Top 10 Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for the Management of Immunoglobulin- and Complement-Mediated Glomerular Diseases with a Membranoproliferative Glomerulonephritis (MPGN) Pattern of Injury

1 MPGN is not a disease

MPGN is not a single, specific disease, but is a light microscopic pattern of kidney injury. The older nomenclature of MPGN types 1–3 should be discarded.

2 Classification of MPGNs

Glomerular injury with an MPGN pattern is now classified by pathobiology and relies on the immunofluorescence examination of the kidney biopsy. These entities may be broadly-defined as immunofluorescence-negative, complement-dominant, or immunoglobulin (with or without complement) positive (Figure 1).

3 Differential diagnosis of MPGNs

The differential diagnosis of glomerular injury with an MPGN pattern is broad and includes infection-related glomerular disease, autoimmune diseases, and complement-mediated diseases (Figure 2).

4 Exclude infection

Infection should be excluded in patients with immune complex-mediated GN, followed by evaluation for an autoimmune disease. If monoclonal immunoglobulin deposits are present, evaluate for a hematologic malignancy.

5 Considerations for idiopathic ICGN in adults

Idiopathic immune complex-mediated GN (ICGN) is not common in adults. If no etiology is discovered, evaluate for complement dysregulation and drivers of complement dysregulation. C3 glomerulopathy (C3G) can masquerade as an immune complex-mediated GN.

6 Considerations for C3G

Prior to assigning a diagnosis of C3G, infection should be excluded, and in patients age 50 or older, a monoclonal gammopathy should be excluded.

7 Treatment of ICGN of known cause

The treatment of immune complex-mediated GN should be directed at the underlying cause.

8 Treatment of ICGN of unknown cause

In the absence of an underlying cause, idiopathic immune complex-mediated GN may be treated with glucocorticoids and/or immunosuppressive therapies, based on the severity and activity of the disease.

9 Treatment of C3G

Patients with C3G who have proteinuria over 1 g/d and/or declining kidney function over 6 months should be treated initially with mycophenolate mofetil plus glucocorticoids, and if this fails, eculizumab may be considered.

10 Clinical trials

Patients with C3G who do not respond to therapy should be considered for a clinical trial.

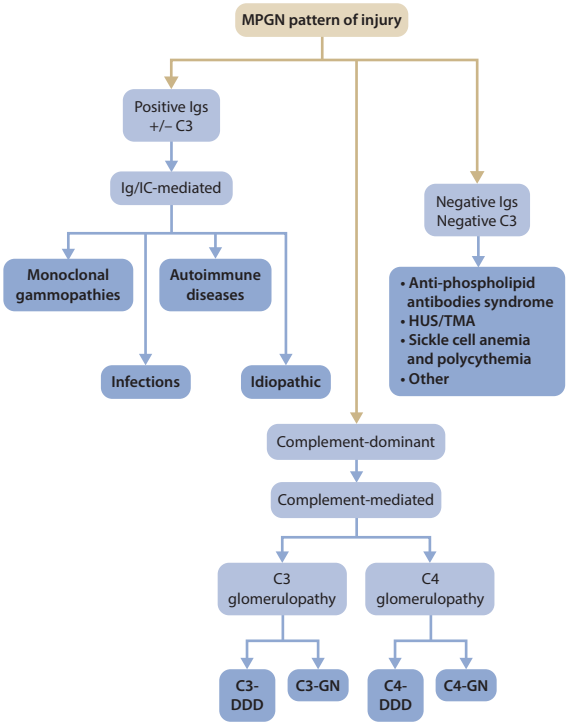

Figure 1

Immunoglobulin-/immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

Figure 2