Therapeutic approach to MPGN

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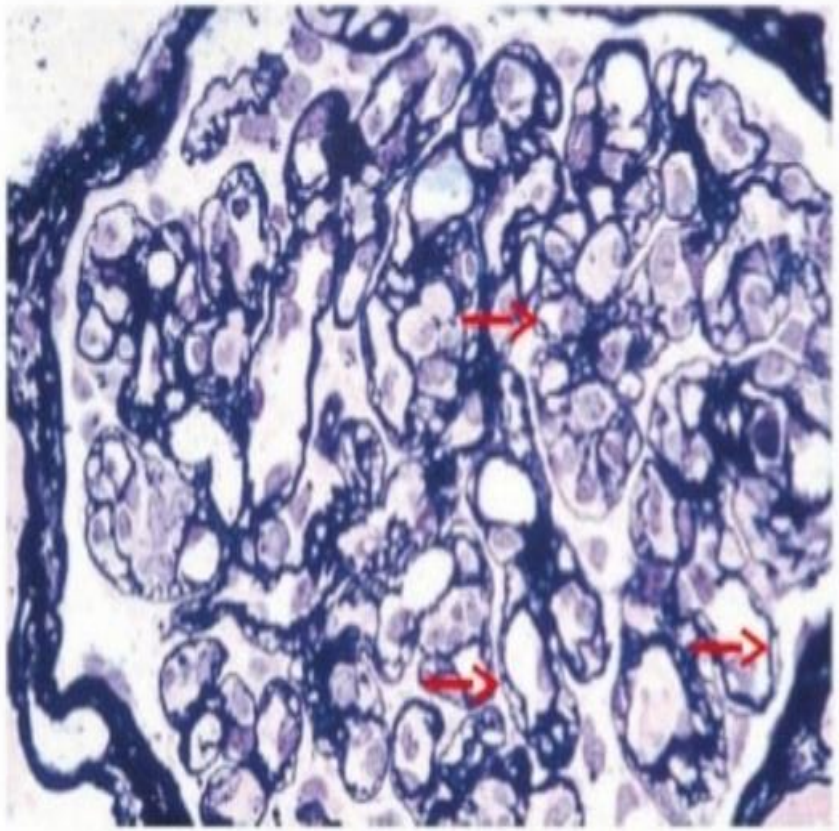
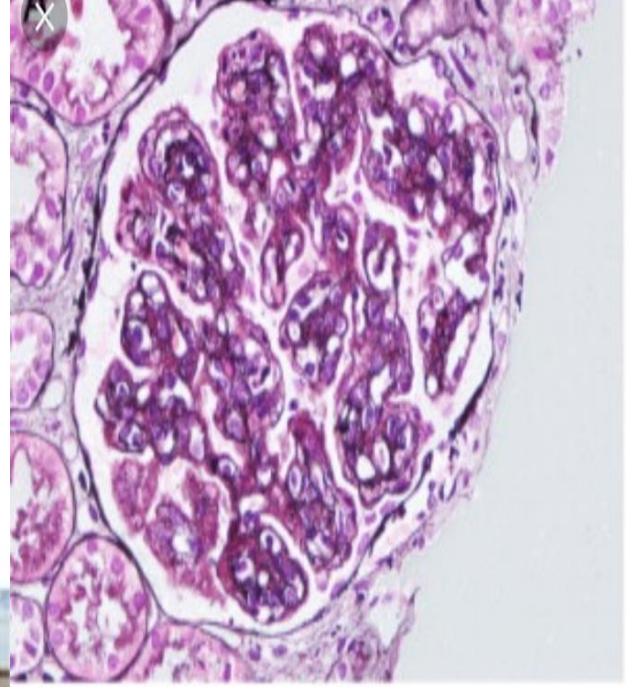
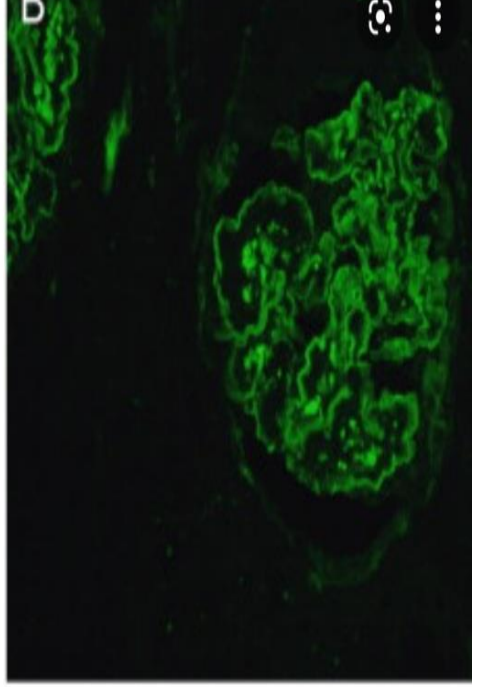
MPGN:

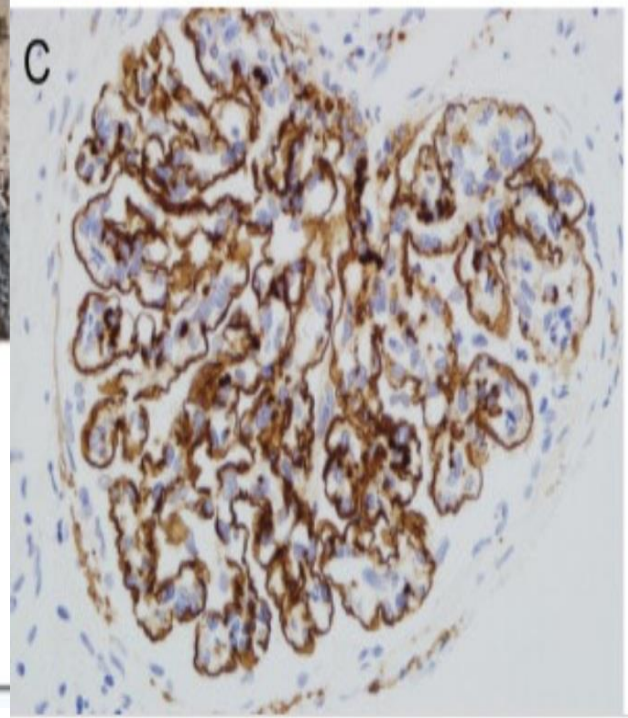
An optical microscopic glomerular lesion, not a disease or a diagnostic term, representing a "pattern of injury" characterized by reduplication of the capillary basement membrane ("double contours") and mesangial expansion (lobularization)

Pathology - LM









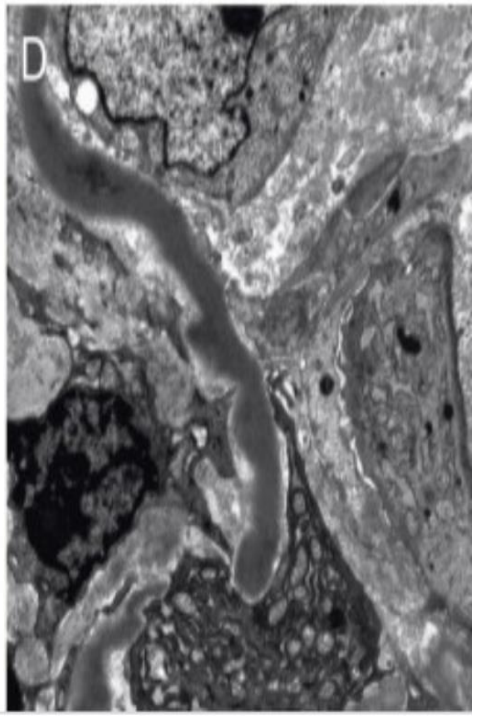


Figure 21.12 "Tram tracks" in membranoproliferative glomerulonephritis (MPGN) type I. By silver stain, a double contouring of the glomerular basement membrane (GBM) can be observed in MPGN type I, resembling tram tracks.

Epidemiology

MPGN accounts for 7 to 10% of all cases of biopsy confirmed glomerulonephritis. (1)

MPGN ranks as the third or fourth leading cause of ESRD among the primary glomerulonephritides. (2)

Classification

Traditional Classification

According to the SITE of deposits

New Classification

According to the TYPE of deposits

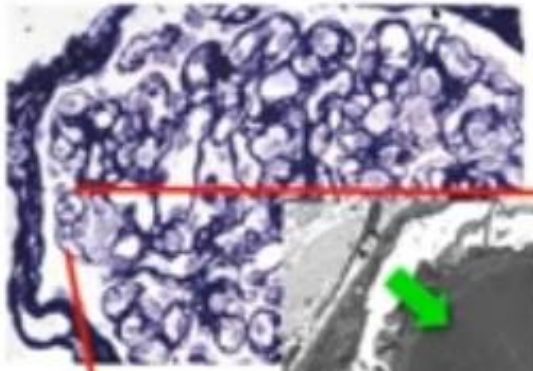
Classification

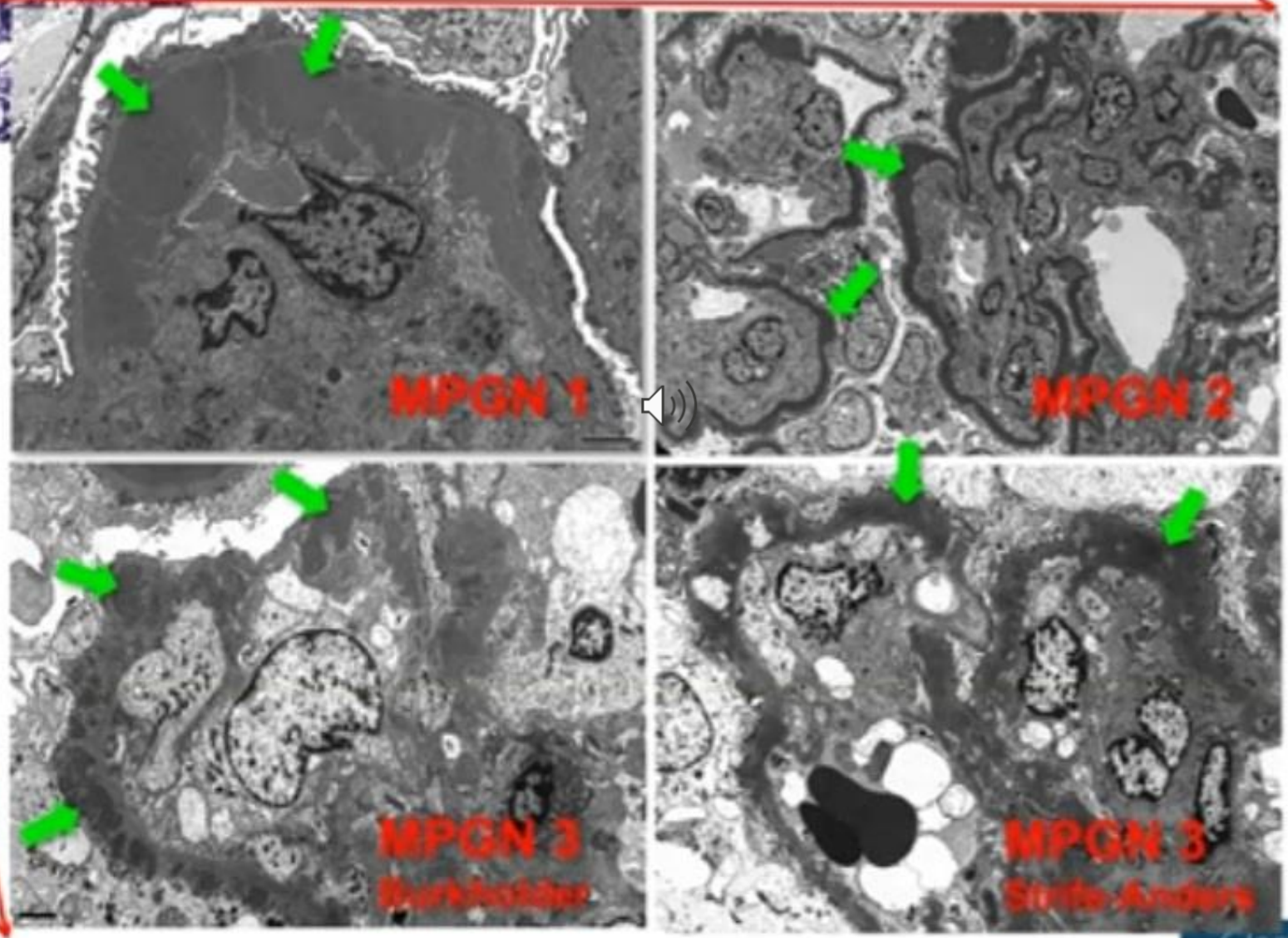
Traditional Classification

According to the SITE of deposits

- MPGN Type I
- MPGN Type II
- MPGN Type III

Historic ultrastructural classificat

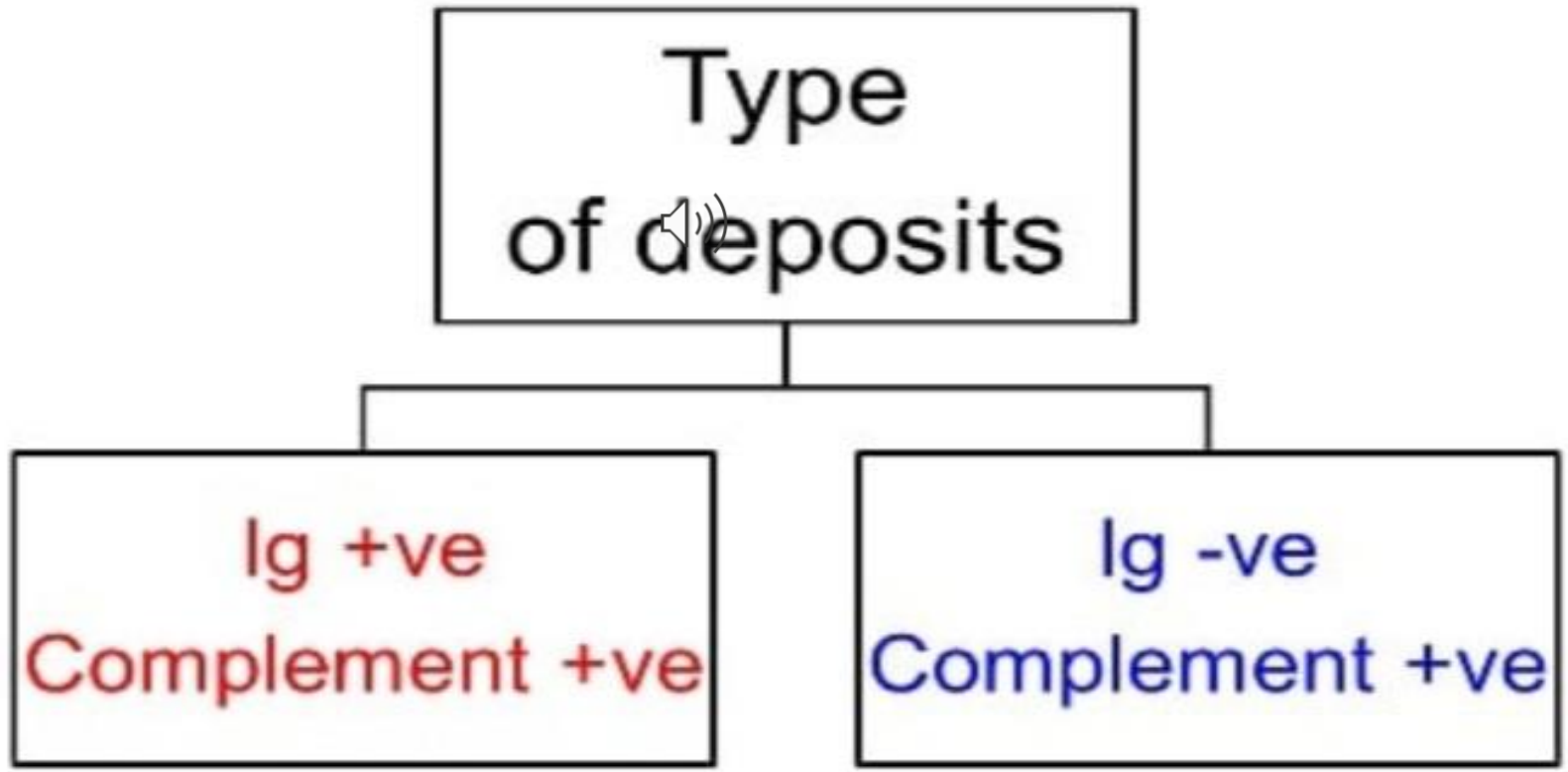




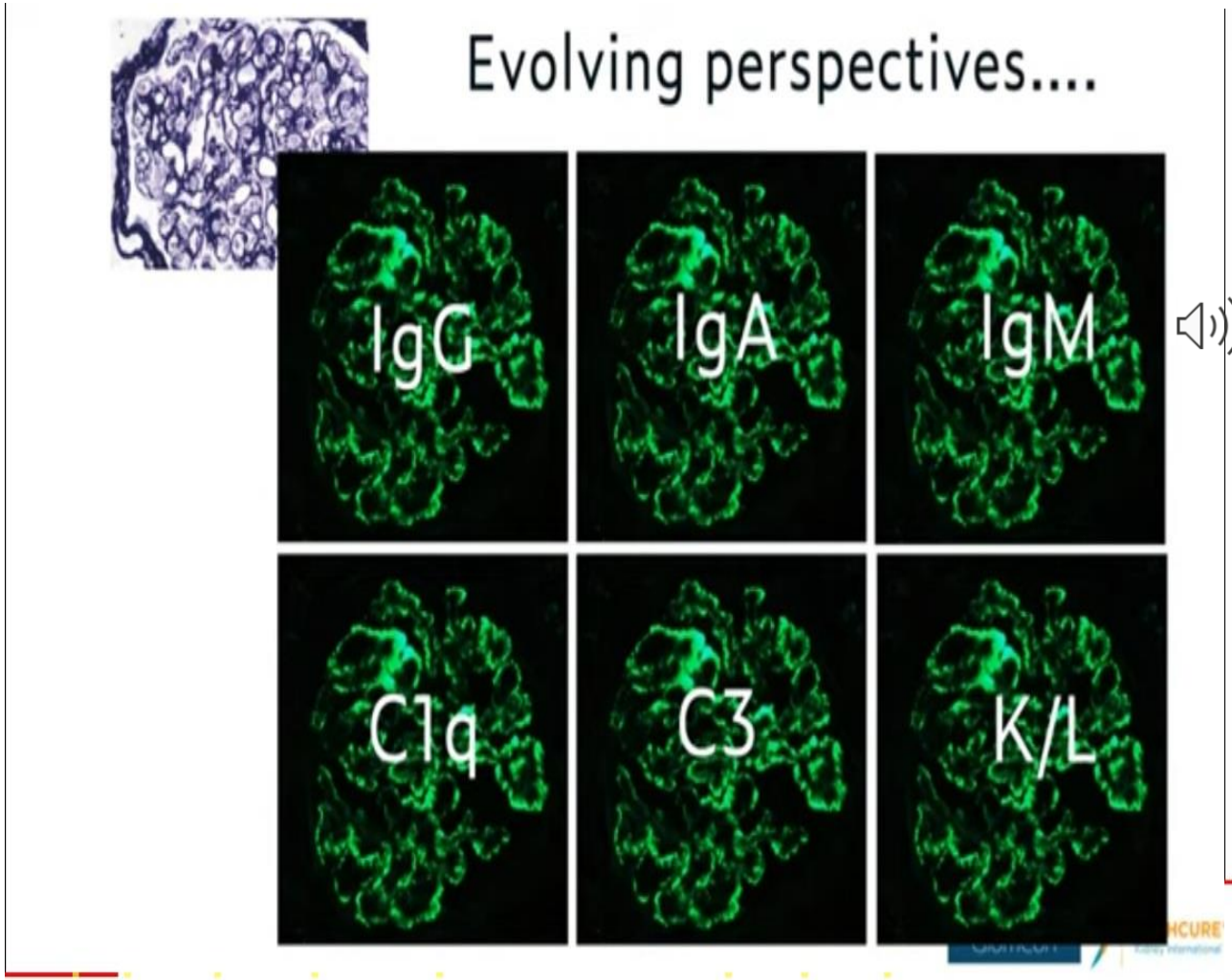
GlomCon

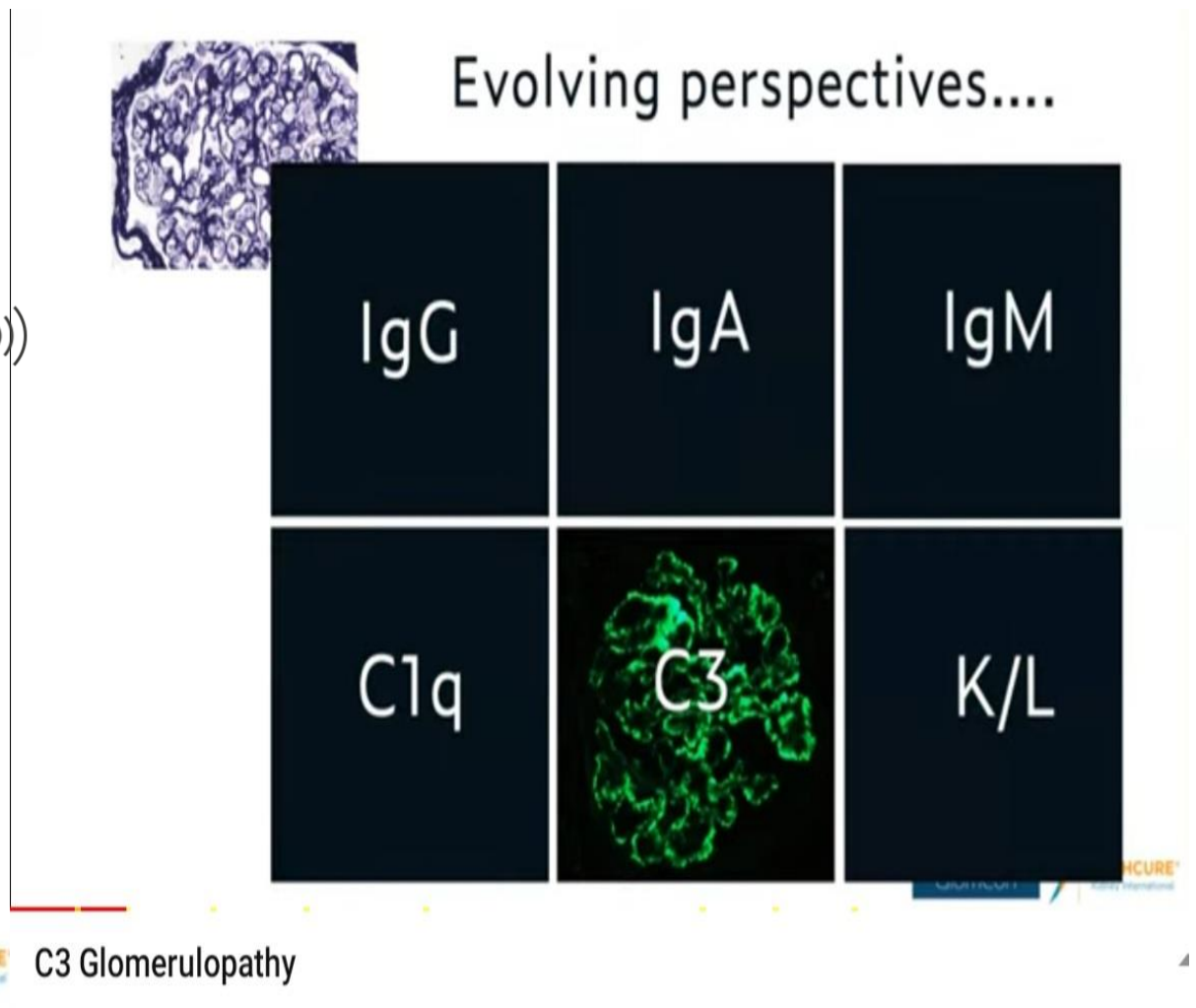
NEPHCURE

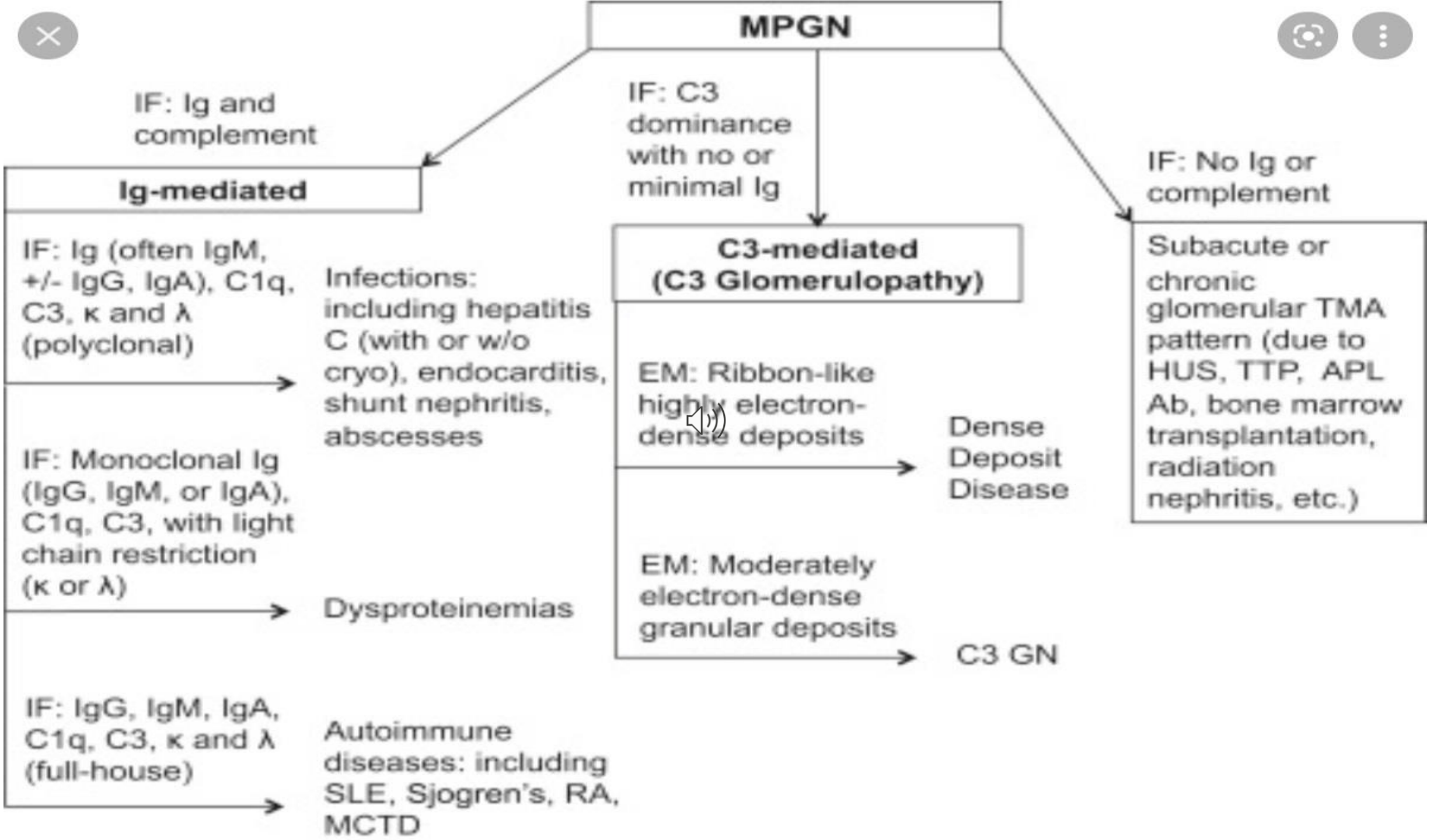
Classification – New: :According to TYPE of deposits

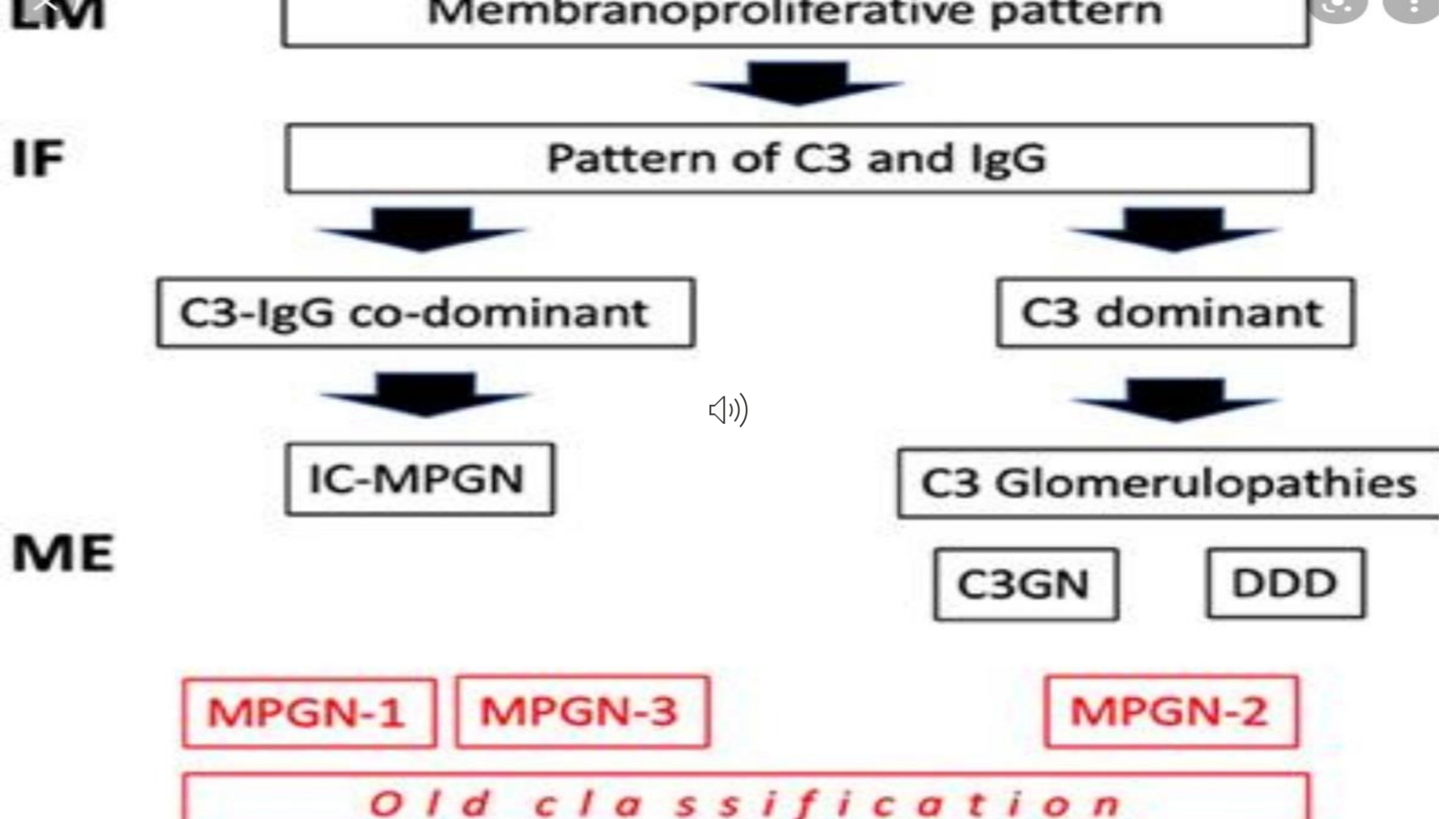


IC MPGN vs C3 GN



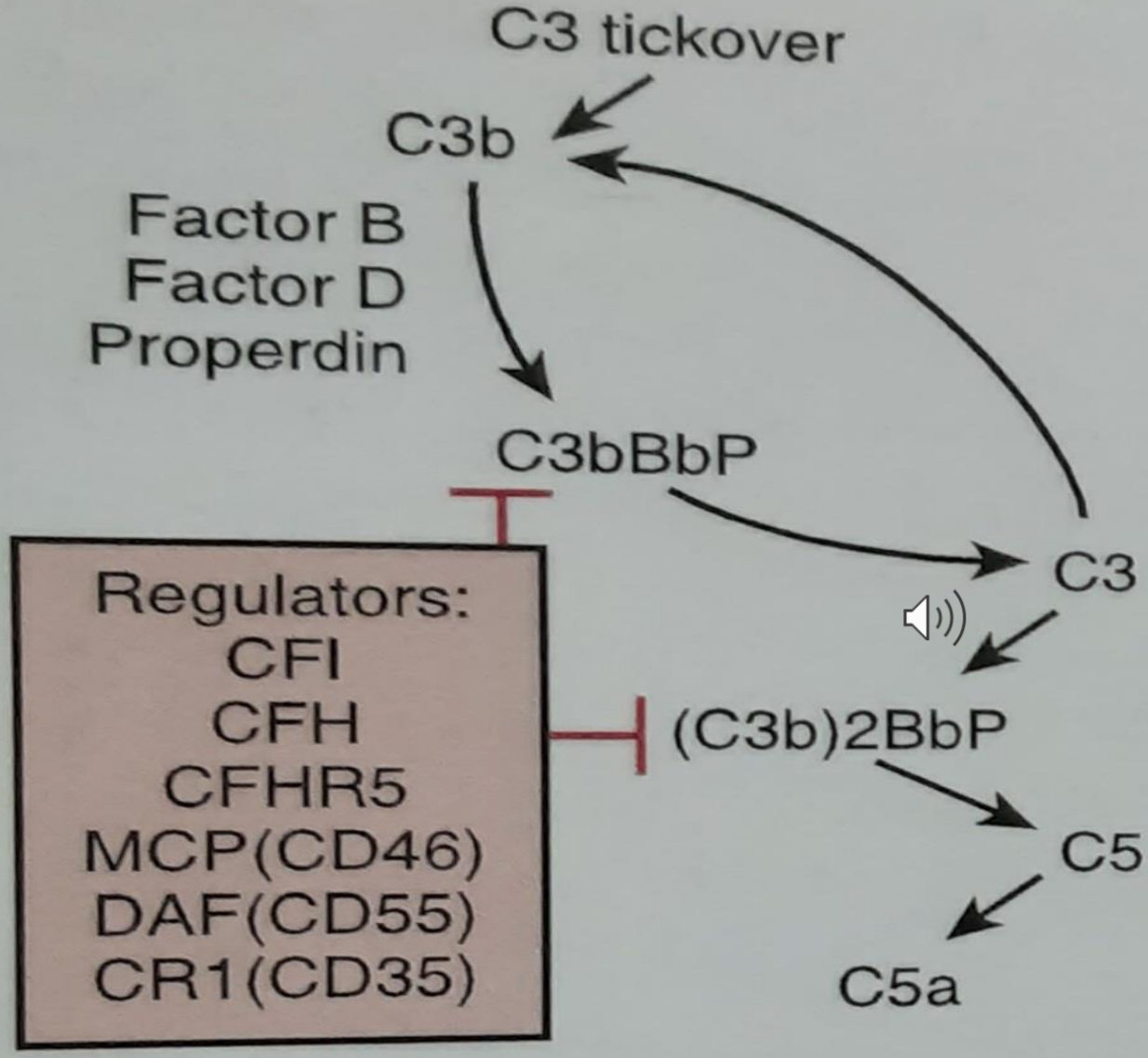



MPGN
IF: Ig and complement
Ig-mediated
IF: C3 dominance with no or minimal Ig
C3-mediated (C3 Glomerulopathy)
IF: No Ig or complement
Subacute or chronic glomerular TMA pattern (due to HUS, TTP, APL Ab, bone marrow transplantation, radiation nephritis, etc.)
IF: Ig (often IgM, +/- IgG, IgA), C1q, C3, κ and λ (polyclonal)
Infections: including hepatitis C (with or w/o cryo), endocarditis, shunt nephritis, abscesses
EM: Ribbon-like highly electron-dense deposits
Dense Deposit Disease
IF: Monoclonal Ig (IgG, IgM, or IgA), C1q, C3, with light chain restriction (κ or λ)
Dysproteinemias
EM: Moderately electron-dense granular deposits
C3 GN
IF: IgG, IgM, IgA, C1q, C3, κ and λ (full-house)
Autoimmune diseases: including SLE, Sjogren's, RA, MCTD


LM
Membranoproliferative pattern
IF
Pattern of C3 and IgG
C3-IgG co-dominant
C3 dominant
IC-MPGN
C3 Glomerulopathies
ME
C3GN
DDD
MPGN-1
MPGN-3
MPGN-2
Old classification

EVALUATION of Apparently "Idiopathic" MPGN

- ***Ig + C3-***
  - **FANA, cryoglobulins, C4, HCV (HBV), blood cultures, occult infections malaria smears, parasites**
- ***Ig ± C3-***
  - **Monoclonality of deposits, serum FLC, immunofixation, bone marrow examination (MGUS can co-exist with an "immune complex" mediated MPGN)**
- ***C3 (or C4) dominant-***
  - **C3/C4, C3Nef, CfH, CfI, MCP, retinal exam, studies for monoclonal paraprotein**
- ***No Ig or C3/C4-***
  - **ADAMST13, blood smear for schistocytes, LDH, indirect bilirubin, Platelet count and volume**



Abnormalities in the regulation of the alternative complement pathway cause C3 glomerulopathy, e.g. antibodies to C3bBbP (C3NeF), CFH, CFI or CFB; or mutations in CFH, CFI, MCP, CFHR5, C3.

Fig. 31.20 Regulators of the alternative complement pathway and abnormalities that cause C3 glomerulopathy. *CF,* Complement factor.

Clinical Presentation

From benign and slowly progressive to rapidly progressive

- Microscopic hematuria and non-nephrotic proteinuria (35%),
- Nephrotic syndrome (35%),
- Chronically progressive GN (20%),
- RPGN (10%).

Systemic hypertension:

- It is resent in 50% to 80% of patients,
- It may occasionally be so severe that the presentation may be confused with that of malignant hypertension.

Box 31.7 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

Modified from references 1106 and 1473 to 1481.

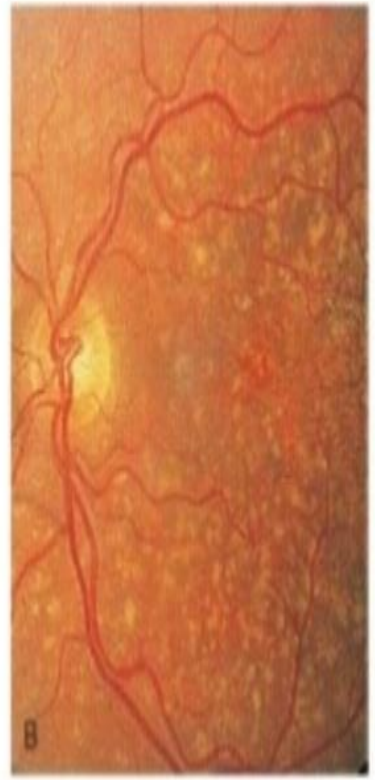
DDD
Clinical Presentation

- **It may precede the renal disease by many years**.
- **Partial lipodystrophy:**
  - preferentially involves the face and upper body

DDD
Clinical Presentation

- **Some patients with DDD will have:**
  - color defects
  - prolonged dark adaptation
  - mottled retinal pigmentation (drusen bodies)
  - sometimes deterioration of vision.

- **Indocyanine green angiography** of the retina may reveal dense deposits in the ciliary epithelial basement membrane (abnormal fluorescent dots) and choroidal neovascularization.



B, Drusen bodies in the retina.

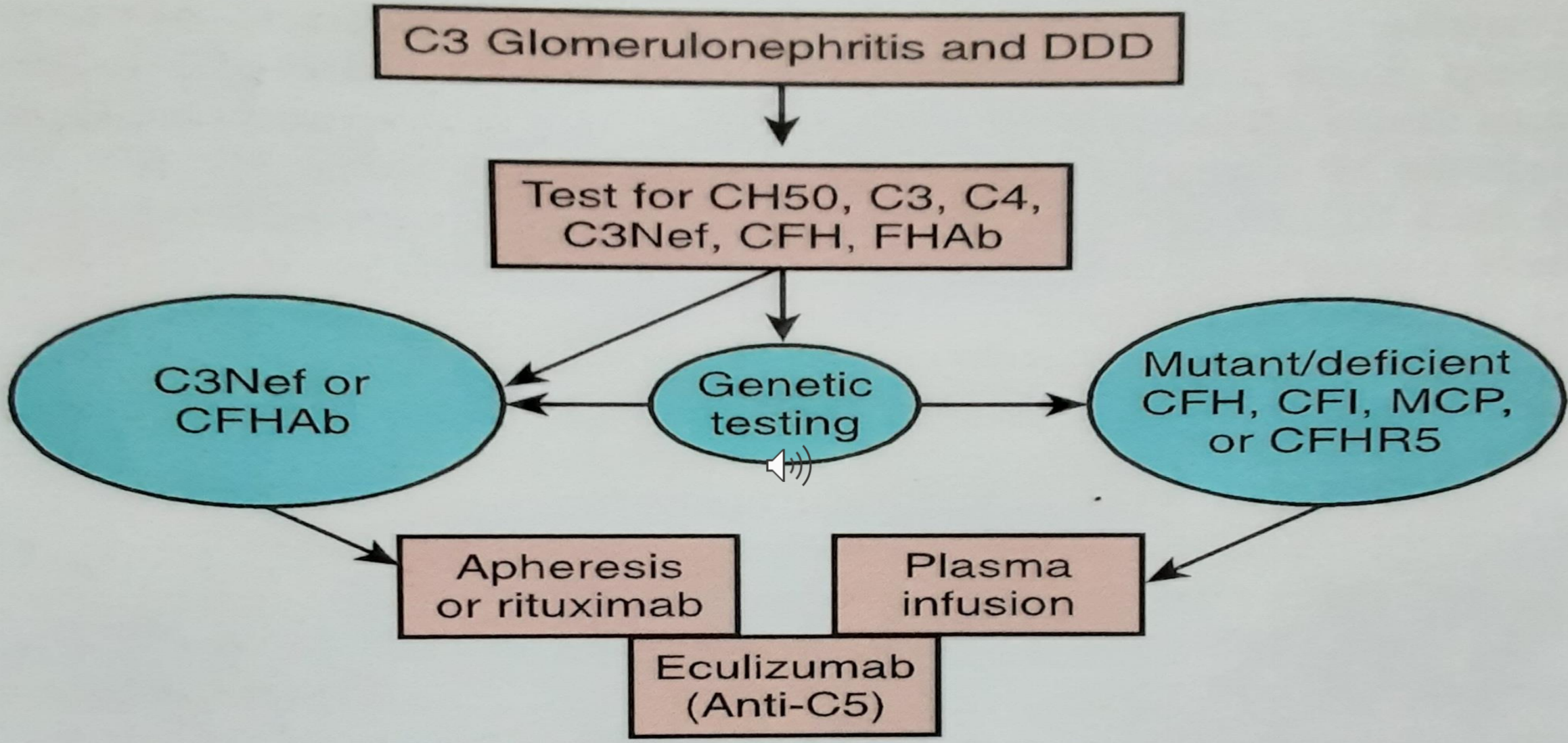


Fig. 31.21 A framework for the diagnosis and management of C3 glomerulopathies, C3 glomerulonephritis, and dense deposit disease (DDD). *Ab,* Antibody; *CF,* complement factor; *C3Nef,* C3 nephritic factor.

MPGN: Therapy- *2019*

- ***"Idiopathic"- very uncertain-*** no agreed upon regimens- if crescentic disease present- CYC + Steroids + PLEX
- ***Immune Complex-*** HCV- RTX and/or DAA; LN- MMF or CYC + steroids ?RTX ?CNI; Other infections-treat underlying disease
- ***C Dysregulation-*** Hereditary CfH deficiency- DDD/C3GN FFP/ Eculizumab; Acquired C3GN- immunosuppression with MMF= steroids-?Eculizumab
- ***Monoclonal Ig Deposition-*** Chemotherapy- Bortezomib/Lenalidomide/Steroids
- ***Chronic TMA-*** Eculizumab (HUS), Warfarin (aPL), PLEX/FFP- ADAMTS-13 deficiency

Treatment

- Antiplatelet agents – uncertain but showed some benefit with ASA and dipyridamole (reduced the incidence of progression to ESRD – 14 vs. 47% in 3-5 yrs)
- Immunosuppressive drugs – limited data

Kidney International
Volume 88, Issue 5, November 2015, Pages 1153-1160

clinical investigation

Effectiveness of mycophenolate mofetil in C3 glomerulonephritis

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C3 glomerulonephritis is a clinicopathologic entity defined by the presence of isolated or dominant deposits of C3 on immunofluorescence. To explore the effect of immunosuppression on C3 glomerulonephritis, we studied a series of 60 patients in whom a complete registry of treatments was available over a median follow-up of 47 months. Twenty patients had not received immunosuppressive treatments. In the remaining 40 patients, 22 had been treated with corticosteroids plus mycophenolate mofetil while 18 were treated with other immunosuppressive regimens (corticosteroids alone or corticosteroids plus cyclophosphamide). The number of patients developing endstage renal disease was significantly lower among treated compared with untreated patients (3 vs. 7 patients, respectively). No patient in the corticosteroids plus mycophenolate mofetil group doubled serum creatinine nor developed end-stage renal disease, as compared with 7 (significant) and 3 (not significant), respectively, in patients treated with other immunosuppressive regimens. Renal survival (100, 80, and 72% at 5 years) and the number of patients achieving clinical remission (86, 50, and 25%) were significantly higher in patients treated with corticosteroids plus mycophenolate mofetil as compared with patients treated with other immunosuppressive regimens and untreated patients, respectively. Thus, immunosuppressive treatments, particularly corticosteroids plus mycophenolate mofetil, can be beneficial in C3 glomerulonephritis.

Review Article | Open Access
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Show citation

Rituximab for Treatment of Membranoproliferative Glomerulonephritis and C3 Glomerulopathies

Michael Rudnicki[1]

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Abstract

Membranoproliferative glomerulonephritis (MPGN) is a histological pattern of injury resulting from predominantly subendothelial and mesangial deposition of immunoglobulins or complement factors with subsequent inflammation and proliferation particularly of the glomerular basement membrane. Recent classification of MPGN is based on pathogenesis dividing MPGN into immunoglobulin-associated MPGN and complement-mediated C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). Current guidelines suggest treatment with steroids, cytotoxic agents with or without plasmapheresis only for subjects with progressive disease, that is, nephrotic range proteinuria and decline of renal function. Rituximab, a chimeric B-cell depleting anti-CD20 antibody, has emerged in the last decade as a treatment option for patients with primary glomerular diseases such as minimal change disease, focal-segmental glomerulosclerosis, or idiopathic membranous nephropathy. However, data on the use of rituximab in MPGN, C3GN, and DDD are limited to case reports and retrospective case series. Patients with immunoglobulin-associated and idiopathic MPGN who were treated with rituximab showed partial and complete responses in the majorities of cases. However, rituximab was not effective in few cases of C3GN and DDD. Despite promising results in immunoglobulin-associated and idiopathic MPGN, current evidence on this treatment remains weak, and controlled and prospective data are urgently needed.

> Arch Iran Med. 2008 Jan;11(1):26-9.

Cyclosporine in the treatment of membranoproliferative glomerulonephritis

Nazila Bagheri [1], Eghlim Nemati, Khosro Rahbar, Ali Nobakht, Behzad Einollahi, Saeed Taheri

Affiliations + expand

PMID: 18154419

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Abstract

Background: Therapeutic approach to patients with idiopathic membranoproliferative glomerulonephritis is still controversial. Because it is more common in developing countries, the studies about it are limited.

Methods: We used cyclosporine to treat 18 patients with membranoproliferative glomerulonephritis who were resistant to other treatment protocols such as using aspirin, dipyridamole, or steroids. All patients were treated with cyclosporine plus low-dose prednisone and were followed for an average 108 weeks.

Results: Partial or complete remission of proteinuria occurred in 94% of the patients ($P<0.01$). Relapse occurred in one (14.2%) of remitters after discontinuation of the drug. But the remainder stayed in remission to the end of the observation period. There was a 507% decrease in the baseline creatinine clearance in one patient (5.5%).

Conclusion: These results suggest that cyclosporine may be an effective therapeutic agent in the treatment of resistant idiopathic membranoproliferative glomerulonephritis. Although the response is appeared later than other types of glomerulonephritis, but a long-term decrease in proteinuria and preservation of filtration function were observed in a significant proportion of the treated patients.

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Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy

Moglie Le Quintrec • Anne-Laure Lapeyraque • Arnaud Lionet • ... Chantal Loirat • Véronique Frémeaux-Bacchi • Fadi Fakhouri • Show all authors

Published: February 08, 2018 • DOI: https://doi.org/10.1053/j.ajkd.2017.11.019

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Results

26 patients (13 children/adolescents) were included. 22 (85%) patients had received steroids, plasma exchange, or immunosuppressive therapy before eculizumab, and 3 of them had rapid progression of their kidney disease despite treatment. At the initiation of eculizumab therapy, 11 (42%) patients had chronic kidney disease, 7 (27%) had rapidly progressive disease, and 3 (12%) required dialysis. After eculizumab treatment (median duration, 14 months), 6 (23%) patients had a global clinical response; 6 (23%), a partial clinical response; and 14 (54%), no response. Compared with those who had a partial clinical or no response, patients who had a global clinical response had lower estimated glomerular filtration rates, a more rapidly progressive course, and more extracapillary proliferation on kidney biopsy. Age, extent of renal fibrosis, frequency of nephrotic syndrome, low serum C3 and C3 nephritic factor and elevated soluble C5b-9 concentrations, or complement gene variants did not differ between responders and nonresponders.

Limitations

Retrospective design without a control group, relatively small number of cases, inclusion of pediatric and adult cases.

Conclusions

Eculizumab appears to be a potential treatment for patients with crescentic rapidly progressive C3 glomerulopathy. Its benefit in patients with non–rapidly progressing forms seems to be limited.

Experimental: Eculizumab Patients will receive Eculizumab and be observed for 60 minutes after the first 5 infusions, then 30 minutes after all subsequent infusions. Patients will not be allowed to take other immunomodulatory therapies during the study period but will continue on their other non-immunomodulatory therapies (e.g. ACE inhibitors, -statins, aspirin) without modifications unless clinically indicated. All patients, if unvaccinated, will be given N. meningitides vaccine at least two weeks prior to first eculizumab exposure. All female patients of childbearing potential will be asked to use adequate contraception methods during treatment and up to 5 months following discontinuation of eculizumab treatment.	Drug: Eculizumab Dosage/Frequency: 900 mg IV once a week for 4 weeks, 1200 mg IV week 5, then 1200 mg IV every 2 weeks through week 53. Other Name: Eculizumab (Soliris®)

MPGN & Transplantation

- In patients with primary MPGN, the recurrence rate is:
  - 20% to 30% in those with type I. (1)
  - 50% to 100% in those with type II. (2)

- In those with secondary disease, the recurrence is directly linked to control of the underlying illness.

GN recurrences after transplant

Disease	Recurrence frequency	Graft loss
SRNS with FSGS	30%	40-50%
MPGN		
Type I	20-30%	30-40%
Type II	80-100%	20%
Membranous nephropathy	10%	40%
IgA nephropathy	30%	15-30%
SHP nephritis	<1%	<1%
Systemic vasculitis	10-20%	<5%
SLE	< 2%	rare
Anti-GBM disease	< 5%	50%
D+HUS	exceptionnal	
Atypical HUS	30-50%	>50%
Amyloidosis	25 %	rare
Primary hyperoxaluria	100%	80%

MPGN vs Transplant glomerulopathy

MPGN recurrence

- Usually early after Tx
- EM: Electrodence deposit
- IF: C1q deposit (glomerul)
- History of MPGN pretransplant

Transplant Glomerulopathy

- Usually late after Tx
- EM: Electrolusent deposit
- IF: c4 d (PTC)
- DSA +

Table 7 Response of post-transplant MPGN recurrence to different treatments

From: Membranoproliferative glomerulonephritis recurrence after kidney transplantation: using the new classification

Treatment	Number of allografts	Response to therapy[a]
High dose steroids	4	1
Rituximab ± plasmapheresis	8	3
Plasmapheresis	1	1
Eculizumab	1[b]	1
No change in therapy	4	3

[a]Response to therapy defined by improvement in GFR and no subsequent graft loss

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8.2 Treatment

8.2.1 ICGN

Practice Point 8.2.1.1: When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process.

Practice Point 8.2.1.2: Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.

Practice Point 8.2.1.3: For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone.

Practice Point 8.2.1.4: For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.

Practice Point 8.2.1.5: For patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.

Practice Point 8.2.1.6: For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.

Practice Point 8.2.1.7: For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.

Practice Point 8.2.1.8: Patients who fail to respond to the treatment approaches discussed in 8.2.1.4 and 8.2.1.5 should be considered for a clinical trial where available.

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8.2.2 C3 glomerulopathy

Practice Point 8.2.2.1: In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.

Practice Point 8.2.2.2: Patients who fail to respond to the treatment approaches discussed in 8.2.2.1 should be considered for a clinical trial where available.