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Diagnosis and Management of C3G

**Announcer:**
Welcome to KDIGO Conversations in Nephrology. This episode in our complement mediated kidney disease series titled, Diagnosis and Management of C3G, is provided by KDIGO and supported by Apellis and Sobi. Here's your host, Dr. Carla Nester.

**Dr. Carla Nester:**
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Carla Nester, professor of Internal Medicine and Pediatrics, Stead Family Children's Hospital, University of Iowa. And joining me to discuss Diagnosis and Management of C3G is Dr. David Kavanagh. Dr. Kavanagh is Professor of Complement Therapeutics at the National Renal Complement Therapeutic Center, Newcastle, England, and his clinical and research interests include complement mediated renal and retinal diseases. Dr. Kavanagh, welcome to the podcast.

**Dr. David Kavanagh:**
Thanks very much, Carla. It's a pleasure to be here. Always great to discuss complement mediated renal disease.

**Dr. Carla Nester:**
Let's begin our discussion with how do patients present, and particularly how do you make the diagnosis of C3G or immune complex MPGN?

**Dr. David Kavanagh:**
C3 Glomerulopathy is an ultra rare kidney disease. We estimate that there will be about 10,000 patients in the United States with C3G. The clinical presentation of C3G can be varied from asymptomatic presentations on routine screening with hematuria or proteinuria on dipstick, nephrotic syndrome, or acute kidney failure. Serum complement C3 levels are low in the majority of cases, and this is one of the first indications that C3G should form part of the differential diagnosis. The diagnosis of C3G however is made on renal biopsy and it's based on the presence of dominant C3 deposition on immunofluorescence. Sub classification of C3G into Dense Deposit Disease and C3 Glomerulonephritis is then based on the appearances on electron microscopy. There is substantial overlap between immune complex MPGN and C3G.

When we see the biopsy feature, then we need to establish what may be driving disease and to exclude any secondary causes. C3 dominant glomerulonephritis is not necessarily C3G.

**Dr. Carla Nester:**
So that's an excellent point that C3 dominant glomerulonephritis is not necessarily C3G. So then the follow-up question becomes, to your mind, is there anything on the biopsy that helps you rule out those confounders?

**Dr. David Kavanagh:**
C3 may accumulate in areas of glomerular or tubular interstitial scarring and due to prior inflammation or ischemia. I do see this very commonly. It tends to be focal and is limited to areas of scarring. The intensity of C3 extending tends to be a bit more modest and moderate at most, and the EM may show non-specific deposits or scarring. However, when we get a biopsy with a C3 dominant picture, we should undertake a diagnostic workup.

**Dr. Carla Nester:**
So what do you consider is the bare minimum diagnostic workup and why?

**Dr. David Kavanagh:**
When we get a renal biopsy that shows a C3 dominant glomerulonephritis, it may point to C3G either due to acquired or inherited complement defects. There are a few caveats, however. This may depend on where in the course of the illness you biopsy.

For instance, 30% of post-infectious glomerulonephritis will be C3 dominant and subepithelial humps are not pathognomonic for post-infectious glomerulonephritis. So I'll ask for a history of pharyngitis or impetigo. I'll measure AS O titres. If it's a post-infectious glomerulonephritis, the haematuria, proteinuria and low complement levels we normally see initially will resolve within about three months.

I will look for a paraprotein mediated disease. The renal biopsy may give us a clue to a monoclonal, gammopathy driven disease. We may see kappa or lambda restriction on immunohistochemistry, and it's really important that this is done. Pronase digestion may reveal hidden immunoglobulin or light chains deposited that would otherwise not be seen, and C4d staining of the biopsy may also help to suggest a paraprotein mediated disease. Clearly we need to do serum and urine protein. Electrophoresis and serum free light chains are important too.

This is a disorder that's more common as you age. About 1.6% of people over 50 will have a monoclonal gammopathy, and this rises to about 6.5%. In those over 80. It must be remembered. However, that rarely younger patients with lymphomas can present like this.

We must also rule out secondary infectious causes such as Hepatitis B and C and other chronic infections such as endocarditis. Depending on the travel history, we should also look for tropical diseases such as Schistosomiasis.

We should also try to exclude autoimmune diseases such as SLE, rheumatoid Arthritis and Cryoglobulinemia.

More specialist complement tests may be available in some centers. Nephritic factors and autoantibodies to complement proteins are frequently found in C3G and provide reassurance as to the diagnosis. Likewise, genetic analysis may be performed, and, in rare cases, an underlying mutation in factor H or C3 may be found. An array of complement tests are available that assess the state of complement activation in C3. However, although these may speak of the underlying pathogenesis, they do not confirm a diagnosis of C3G or as yet guide treatment. It is likely however, that as complement therapeutics enter the real world, we'll work out how to use these tests to guide treatment.

**Dr. Carla Nester:**
Thank you. That's actually a very nice list of ways we can rule out some of these confounders. And I also like the way you portray the finding of autoantibodies, for instance, as quote unquote "reassurance of the diagnosis". I think with that in mind, I'll take that one step further and just ask you, is testing for these autoantibodies required for the diagnosis of C3G or immune complex MPGN?

**Dr. David Kavanagh:**
No, the diagnosis of C3G and immune complex MPGN is a biopsy diagnosis. These are really just additional tests that may allow you to confirm that this is driven by complement overactivation.

**Dr. Carla Nester:**
If you're just tuning in, you're listening to the KDIGO Podcast on Diagnosis and Management of C3G. I'm Carla Nester and I'm speaking with Dr. David Kavanagh. So let's jump to our next question. How do you treat your newly diagnosed C3G patient?

**Dr. David Kavanagh:**
As with most proteinuric renal diseases, I start with non-specific approaches such as optimization of blood pressure and proteinuric control with renal-angiotensin inhibition and SGLT2 inhibitors, I'll give lipid lowering agents when required.

In patients with more than half a gram of proteinuria, worsening renal function or severe inflammation in the renal biopsy, I will try non-specific immunosuppression in the form of steroids and MMF. I would say the evidence for this is all retrospective, but until now, it's the only treatment I had, and despite that, most patients progressed to end stage kidney failure.

We know that C3G is a disorder of the alternative pathway of complement, and therefore Eculizumab acts too far downstream to effectively treat C3G. The new alternative pathway targeted agents Iptacopan and pegcetacoplan are a pivotal moment for patients with C3G as we can now effectively target the site of complement overactivation. That is a really exciting time for patients with C3G.

**Dr. Carla Nester:**
I agree a hundred percent. But before we get to the new therapeutics, I'm sure as glomerular disease doctors, we've both had some successes with mycophenolate and steroids with other diseases. Would you like to take a stab at why this approach may be effective or for that matter, not effective in this particular setting?

**Dr. David Kavanagh:**
Yeah, that's a very interesting point, Carla. I mean, we have all treated some patients with steroids and MMF and seen good response. Now, I suppose all the evidence is retrospective, so we don't know if people would've got better anyway. And indeed, I've seen some patients just get better without any treatment. So, the evidence for this is all retrospective. However, as I said, most patients in MMF and steroid will progress to end stage whatever we do. Now, I think that's because we might see an initial response to steroids, and that's just treating the nonspecific inflammation we see in the kidney. However, we do not get rid of the underlying driver of disease. That's complement activation C3 depositing in the kidney, and that ultimately leads to end stage renal failure. And although we might feel MMF may be targeting autoantibodies as it may do in other diseases, we've had really poor success in eliminating the nephritic factors. Whatever we do, we have not really been able to get rid of these nephritic factors, and I believe you don't require terribly much C3 NEF to cause disease.

**Dr. Carla Nester:**
That all makes sense to me. Thank you. Now, let's move forward. So when the new therapeutic options are available to you, how do you plan to use them moving forward?

**Dr. David Kavanagh:**
Clearly, we all await the updated KDIGO guidance on treatment, but as a personal view, I will start ACE inhibitors and SGLT2 inhibitors. As I would in any proteinuric renal disease. I view alternative pathway inhibition as first line therapy. I will not start MMF and steroids first and see if there's a response.

We exquisitely know the pathogenesis of C3G and these alternative pathway agents target this. Iptacopan and pegcetacoplan have been shown to be effective in gold standard randomized placebo controlled trials.

There has never been a randomized controlled trial of MMF and steroids in C3G, and these agents come with marked side effects. Despite their use, most patients progress to end stage renal failure anyway. Thus, I would not want to see a gatekeeper role for MMF and steroids prior to us accessing the evidence-based treatment pegcetacoplan and Iptacopan.

Many questions remain about alternative pathway agents optimal use, such as how long we need to continue and what constitutes successful treatments and whether we need to swap between agents if we're not seeing successful treatment. I think however, many of these questions will only be answered when we use these agents in the real world.

**Dr. Carla Nester:**
I think that those are all excellent points. So I'm going to push back a little bit and ask you maybe a harder question. What if your ACE inhibitor plus your SGLT2 inhibitor takes a patient, let's say from 1.9 grams of urine protein down to 0.7 grams of urine protein, are you still going to consider one of the new therapies?

**Dr. David Kavanagh:**
Yes. Not all reduction in proteinuria is the same. ACE inhibitors, SGLT2 inhibitors will have a non-specific effect on proteinuria. However, they're not going to prevent that ongoing complement activation damaging the kidney. It's really the alternative pathway agents that hit the disease at the source.

**Dr. Carla Nester:**
Well, I think that's pretty straightforward. Thank you very much for that. So now let's jump over to transplantation. Are there issues about

transplantation that you would like to chat about?

**Dr. David Kavanagh:**
One of the most desperately disappointing features of this disease for our patients was that in up to 80% of cases, the disease relapsed after transplantation. Our patients had seen their native kidney function deteriorate to the point where they needed dialysis, and then they were fortunate enough to get a transplant. But frequently we had to tell them that the disease had come back and there was little we could do to stop this.

Both iptacopan (in phase two trials) and pegcetacoplan (in phase two and three trials) have been used in transplant recurrence with good result. There does not appear to be a safety signal when used in combination with transplant immunosuppression. The infectious risks of complement blockade is well known but can be mitigated with antibiotic prophylaxis, vaccination and patient awareness.

**Dr. Carla Nester:**
That's been my experience also, that the prognosis post-transplant can be just as daunting as it was in the native kidney. Can I ask you just for our audience more than anything, what constitutes recurrence in that transplant for you?

**Dr. David Kavanagh:**
Well, that does seem like an easy question, but actually it's not quite as straightforward. You could say, I need to see evidence of proteinuria or worsening renal function or should we do a renal biopsy? But if we do a renal biopsy, is C3 deposition enough or do I also need to see a glomerular nephritis? My feeling is that we know the pathogenesis of disease and, I don't want to wait until there's marked proteinuria and worsening renal function. If I do a kidney biopsy and I'm seeing pathological recurrence with a glomerulonephritis, I'm going to want to treat.

Now, that is a reactive treatment and there is one other complement mediated condition, atypical HUS, that also recurs post-transplant. But in that we give eculizumab prophylactically to prevent disease. Now that's a very acute presentation, and these patients with atypical HUS can lose their kidneys very quickly. In C3G, it tends to be far slower, so we will have time to react and do a biopsy. I don't, however, rule out giving prophylactic iptacopan or pegcetacoplan in certain cases where there might be a high risk of recurrence, but as yet, we'll need to see how this pans out in the real world.

**Dr. Carla Nester:**
Again, all excellent points I think you're making, and thank you for a wonderful discussion about the C3G. I want to thank my guest, Dr. David Kavanagh for joining me. Dr. Kavanagh. It was great having you on the podcast.

**Dr. David Kavanagh:**
It's always a pleasure.

**Dr. Carla Nester:**
I'm Dr. Carla Nester. To access this and other episodes in our series, visit kdigo.org/podcast. Thanks for listening.