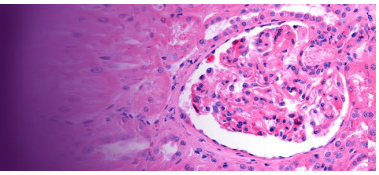

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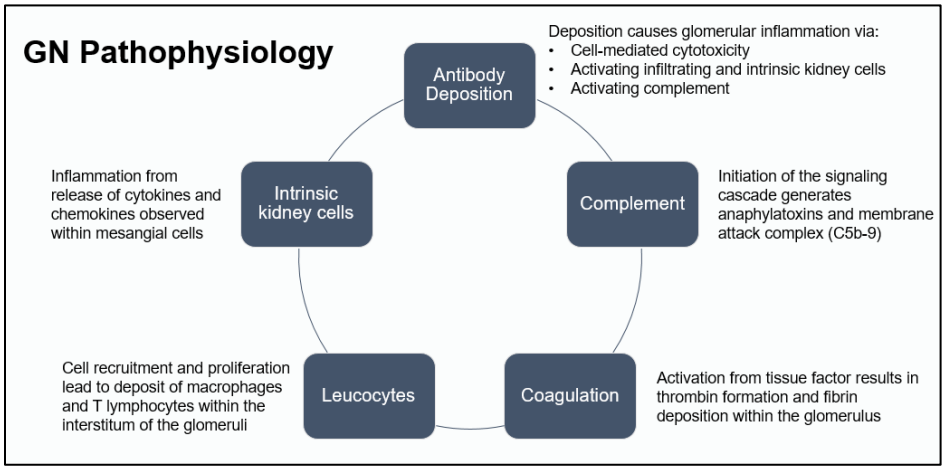
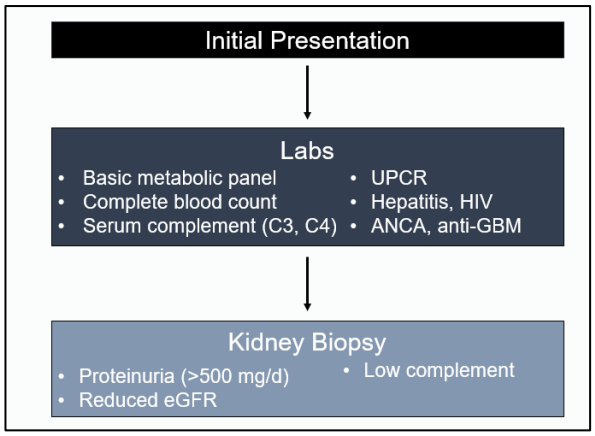
Key Concepts

Glomerular Disease

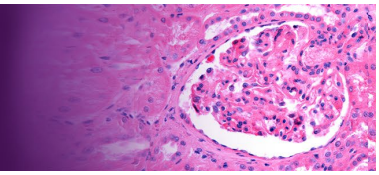
Glomerular disease comprises 25% to 30% of the end-stage kidney disease (ESKD) population and is the third leading cause of chronic kidney disease (CKD) in the United States.[1] Glomerular disease can be caused by diverse etiologies, including malignancy, infection, vascular disease, and medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and penicillinamine.[2] Activation of 1 or multiple pathways leading to kidney insult, including antibody deposition, complement, coagulation, leucocytes and intrinsic kidney cells, contribute to the pathophysiology.[2-4] Left untreated, progression to ESKD will be observed, with associated complications such as hypertension (HTN), proteinuria, acid-base disorders, anemia, bone mineral abnormalities, and cardiovascular disease.[1]



C3 Glomerulopathy



C3 glomerulopathy (C3G) is a form of membranoproliferative glomerulonephritis (MPGN) and is characterized by dysregulation of the alternative complement pathway and deposition of complement 3 (C3) complexes within the glomeruli.[5] It is classified as a rare kidney disease with an estimated 0.2-3 cases/million worldwide.[6] There are 2 forms of C3G disease, C3 glomerulonephritis (C3GN) and dense deposit disease (DDD); DDD patients exhibit a worse prognosis with progression to ESKD in 10 years as compared to C3GN.[7] The estimated overall progression to ESKD in 10 years is estimated in 30% to 70% of patients.[8] C3G disease is not specific to any one age range and presentation may be similar to other forms of GN.[5] There is a major negative impact on patient quality of life.



Presenting symptoms are dependent on the severity of disease, but may include HTN, proteinuria, hematuria, edema, drusen in the eyes, and lipodystrophy.[1] From initial presentation, the next step in C3G workup should include laboratory assessment.[9] If parameters are met, a kidney biopsy should be performed for definitive diagnosis. Once a diagnosis is made, further evaluation may include overall assessment of complement activity, screening for autoantibodies and genetic workup to identify an underlying etiology of disease and/or if specific abnormalities are present that may guide treatment.[5,10]

Treatment Options

Current treatment regimens can be divided into supportive care, general immunosuppressive and immunomodulatory therapies, and disease-specific targets in C5- and C3-directed medications. [Currently, no treatments have been approved by the US Food and Drug Administration for C3G.] An angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) should be initiated in all patients with C3 disease who do not have contraindications, to improve renal survival within this population.[1] Nonspecific immunomodulatory or immunosuppressive regimens, eg, corticosteroids and mycophenolate mofetil, have variable success in rates of remission and long-term renal survival.[11-14]

C5- and C3-directed therapies have specific targets in either the proximal or terminal complement pathways. Eculizumab and raviluzumab are 2 monoclonal antibodies targeted against C5 that prevent assembly of the soluble C5b-9 membrane attack complex. A small cohort study of 26 children and adults with C3G treated with eculizumab for a median of 14 months observed ~50% with either a global or partial clinical response.[15] Avacopan is a C5a antagonist, iptacopan is a factor B inhibitor, and pegcetacoplan is a C3 inhibitor. Kidney transplantation may serve as an option for patients who have failed pharmacologic treatment.[16] However, ongoing dysregulation of the alternative complement system will still be present. Recurrence of C3G disease and/or resultant graft failure is common within 10 years after kidney transplantation.

Patient Resources and Supportive Measures

The National Kidney Foundation held a patient-focused drug development meeting on C3G in August 2017, with attendees including patients living with C3G and their caregivers.[17] Key themes and discussion surrounded symptoms, experiences with treatments, and insight on future therapies. Several organizations exhibit patient resource pages and support groups, including the National Organization for Rare Disorders, Inc, National Kidney Foundation, and Nephcure Kidney International. As a provider, awareness in the global effects of complement system dysregulation may involve concomitant health issues and need for specialists in comanagement of patients with the disease.[5]

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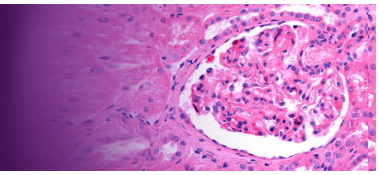

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