
بسم الله الرحمن الرحیم

Mangement of MPGN and C3G

Dr.Mehdi Khajeazad

Outline

1.Definition

2.Classification

3.Pathogenesis

4.Clinical Features

5.Complement work up

6.Renal transplantation

7.Prognosis

8.Treatment

9.Conclusion

Definition

MPGN is a pattern of kidney biopsy that characterized in light microscopy by:

1.An increased number of intraglomerular cells

2.Diffuse thickening of the glomerular capillary walls

Brenner2020

Traditionally classification of MPGN

Type I: Mesangial and subendothelial deposits

Type II: (dense deposit disease DDD) : Electron dense deposits along the GBM

Type III: Both subepithelial and subendothelial deposits

Berenner2020

New Classification system

1)Immune complex Mediated MPGN: Both immunoglobulin and complement staining on IF

2) Complement Mediated MPGN = C3 Glomerulopathy: predominant C3 staining on IF

Brenner2020

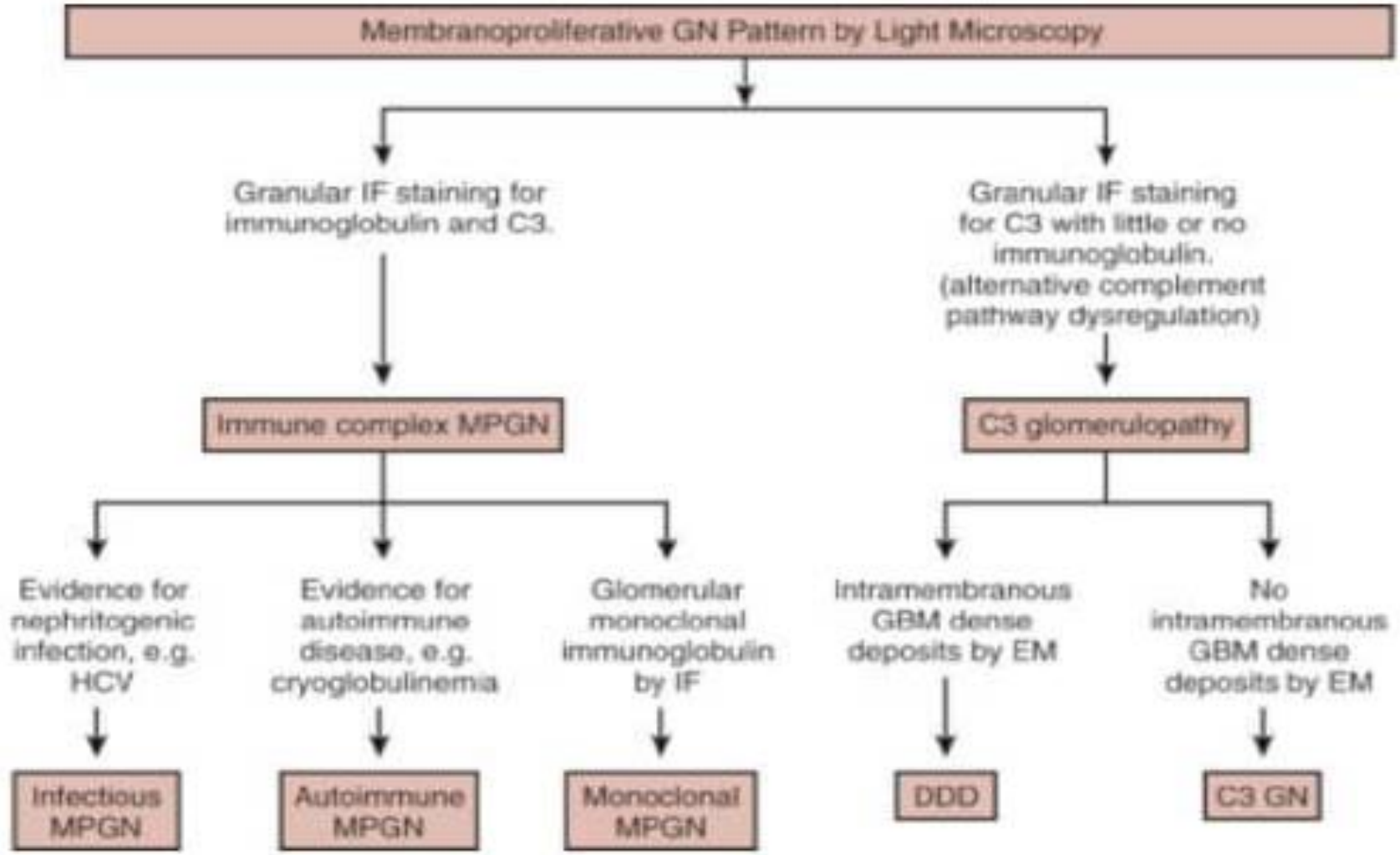
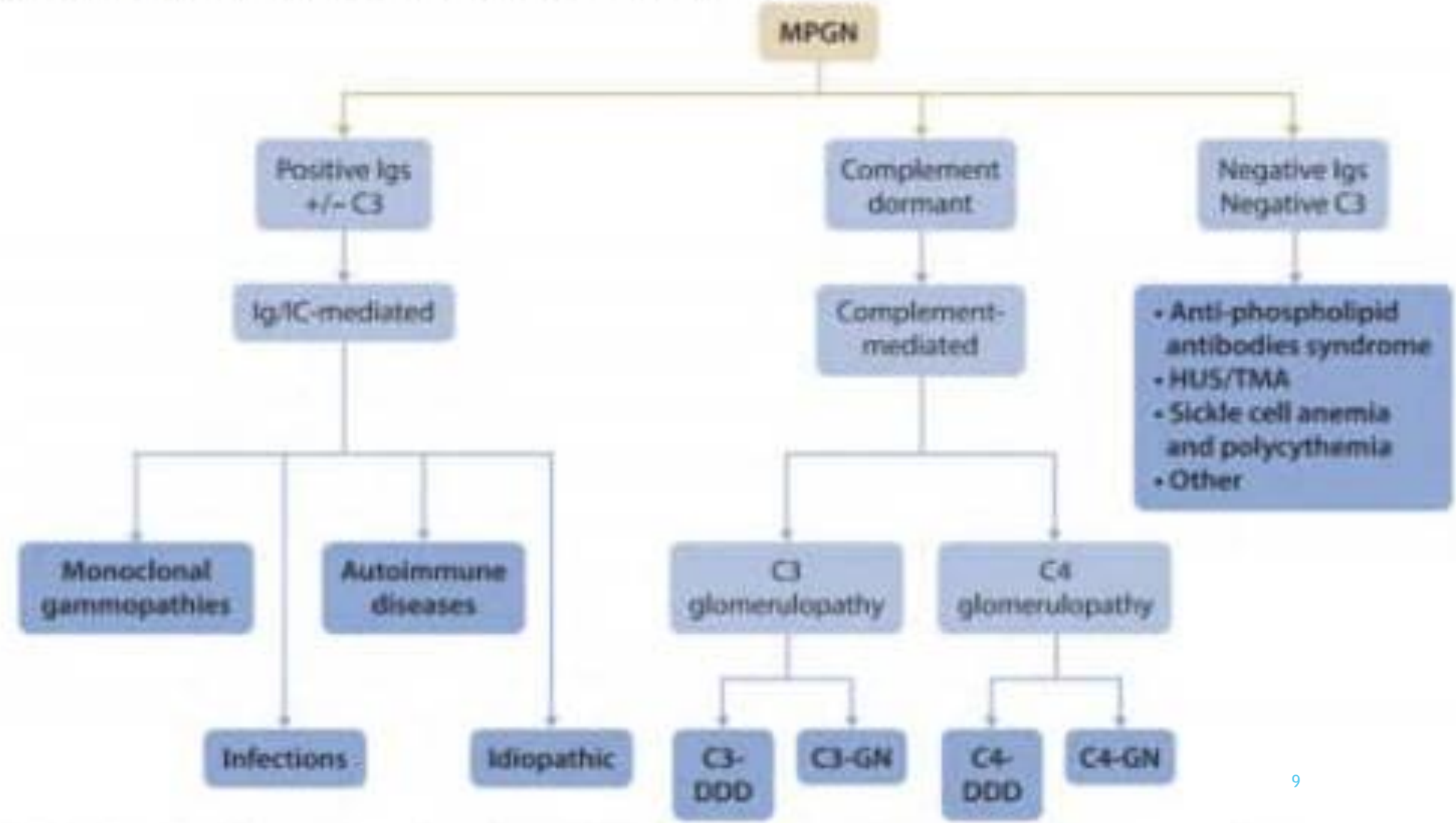

Membranoproliferative GN Pattern by Light Microscopy
Granular IF staining for immunoglobulin and C3.
Granular IF staining for C3 with little or no immunoglobulin. (alternative complement pathway dysregulation)
Immune complex MPGN
C3 glomerulopathy
Evidence for nephritogenic infection, e.g. HCV
Evidence for autoimmune disease, e.g. cryoglobulinemia
Glomerular monoclonal immunoglobulin by IF
Intramembranous GBM dense deposits by EM
No intramembranous GBM dense deposits by EM
Infectious MPGN
Autoimmune MPGN
Monoclonal MPGN
DDD
C3 GN

Table ICMG1. Causes of a membranoproliferative pattern of injury

Immunoglobulin/ immune-complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** - Viral: hepatitis C, 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**
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**
MPGN without immune complexes or complement	- Healing phase of HUS/TTP - Anti-phospholipid (anti-cardiolipin) 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 - Anti-trypsin deficiency
"Idiopathic" forms of MPGN	- None of the conditions above are present

Figure ICMG1. Pathophysiology of MPGN lesions



Modified from references

Secondary Causes of Membranoproliferative Glomerulonephritis

Associated With Infection

- Hepatitis B and C
- Visceral abscesses
- Infective endocarditis
- Shunt nephritis
- Quartan malaria
- *Schistosoma* nephropathy
- *Mycoplasma* infection

Associated With Rheumatologic Disease

- Systemic lupus erythematosus
- Scleroderma
- Sjögren syndrome
- Sarcoidosis
- Mixed essential cryoglobulinemia with or without hepatitis C infection
- Anti–smooth muscle syndrome

Associated With Malignancy

- Carcinoma
- Lymphoma
- Leukemia

Associated With an Inherited Disorder

- α_1-Antitrypsin deficiency
- Complement deficiency (C2 or C3), with or without partial lipodystrophy

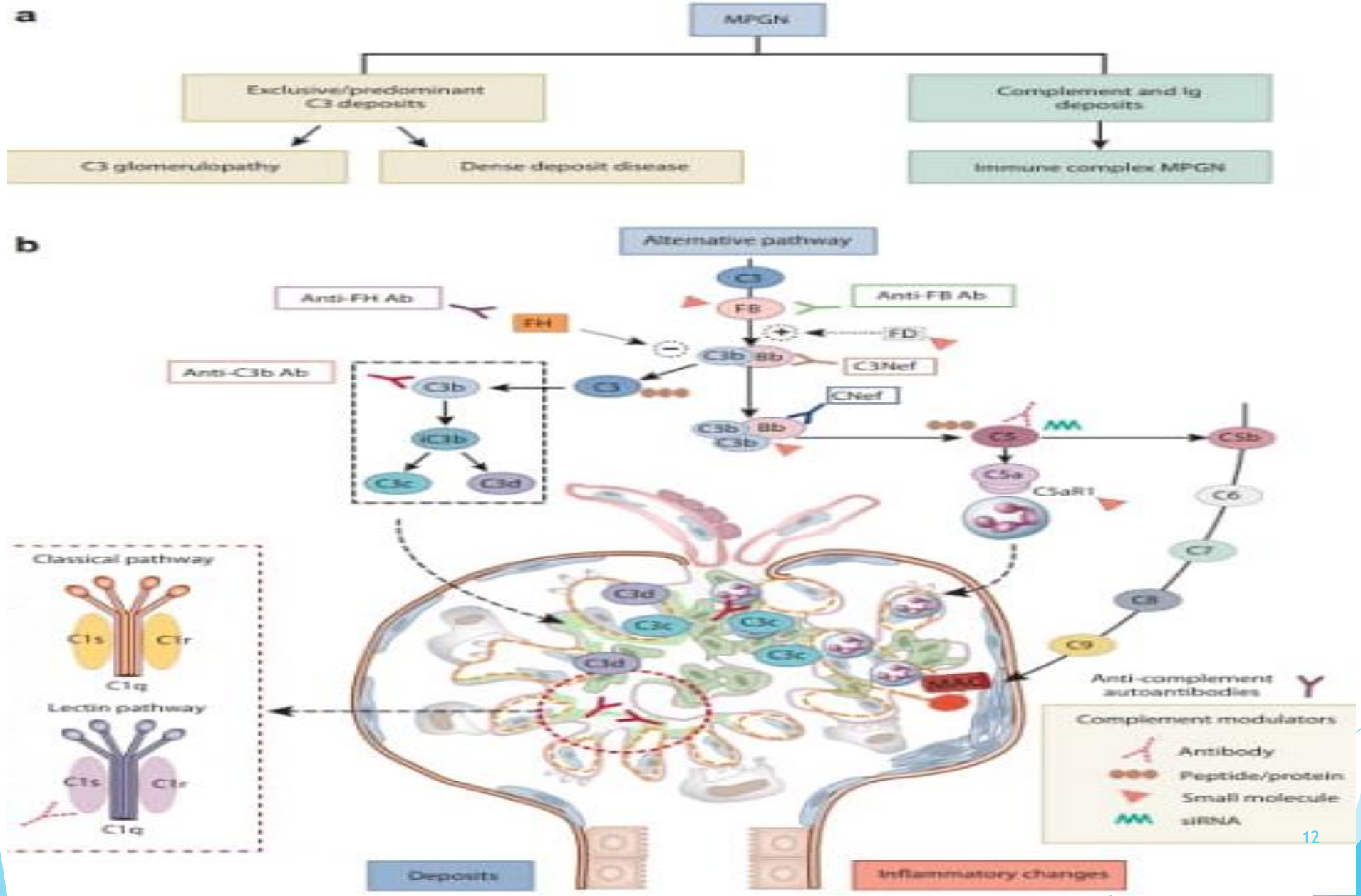
Pathogenesis

1)Immune complex localization

2)Dysregulation of alternative pathway complement activation

3) Glomerular deposition of monoclonal Ig is a rare cause

Brenner2020


a
MPGN
Exclusive/predominant C3 deposits
Complement and Ig deposits
C3 glomerulopathy
Dense deposit disease
Immune complex MPGN
b
Alternative pathway
C3
FB
Anti-FH Ab
Anti-FB Ab
FH
FD
C3b Bb
C3Nef
Anti-C3b Ab
C3b
C3
CNef
iC3b
C3c
C3d
C3b Bb C3b
C5
C5b
C5a
C5aR1
C6
C7
C8
C9
MAC
Classical pathway
C1s
C1r
C1q
Lectin pathway
C1s
C1r
C1q
Anti-complement autoantibodies
Complement modulators
Antibody
Peptide/protein
Small molecule
siRNA
Deposits
Inflammatory changes

Clinical Features in Type I MPGN

1) Proteinuria often nephrotic range

2)Hematuria

3)Hypertension

4)Renal failure is usually present

Brenner2020

Clinical Features in C3G

1) Hematuria

2) Proteinuria

3)One- third of patients have nephrotic syndrome

4) %25 of patients have acute nephritic syndrome

5)Respiratory infections precede of MPGN in %50 of patients

6) Ocular involvement (drusen) in DDD patients

7)Lypodystrophy in DDD patients

Brenner2020

Complement work up

Recommended in all patients with C3G and Ig – MPGN.

Includes:

1.biochemical evaluation of the CAP

2.Assays for Autoantibodies targeting the CAP

3.Complement gene profiling

Practical management of C3 glomerulopathy and Ig-mediated MPGN .KI

Table 2 | Main anti-complement autoantibodies detected in patients with C3G and Ig-MPGN

Anti-complement autoantibody	Characteristics
C3 nephritic factor	Binds to a neoepitope on the assembled C3 convertase (C3bBb). Detected in C3G and Ig-MPGN (50%–80%) and may be associated with acquired partial lipodystrophy
Anti–factor H antibodies	Bind to the N-terminal portion of factor H (short consensus repeats 1–4). Detected in 4%–12% of C3G and Ig-MPGN
Anti–factor B antibodies	Bind to an epitope in von Willebrand type A and serine protease domain of Bb. Detected in 90% of children with post-infectious glomerulonephritis
Anti-C3b antibodies	Bind to C3, C3b, iC3b, and C3c with variable affinity. Detected in 2%–3% of patients with C3G and infection-related Ig-MPGN
C5 nephritic factor	Binds to a neoepitope on the assembled C5 convertase (C3bC3bBb properdin). Detected in ~50% of patients with C3 glomerulonephritis

C3G, C3 glomerulopathy; Ig-MPGN, Ig-mediated membranoproliferative glomerulonephritis.

Table ICMG2. Evaluation of abnormalities of the alternative pathway of complement*

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, CFHR-5
Plasma cell disorders†	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3 negative or minimal Ig, negative C4d)

Importance

1.Low C3 with normal C4 is hallmark of CAP activation that is found in %50 of C3G and Ig-MPGN patients

2.C3Nef is the most important autoantibodies

3. C3Nef are detected in %80 DDD and %50 of C3G and

% 40-54 Ig-MPGN

4.CAP dysregulation underlies the pathogenesis of C3G

5.Glomerular C4d staining positive in %80 of primary and secondary Ig-MPGN and only in %13 of C3G cases.

6.In Ig-MPGN and C3G classic and alternative pathways are activated; respectively.

Impact of compelement work up on management is limited.

Because :

1.Normal assays compelement do not rule out active C3G or MPGN

2.Clinical pathogenicity of autoantibodies is not clearly

3.No available complement biomarker accurately predicts the outcome

4.Pathogenic complement variants are detected in minority of patients(lower than %20)

Practical management of C3 glomerulopathy and Ig-mediated MPGN .KI

Renal transplantation

High rates of post-RT recurrence have been reported in patients with:

1.C3GN 60-86 %

2.DDD 55-86%

3.Ig-MPGN 42-53%

Factors associated with recurrence

1.Low C3 level at the time of transplantation

2.Presence of crescents in a native kidney biopsy

3.Presence of monoclonal protein

4.Living related donor

5.Preemtive transplantation

Practical management of C3 glomerulopathy and Ig-mediated MPGN .KI

Prognosis of MPGN type I

1.Renal survival 10 years is 65% without significant differences between treated and untreated patients.

2.Minority of patients may have a spontaneous remission

3.The best predictors of disease progression are kidney biopsy findings and e GFR

4.Risk factors for poor prognosis include :HTN ; Impaired GFR and cellular crescents in biopsy

Brenner2020

Prognosis of C3G

1.Prognosis for DDD is worse than type I MPGN

2.In DDD clinical remission are rare

3.Patient reech ESRD in 8-12 years from onset of disease

4.In DDD prognosis is worse in adults than in children

5.Prognosis of C3GN is poor but better than DDD

Brenner2020

Treatment Of MPGN type I

1.In patients with a defined underlying disease treatment should be directed at the underlying condition

2.In idiopathic MPGN type I the use of MMF and corticosteroids has been suggested

3.Using of anticoagulant or antiplatletes is contraversia

Brenner2020

Treatment of C3G

1.There is currently no widely agreed on treatment

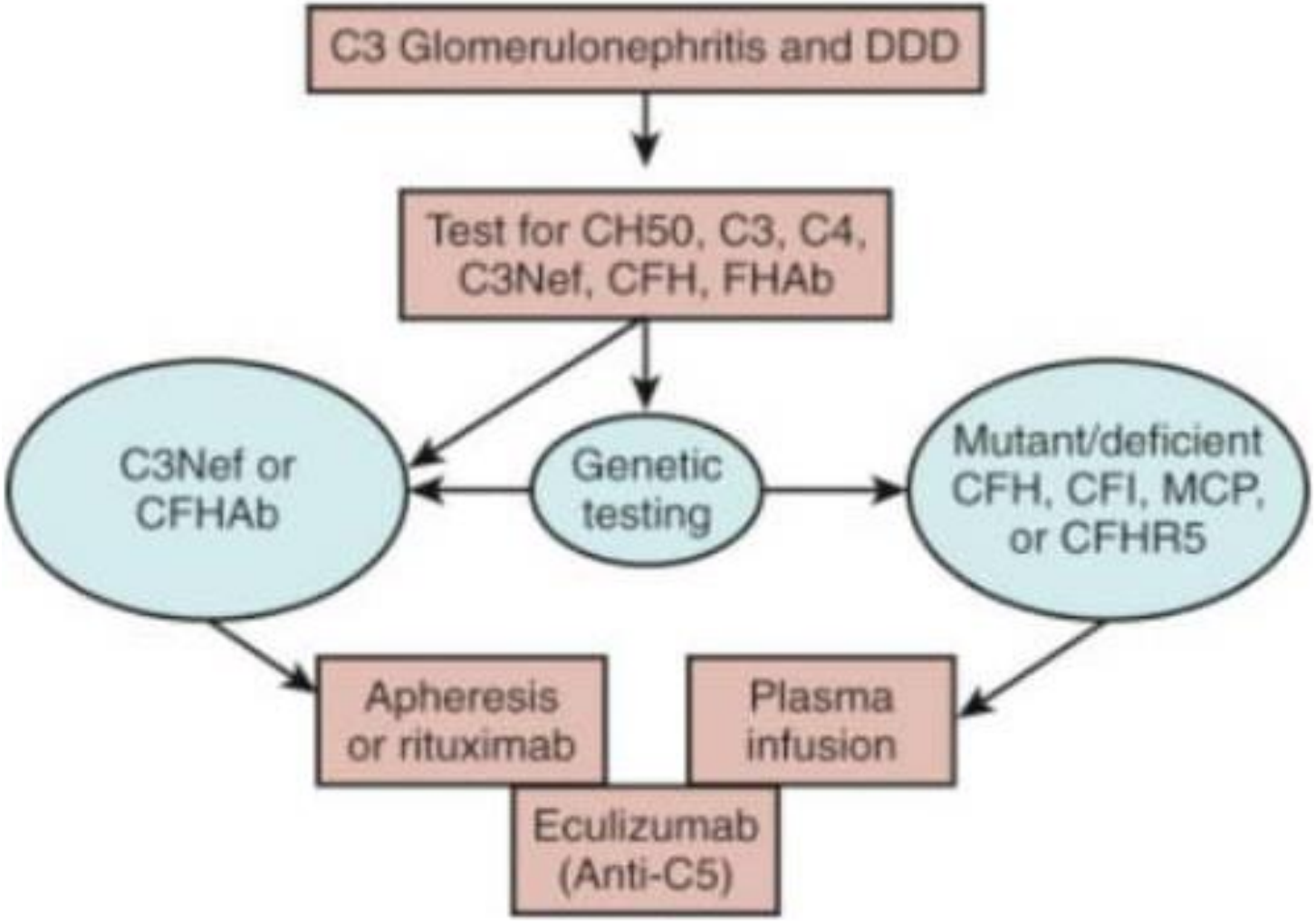
2. The use of corticosteroid therapy is probably not effective

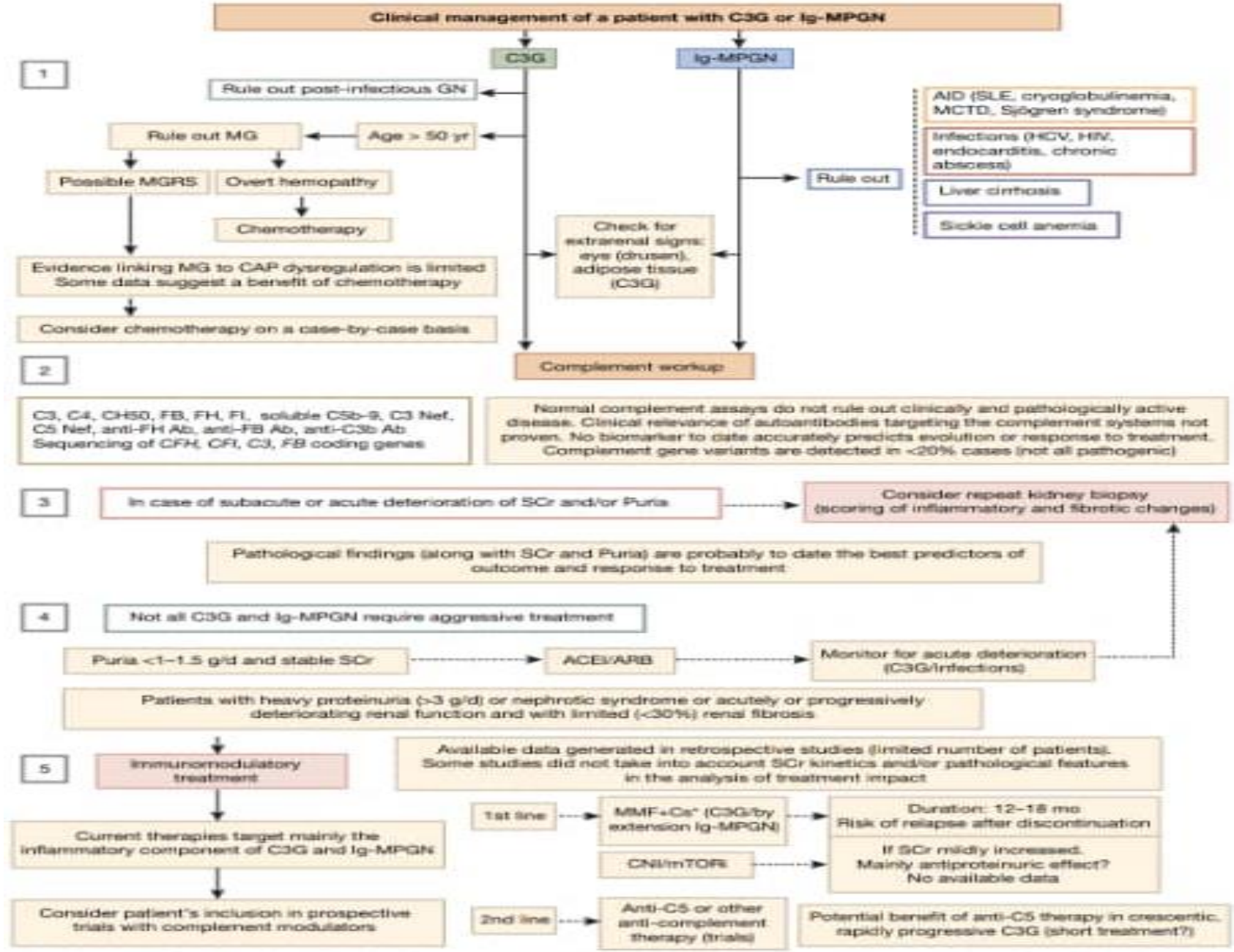
3.Immunosuppressive therapy with agents such as MMF and rituximab has been suggested

4.Patients with defined deficiency of complement factor H : FFP infusion every 2 weeks

5.Eculizumab by inhibition of C5 activation

Brenner2020


C3 Glomerulonephritis and DDD
Test for CH50, C3, C4, C3Nef, CFH, FHAb
C3Nef or CFHAb
Genetic testing
Mutant/deficient CFH, CFI, MCP, or CFHR5
Apheresis or rituximab
Plasma infusion
Eculizumab (Anti-C5)


Clinical management of a patient with C3G or Ig-MPGN
C3G
Ig-MPGN
1
Rule out post-infectious GN
Rule out MG
Age > 50 yr
Possible MGRS
Overt hemopathy
Chemotherapy
Evidence linking MG to CAP dysregulation is limited
Some data suggest a benefit of chemotherapy
Consider chemotherapy on a case-by-case basis
AID (SLE, cryoglobulinemia, MCTD, Sjögren syndrome)
Infections (HCV, HIV, endocarditis, chronic abscess)
Liver cirrhosis
Sickle cell anemia
Rule out
Check for extrarenal signs: eye (drusen), adipose tissue (C3G)
2
Complement workup
C3, C4, CH50, FB, FH, FI, soluble C5b-9, C3 Nef, C5 Nef, anti-FH Ab, anti-FB Ab, anti-C3b Ab
Sequencing of CFH, CFI, C3, FB coding genes
Normal complement assays do not rule out clinically and pathologically active disease. Clinical relevance of autoantibodies targeting the complement systems not proven. No biomarker to date accurately predicts evolution or response to treatment.
Complement gene variants are detected in <20% cases (not all pathogenic)
3
In case of subacute or acute deterioration of SCr and/or Puria
Consider repeat kidney biopsy (scoring of inflammatory and fibrotic changes)
Pathological findings (along with SCr and Puria) are probably to date the best predictors of outcome and response to treatment
4
Not all C3G and Ig-MPGN require aggressive treatment
Puria <1–1.5 g/d and stable SCr
ACEi/ARB
Monitor for acute deterioration (C3G/infections)
Patients with heavy proteinuria (>3 g/d) or nephrotic syndrome or acutely or progressively deteriorating renal function and with limited (<30%) renal fibrosis
5
Immunomodulatory treatment
Available data generated in retrospective studies (limited number of patients).
Some studies did not take into account SCr kinetics and/or pathological features in the analysis of treatment impact
Current therapies target mainly the inflammatory component of C3G and Ig-MPGN
1st line
MMF+Cs* (C3G/by extension Ig-MPGN)
Duration: 12–18 mo
Risk of relapse after discontinuation
CNI/mTORi
If SCr mildly increased.
Mainly antiproteinuric effect?
No available data
Consider patient's inclusion in prospective trials with complement modulators
2nd line
Anti-C5 or other anti-complement therapy (trials)
Potential benefit of anti-C5 therapy in crescentic, rapidly progressive C3G (short treatment?)

Treatment of ICGN on basis KDIGO 2020

1.Indolent disease :should be treated with RASi alone

2.Proteinuria < 3.5 g/d and normal e GFR : supportive therapy with RASi alone

3.Nephrotic syndrome and normal e GFR: Treatment with prednisolone 1mg/kg/d for 3-4 months.

Patients who respond: Gradually tapering over 6-8 months.

If there is < %30 reduction in proteinuria: taper and discontinue.

Patient with a contraindication for corticosteroides :Treatment with CNI

KDIGO2020

4.Abnormal kidney function without cresent; active urine sediment :Add corticosteroids and immunosuppressive therapy to supportive care.

Satisfactory response to 1mg/kg/d prednisolone for 3-4 months:Gradually taper and discontinue.

Unsatisfactory response: Reduce dose of prednisolone to

20 mg/d and add MMF.

If no response to prednisolone and MMF after 6-12 months : Discontinue therapy and repeat kidney biopsy.

If kidney biopsy show active GN : consider using cyclophosphamide or rituximab .

5.Rapid progressive crescentic GN :Treat with high dose corticosteroids and cyclophosphamide or rituximab.

6. e GFR<30 without active necrotizing crescentic GN : Supportive care alone .

Treatment of C3G on basis KDIGO 2020

1.An optimal treatment strategy for C3G has not been established

2. Moderate to severe C3G : Should be treated initially with MMF; and if this fails eculizumab.

3.We consider using eculizumab in patients with progressive disease who fail to respond to other therapies.

4.Patient who fail to respond to the treatment approaches discussed; should be considered for a clinical trial

KDIGO2020

Conclusion

1.Several uncertainties surrounding the complement biomarkers and current treatment remain

2.Future studies should be about complement –targeted drugs