsulated bacterial infections (*Neisseria*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) as expected with complement inhibition; vaccination required before initiation

REGULATORY STATUS (2024-2025):

The APPEAR-C3G data has been submitted to the FDA and EMA for C3G indication approval. If approved, iptacopan becomes the first specifically approved complement inhibitor for C3G.

What this means for patients:

If you have C3G with significant proteinuria: ask specifically whether iptacopan is available through clinical trial, compassionate use, or approved indication in your country. The regulatory timeline is moving rapidly.

PEGCETACOPLAN (ASPAVELI/EMPAVELI — APELLIS):

Pegcetacoplan targets C3 itself — the most upstream intervention currently available, blocking the central protein of the complement cascade before it deposits in the glomerulus.

Mechanism: pegcetacoplan is a cyclic peptide that binds C3 and C3b, preventing their cleavage and deposition. Unlike eculizumab (which blocks downstream C5), pegcetacoplan prevents the C3 deposition that is the defining feature of C3G.

Clinical data:

- FDA approved for PNH (2021)
- VALIANT trial (C3G and IC-MPGN): Phase II/III data published 2023-2024 showing significant reduction in proteinuria and C3 deposits compared to placebo
- Administered as twice-weekly subcutaneous injection — a practical consideration for long-term management

REGULATORY STATUS: C3G indication application under review in US and EU; likely approval 2025 if data confirmed.

AVACOPAN (TAVNEOS — AMGEN/VIFOR):

As covered in Day 111 (ANCA vasculitis), avacopan is a C5a receptor antagonist — blocking the inflammatory amplification signal downstream of C5 cleavage. Unlike its established role in ANCA vasculitis, avacopan's role in C3G is less established. The mechanism is theoretically relevant — C5a drives the inflammatory component of complement-mediated glomerular injury. Small case series suggest benefit in some C3G patients; no Phase III C3G trial data yet. May be particularly useful for the inflammatory/crescentic presentations.



PART 5 — VACCINATION: THE CRITICAL SAFETY REQUIREMENT

All complement inhibitors — by blocking the complement system that is essential for defence against encapsulated bacteria — increase the risk of life-threatening infections with:

- *Neisseria meningitidis* (meningococcal disease)
- *Streptococcus pneumoniae* (pneumococcal disease)
- *Haemophilus influenzae* type b

VACCINATION REQUIREMENTS BEFORE STARTING COMPLEMENT INHIBITOR THERAPY:

These vaccines are mandatory, not optional, before initiating iptacopan, pegcetacoplan, or any complement inhibitor:

- Meningococcal vaccines: MenACWY + MenB — both required; if not previously vaccinated, a waiting period of at least 2 weeks after vaccination before starting therapy (or antibiotic prophylaxis if urgent initiation is required)
- Pneumococcal vaccine: PCV13 (or PCV15/20) and PPSV23
- Haemophilus influenzae type b vaccine

Patients on complement inhibitors should carry an emergency card identifying their complement inhibitor status and instructing healthcare providers to treat fever with immediate antibiotic cover pending culture results.

PART 6 — POST-TRANSPLANT C3G: THE RECURRENCE CHALLENGE

The high recurrence rate of C3G post-transplant (50-70%) represents a specific clinical challenge — and an area where complement-targeted therapy may have its most significant impact.

THE RECURRENCE MECHANISM:

C3G recurs in transplanted kidneys because the underlying complement dysregulation (factor H mutation, C3NeF, anti-factor H antibody) persists in the recipient regardless of the new kidney. The new kidney is exposed to the same dysregulated complement environment as the native kidney was.

IMPLICATIONS:

- Pre-transplant complement evaluation is essential to quantify recurrence risk
- In patients with high-risk profiles (positive C3NeF, anti-factor H antibodies, genetic mutations with prior aggressive course), complement inhibitor therapy started before or immediately after transplantation may reduce recurrence risk
- Post-transplant protocol biopsies monitoring C3 deposits are increasingly used at specialist centres
- Living donation requires particular care — using a family member's kidney in a patient with C3G who has a high recurrence risk risks losing a precious living donor kidney to recurrent disease

✔ WHAT EVERY C3G PATIENT SHOULD ASK IN 2024-2025:

AT DIAGNOSIS OR REVIEW:

- 1 "Has my complete complement workup been performed — including C3NeF, anti-factor H antibodies, and genetic panel for CFH, CFI, C3, CFB mutations?"
- 2 "Am I being managed at or in consultation with a specialist complement nephrology centre?"
- 3 "Is iptacopan or pegcetacoplan available to me through trial, compassionate use, or approved indication?"
- 4 "What is my specific complement defect — and does it point toward a particular treatment approach?"

IF CONSIDERING TRANSPLANT:

- 5 "What is my predicted recurrence risk in a transplanted kidney based on my complement profile?"
- 6 "Should complement inhibitor therapy be started before or immediately after transplantation?"
- 7 "Is a protocol post-transplant biopsy schedule recommended for monitoring recurrence?"

REGARDING SAFETY:

- 8 "Are my meningococcal, pneumococcal, and Haemophilus vaccines up to date before starting complement inhibitor therapy?"

💬 The bottom line:

C3 glomerulopathy has been, for most of the history of nephrology, a disease without a specific treatment. Patients were managed with immunosuppression borrowed from other conditions, watched their kidney function decline, and faced dialysis and transplantation with the knowledge that recurrence would likely follow.

The complement biology of C3G was understood before the treatments existed to target it. What 2024 has changed is the availability of those treatments — iptacopan blocking factor

B upstream, pegcetacoplan blocking C3 itself, the Phase III data demonstrating proteinuria reduction and complement engagement.

This is not a cure. It is the beginning of specific treatment for a disease that has had none. For the 1-3 people per million who develop C3G each year — many of them young, many of them losing kidney function in their most productive decades — this beginning matters enormously.

Know the diagnosis. Know the biology. Demand the workup. And ask specifically about the new treatments that 2024 has brought to this disease.

RESOURCES:

- C3G Consortium: c3gconsortium.org
- Complement UK: complementuk.org
- Rare Kidney Disease Registry (UK): rkd.org.uk
- NKF - C3 Glomerulopathy: kidney.org
- APPEAR-C3G Trial Data: clinicaltrials.gov (NCT04557657)
- VALIANT Trial Data: clinicaltrials.gov (NCT04572854)
- European Complement Network: complement-network.eu

Please SHARE this post - C3G is rare enough that many patients are diagnosed without a specialist who understands it fully. This post is the map to the right questions and the right expertise.