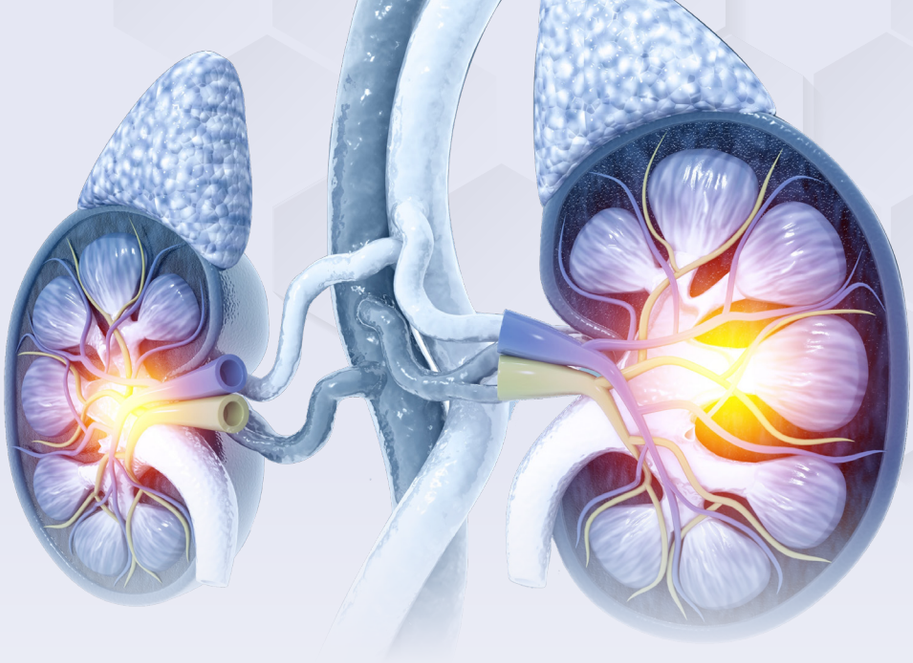

Acute Glomerulopathies

Glomerulonephritis (GN) is a common cause of end-stage kidney disease.[1] This heterogeneous group of disorders is undergoing reclassification based on new discoveries about their pathogenesis.[2]

This primer summarizes the diagnostic approach for GN as discussed in the accompanying review article, with a special focus on a rare, complement-mediated form of GN called C3 glomerulopathy (C3G). The author of the review article, Dr Sanjeev Sethi, provides his expert commentary and key takeaways throughout this primer.

Typical symptoms of GN, including C3G

Classification of glomerulonephritides based on underlying pathophysiology

Overall approach to the diagnosis of glomerulonephritides, with a focus on the diagnosis of C3G

This piece was developed in partnership with Sanjeev Sethi, MD, PhD.
Perspectives provided are his own and reflective of his affiliation.

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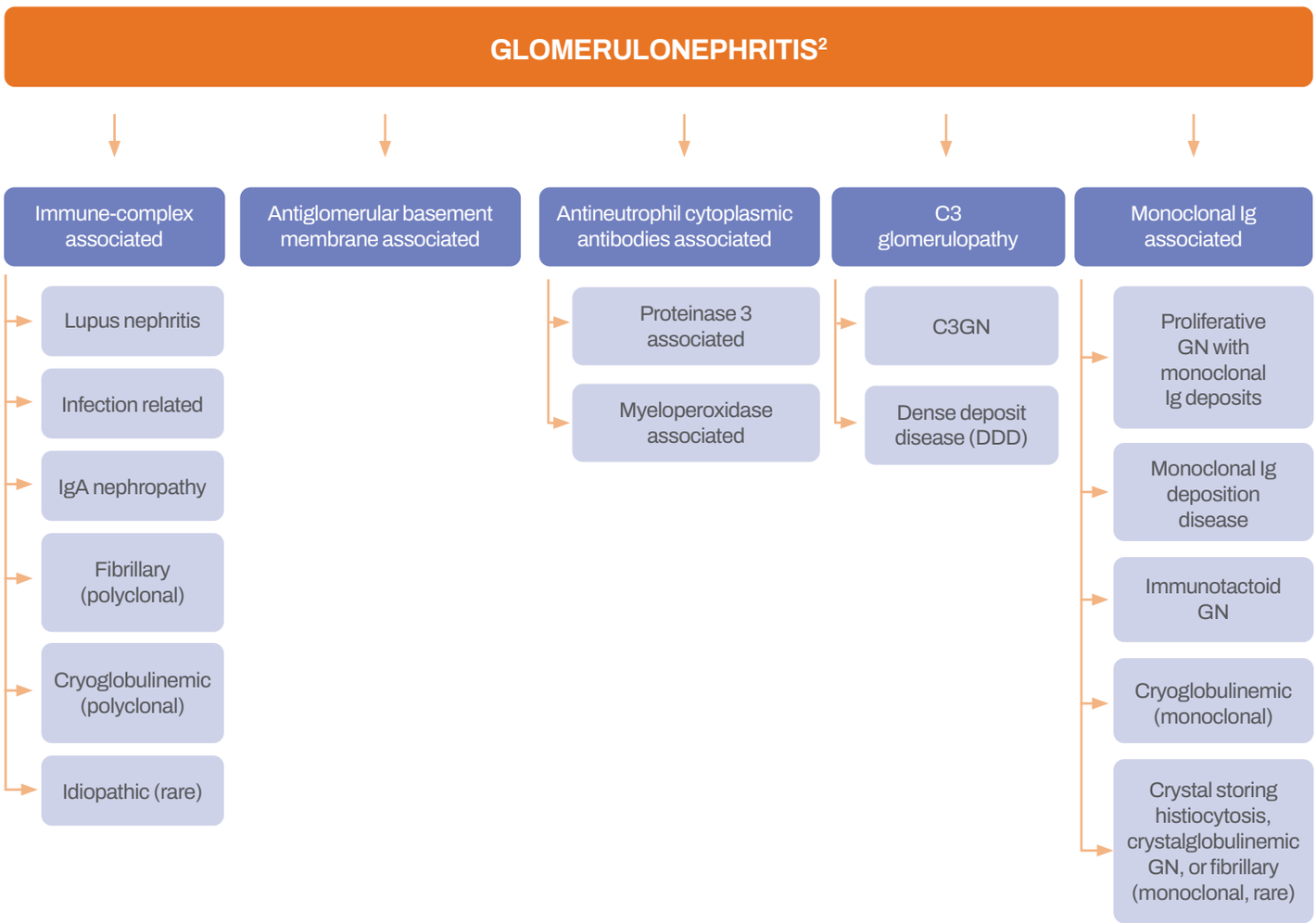
Glomerulonephritis (GN) is a heterogeneous group of disorders that might present as many different clinical patterns or syndromes. Patients present most frequently with asymptomatic hematuria and proteinuria with or without reduced kidney function, though the combination, intensity, and time course of symptoms can vary. Clinical presentations characteristic of glomerular disease include asymptomatic proteinuria or microscopic hematuria, nephrotic syndrome, autoimmune diseases, nephritic syndrome, rapidly progressive glomerulonephritis, and chronic glomerulonephritis. In some cases, the kidney is the sole organ affected. Glomerulonephritides may also occur as part of a multisystemic disease (eg, malignancy, monoclonal gammopathy, infections, drugs).[2]

Classification of glomerulonephritides based on the underlying pathophysiology is now favored over a pattern-based approach as mechanisms of disease are discovered and targeted therapies become available. The underlying causes can be mostly inferred from immunofluorescence studies, which are typically used for diagnosis.[2] Based on underlying cause, GN can be broadly classified into 5 main classes:



C3G is a rare disease caused by dysregulation of the alternative complement pathway and ensuing glomerular deposition of complement factor C3. Deposition of complement factors subsequently drives glomerular inflammation, resulting in proliferative GN. Being a complement disorder, 47% to 65% of patients present with low serum C3 and 12% to 14% of patients present with low serum C4.[2]

Dysregulation of the alternative pathway is caused by genetic variants in complement system factors or auto-antibodies against complement system proteins (eg, C3 nephritic factors, anti-factor H antibody, and anti-factor B antibody), either of which are detected in approximately one-third of C3G patients.[2] A recent infection, autoimmune disease, and monoclonal gammopathy can be identified as the triggering condition in approximately one-third of patients and are common differential diagnoses for C3G.[2,3]

C3, complement component 3; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; C4, complement component 4; IgA, immunoglobulin A.

Clinical symptoms in C3G are similar to those for other glomerulonephritides and include hematuria and proteinuria, sometimes in the nephrotic range. Disease flairs characteristically occur in patients with C3G, and rates of progression vary widely. Predictors of poor prognosis include increased serum creatinine, proteinuria >3 g/day, and extensive chronic damage on kidney biopsy.[2]

Overview of the different forms of glomerulonephritis[2]

	Extrarenal Manifestations	Laboratory Markers	Key Pathological Features
Infection-related GN*	Impetigo, pharyngitis, endocarditis, and abscess	Positive blood cultures and low C3	Diffuse proliferation; immunofluorescence: IgG and C3
C3 glomerulopathy	Synpharyngitic hematuria, Drusen, and autoimmune disease	Low C3 or C4 and monoclonal Ig C3 nephritic factor	Mesangial, endocapillary proliferation, membranoproliferative, and crescentic; immunofluorescence: C3 dominant
Monoclonal Ig-associated GN	Hematological malignancy or monoclonal gammopathy of renal significance	Low C3 or C4 and monoclonal Ig	Membranoproliferative; immunofluorescence: IgG (monotypic), κ or λ light chain restriction

*Immune-complex GN.

The overall diagnostic approach for identifying a suspected GN, including C3G, involves a multi-step process that includes urinalysis, serological analysis, and biopsy.[2]

Panel: Initial laboratory evaluation in patients suspected as having GN[2]

- Complete blood count
- Urinalysis with a careful search for red blood cell casts
- Proteinuria quantification (on a 24 h urine sample)
- Complete metabolic panel
- C3 and C4 complement concentrations
- Anti-double stranded DNA antibody
- Antineutrophil cytoplasmic antibodies and antiglomerular basement membrane serology
- Hepatitis B, hepatitis C, and HIV serology
- Monoclonal protein studies and plasma free light chains (in patients aged >50 years)
- C-reactive protein
- Cryoglobulins and rheumatoid factor (in patients presenting with palpable purpura, arthralgia, or arthritis; peripheral neuropathy; and hypocomplementemia [low C4 concentration] or both)
- Antistreptolysin O titer, antideoxyribonuclease B, and blood cultures (when infection-related GN is suspected)

STEP 1: Recognize symptoms[2]

Recognize common symptoms to create a tentative differential diagnosis.

STEP 2: Urinalysis[2]

Microscopic and biochemical analysis of urinary sediment.

STEP 3: Serological analysis[2]

Serological analysis and immunological evaluation.

STEP 4: Kidney biopsy[2]

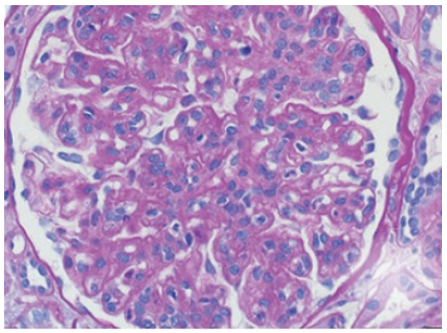
Kidney biopsy is the gold standard for diagnosis and is analyzed via light microscopy, immunofluorescence, and electron microscopy.

C3, complement component 3; C3G, complement 3 glomerulopathy; C4, complement component 4; GN, glomerulonephritis; DNA, deoxyribonucleic acid; h, hour; HIV, human immunodeficiency virus; Ig, immunoglobulin; IgG, immunoglobulin G.

Histological patterns of injury are examined via light microscopy (LM) and can reveal several distinct patterns such as membranoproliferative glomerulonephritis (MPGN). However, **because different causes of GN can result in the same pattern of injury on LM, immunofluorescence is typically used to detect the type and semi-quantitate.[2]** Immunofluorescence can detect the relative quantity of immune system components. Finally, electron microscopy is used to detect the presence and location of immune protein deposits and changes in glomerular anatomy.

Biopsy findings inform the diagnosis and management of GN. Biopsy reporting includes the primary cause (diagnosis) of GN, the severity and pattern of injury (eg, MPGN), classification and grading of specific diseases, and grading of chronic changes.[2]

Biopsy analysis is required to diagnose C3G.[2]



LM most commonly reveals an MPGN, though mesangial proliferative and crescentic patterns of injury may occur.[2]

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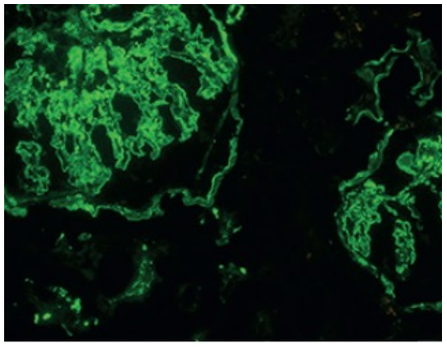

Immunofluorescence is required for diagnosis. The defining feature of C3G is bright C3 staining with no or minimal immunoglobulin staining.[2]

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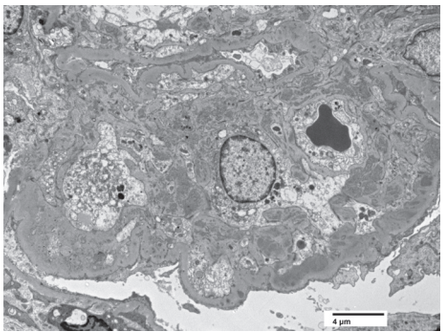

C3 is subdivided into C3GN and DDD. Electron microscopy can distinguish C3GN from DDD.[2]

Image provided courtesy of Sanjeev Sethi, MD.

Scan the QR code to learn more about C3G

C3, complement component 3; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; GN, glomerulonephritis.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080