# C3 Glomerulopathy: From Early Recognition to Individualized TargetedTherapy

**Editor's Note:** This is a transcript of a discussion on August 11, 2026. It has been edited and condensed for clarity. To obtain credit for participation CLICK HERE.

**Module 1: Burden of Disease**

Complement 3 (C3) glomerulopathy is a form of glomerulonephritis that's caused by the deposition of C3 complexes. It's a glomerulonephritis that is marked by isolated deposits of C3 on immunofluorescence, which in turn points to an overactive alternative complement pathway. There are 2 main forms of C3 glomerulopathy. The most common form is called C3 glomerulonephritis (C3GN). The less common form, which is a more aggressive form, is called dense deposit disease (DDD). The way we make the distinction between the 2 of these is based on how the biopsy looks under highest power electron microscopy.

C3 glomerulopathy is a very rare disease. The prevalence is estimated to be 2 to 3 cases per million people in the United States (US), and 0.2 to 1 case per million in Europe. It's a rare disease, but an extremely progressive disease. The estimates are that about 30% to 50% of patients with newly diagnosed C3 glomerulopathy will progress to end-stage kidney disease within 10 years of diagnosis. Unfortunately, the story doesn't end at the time of progression to end-stage kidney disease when a patient gets a kidney transplant. Unlike other kidney diseases, the kidney transplant is at risk for recurrent C3 glomerulopathy. This has been shown in series done at our center and across the world. The rate of recurrence of C3 glomerulopathy is as high as 80% to 100%. When the disease recurs in the transplant, there are high rates of kidney transplant failure, what we call allograft failure. This is not what you would expect in a disease like C3 glomerulopathy that preferentially affects young people who don't have other comorbidities. They should have the best kidney outcomes, but unfortunately we're seeing the disease come back in the transplant and leading to loss of the transplant itself.

**Module 2: Pathogenesis**

To understand the pathogenesis of C3 glomerulopathy, it's important to make a distinction between C3 glomerulopathy and other forms of glomerulonephritis that are more likely described as immune complex-mediated. C3 glomerulopathy is a complement-mediated lesion, but let's go to the more common forms of glomerulonephritis that are immune complex-mediated.

When you do a kidney biopsy and you see immunoglobulins accompanying complement on the immunofluorescent staining, you know that immune complexes have activated complement pathways, like the classical pathway and the lectin pathway. As the physician caring for a patient with an immune complex-mediated form of glomerulonephritis, you're looking for the antigen-antibody interactions that triggered consumption of complement proteins in the classical and lectin pathways. You're basically trying to figure out why did these immune complexes form? Is it from an autoimmune disease like lupus? We see this in lupus nephritis. Is it from an infection,

as we might see in post-streptococcal glomerulonephritis, or any form of infection-related glomerulonephritis? Is it part of a malignancy-associated form of glomerular disease?

Then, let's shift now to C3 glomerulopathy, because the hallmark finding on a kidney biopsy of C3 glomerulopathy is that the immunofluorescence only stains for C3. This means that you're only seeing a complement protein from the alternative complement pathway. Yes, there are some cases where we see a little bit of trace staining of immunoglobulin, but the definition is that the C3 staining has to be at least 2 orders of magnitude higher than any other immunoreactant. You're seeing either isolated or clearly dominant C3 staining on the immunofluorescence, which points to the complement proteins being activated independent of immune complexes. It's a purely complement-mediated lesion.

One of the interesting things about the alternative complement pathway, as opposed to the classical and lectin pathways, is that the alternative pathway is constitutively active. It is always on at a low level due to spontaneous hydrolysis of C3 to C3b. There is always some low-level construction of the C3 convertase and subsequent low-level activity of the entire alternative pathway. In contrast to the classical and lectin pathways, those are off and need immune complexes to turn them on. But the alternative pathway is always on at a low level in all of us.

What happens in C3 glomerulopathy is that we go from low level to hyperactivity. We've basically lost control of the system. I like to describe this to patients as the difference between a dripping faucet and a gushing faucet. In states of health, our alternative pathway is going at a very low level, almost like a dripping faucet. In states of disease, like C3 glomerulopathy, where we've lost control of the system, the alternative pathway is hyperactive, like a gushing faucet. Now, why would the pathway become hyperactive? Again, we're looking at where control of the system may have been lost, because the alternative pathway has proteins that push it forward, what we call promoter proteins, and then there are proteins throughout that are inhibitory, regulator, or break proteins on the system. If you have a genetic variant in a promoter protein causing a gain of function variant that makes the promoter protein overactive, or a genetic variant in an inhibitory protein causing a loss of function variant that makes the inhibitory protein not work, that genetic variant can explain why the alternative pathway is overactive. We detect that in about 5% to 10% of C3 glomerulopathy cases, and it is much more common in patients who present at a very young age.

You can also acquire, over the course of your lifetime, autoantibodies that target proteins in the alternative pathway. These are autoantibodies that can stabilize enzymes in the pathway. There's an autoantibody called a C3 nephritic factor, which can be detected in over half of the cases. In some series, that autoantibody stabilizes the C3 convertase and makes it immune to any regulatory proteins. That's the most common autoantibody, but you can also have autoantibodies that target some of the brakes on the system, such as an antifactor B antibody or an anti-C3 antibody. These things turn off some of the functions of complement proteins and make the pathway overactive.

Finally, in older individuals and C3 glomerulopathy, we think of anybody diagnosed over the age of 40 or 50 years as being an older patient for this disease. The older the patient gets, the more likely we detect what are called monoclonal gammopathies. These are abnormal clonal proteins made by the bone marrow that interfere with some of the regulatory proteins of the alternative complement pathway. When somebody is newly diagnosed with C3 glomerulopathy, the physician taking care of that patient really has to get into the pathogenesis of the disease. We are trying to figure out why my patient has gone from low level, drippy faucet, normal functional activity of the alternative pathway to hyperactivity, abnormally high activity of the alternative pathway, a gushing faucet. What we're really trying to figure out, is there a genetic variant, an autoantibody, or a monoclonal protein that led to this loss of control?

**Module 3: Diagnosis**

The clinical features of C3 glomerulopathy, and in many respects, the overall disease course, can be quite heterogeneous. The features can be heterogeneous based on disease severity and duration. What we know is that many patients are asymptomatic, especially early in the disease process. If you can diagnose C3 glomerulopathy early, sometimes you're just picking it up on abnormal laboratory values without the patient having any symptoms or signs on exam. There are some extra kidney manifestations, including lipodystrophy and retinal drusen, but you would need specialists to be able to detect those. So, you need to have suspicion for this and make the appropriate referral to specialists. As the disease progresses, you will see patients present in the clinic with hypertension and often lower extremity edema in more advanced forms of the disease. If the disease is picked up late in the course, you'll see the hallmark findings of blood and protein in the urine and evidence of reduced kidney function.

C3 glomerulopathy is not specific to one age range. It can present at any time, but the average age of diagnosis is late teenage years and early adulthood. If you see it in older individuals, which for this disease would be patients 40 or 50 years of age and older, it's much more commonly associated with a monoclonal gammopathy of kidney significance. The truest forms of C3 glomerulopathy are typically going to present in pediatric, adolescent, and young adult populations. It's not specific to one age range, but it is more heavily seen in its purest form in younger patients.

The diagnostic evaluation of C3 glomerulopathy is multifold. You want to start by getting a thorough history of the patient and getting a better idea of what their underlying disease burden is. The initial laboratory assessment includes some of our basic tests that we do in all patients with glomerular disease, including a basic metabolic panel, a complete blood count, and serum complement levels, along with urine protein-to-creatinine ratio for quantification of protein. Then, there are some other serologies to make sure we're not dealing with other forms of glomerular disease. This would be screening for hepatitis and human immunodeficiency virus (HIV) and looking for autoantibodies against antineutrophil cytoplasmic antibody (ANCA) and antiglomerular basement membrane (anti-GBM) disease. The ultimate diagnosis is coming from the kidney biopsy.

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Who do we perform kidney biopsies on? Well, pretty much anybody with hematuria and proteinuria above 500 mg a day should be getting a kidney biopsy. C3 glomerulopathy won't be the most common finding in that setting. It will be immunoglobulin A (IgA) nephropathy, but this is the way you'll make your diagnosis of C3 glomerulopathy. If somebody has low complement levels, we should be lowering our threshold for kidney biopsy even below 500 mg a day. For me, if somebody has low complement levels, hematuria, and proteinuria above 300 mg a day, that's someone who should get a kidney biopsy. With the low complement level, the potential of having C3 glomerulopathy goes up in your pretest probability.

Once you have a biopsy diagnosis of C3 glomerulopathy, that's when you need to do further evaluation of the disease and specifically more further assays into what has led to loss of control of the alternative complement pathway. This is the key pathogenesis stage of why people get C3 glomerulopathy. We're going to try to do a comprehensive assessment of the complement cascade. We'll look at levels of activation. For example, you can test factor B breakdown products, like activated factor B (BB). You can test for terminal complement activity with a serum membrane attack complex assay (sMAC) of C5b-9. We're going to look for autoantibodies that might interfere with regulation of the alternative pathway, the most common being nephritic factors, like the C3 nephritic factor, but there are also antifactor B antibodies and antifactor H antibodies. There are functional assays where you can get readouts of just how much complement activation is present, both of the alternative pathway and the total complement pathways. Then, there are assays specifically for levels of complement proteins, particularly regulators like factor H and factor I. Most of these tests that I've mentioned are really only being done in research labs.

There are some labs that are commercial and test for nephritic factors and membrane attack complex levels. A complement hemolytic activity 50% (CH50) level and a complement alternate pathway 50% (AP50) level are the kinds of tests you could also get in commercial labs. But the complement proteins themselves, and many of these autoantibodies, are only being tested currently in research labs.

In genetic testing, there's a distinction between what you can get done commercially and what you can do in research labs. Most commercial renal genetics panels now will have a number of complement genes available. The typical commercial renal genetics panel can test for the main complement genes that have been identified in C3 glomerulopathy. For most of our patients, this is the step that we use to check for complement gene variants that might explain their disease. These are variants in complement proteins that are either promoters or regulators of the alternative complement pathway. In some patients, if the commercial panels are negative, and we still suspect that there's a genetic variant at play in the disease, you'll move on to research levels of genetic testing, whether it's whole exome sequencing or whole genome sequencing. Those places that see a lot of C3 glomerulopathy and have a strong genetics laboratory should be able to offer that to patients in a research setting.

**Module 4: Targeted Treatment**

The treatment of C3 glomerulopathy has been an evolving field. Fortunately, we've made some great advances over the last decade to get us to a point where we can actually move to targeted treatment of C3 glomerulopathy.

When we think about treatment, we will start by trying to identify and treat any of the primary processes that might be available. But, in most C3 glomerulopathies, we are treating the disease itself and not actually treating an underlying etiology, other than knowing that the alternative pathway is overactive. The exception being in older individuals who have monoclonal gammopathies of renal significance, where we can detect a monoclonal protein and say that that is the protein that's interfering with complement. In those instances, we treat with clone-directed therapy and have seen excellent results.

For the majority of patients, we're just saying we're going to go after the alternative pathway. Before we do that, we use conservative or foundational therapies. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are widely used for both blood pressure and proteinuria control. I think you could also throw on sodium-glucose cotransporter-2 (SGLT2) inhibitors as part of that foundational conservative therapy.

Up until recently, we've had to rely on nonspecific immunosuppression to treat C3 glomerulopathy. Mycophenolate mofetil plus glucocorticoids, essentially using a lupus nephritis regimen, has been the most commonly used regimen. It's typically been used in patients who have more than a gram per day of proteinuria, and it's shown some benefit, especially in patients with nephritic factors and autoantibodies in at least stabilizing the disease. But it's a nonspecific approach to treating, because it doesn't go after complement.

The first complement-targeting drug to be used in C3 glomerulopathy, in both small trials and case series, was eculizumab, a complement 5 (C5) monoclonal antibody. This was used principally in patients who were progressing or had not responded to a mycophenolate mofetil and glucocorticoid regimen. Unfortunately, the results with eculizumab have been very disappointing, and it's not considered a standard therapy at this point. Because we didn't have good treatment options, we often were recommending our patients go into clinical trials of complement-targeting drugs that targeted at C3 rather than at C5 like eculizumab. And of course, when patients went into kidney failure, they were offered a kidney transplant. We know with this disease, when you get a kidney transplant, the disease has a very high rate of recurrence, 80% to 100%, and those patients also would need targeted therapy.

In terms of treatment targets, as I mentioned, eculizumab targets C5. Avacopan was the next complement inhibitor to be approved for antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis. Avacopan was studied in the first large, randomized trial in C3 glomerulopathy, and it is a C5a targeting drug. Then, we moved on to trials of drugs that

targeted higher up in the alternative pathway, particularly at the level of C3, with pegcetacoplan, a C3-targeting drug, and iptacopan, a factor B inhibitor. It really was iptacopan and pegcetacoplan, the C3 targeting drugs, where we saw our first true successes in using complement-targeted therapy in C3 glomerulopathy. Whereas eculizumab and avacopan were unable to show long-term benefits in the disease, iptacopan and pegcetacoplan were able to show significant changes in disease trajectory, which got these drugs approved by the US Food and Drug Administration (FDA).

We'll start with iptacopan, a factor B inhibitor. This drug had already been approved for IgA nephropathy when the results from the phase 3 study in C3 glomerulopathy, called the APPEAR-C3G study, were published and eventually led to approval by the FDA. This study looked at patients with native kidney C3 glomerulopathy, and they randomized them to iptacopan vs placebo. The reduction in proteinuria, which was observed as early as day 14 and sustained out to 12 months, was statistically significant. We also saw a stabilization of glomerular filtration rate (GFR). Patients who were in the study provided GFR data for up to 2 years before enrollment in the study. Patients, on average, were losing about 7 mL/min/1.73m$^2$ per year of GFR before they went onto iptacopan. The GFR slopes essentially flattened where they weren't losing any more GFR, on average, once they were put onto iptacopan. The other thing we have from this study is kidney biopsy data. Everybody did a repeat biopsy after being on iptacopan for 6 months, and there was a large reduction in the C3 deposits on immunofluorescence, showing that the drug was able to get control of the alternative complement pathway and prevent any further complement-mediated kidney injury.

There is a long-term extension study evaluating the efficacy and safety of iptacopan in patients with C3 glomerulopathy. There is also a separate study looking at iptacopan in immune complex membranoproliferative glomerulonephritis (IC-MPGN) called the Apparent MPGN study.

Pegcetacoplan, which is a C3 targeting drug, was also approved by the FDA after they published their very impressive results from a phase 3 study called the VALIANT study. This study enrolled both C3 glomerulopathy and IC-MPGN, but was primarily studied in C3 glomerulopathy patients (over 80%). Here they showed, again, significantly greater reduction in proteinuria with pegcetacoplan compared to placebo. A really remarkable drop in proteinuria when you look at the numbers of -67.2% (with pegcetacoplan) as compared to placebo (2.9%). These patients showed a statistically significant improvement in GFR. They also showed an overall combined endpoint of stabilization of GFR and reduction of more than 50% proteinuria with pegcetacoplan as compared to placebo. Like we saw with iptacopan, there was a very impressive reduction in C3 staining on immunofluorescence in patients in the VALIANT study, all of whom did repeat biopsies after being on pegcetacoplan for 6 months. In fact, almost 75% of the patients went to zero C3 staining on immunofluorescence at 6 months. Again, this showed that pegcetacoplan was able to get control of the alternative complement pathway and prevent any further complement-mediated damage.

As we saw with the iptacopan, there is a long-term extension study to look at the efficacy and safety of pegcetacoplan, called the VAIL study. It is ongoing at this moment.

Moving from nonspecific immunosuppression to targeted treatment options provides our patients with many benefits. Number one is that we're actually getting to target the disease. With a nonspecific immunosuppressive approach, we never really were getting control of complement. If you rebiopsied any patient who was on mycophenolate mofetil and glucocorticoids, there may be less inflammation on immunofluorescence, but the biopsies looked identical. There was no control of complement with nonspecific immunosuppression. Now, you are able to get control with targeted complement-addressing therapies.

The more specific the treatment option, the better the overall toxicity profile will be. I tell my patients that these complement drugs are like designer drugs. They're only going after one target. Yes, they do imply a fair amount of immune suppression, but we know from these studies that the safety outcomes can be quite good with appropriate vaccinations against encapsulated bacteria organisms. As long as we're vaccinating against *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* type B, the safety of using these C3 targeting drugs is excellent, and there really is no other widely expected side effect beyond immune suppression with these targeted designer drugs. We're getting all the efficacy, and with appropriate vaccinations, there are good safety signals to use these drugs in our patients.

**Module 5: Optimizing Care**

Our treatment goals in C3 glomerulopathy are to reduce proteinuria, which, in turn, should slow disease progression. A good initial goal is to reduce proteinuria by at least 50% over the first 6 months of therapy, with a long-term goal of getting proteinuria below 500 mg per day as a sustained proteinuria goal, which gives us our best chances of preserving long-term kidney function. What we know from natural history studies that have been done in multiple centers, looking at C3 glomerulopathy, is that the faster and more profound reductions in proteinuria, the earlier you can get proteinuria below 500 mg per day. This level gives the patient the best chance at preserving long-term kidney function, which would be followed, over time, with stable GFR curves. This is true of all glomerular diseases, but it's particularly true of C3 glomerulopathy. We want to get our patients to as low a proteinuria goal as possible, and as early as possible, to give them the best long-term chances, overall, to preserve kidney function.

While we're treating C3 glomerulopathy, we have to keep in mind safety concerns. If we're going to get our patients to the treatment goal of proteinuria less than 500 mg a day, and sustain proteinuria in that level, we're likely going to require long-term use of complement targeting therapies. The 2 complement therapies that have been approved for C3 glomerulopathy are iptacopan, a factor B inhibitor, and pegcetacoplan, a C3 targeting drug. Both iptacopan and pegcetacoplan have shown very good efficacy data, and in clinical trials, very good safety data. In those clinical trials, all patients were required to have vaccinations against *Streptococcus*

*pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. These vaccines must be completed at least 2 weeks prior to the initial dose of iptacopan or pegcetacoplan, unless it's urgent. In those cases, you can start the drug under cover of penicillin antimicrobial prophylaxis. If the patient has a penicillin allergy, there are other potential antimicrobial prophylaxis options that can be used. Penicillin is the most commonly used antimicrobial prophylaxis. Very commonly, what we will do, because we don't want to lose the time needed to get our patients to goal, is to put them on penicillin antimicrobial prophylaxis while we're doing these series of vaccinations.

When you think about these patients, it's going to be an interprofessional approach that's required to get our patients to the best possible outcomes. There needs to be collaboration between multiple team members, including referrals to specialty centers. There is a heavy reliance on primary care physicians to make sure we're getting our vaccines updated and that we're doing our appropriate follow-up screening of patients. A specialty center will basically guide all treatment decisions and do routine surveillance of how the patient is responding to therapy. Communication between the centers, physicians, patients, and their families is routinely going to be needed to make sure that we keep the patient on the optimal course, and we're keeping them as safe as possible throughout this course.

We have to incorporate patients' goals. We do have 2 complement targeted therapies now, and we need to let patients know what their options are. Some patients prefer an oral regimen to a subcutaneous regimen. Some people will say, I think I'll do better from an adherence standpoint with a twice-a-week medicine rather than a daily medicine. While we're incorporating these treatment decisions, hearing from the patient about their disease burden, whether we're making impacts on their quality of life, is crucially important as well. We're not just treating lab values, we're treating actual patients, and we want to make sure that we're improving their lives as we work towards improving their long-term kidney outcomes.