بسم الله الرحمن الرحیم

C3 glomerulopathy

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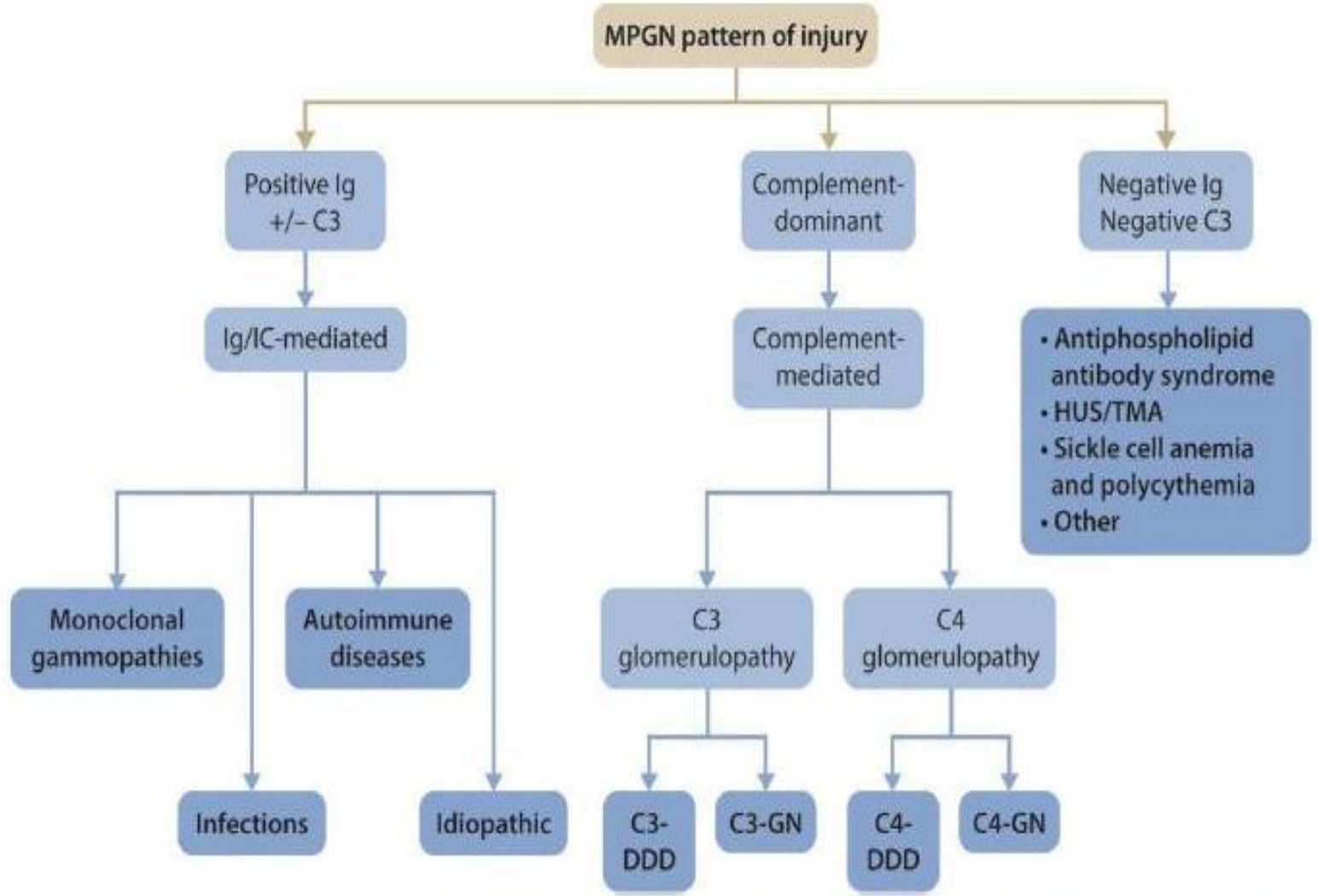


Figure 19| Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolyt uremic syndrome; IC, immune complex; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

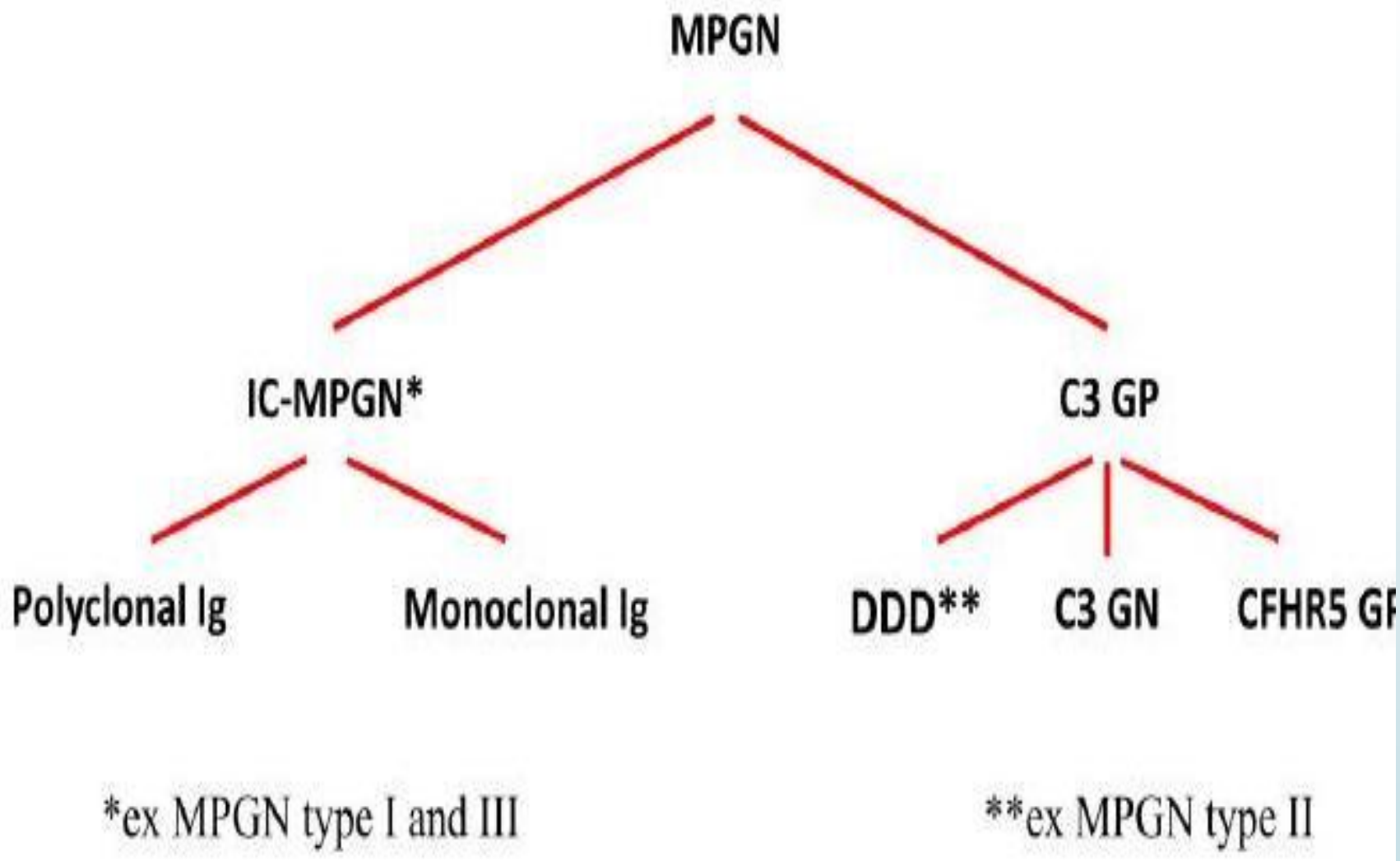
Introduction

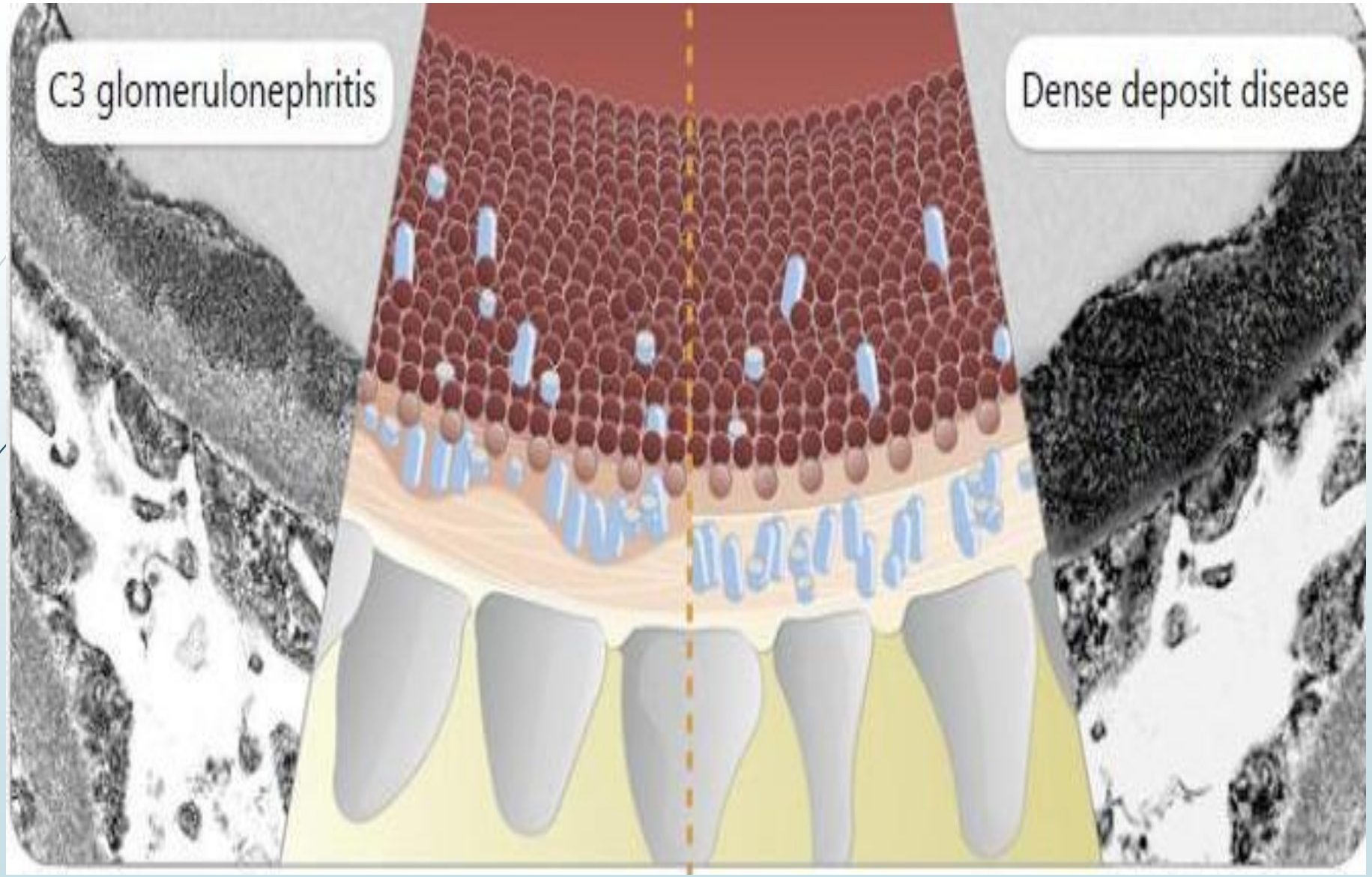
- Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) are rare forms of glomerulonephritis that affect both children and adults.
- Both diseases result from abnormal regulation of the alternative complement pathway and are classified under the heading of "C3 glomerulopathies."
- The clinical presentation is variable, and the diagnosis is made by immunofluorescence examination of a kidney biopsy specimen, supplemented by studies of the complement system.

Morphological classification of C3 glomerolupathies

DDD – The term "dense deposit disease" reflects the characteristic appearance of linear-appearing, highly electron-dense material in the glomerular basement. membrane (GBM) observed on kidney biopsy electron microscopic examination Historically, DDD was classified as a subgroup of primary membranoproliferative glomerulonephritis (MPGN type II), but it has been reclassified as a complement-mediated glomerular disease.

C3GN – First described in 2007, C3GN is characterized by isolated deposits of C3 on immunofluorescence , but instead of dense intramembranous deposits as in DDD , electron microscopy reveals predominant subendothelial and mesangial electron-dense deposits of lesser intensity . In some cases, subepithelial deposits can also be seen.


MPGN
IC-MPGN*
C3 GP
Polyclonal Ig
Monoclonal Ig
DDD**
C3 GN
CFHR5 GN
*ex MPGN type I and III
**ex MPGN type II


C3 glomerulonephritis
Dense deposit disease

Epidemiology

- The C3 glomerulopathies are rare, with an estimated incidence of one to three cases per million and point prevalence of 14 to 140 cases per million.
- DDD is primarily, although not exclusively, a disease of children. The age range at diagnosis extends into adulthood.
- By contrast, patients with C3GN are generally older. *C3 glomerulopathy is also occasionally diagnosed in older adults, the majority of whom have been found to have an underlying monoclonal gammopathy.* DDD appears to affect both sexes equally although the data vary from study to study

Pathogenesis

The major defect underlying DDD and C3GN is excessive activation of the alternative complement pathway. This results in the deposition of multiple complement components in the glomerulus. The mechanism by which complement deposition leads to dense deposit formation or to the clinical manifestations of glomerulonephritis has not been established but most likely involves chemotaxis of leukocytes and possibly the cytolytic effects of C5b-9 (also called the membrane attack complex of complement or MAC).

Pathogenesis

The alternative complement pathway is normally autoactivated by low-level, spontaneous cleavage of C3 to C3b, which leads to the formation of the C3 convertase by the binding of factor B and properdin . The C3 convertase (C3bBb) amplifies the cascade by enzymatically cleaving more C3 in addition to generating the downstream C5 convertase ($[C3b]_2Bb$). The C5 convertase cleaves C5 to the potent chemoattractant C5a and initiates assembly of C5b-9.

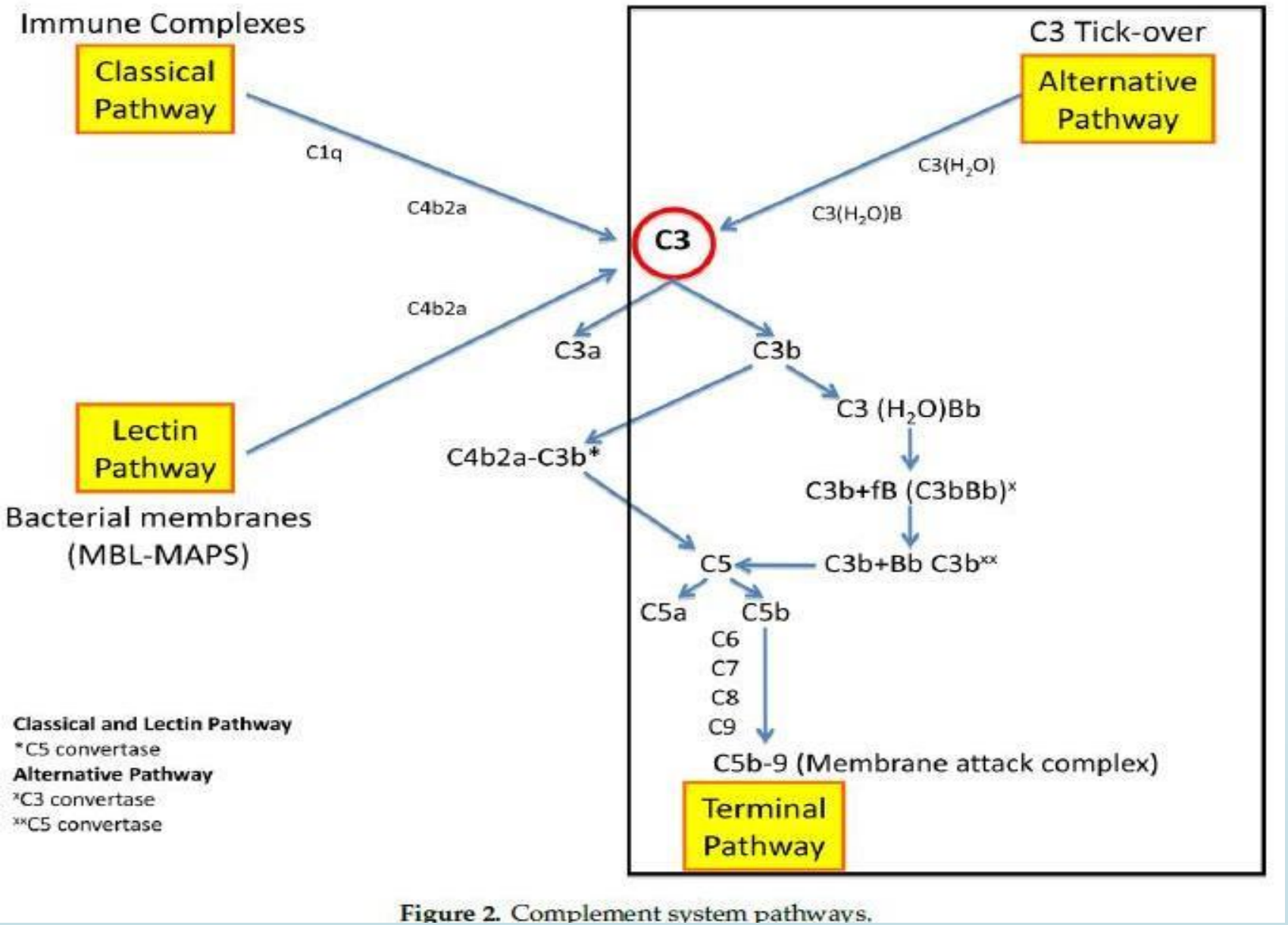
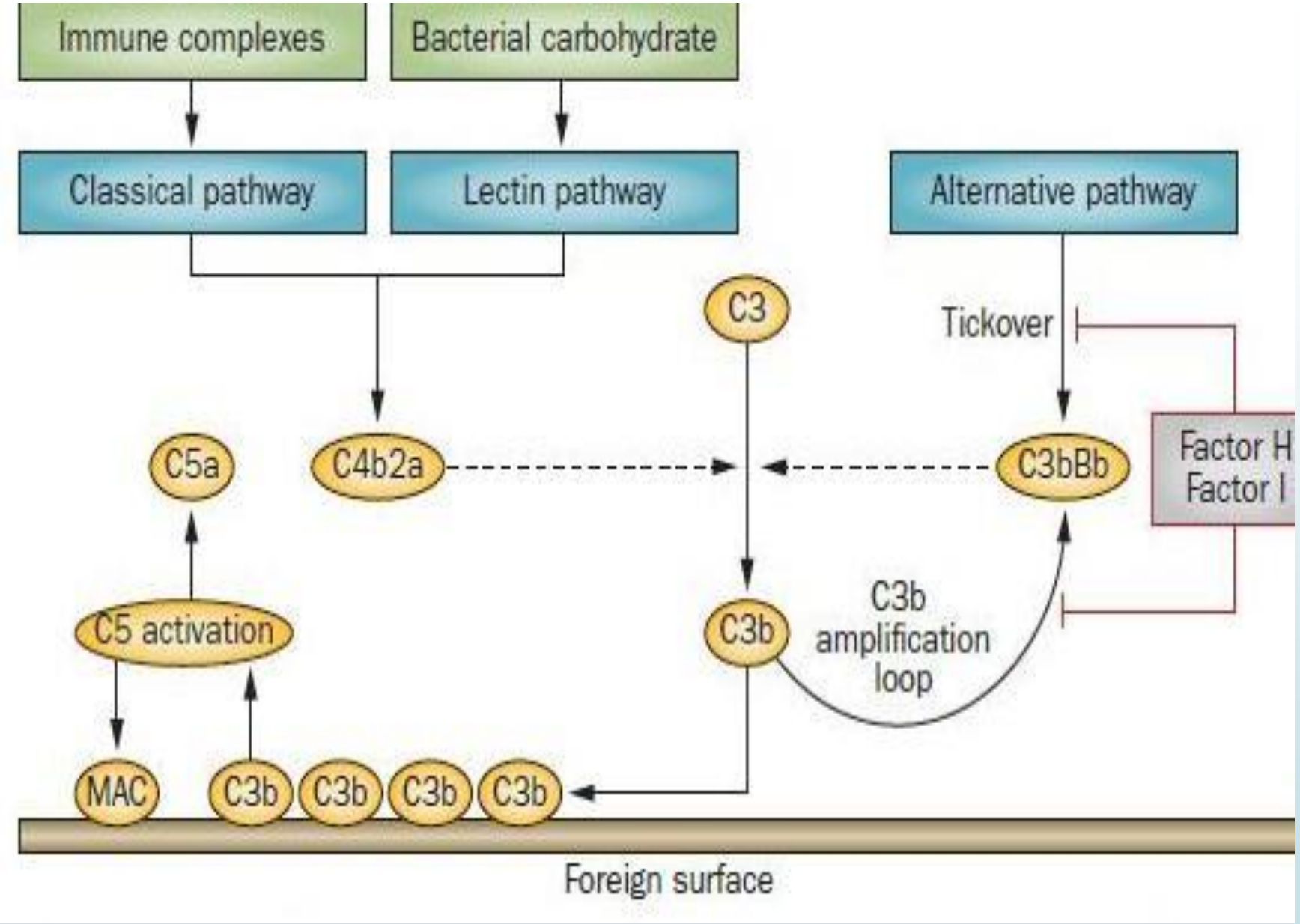


Figure 2. Complement system pathways.


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

Pathogenesis

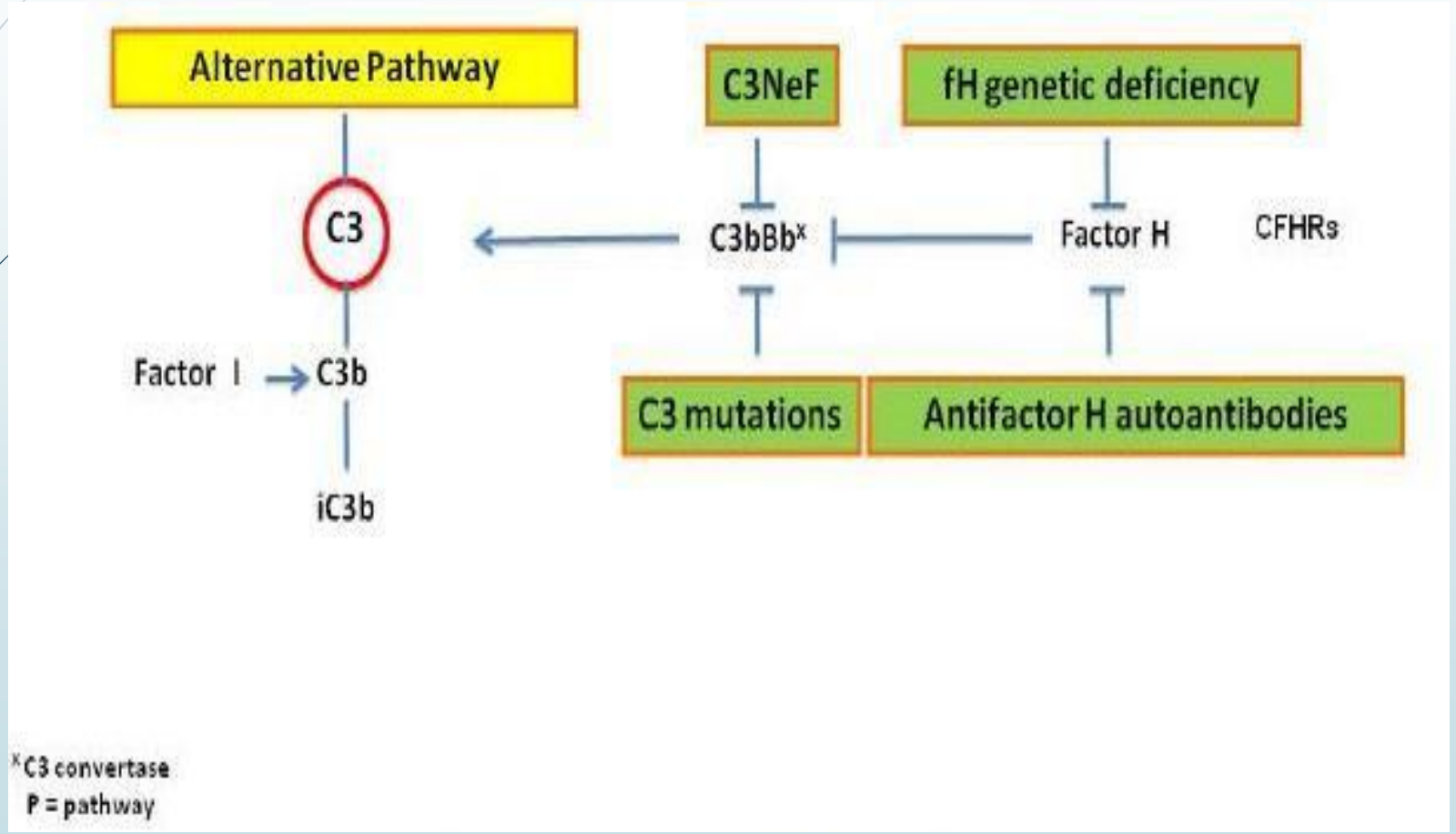
Normally, the activity of this pathway is tightly regulated and directly related to the activity of the C3 convertase . The serum protein factor H regulates the activity of the alternative pathway in the fluid phase by directly promoting the decay of the C3 and C5 convertases. Factor H also combines with the regulator factor I to bind and rapidly inactivate free C3b.

The alternative pathway is tightly regulated on cell surfaces by membrane cofactor protein (MCP, also called CD46), complement receptor 1 (CR1), and decay accelerating factor (DAF, also called CD55). CR1 also combines with factor I to bind and inactivate cell surface C3b.

Pathogenesis

Deregulation of the complement alternative pathway in C3 glomerulopathy is most commonly induced by autoantibodies that stabilize C3 convertase or are directed against other complement regulatory proteins and less commonly by an inherited defect. Some patients are found to have more than one abnormality.

Schematic dysregulation of the C3 activation in C3 GP



C3 nephritic facors(C3NeF)

- Generation of C3 convertase stabilizing autoantibodies called C3NeFs, usually of the immunoglobulin G class. C3NeF is found in 80 percent of patients with DDD and somewhat less often in patients with C3GN but is not unique to these patients. C3NeF has also been found in the serum of healthy individuals, in those with meningococcal disease, and in patients with acquired partial lipodystrophy (APL).
- In some patients, the activity of the terminal complement pathway is increased by a C5 convertase stabilizing autoantibody called C5 nephritic factor (C5NeF). Patients may have C3NeF alone or a combination of C3NeF and C5NeF autoantibodies. C5NeF-positive patients are more likely to have higher levels of C5b-9 and are more likely to have C3GN than DDD .

Loss of regulator activity

Factor H normally inhibits the C3 convertase and activated C3 (C3b). Loss of functional factor H activity can result from the following inherited or acquired defects:

- Autoantibodies to factor H that inhibit its action on C3b
- Monoclonal immunoglobulins that inhibit factor H
- Hereditary deficiency of factor H from particular mutations
- Familial mutations in complement factor H-related proteins, which compete with factor H for binding to C3b

- Although case studies have implicated autoantibodies and genetic mutations in the pathogenesis of the C3 glomerulopathies*, it is important to recognize that the causality of C3NeFs is still unresolved, that their presence does not always correlate with disease activity,* and that most patients with DDD or C3GN do not have disease-causing mutations in the factor H, C3, or other complement genes.
- It is possible that subtle differences in factor H levels or activity confer a risk for C3 glomerulopathy since several allelic variants of the factor H gene and a closely related gene, complement factor H related 5 (*CFHR5*), have been associated with DDD.

Urinary abnormality

- All patients with DDD and C3GN have proteinuria and/or hematuria. The degree of proteinuria is variable and may be nephrotic range.
- Patients with DDD may present with the acute nephritic syndrome (16 to 38 percent), isolated macroscopic hematuria (21 to 36 percent), nephrotic syndrome (12 to 55 percent), microscopic hematuria with sub-nephrotic-range proteinuria (15 percent), and isolated proteinuria (15 to 41 percent) . DDD may also be associated with sterile pyuria .
- Patients with C3GN may present with hematuria and proteinuria and preserved kidney function (41 percent), nephrotic syndrome (33 percent), or, less commonly, acute kidney injury or rapidly progressive glomerulonephritis (8 percent).

Complement abnormality

- Many, but not all, patients with C3 glomerulopathy have low serum C3 levels. Low C3 levels are more common among patients with DDD than among those with C3GN.
- Other complement abnormalities may be present. Serum levels of classical pathway components C1, C2, and C4 are usually normal although a minority of patients can have low serum C4 levels at some point in the disease course. Elevated serum levels of sC5b-9 (ie, soluble membrane attack complex or sMAC), the terminal complement complex, may be present and provide additional evidence of complement activation. Elevated serum levels of sC5b-C9 are more commonly observed in C3GN than in DDD.
- C3 nephritic factor (C3NeF) is found in approximately 80 percent of patients with DDD and roughly 40 percent of patients with C3GN.

Kidney function impairment

Patients with DDD and C3GN have variable degrees of kidney function impairment at presentation and variable rapidity of kidney function decline. Occasionally, patients with DDD or C3GN can develop rapidly progressive (crescentic) glomerulonephritis.

Extra renal abnormality

- **Drusen** – Many patients with DDD, and some with C3GN, develop drusen in Bruch's membrane of the retina . Drusen are macular deposits and are a prominent feature of age-related macular degeneration (AMD). In contrast to the drusen in AMD, DDD-associated drusen develop at a much younger age and infrequently lead to vision loss.
- There does not appear to be a close correlation between kidney disease activity and drusen formation in DDD. Nonetheless, given the similarities of electron-dense deposits in the retinal basement membrane and those in the glomerular basement membrane (GBM) in DDD, the two disorders are thought to share a common pathogenesis.

Acquired partial lipodystrophy

Patients with DDD may also have APL. APL is characterized by loss of subcutaneous fat in the upper half of the body. Up to 22 percent of patients with APL are also affected by DDD, which may develop years after the onset of APL . Sixty-seven to 74 percent of patients with APL have low C3 levels, and up to 83 percent have C3NeF. The putative link between both disorders is believed to be dysregulation of the alternative pathway of complement affecting both kidney and adipose tissue.

Diagnosis and evaluation

- The diagnosis of C3 glomerulopathy should be suspected in any patient who presents with hematuria and/or proteinuria, particularly if accompanied by kidney function impairment, hypertension, and a low serum C3 level.
- All patients presenting with proteinuria and hematuria should undergo a thorough evaluation for glomerular disease and other disorders, which generally involves laboratory testing and, in most patients, a kidney biopsy to obtain a definitive diagnosis.

Establishing the diagnosis

- The diagnosis of DDD or C3GN is established by kidney biopsy demonstrating the characteristic findings on immunofluorescence microscopy in a patient with suspected glomerulonephritis. Electron microscopy is required to distinguish DDD from C3GN.
- In patients with biopsy-confirmed DDD or C3GN, additional testing should be performed to help identify the underlying etiology of the glomerulopathy since this knowledge may help determine therapy

Further work up

Evaluation for monoclonal gammopathy – *In all patients with DDD or C3GN, particularly those aged older than 50 years, monoclonal gammopathy should be excluded by serum protein electrophoresis and immunofixation, serum free light chains, and urine protein electrophoresis and immunofixation.*

Complement testing – Patients with DDD or C3GN should be evaluated for activation of the alternative pathway of complement.

Measurement of serum complement protein

Serum C3 and C4 – A low serum C3 level supports the diagnosis of C3GN or DDD but is not specific. Serum C4 levels are usually normal but may be low in a minority of patients.

Soluble C5b-9 (soluble membrane attack complex or sMAC) – Elevated levels of sMAC reflect activation of the C5 convertase and are found in approximately 25 and 50 percent of patients with DDD and C3GN, respectively.

Serum factor H – As noted above, factor H promotes the decay of the C3 and C5 convertases. If factor H activity is diminished, factor H levels should be measured and assays for possible mutations in the factor H gene and autoantibodies to factor H should be performed.

Testing for autoantibodies

C3 nephritic factor (C3NeF) – C3NeF is an autoantibody that stabilizes the C3 convertase (C3bBb). C3NeF is detected in approximately 80 percent of patients with DDD and 40 percent of those with C3GN. *Detection of C3NeF in the serum supports the diagnosis of C3GN or DDD but is not specific.*

C5 nephritic factor (C5NeF) – C5NeF is an autoantibody that stabilizes the C5 convertase ($[C3b]_2Bb$) in the presence of properdin. It is found most commonly in C3GN and is associated with high sC5b-9 levels.

Genetic testing

- The frequency of complement gene variants in C3 glomerulopathy is estimated at approximately 20 percent. Testing for mutations in the genes encoding factor H, factor I, C3, and complement factor H-related (CFHR) proteins (CFHR1-5) should be performed.
- The CFHR proteins CFHR1, CFHR2, and CFHR5 are able to compete with factor H for binding to tissue-bound complement fragments, thereby deregulating the control of the alternative pathway by factor H. This balance can be disturbed by CFHR mutations.

Pathology

Immunofluorescence is necessary to make a diagnosis of C3GN and DDD, and electron microscopy is required to distinguish them from one another. Light microscopic findings are not specific for C3GN or DDD.

Light microscopy – There are no characteristic light microscopic findings in C3 glomerulopathy; mesangial proliferative, membranoproliferative, and endocapillary proliferative glomerulonephritis may be present, as may crescentic glomerulonephritis.

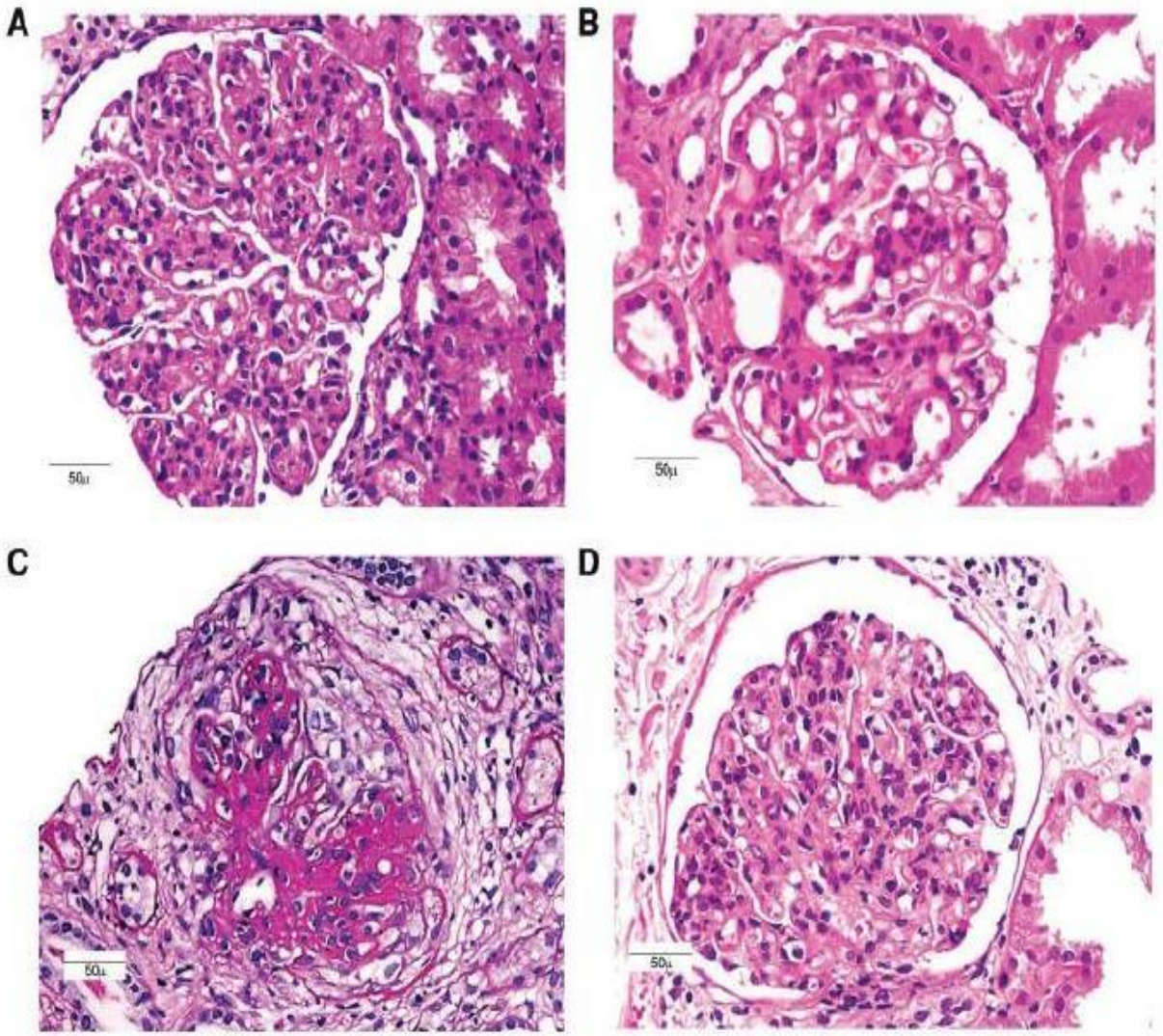


FIGURE 1: Light microscopic patterns. (A) Membranoproliferative pattern showing mesangial hypercellularity and capillary wall double contours (haemotoxylin and eosin, original magnification ×400); (B) mesangial hypercellularity (haemotoxylin and eosin, original magnification ×400); (C) crescentic pattern (PAS, original magnification ×400); (D) endocapillary proliferative pattern with many neutrophils (haemotoxylin and eosin, original magnification ×400).

Pathology

Immunofluorescence microscopy almost always shows bright deposits of C3 along the glomerular, tubular, and Bowman's capsule basement membranes, as well as mesangial rings.

Immunoglobulin deposits, including kappa and lambda light chains, are typically absent, or present at lower intensity than C3, which indicates that DDD and C3GN are not immune complex deposition diseases.

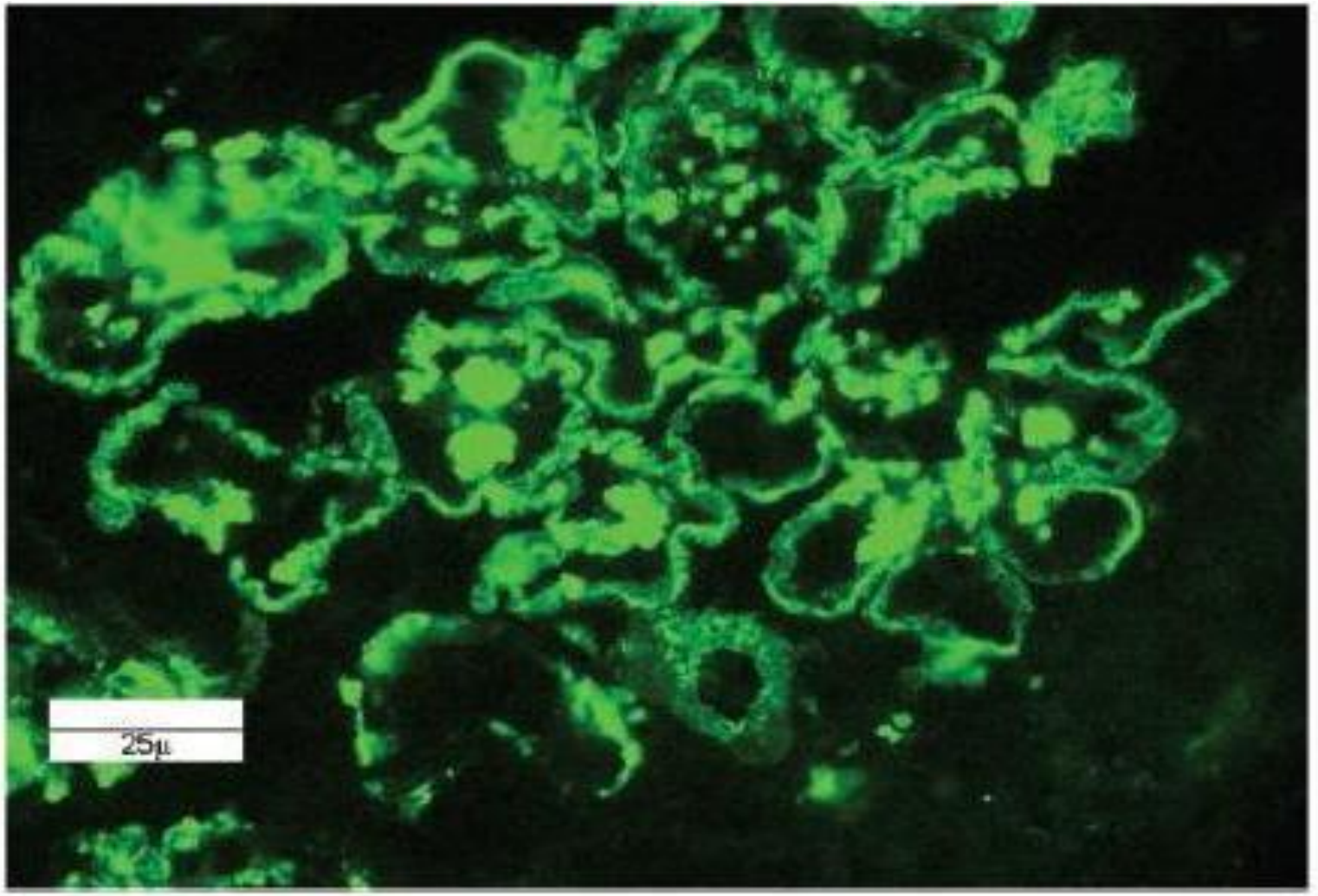


FIGURE 2: IF pattern: intense staining for C3 along the glomerular capillary loops in a semi-linear ribbon-like pattern and as 'ring' forms in the mesangium (fluo-

Pathology

Electron microscopy should be used whenever possible to confirm the presence and distribution of glomerular deposits. It is required to distinguish between DDD and C3GN. Electron microscopy in patients with DDD reveals pathognomonic abnormal electron-dense material within the GBM, which replaces and widens the lamina densa . The GBM changes may be uniform or vary from loop to loop in DDD. Electron-dense material may also be found in the mesangium, paramesangial areas, and the basement membranes of the renal tubules and Bowman's capsule

Pathology

- Such intramembranous electron-dense material is absent in C3GN. Rather, patients with C3GN have predominant subendothelial, mesangial, and sometimes subepithelial deposits of lesser intensity.
- Subepithelial "humps" may be seen in both DDD and C3GN that are identical to those present in poststreptococcal glomerulonephritis In some cases, kidney biopsies of C3 glomerulopathy are difficult to label as either DDD or C3GN, as there is an overlap in ultrastructural findings, although one pattern may dominate over the other.

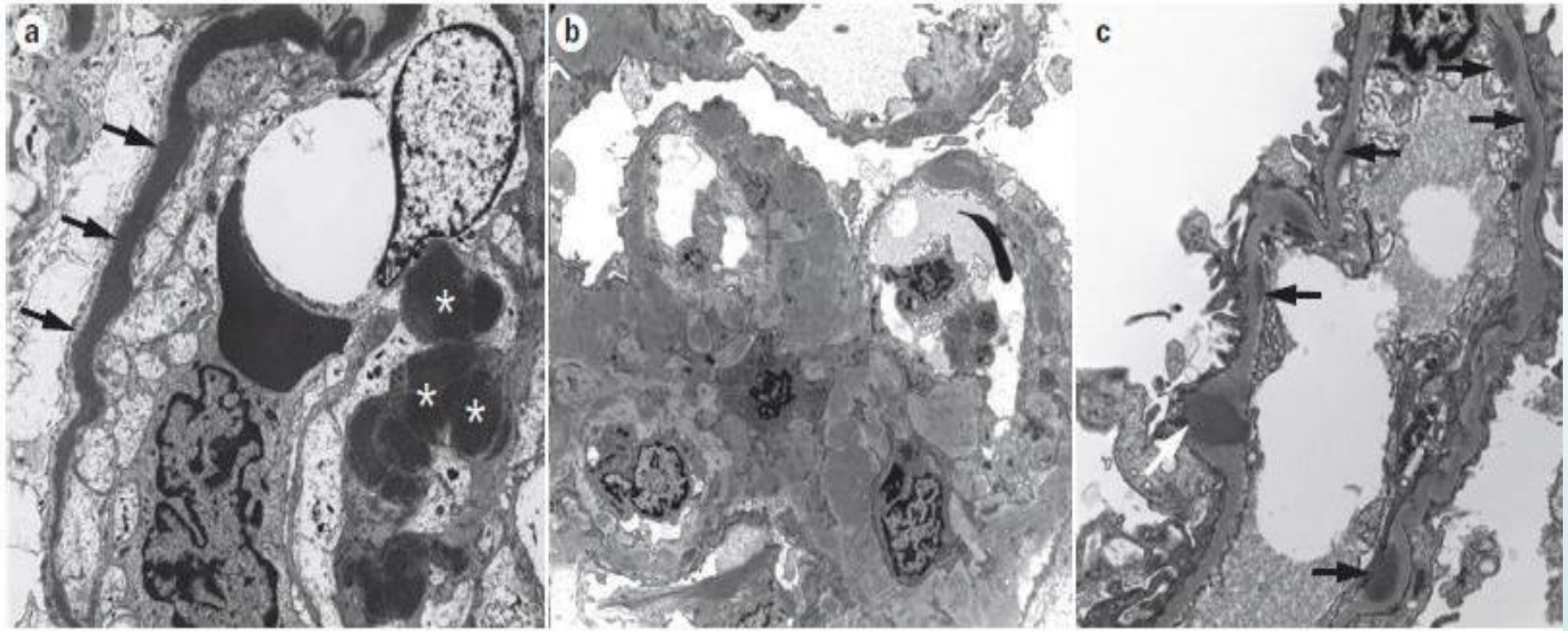


Figure 3 | Histopathology of MPGN and C3 glomerulopathy. **a** | A case of dense deposit disease. The electron micrograph shows very electron-dense transformation of the glomerular basement membrane (arrows) and globular electron material in the mesangium (asterisks). **b** | A case of C3 glomerulopathy. The electron micrograph shows marked thickening of the capillary wall with intramembranous electron-dense deposits and complex disruption of the glomerular basement membrane. This appearance was historically recognized as the Strife and Anders variant of MPGN type III. **c** | A case of CFHR5 nephropathy. An electron micrograph of a glomerulus shows a number of subendothelial deposits (black arrows) and one transmembrane deposit (white arrow). Abbreviations: CFHR5, complement factor H related protein; MPGN, membranoproliferative glomerulonephritis. Part a, permission obtained from Nature Publishing Group © Pickering, M. C. *et a* *Kidney Int.* **84**, 1079–1089 (2013).

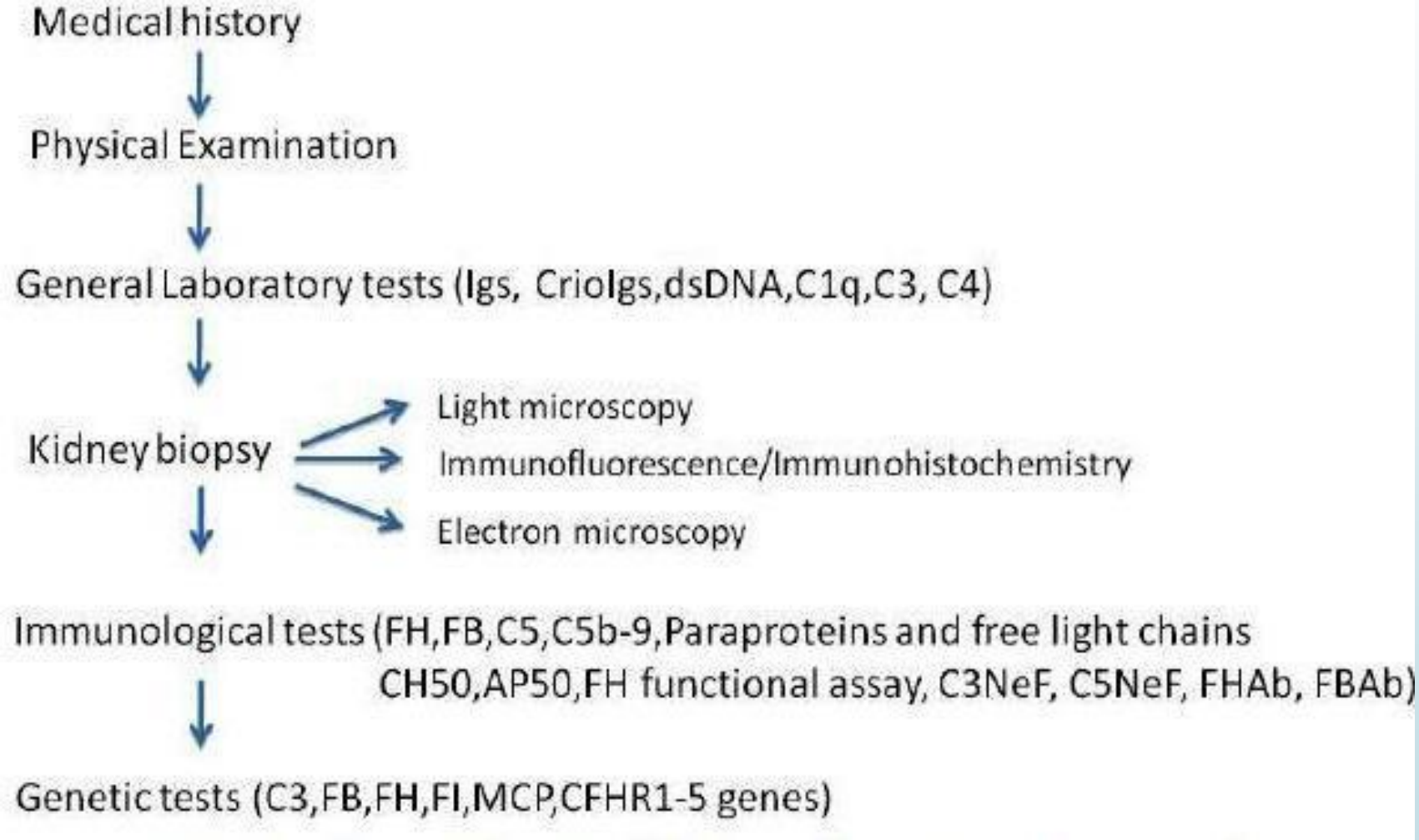
DIFFERENTIAL DIAGNOSIS

- IgA nephropathy, lupus nephritis, fibrillary glomerulonephritis, vasculitis, poststreptococcal glomerulonephritis, and staphylococcus-associated glomerulonephritis.
- Atheroembolic disease and complement-mediated thrombotic microangiopathy (also known as atypical hemolytic uremic syndrome), which may also present with acute kidney injury and a low C3 level, and monoclonal immunoglobulin-related glomerular diseases in patients with monoclonal gammopathy.
- *Decreased serum C3 and a normal C4 may help distinguish DDD and C3GN from other types of glomerulonephritis*. However, poststreptococcal and, to a lesser extent, staphylococcus-associated glomerulonephritis are also characterized by this pattern of complement activation.

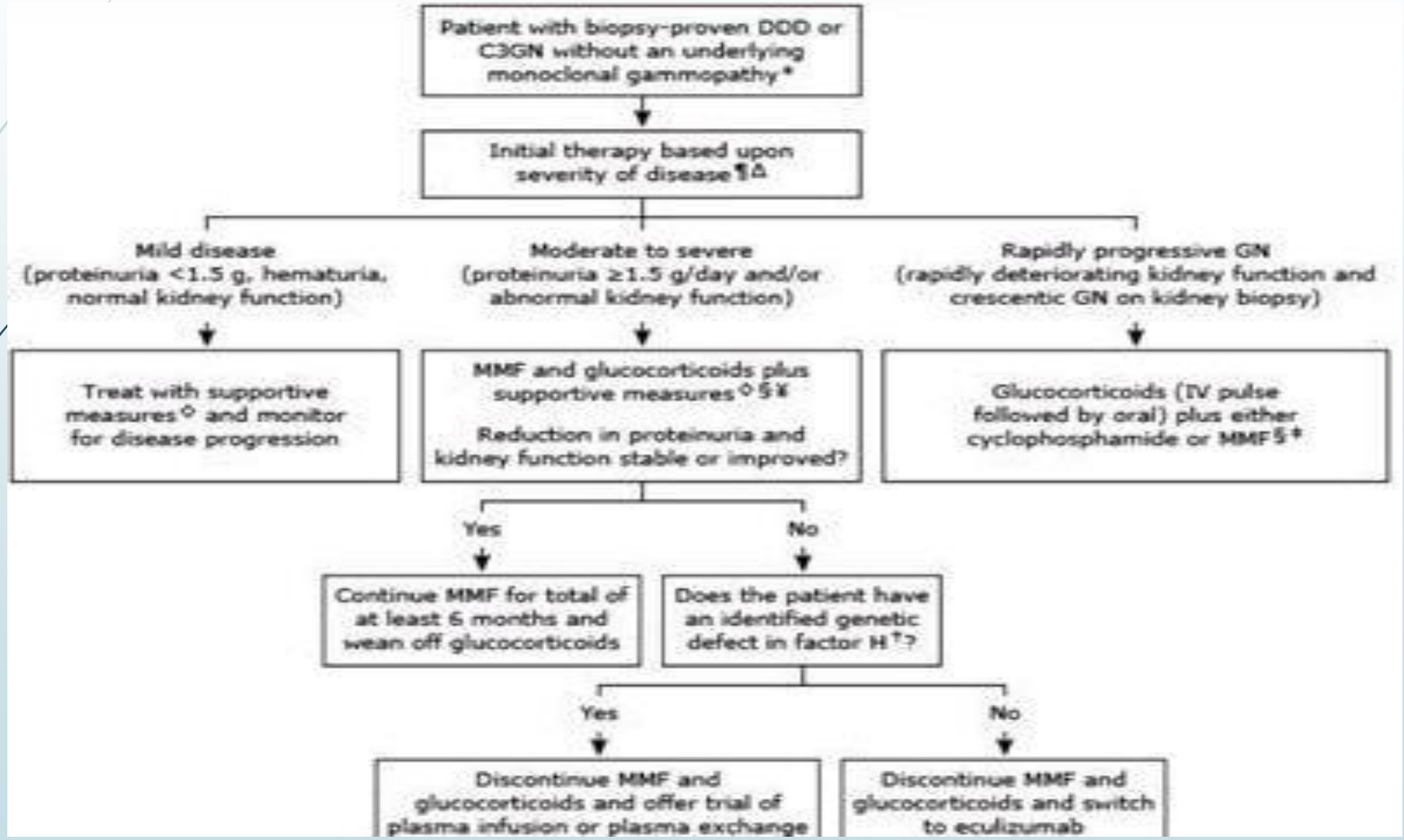
Distinction from postinfectious glomerulonphritis

- Persistent or recurrent glomerulonephritis over a prolonged period is common with DDD and C3GN, whereas poststreptococcal and IgA-dominant, staphylococcus-associated glomerulonephritis typically resolve, although signs of irreversible injury (ie, persistent azotemia and proteinuria) may be present.
- Depression of C3 usually persists in DDD and C3GN, whereas it is transient in poststreptococcal and staphylococcus-associated glomerulonephritis.
- Immunofluorescence microscopy usually demonstrates immunoglobulin deposition in poststreptococcal and IgA-dominant, staphylococcus-associated glomerulonephritis; by contrast, there is typically intense C3 staining with scant or no immunoglobulin staining in DDD and C3GN.

Clinical and laboratory work up for diagnosis for C3 glomerulopathy



Approach to the treatment of C3 glomerulopathy in patients



Monoclonal gammapathy

- Patients with DDD or C3GN who are found to have a monoclonal gammopathy should be evaluated further for underlying malignancy (such as multiple myeloma) or evidence of other end-organ involvement and treated accordingly. In the absence of an assay to confirm that the monoclonal gammopathy is responsible for the complement dysregulation, treatment is based upon this presumption given the unusually strong association between monoclonal gammopathy and C3 glomerulopathy in older patients.
- *The treatment of C3 glomerulopathy associated with monoclonal gammopathy is primarily directed against the pathologic clone responsible for producing the monoclonal protein*.

Mild disease

- Patients with mild disease should be monitored periodically for disease progression that might warrant therapy.
- *Serum creatinine and urine protein excretion (initially by 24-hour urine collection and then by spot urine protein-to-creatinine ratio [UPCR] if stable) was cheked every three months for one year and then every six months if stable.*
- If proteinuria and kidney function remain stable or improve, we continue supportive measures indefinitely with follow-up every six months. Patients who develop increasing proteinuria or worsening kidney function should be considered for immunomodulatory therapies

Moderate to severe disease

- *MMF and oral glucocorticoids plus supportive measures are suggested as initial therapy for moderate kidney disease rather than supportive measures alone or combined with other immunosuppressive agents*.
- MMF 1000 mg twice daily and prednisone 20 mg daily or 40 mg every other day
- Monitor serum creatinine and urine protein excretion (by spot UPCR), initially on a monthly basis and then every three months if these parameters remain stable.

Moderate to severe disease

If proteinuria improves and kidney function stabilizes, treatment with MMF continue for a total of at least six months.

Prednisone at the initial dose is adminstered for a total of at least three months, followed by a gradual taper to discontinuation by nine months.

The optimal duration of MMF therapy is uncertain, and up to 50 percent of patients relapse when the treatment is stopped.

If MMF is discontinued after six months of therapy, serum creatinine and urine protein excretion are cheked every three months to monitor for signs of relapse (eg, increasing proteinuria or worsening kidney function).

In patients who develop relapsing disease, we restart MMF and glucocorticoids and continue treatment with MMF indefinitely after tapering off the glucocorticoids.

Moderate to severe disease

- If there is no improvement in proteinuria or kidney function after six months of MMF plus glucocorticoid therapy, or if kidney function rapidly deteriorates prior to the completion of six months of therapy:
- If the patient has a genetic defect in factor H, MMF and glucocorticoids are discontinued and a trial of plasma infusion or plasma exchange is offered.
- If the patient does not have a genetic defect in factor H, we discontinue MMF and glucocorticoids and either switch to eculizumab .

Rapidly progressive glomerulonephritis

Glucocorticoids in combination with either cyclophosphamide or MMF are suggested. Methylprednisolone 500 to 1000 mg daily for three days, followed by a tapering course of oral prednisone (eg, starting dose 60 mg/day until remission is achieved, then tapered to discontinuation by six months).

If cyclophosphamide is used, 1.5 to 2 mg/kg/day orally is administered for three to six months, depending upon the clinical response.

If MMF is used, we give 1.5 to 2 g/day orally in two divided doses as tolerated for at least six months.

Rapidly progressive glomerolunephritis

The decision between cyclophosphamide and MMF is determined by clinician and patient preference, and there is no evidence to support the use of one agent over the other in patients with C3 glomerulopathy who present with RPGN.

In addition to the combination therapy described above, some experts would also administer eculizumab, based upon the results of one case series suggesting a potential benefit in patients with RPGN. If eculizumab is used, 1200 mg IV is adminstered every two to four weeks

Rapidly progressive glomerulonephritis

- *If there is no evidence of disease stabilization or improvement after three months of therapy, eculizumab should be discontinued.*
- Dialysis dependence of less than two weeks' duration should not preclude the use of eculizumab in patients with extensive cellular crescents on kidney biopsy.
- In patients who have a genetic defect in factor H, some of the contributors to this topic would use plasma exchange or plasma infusion in addition to glucocorticoids with cyclophosphamide or MMF, given the success of this therapy in two case reports

Rapidly progressive glomerulonephritis

Plasma exchange can be performed with three exchanges per week for two weeks. If there is evidence of disease stabilization or improvement at two weeks, plasma exchange can be continued; if not, plasma exchange should be discontinued, and the patient should be offered a trial of eculizumab.

Supportive measures in all patients

Dietary sodium and protein

Antihypertensive therapy

Renin-angiotensin system inhibition

Lipid lowering agents

Treatment of edema

Maintenance of adequate nutrition

Eculizumab for refractory disease

- For patients with C3GN or DDD and moderate to severe disease , eculizumab is suggested rather than continuation of MMF plus glucocorticoid therapy.
- Eculizumab is a monoclonal antibody that binds with high affinity to C5, preventing its cleavage and thereby inhibiting the formation of C5a and the terminal complement complex (C5b-9), which have been implicated in the pathogenesis of both DDD and C3GN.
- *Eculizumab is adminstered 900 mg intravenously (IV) per week for four to five weeks, followed by 1200 mg IV every two weeks*.
- Serum creatinine and urine protein excretion (by spot UPCR) was monitored on a monthly basis during therapy. The optimal duration of eculizumab therapy is uncertain.

Eculizumab for refractory disease

In patients who respond with an improvement or stabilization of kidney function and proteinuria within three months, we continue eculizumab for a total of approximately one year.

Since some patients will relapse when the treatment is stopped or frequency of treatment is reduced, serum creatinine and spot UPCR is monitored monthly for three months, then every two months for six months, and then every three months for one year.

Subsequent monitoring then varies on a case-by-case basis. In patients who experience a relapse, we restart eculizumab and continue treatment indefinitely.

Eculizumab for refractory disease

- *In patients who have no improvement or stabilization of kidney function or proteinuria after three months of eculizumab therapy, treatment is dicontinued since the benefits of eculizumab are likely to be seen within a few weeks to months*.
- Some clinicians would consider a trial of plasma infusion or plasma exchange in such patients; however, data to support this approach are limited to a few case reports of patients with C3 nephritic factor (C3NeF) or factor H defects

Eculizumab for refractory disease

- Treatment with eculizumab may be associated with life-threatening and fatal meningococcal infections. *Patients should receive meningococcal vaccination at least two weeks prior to initiation of eculizumab whenever possible. Daily antimicrobial prophylaxis for prevention of meningococcal infection is administered in patients treated with eculizumab, despite vaccination, due to increased infection risk with immunosuppression.*
- Data on the efficacy of eculizumab are derived from one small, open-label, phase I clinical trial and several case reports and series. These suggest that some, but not all , patients with C3 glomerulopathy may benefit from treatment with eculizumab. In the small number of patients included, there were no reported adverse effects of eculizumab therapy. The patients who had posttreatment kidney biopsies appeared to have eculizumab deposition in kidney tissues. The long-term effects of this deposition are unknown.

Eculizumab for refractory disease

- The largest case series of patients with C3 glomerulopathy treated with eculizumab included 13 children/adolescents and 13 adults. Most patients (85 percent) had received other immunosuppressive therapy prior to eculizumab, and three had rapid progression of their kidney disease despite treatment. At the time of eculizumab initiation, 11 patients (42 percent) had chronic kidney disease, 19 (73 percent) had nephrotic syndrome, seven (27 percent) had rapidly progressive disease, and three (12 percent) required dialysis. None of the patients had monoclonal gammopathy. Patients were treated with eculizumab 900 mg IV per week for four weeks, followed by 1200 mg every other week; median duration of eculizumab therapy was 14 months. Six patients (23 percent) had a global clinical response, six (23 percent) had a partial clinical response, and 14 (54 percent) had no response. Patients with a global response tended to have a more rapidly progressive disease course and more extracapillary proliferation on kidney biopsy. Other factors, including age, extent of kidney fibrosis, frequency of nephrotic syndrome, complement levels, and gene variants, did not differ between responders and nonresponders.

Plasma infusion or exchange for factor H defects

- For patients with moderate to severe disease that does not respond to initial treatment with mycophenolate and glucocorticoids and who have identified genetic defects in factor H, a trial of plasma infusion of fresh frozen plasma (FFP) or plasma exchange is suggested to replace the missing or mutant protein.
- Plasma exchange (with FFP, not albumin) may be preferred to plasma infusion if there is concern about volume overload. Plasma exchange may also be of value in those patients with an acquired functional deficiency of factor H due to the presence of inactivating proteins, such as an autoantibody, to remove the antibody while replacing factor H.

Plasma infusion or exchange for factor H defects

- A trial of plasma infusion or exchange once every 14 days may be continued for 6 to 12 weeks while monitoring for signs of kidney recovery as measured by a decline in proteinuria and serum creatinine. If the patient responds, plasma infusion or exchange should be continued indefinitely.
- *If the patient does not respond after 6 to 12 weeks, plasma infusion or exchange should be discontinued, and the patient should be offered eculizumab* .
- The data supporting the use of plasma infusion come from a case report of two siblings with C3NeF and defective factor H secretion; normal kidney function was maintained with a regimen of 10 to 15 mL per kg body weight of FFP infused regularly every 14 days.
- *Plasma exchange with albumin has also been shown to stabilize disease progression in some patients with circulating C3NeF, presumably by removal of the pathologic autoantibody*.

Screening family members

- Family members of affected patients should undergo genetic testing if a potentially causative mutation is identified in the patient (eg, factor H mutation in a patient with low serum factor H levels).
- *If the family member is found to have the same mutation, they should be evaluated for the presence of hypocomplementemia and an abnormal urinalysis or elevated serum creatinine. A kidney biopsy should be done to exclude DDD and C3GN if there is clinical evidence of glomerular disease*. Asymptomatic siblings and other young family members who have a demonstrated genetic mutation should be followed prospectively for signs of glomerular disease.
- However, it is reasonable to perform urinalysis and assessment of kidney function in such patients annually and following infections that might trigger complement activation and precipitate the onset of glomerulonephritis.
- *Periodic measurements of complement levels and C3 nephritic factor (C3NeF) should also be done.*

Thank for attention