
بسم الله الرحمن الرحيم

MPGN and related disorders

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NEPHROLOGY - ORIGINAL PAPER

Renal biopsy findings in Iran: case series report from a referral kidney center

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Table 1 Frequency of different pathologic diagnoses in 1,407 renal biopsy specimens

Pathologic category and diagnosis	Frequency (No.)	Percentage of all	Percentage of subgroup
Primary glomerular disease			
Membranous glomerulopathy	377	26.8	35.8
IgA nephropathy	155	11.0	14.7
Focal segmental GS (FSGS)	141	10	13.4
Minimal change disease (MCD)	117	8.3	11.1
Diffuse crescentic GN	81	5.8	7.7
Membranoproliferative GN	77	5.5	7.3
Chronic GN	39	2.8	3.7
MCD versus FSGS	24	1.7	2.3
Proliferative GN	21	1.5	2
Mesangial proliferative GN	13	0.9	1.2
Others	7	0.5	0.7
Total	1,052	74.8	100

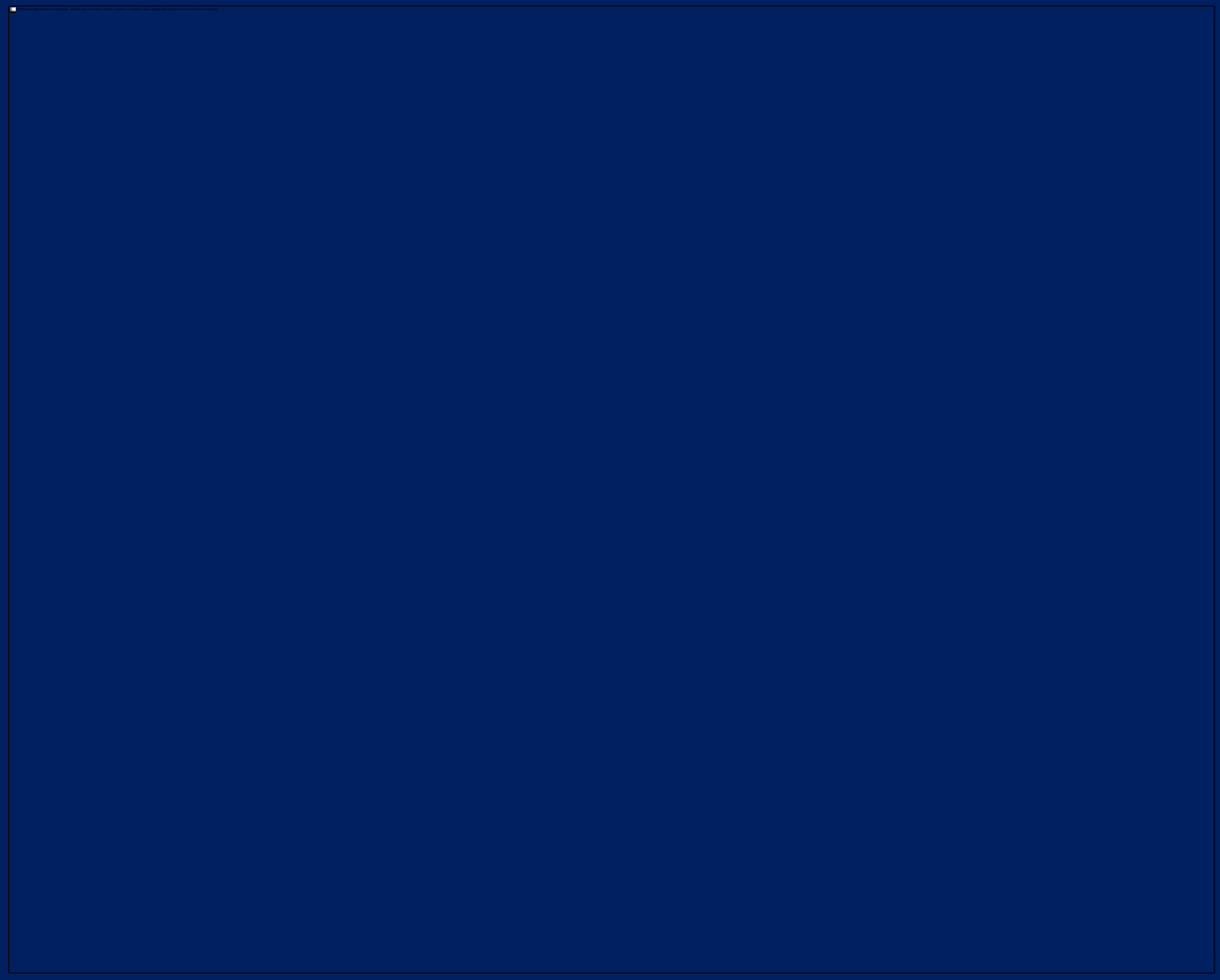
MPGN

- Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury .
- The clinical presentation is similar to that in other types of glomerulonephritis.

MPGN

- The typical features of MPGN on light microscopy include mesangial hypercellularity, endocapillary proliferation, and capillary-wall remodeling (with the formation of double contours) — all of which result in lobular accentuation of the glomerular tufts.
- These changes result from the deposition of immunoglobulins, complement factors, or both in the glomerular mesangium and along the glomerular capillary walls.

showing thickening of all capillary walls with double contours (long arrows and focal areas of cellular proliferation (short arrow)



Electron-microscopical findings

- MPGN I, the most common form, is characterized by subendothelial deposit.
- MPGN III has both subepithelial and subendothelial deposits
- MPGN II is characterized by dense deposits in the glomerular basement membrane (“dense-deposit disease”).

MPGN type I

- MPGN type I is the most commonly seen subclass.
- Typically well-defined double contours are seen by light microscopy and EM reveals mesangial and subendothelial electron-dense deposits with new subendothelial basement membrane and frequent mesangial cell interposition.

Electron micrograph of a normal glomerulus

Electron microscopy in type I membranoproliferative glomerulonephritis

Marked thickening of the glomerular capillary wall by immune deposits and by interposition of mesangial cell processes .

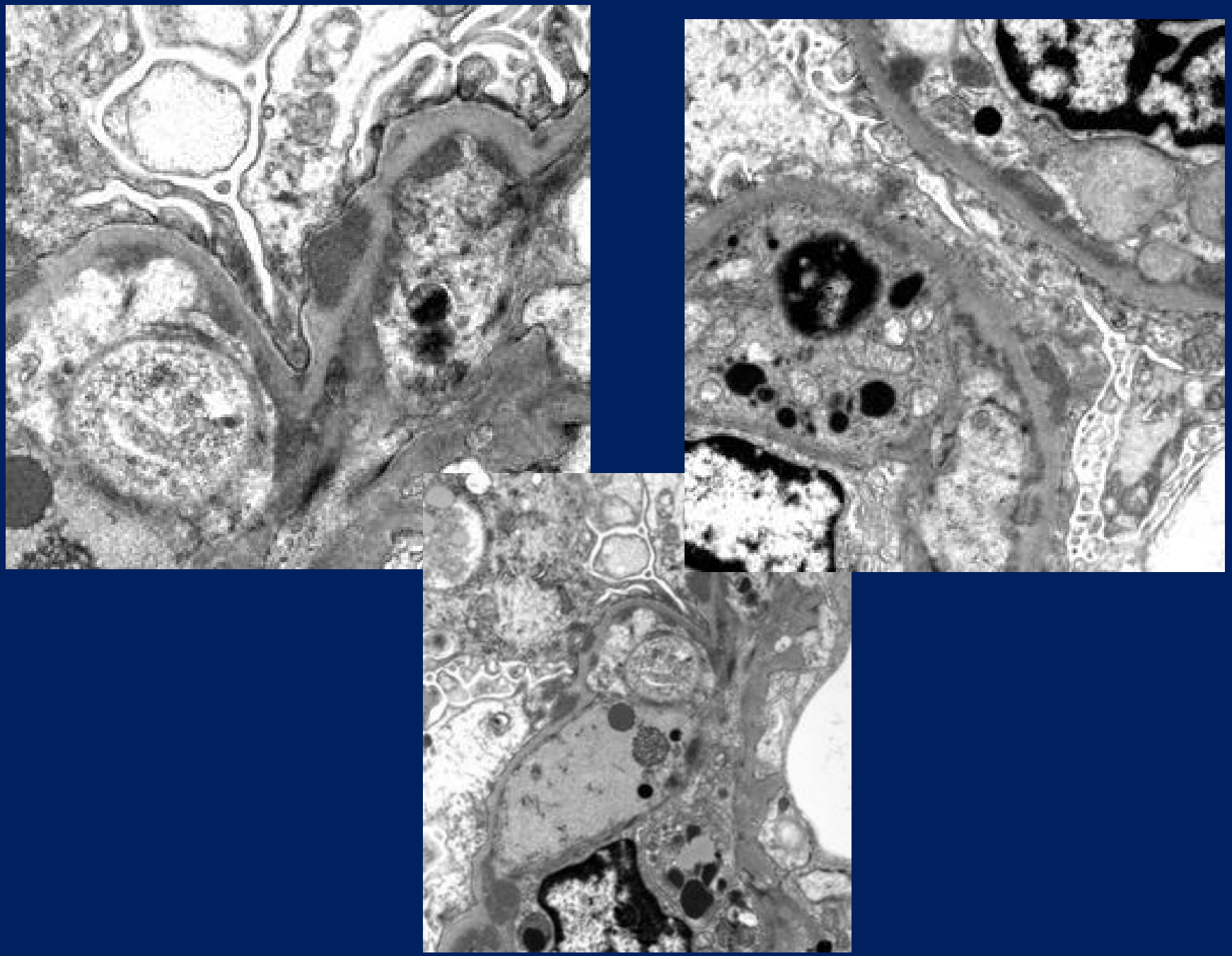
MPGN type II

- MPGN type II was first recognized in 1963 as a form of MPGN with a distinctive EM appearance.
- Extremely electron-dense material that fills and expands the glomerular basement membrane Dense deposit disease (DDD).

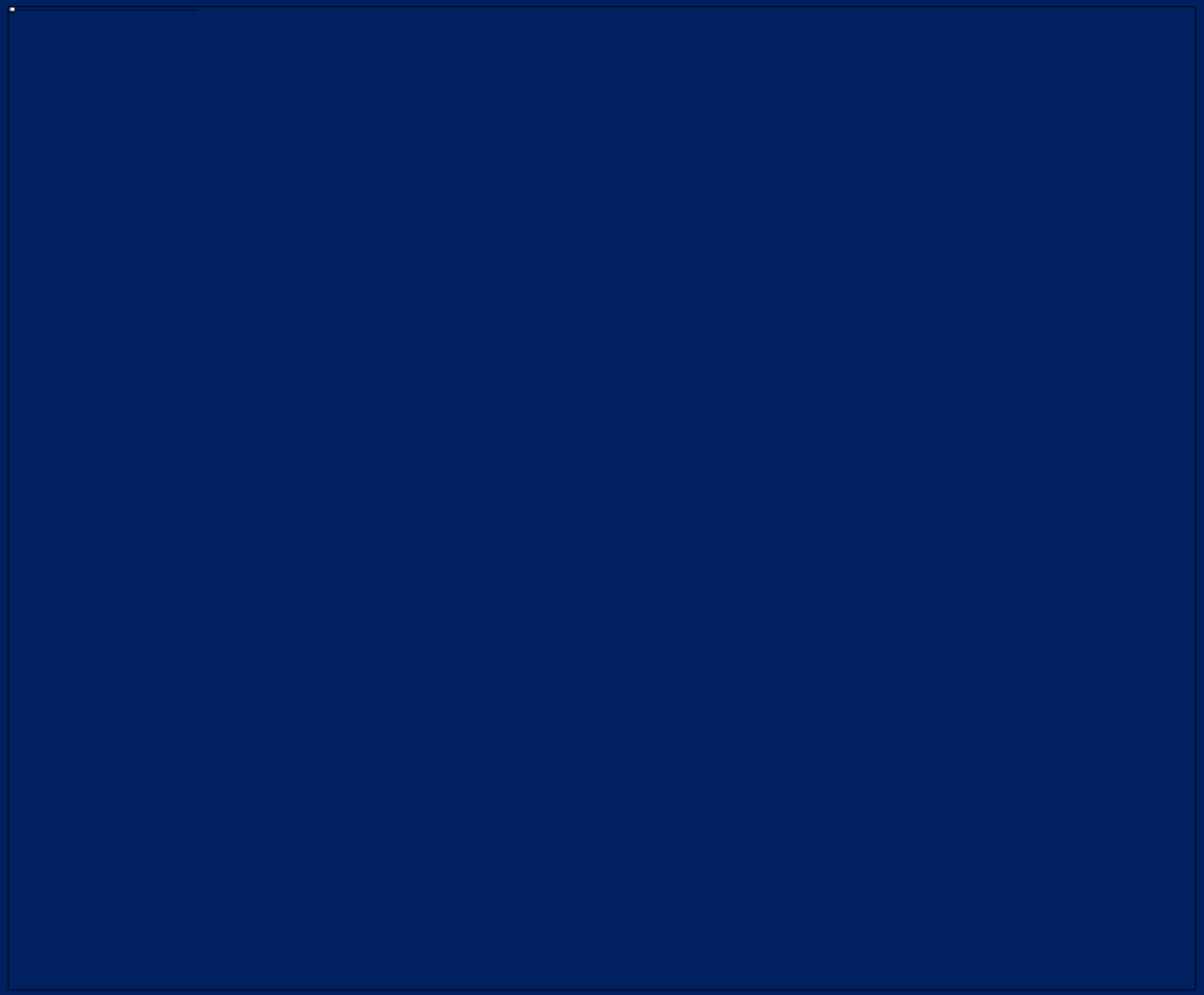
Electron micrograph in dense deposit disease (DDD) showing dense, ribbon-like appearance of subendothelial and intramembranous material (arrow) and narrowing of the capillary lumen due to proliferation of cells (double arrow).

MPGN type III

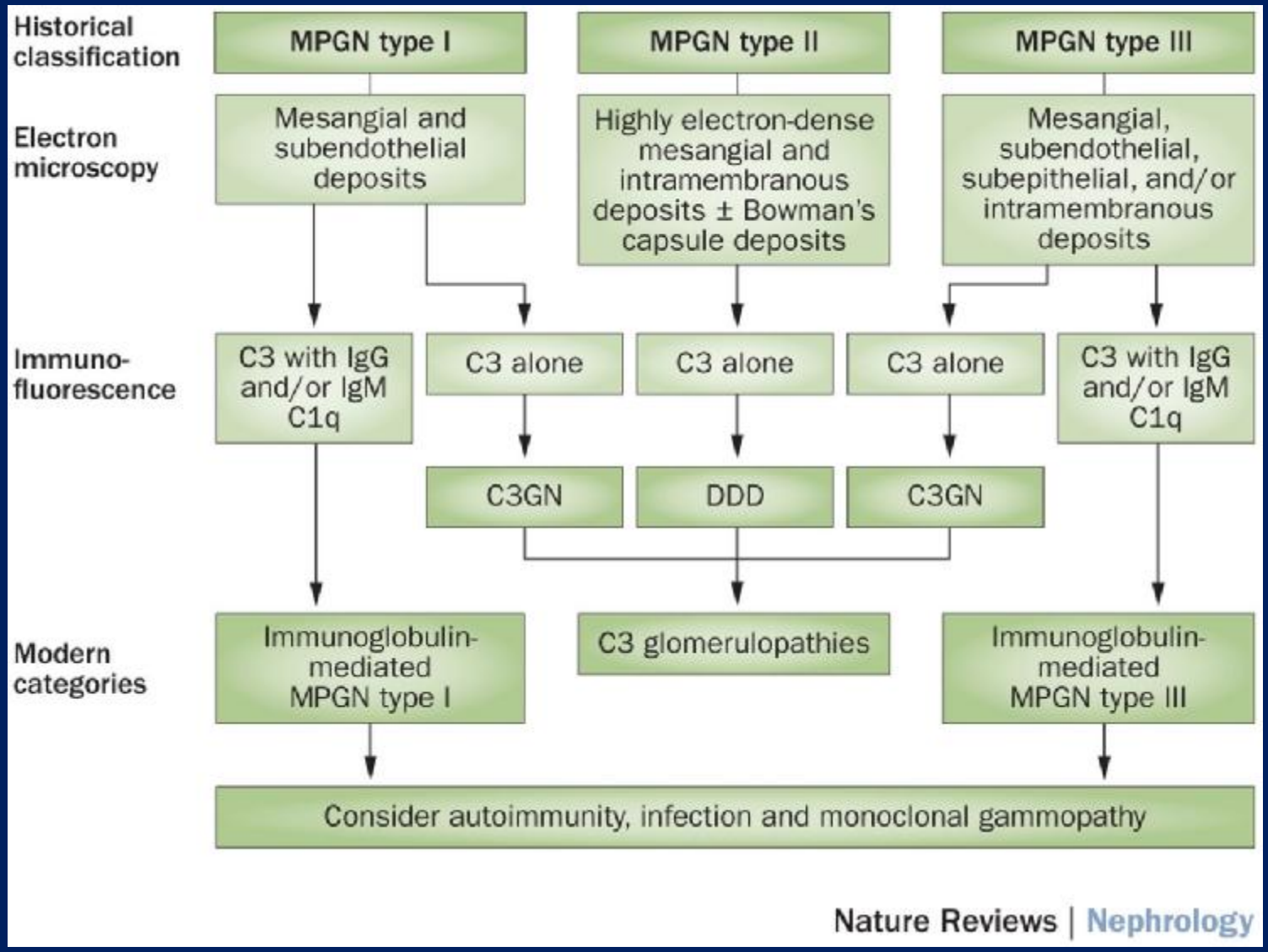
- In the Burkholder variant of MPGN type III, subepithelial immune deposits in addition to subendothelial and mesangial deposits are present.
- The other variant of MPGN type III is known as the Strife and Anders variant. It shows extensive glomerular capillary wall thickening by EM with multilayering and complex disruption of the glomerular basement membrane[1]



The older ultrastructural classification of MPGN based on the extent and site of electron-dense deposits (MPGN type I, II, III, *etc.*) is now being replaced with a more mechanistic classification based on the presence of Ig (polyclonal or monoclonal) and/or C3 deposits by immunofluorescence microscopy. This new classification system recognizes the diversity of pathogenic factors responsible for the light microscopy pattern of MPGN.



The relationship between historical and modern classification of glomerulonephritis with membranoproliferative morphology



D'Agati, V.D. & Bomback, A.S. *Kidney Int.* **82**, 379-381 (2012)

Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies
Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.217

C3 glomerulonephritis

- C3 glomerulonephritis (C3GN) was first described in 2007 in a clinicopathologic and genetic study of 19 patients .
- The term "C3 glomerulopathy" was introduced to encompass all glomerular lesions with predominant C3 accumulation .
- Thee are two varients ;DDD and C3GN.
- Like DDD, C3GN is characterized by isolated deposits of C3 on immunofluorescence but instead of dense intramembranous deposits as in DDD electron microscopy reveals subendothelial and mesangial electron-dense deposits . In some cases, subepithelial deposits can also be seen.

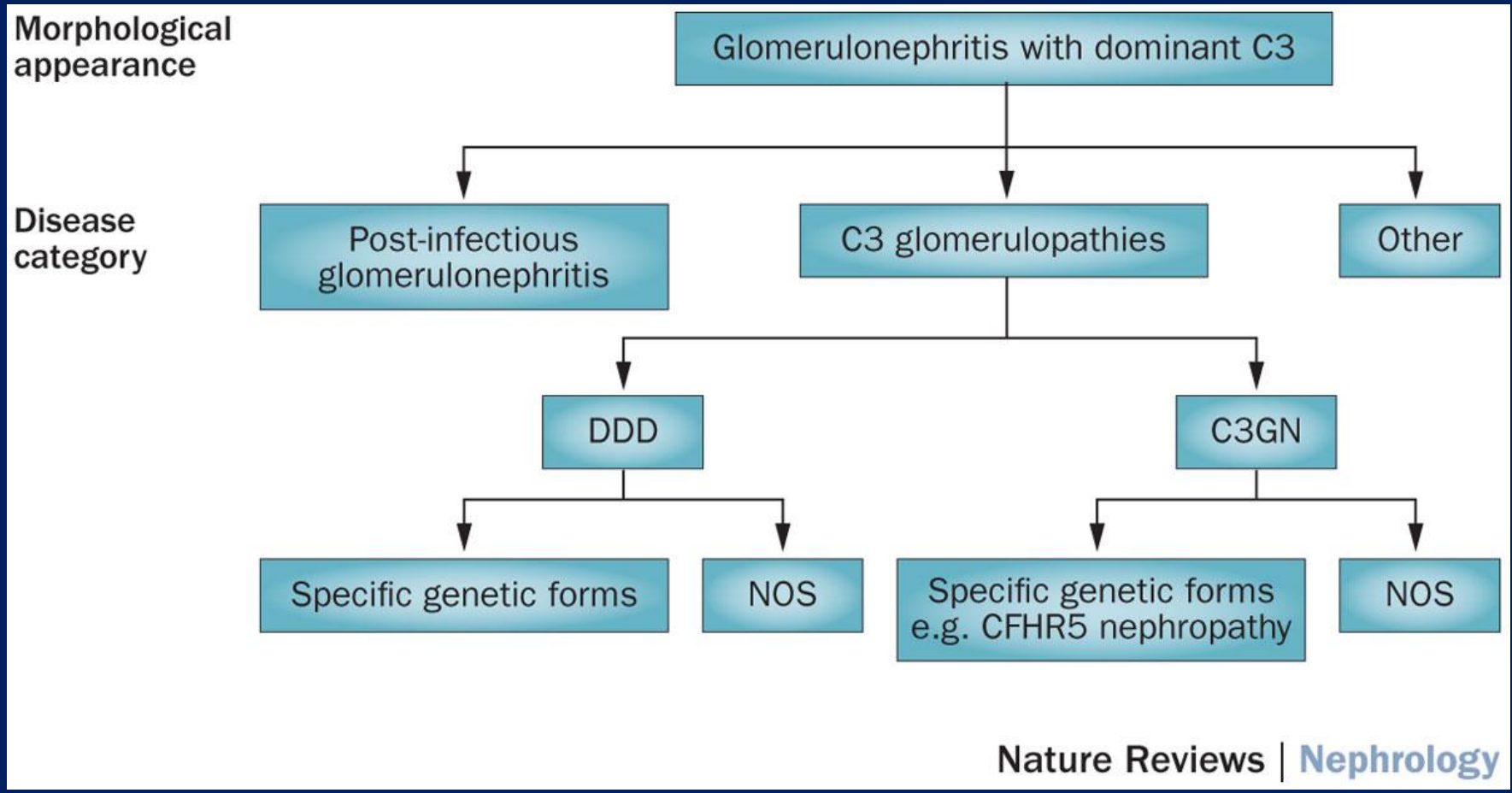
Immunofluorescence micrographs stained for IgG (A) and C3 (B) in a case of C3 glomerulonephritis. Note the weak or absent staining for IgG and strong glomerular capillary wall staining for C3

Electron micrograph in dense deposit disease (DDD) showing dense, ribbon-like appearance of subendothelial and intramembranous material (arrow) and narrowing of the capillary lumen due to proliferation of cells (double arrow).

Electron microscopy of a glomerulus in a patient with C3 glomerulonephritis

Electron micrograph in C3 glomerulonephritis showing subendothelial electron-dense deposits (arrows). Mesangial deposits are also present in C3 glomerulonephrit

An approach to the classification of disease in a biopsy sample showing the morphological changes of a glomerulonephritis with dominant C3



Pickering, M. C. et al. *Kidney Int.* **84**, 1079-1089 (2013)

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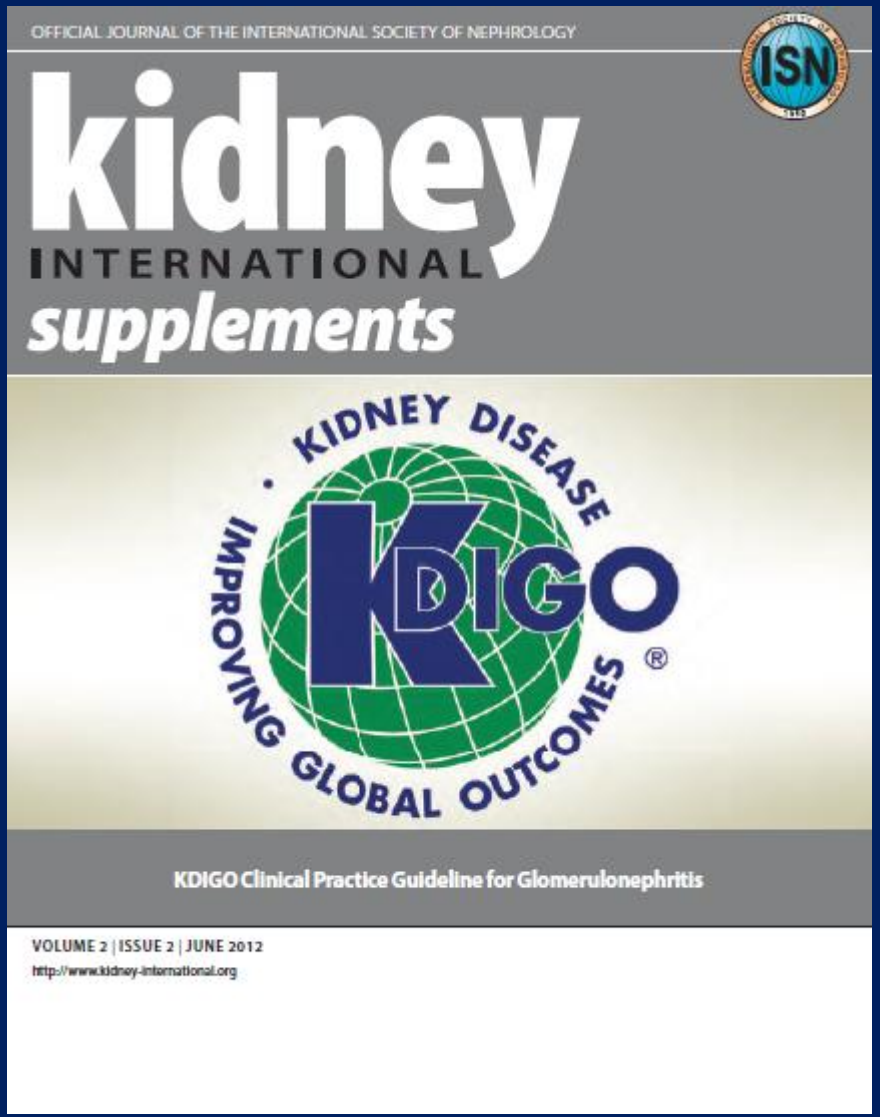
Table 5. Evaluation of patients with an optical microscopic lesion of membranoproliferative GN, based on immunofluorescence microscopy

Ig and C3 Immunofluorescence Pattern	Diagnostic Evaluation Strategy	Associated Disorders	Comment
Polyclonal Ig^+ and $C3^+$	Evaluate for "immune complex" disorders	Lupus nephritis Chronic viral infections: HCV or others Cryo-immunoglobulinemia Occult chronic infections: bacterial, protozoal, fungal, or helminthic infections	IgAN is very rarely present
Monoclonal Ig^+ and $C3^+$	Evaluate for underlying B cell neoplasia	Multiple myeloma B cell lymphoma Light chain deposition disease	
Ig^- or trace + and C3 (dominant)	Evaluate for C3 glomerulopathy	Dense deposit disease or C3GN, depending on electron microscopic appearance	Older adults should also undergo evaluation for an underlying B cell neoplasia If "humps" present by electron microscopy, evaluate for "atypical postinfectious GN"
Ig^- or trace and $C3^-$	Evaluate for underlying chronic thrombotic microangiopathy		

Modified with permission from Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 366: 1119–1131, 2012; Hou J, Markowitz GS, Bomback AS, Appel GB, Herlitz LC, Barry Stokes M, D'Agati VD: Toward a working definition of C3 glomerulopathy by immunofluorescence. *Kidney Int* 85: 450–456, 2014; Sethi S, Nester CM, Smith RJ: Membranoproliferative glomerulonephritis and C3 glomerulopathy: Resolving the confusion. *Kidney Int* 81: 434–441, 2012; and Fervenza FC, Sethi S, Glassock RJ: Idiopathic membranoproliferative glomerulonephritis: Does it exist? *Nephrol Dial Transplant* 27: 4288–4294, 2012. IgAN, IgA nephropathy; HCV, hepatitis C virus.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VOLUME 2 | ISSUE 2 | JUNE 2012
http://www.kidney-international.org

8.1: Evaluation of MPGN

8.1.1: Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (*Not Graded*)

8.2: Treatment of idiopathic MPGN

8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome *AND* progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

General measures

- Patients with idiopathic MPGN, DDD and C3GN who have hypertension and proteinuria (more than 500 to 1000 mg/day) receive an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) .
- These patients with should also be evaluated and treated for dyslipidemia to lower the risk of cardiovascular disease.

Mild disease

In patients with mild disease characterized by hematuria, mild proteinuria (ie, less than 500 mg/day), and normal kidney function, suggestion is general measures alone rather than therapy with plasma infusion, rituximab, or eculizumab .

Use these other therapies only if the clinical status worsens.

Moderately severe disease

In patients with more severe proteinuria, nephrotic syndrome, and/or azotemia (but not rapidly progressive disease), treatment is based upon the underlying etiology, if known.

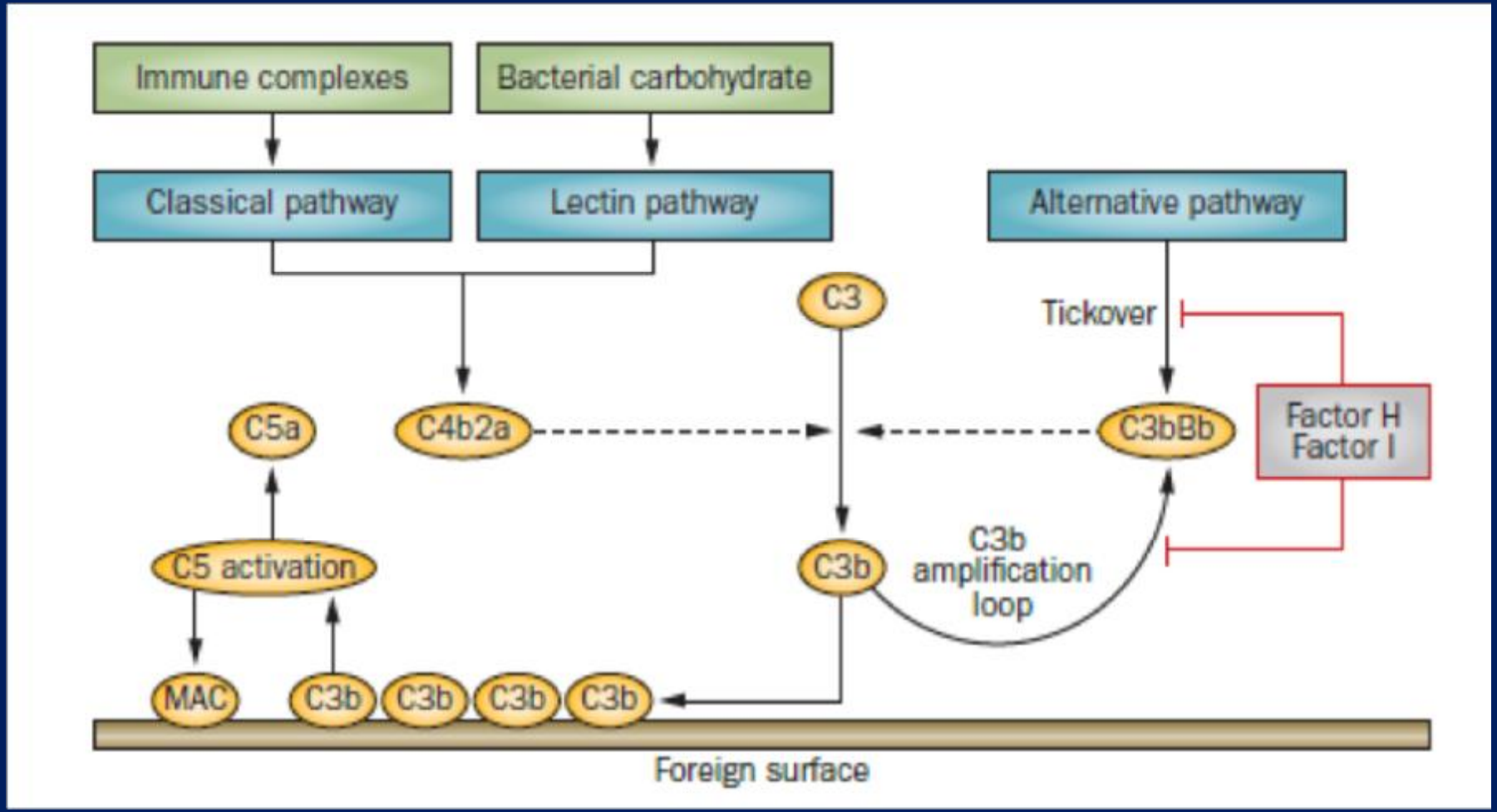
Corticosteroids and MMF,CTX are usually recommended.

Patients with rapidly deteriorating renal function

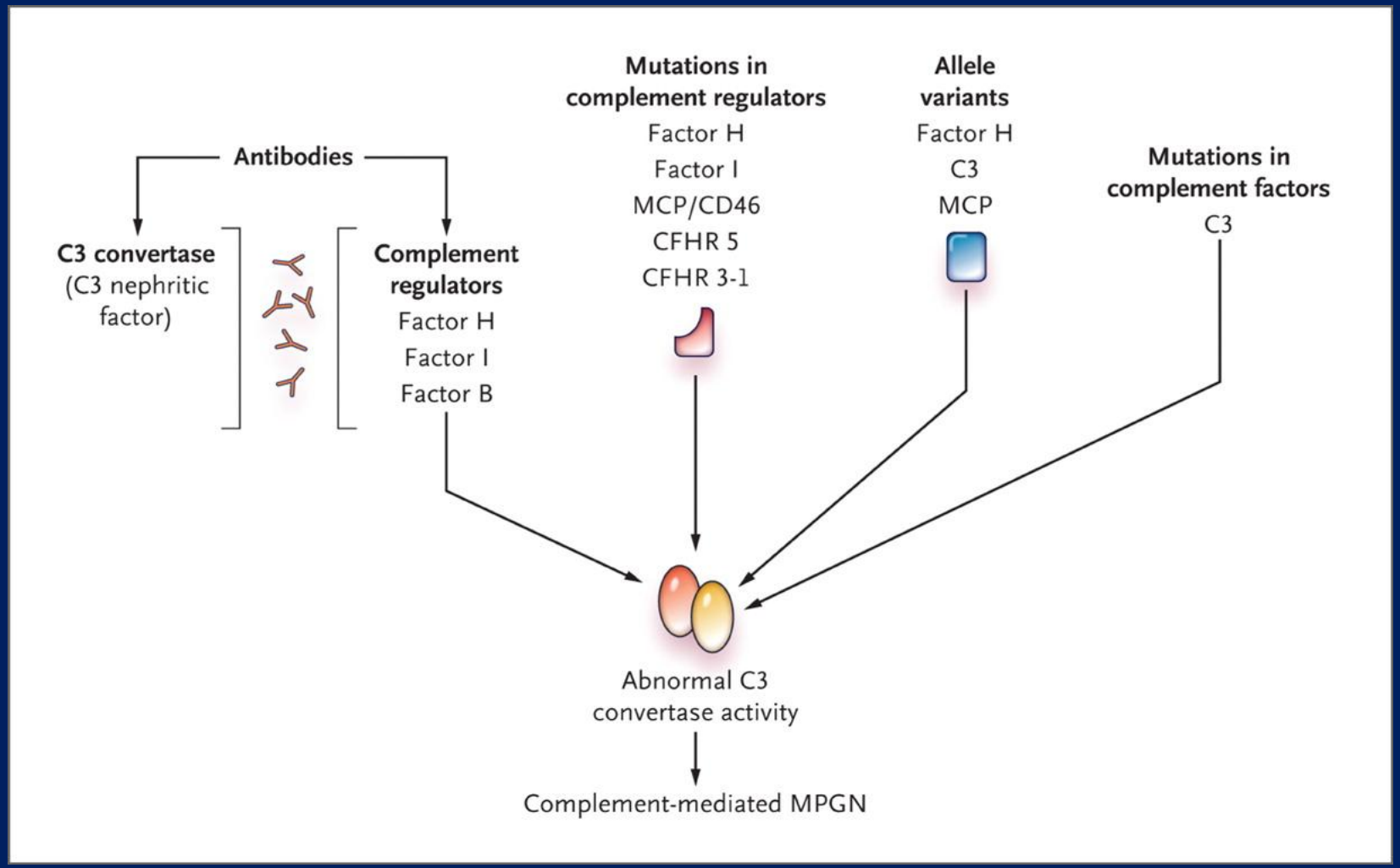
In patients with rapidly progressive disease (eg, crescentic glomerulonephritis), suggestion is immunosuppressive therapy with glucocorticoids in combination with either cyclophosphamide or mycophenolate mofetil .

Some would also treat such patients with plasma exchange in addition to immunosuppressive therapy.

In patients with a genetic serum factor deficiency, they would treat with periodic FFP infusion after remission is achieved.


Immune complexes
Bacterial carbohydrate
Classical pathway
Lectin pathway
Alternative pathway
C3
Tickover
C5a
C4b2a
C3bBb
Factor H
Factor I
C5 activation
C3b
C3b
amplification
loop
MAC
C3b
C3b
C3b
C3b
Foreign surface

Acquired and Genetic Abnormalities Associated with Complement-Mediated MPGN.



Sethi S, Fervenza FC. N Engl J Med 2012;366:1119-1131.

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Disease due to an autoantibody

- In patients whose disease is presumably due to a circulating autoantibody, for example, C3NeF or an anti-factor H antibody, there is no consensus among the authors and reviewers of this topic. Suggestion is that initial therapy include plasma exchange, rituximab, or eculizumab rather than other therapies such as glucocorticoids .
- Disease due to a genetic deficiency for example, inherited factor H deficiency, periodic infusions of fresh frozen plasma (FFP) to replace the missing or mutant protein may be helpful.
- Disease due to a genetic activating mutation in C3 , plasma exchange , which theoretically can remove the abnormal C3 protein and replace it with a normal protein that can be inactivated by factor H.
- If diagnostic tests are unavailable and the underlying etiology cannot be identified. In such patients, we suggest a trial of plasma infusion .


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