Πρωτοπαθείς Σπειραματικές Παθήσεις
Primary Glomerular Diseases

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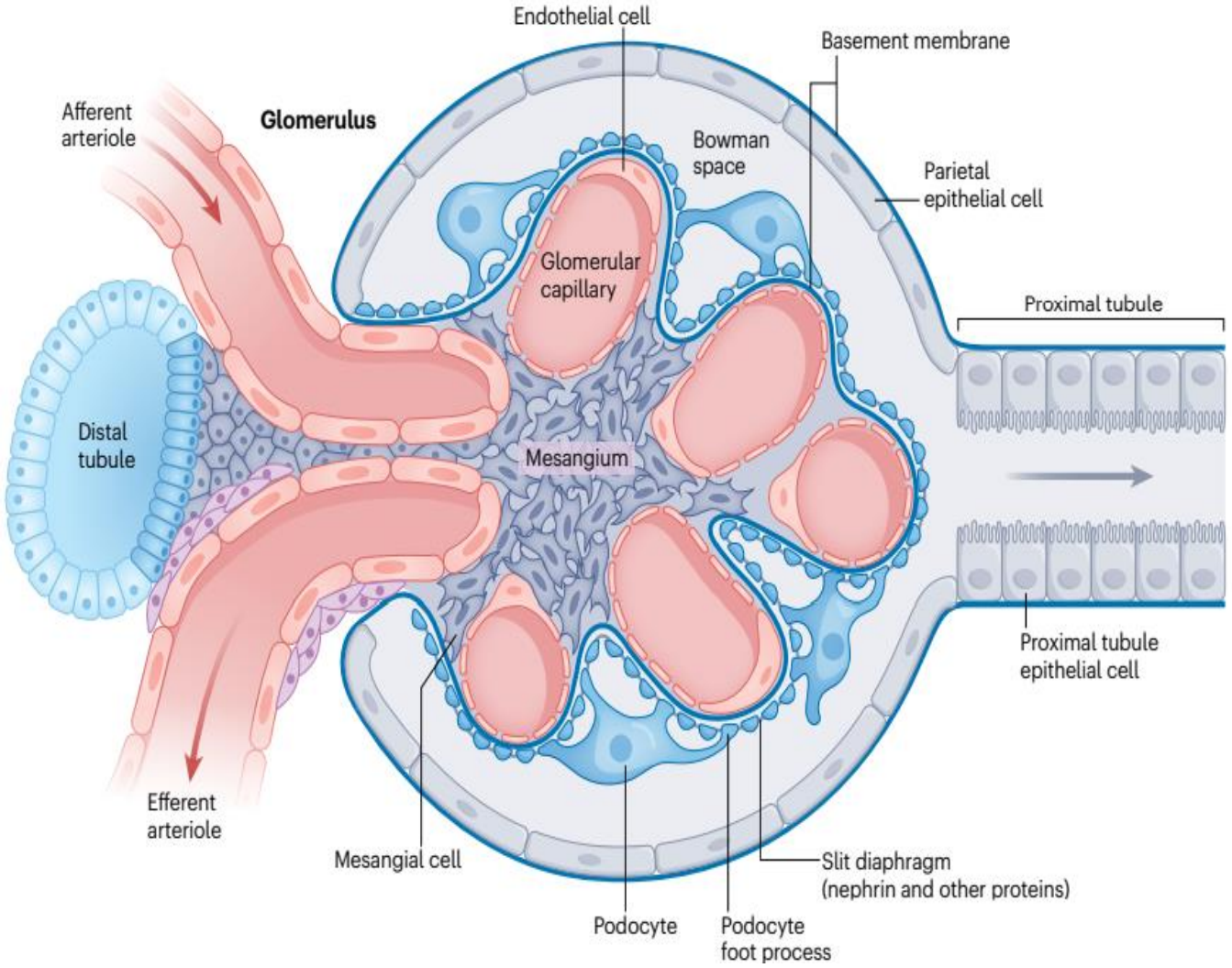
Ιατρική Σχολή ΕΚΠΑ, Γ.Ν.Αθηνών «Λαϊκό»

The glomerulus



Nephron = glomerulus + associated renal tubules

Anders HJ. Nat Rev Immunol. 2023 Jul;23(7):453-471

Glomerular filtration barrier

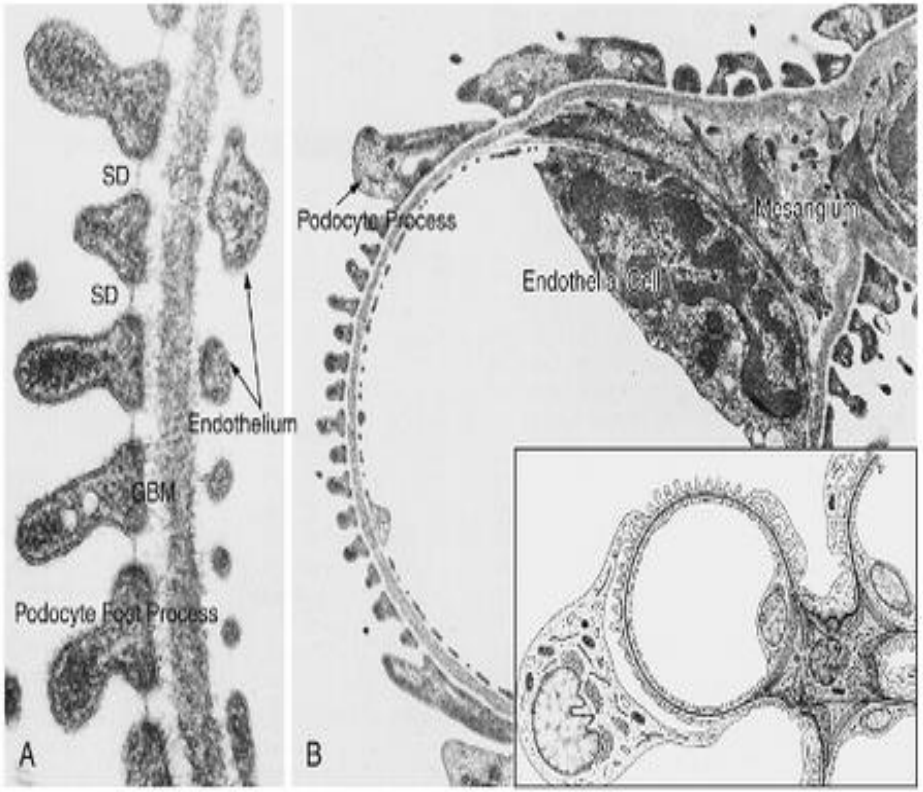
Fenestrated endothelium

+

Glomerular Basement Membrane (GBM)

+

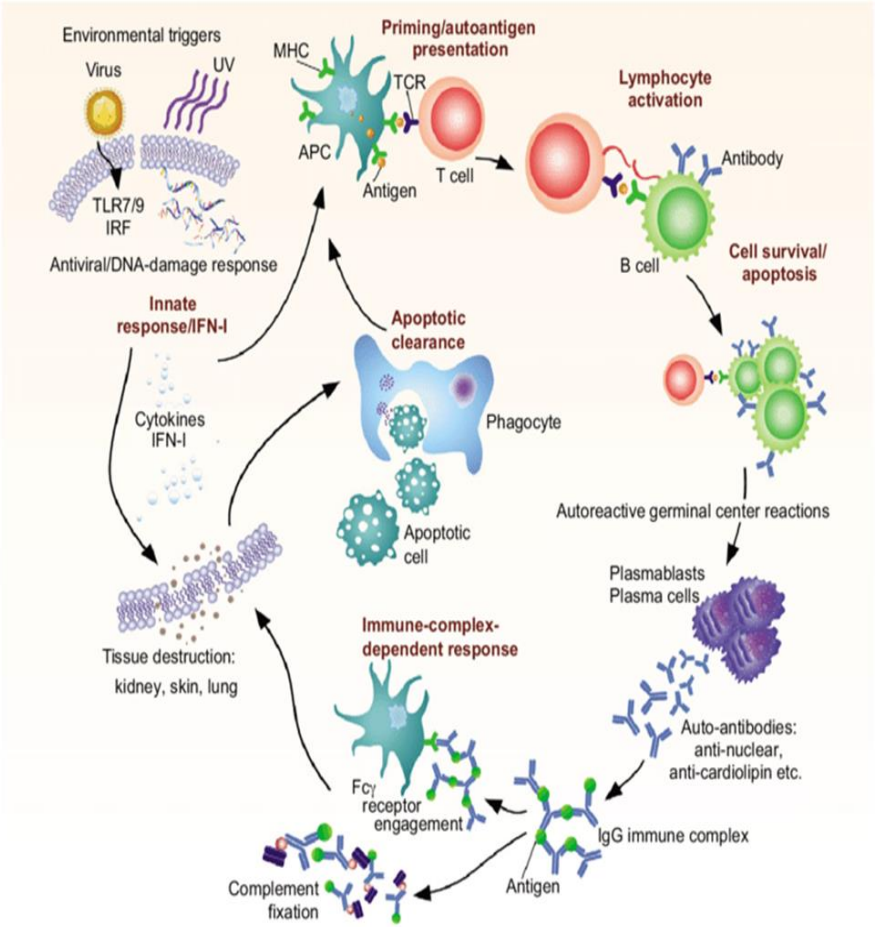
Epithelial cells (pocytes)



Gilbert SJ, Weiner DE, Primer on Kidney Diseases, 6th Edition

Pathogenesis of glomerular diseases

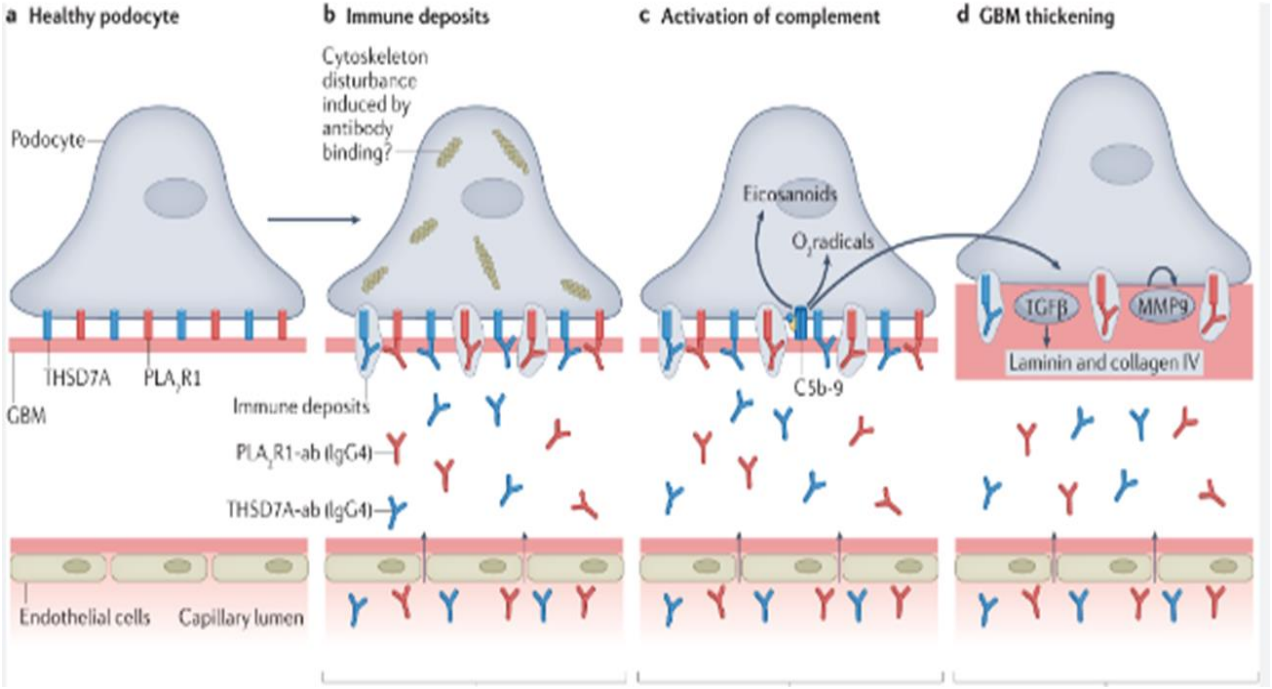
- ❑ Loss of immune tolerance
- ❑ Immune response against auto-antigens



Anders HJ. Nat Rev Immunol. 2023 Jul;23(7):453-471

Pathogenesis of glomerular diseases

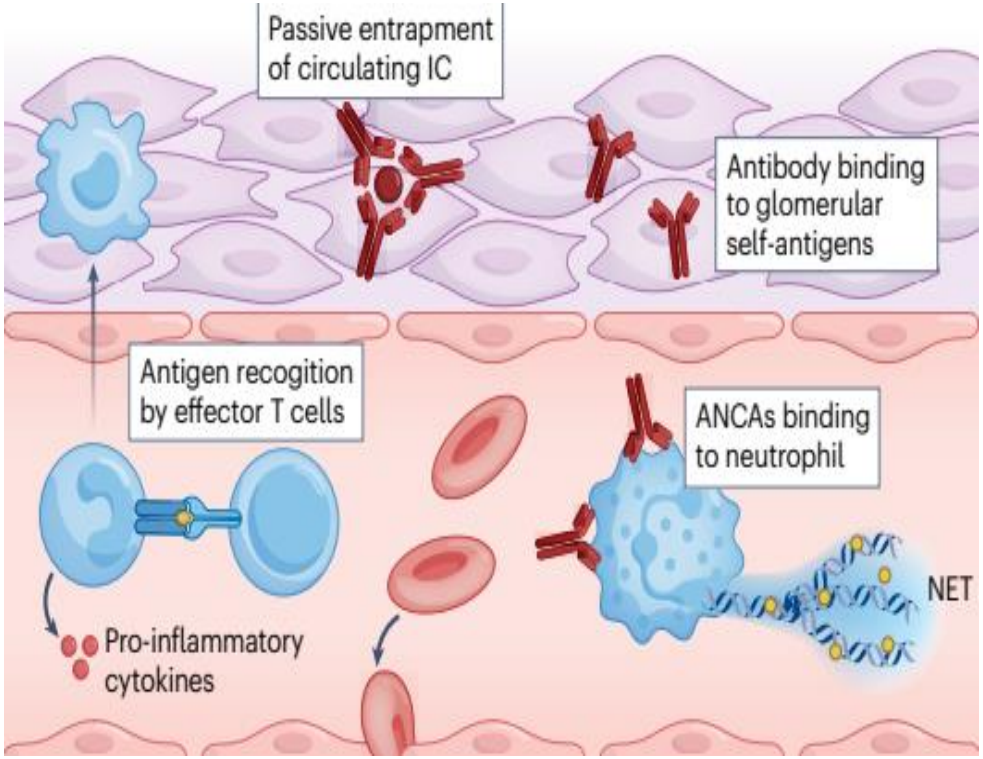
- Auto-antigens located in the glomerulus (GBM, podocytes)
- In situ formation of immune complexes



Hoxha E. Nat Rev Nephrol. 2022 Jul;18(7):466-478

Pathogenesis of glomerular diseases

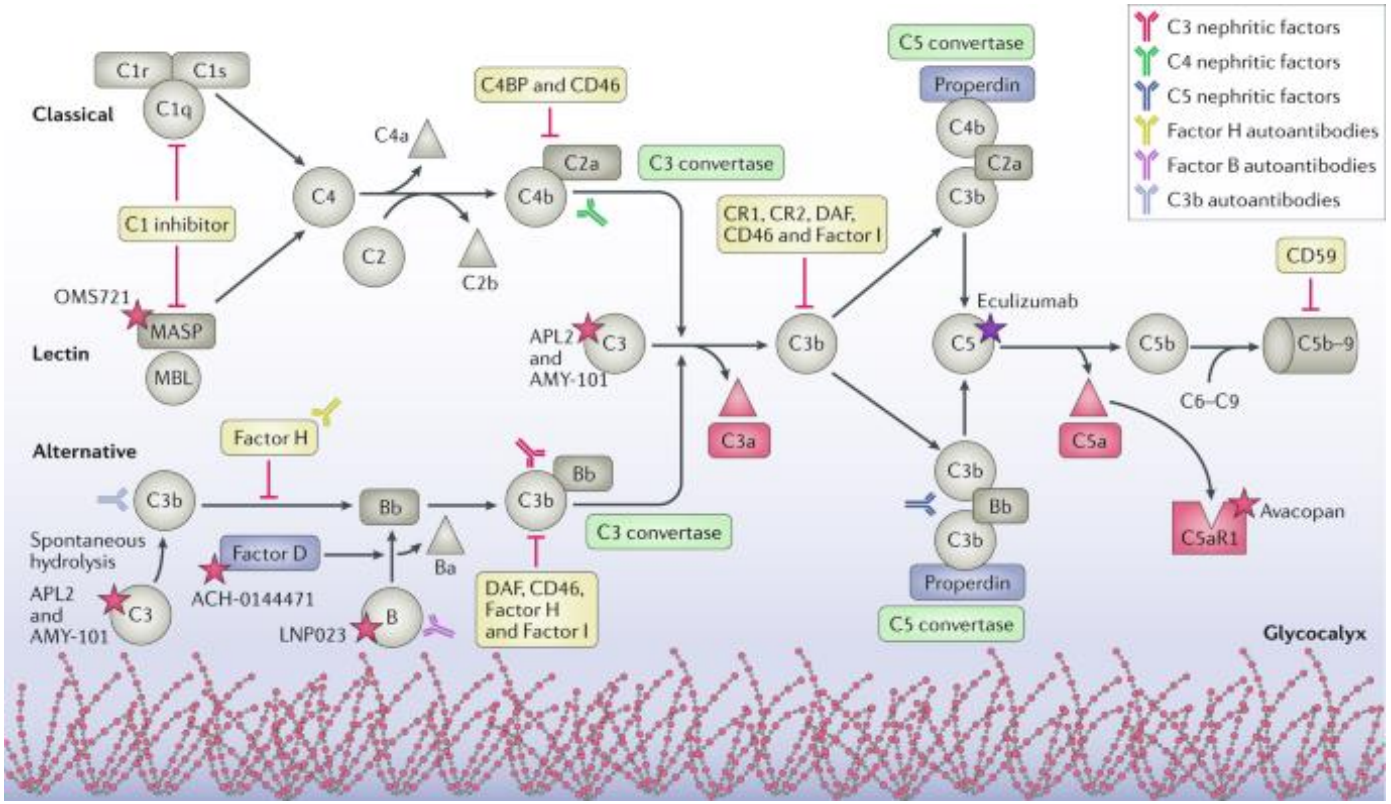
- Circulating auto-antigens form immune complexes which are trapped in the glomerulus (i.e. gd-IgA1, ANCA)



Anders HJ. Nat Rev Immunol. 2023 Jul;23(7):453-471

Pathogenesis of glomerular diseases

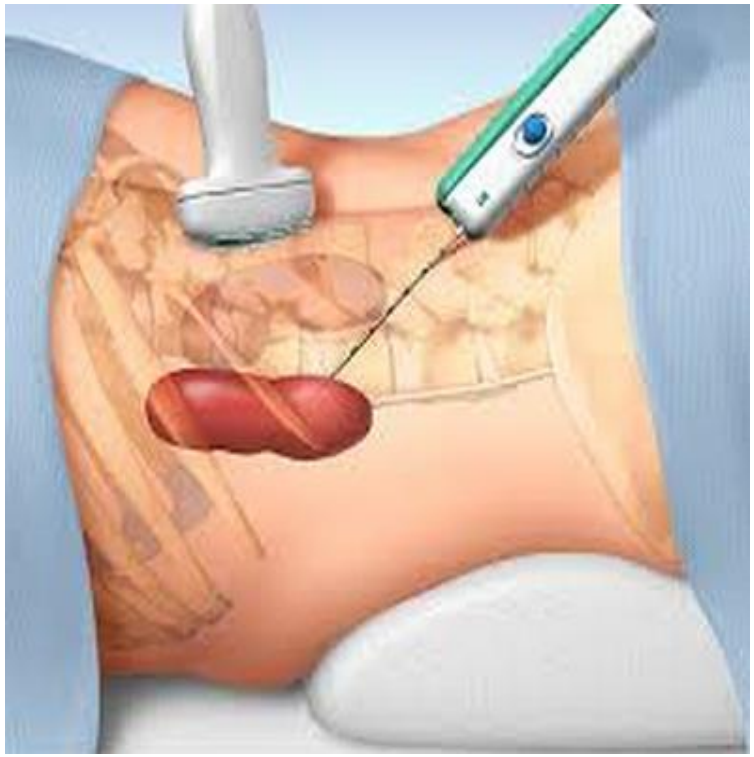
- Auto-antibodies against regulatory proteins of the complement system can cause an uncontrolled activation of the complement



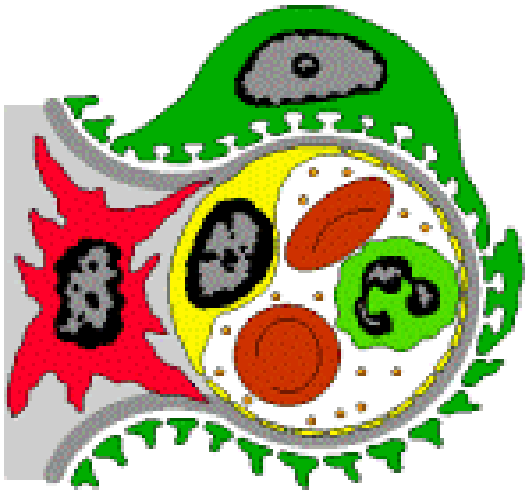
Smith RJH. Nat Rev Nephrol. 2019 Mar;15(3):129-143

Diagnosis of glomerular diseases

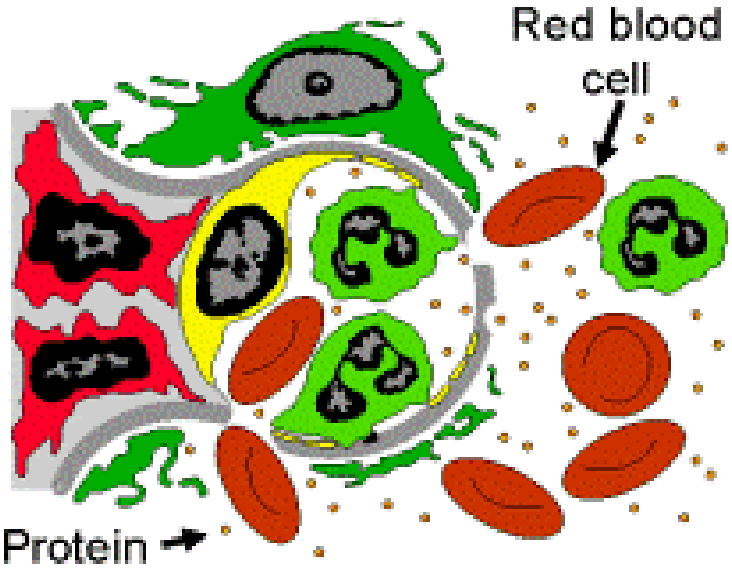
- Patient history
  - Systemic diseases (i.e. hypertension, diabetes, auto-immune diseases, chronic infections)
  - Drugs
- Family history
- Physical examination
- Blood examinations
- Urine examinations
- Imaging studies
  - To exclude non-glomerular cause of renal disease
- **Renal biopsy**



Clinical manifestations of glomerular diseases
Proteinuria - Hematuria



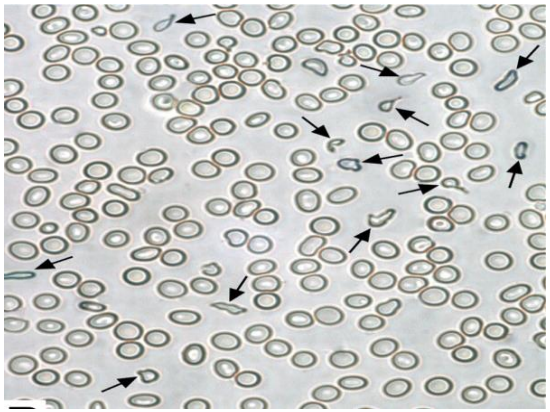
A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine.

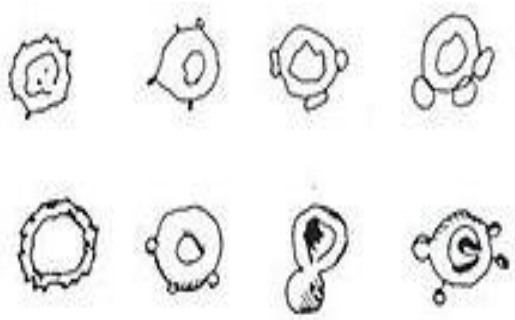


A capillary in a diseased glomerulus lets protein into the urine (proteinuria) and red blood cells into the urine (hematuria).

Isolated glomerular hematuria

- Microscopic detection of erythrocytes (>3 RBC per high power field) of **glomerular origin** in the urine





- May be accompanied by episodes of macroscopic hematuria, usually associated with an infection of the respiratory system

Nephrotic syndrome

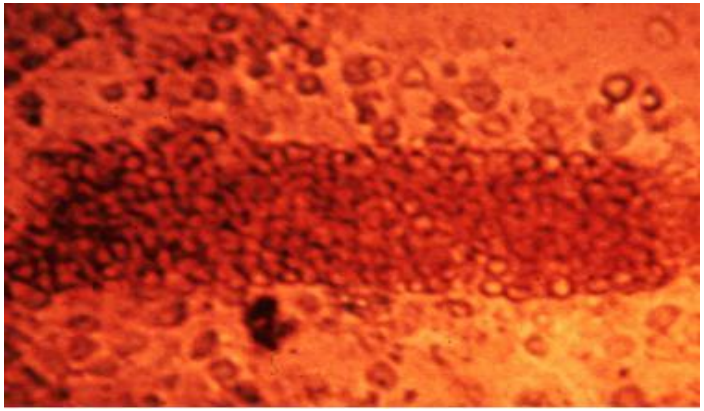
- ❑ Proteinuria >3.5g/24h
- ❑ Hypoalbuminemia <3 g/dl
- ❑ Oedema (of lower limb, periorbital, ascites, ana sarca)
- ❑ Hyperlipidemia
- ❑Hypertension

Neprotic syndrome may be complicated by:

- ✓**Infections**
- ✓**Thromboses**
- ✓**Acute renal injury**

Nephritic syndrome

- ❑ Glomerular hematuria with RBC casts
- ❑Proteinuria (usually subnephrotic)
- ❑ Acute kidney injury (may be oliguric)
- ❑Hypertension



Rapidly progressive glomerulonephritis

RPGN

- Clinicohistological definiton

- Refers to a rapid (within days or weeks) deterioration of renal function in the presence of a glomerulonephritis and glomerular crescent formation in at least 50-75% of glomeruli

- In 50% of cases RPGN is associated with:
  - Anti-GBM disease
  - Small vessel vasculitis
  - Systemic lupus erythematosus

- Other causes of RPGN
  - IgA vasculitis
  - Membranoproliferative glomerulonephritis (endocarditis, post-streptococcal glomerulonephritis)
  - Idiopathic

Chronic glomerulonephritis

❑ Syndrome characterized by gradual progression of kidney disease/renal function impairment, hematuria, proteinuria and/or hypertension in patients with an inflammatory glomerular disease.

❑ It should be considered and treated as chronic kidney disease.

IgA nepropathy

IgA nephropathy

- The **most common primary** glomerular disease (20-40%)
- Mainly sporadic disease, familiar cases may exist
- **20-30%** of patients reach **ESRD in 20 years**

KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276
O'Shaughnessy MM. Nephrol Dial Transplant. 2018 Apr 1;33(4):661-669

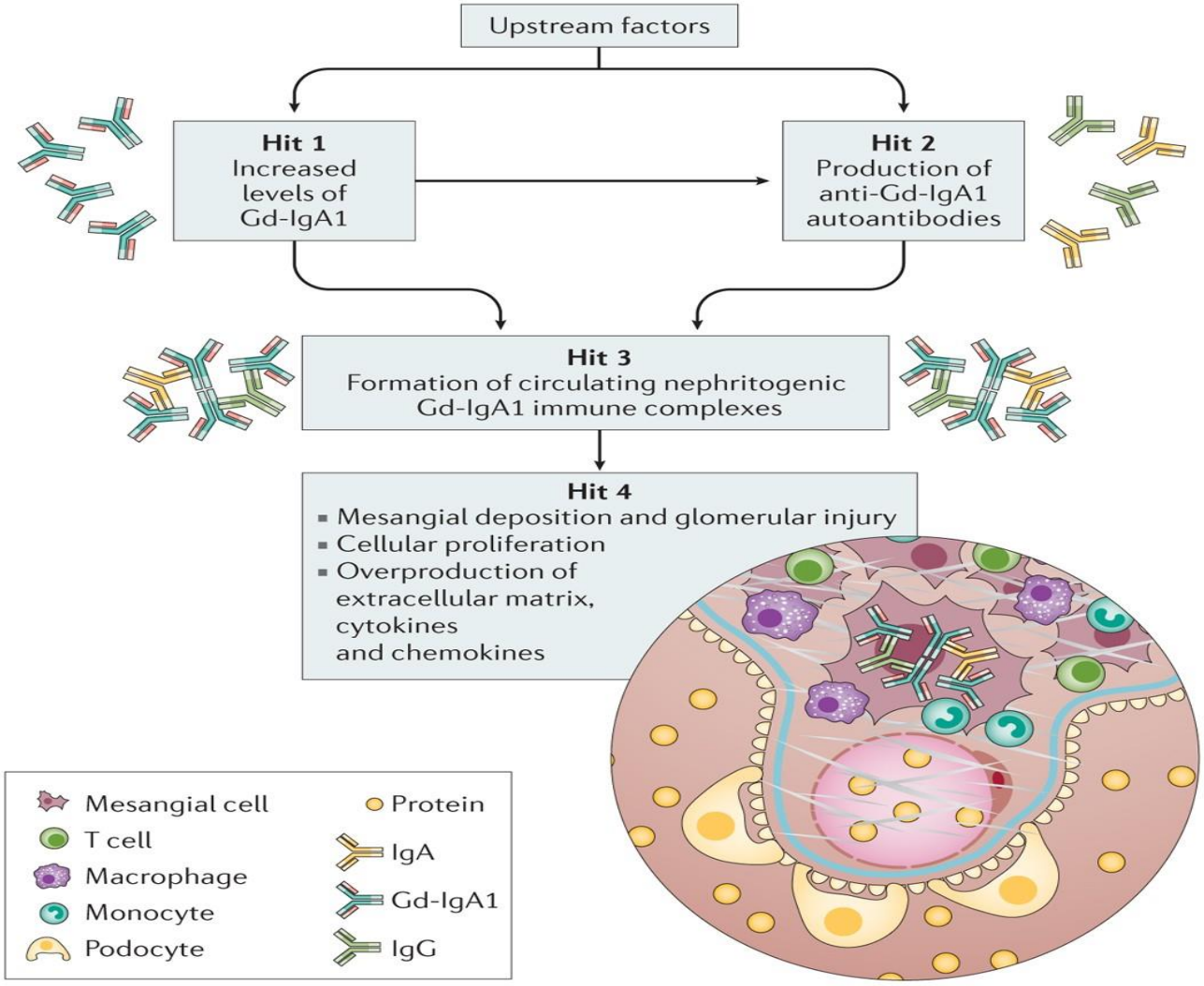
Clinical presentation of IgA nephropathy

- Great **phenotypic and histologic heterogeneity**

- Clinically manifested as **microscopic hematuria** ± episodes of **macroscopic hematuria** (associated with respiratory tract infections) ± **low grade proteinuria** but, in rare occasions, can present as rapidly progressive glomerulonephritis (**RPGN**)

KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276
O'Shaughnessy MM. Nephrol Dial Transplant. 2018 Apr 1;33(4):661-669

Pathogenesis of IgA nephropathy
The four-hit hypothesis

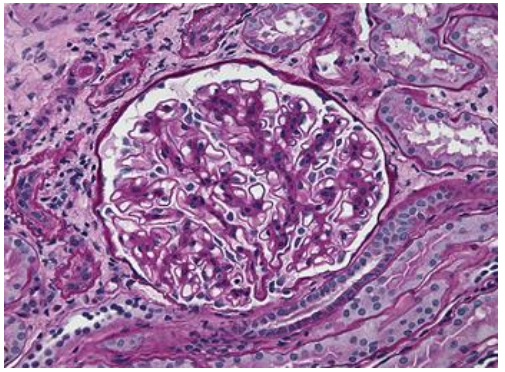


Nature Reviews | Disease Primers

Histological findings in IgA nephropathy

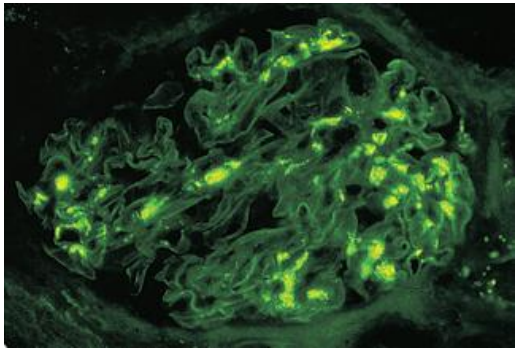
Light microscopy

- Mesangial proliferation



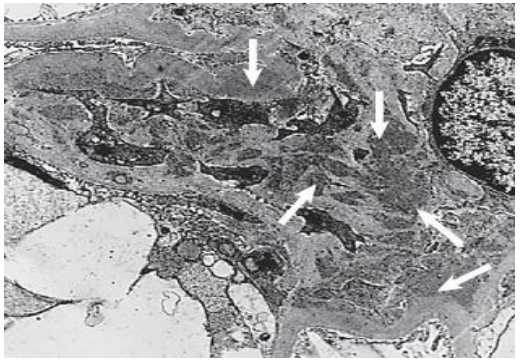
IF

- Positive for IgA



Electron microscopy

- Electron dense deposits in the mesangium



Comprehensive Clinical Nephrology 4th edition

Treatment of IgA nephropathy

- Lifestyle modifications (smoking cessation, weight loss)
- Blood pressure control **<120/70mmHg**
- **RAAS inhibitors**
- **SGLT2 inhibitors**
- **Sparsentan** (dual angiotensin-endothelin receptor antagonist)
- In patients at high risk of renal disease progression (**proteinuria >0.5g/24h** despite maximum supportive treatment):
  - **Targeted-release budesonide**
  - **Systemic oral corticosteroids**
  - **Participation in clinical trial**

Minimal Change Disease

Minimal Change Disease
MCD

- ❑ The most frequent cause of nephrotic syndrome in children

- ❑ Cause of **nephrotic syndrome** in **10-25%** of adults

- ❑ **Idiopathic** in **80-90%**

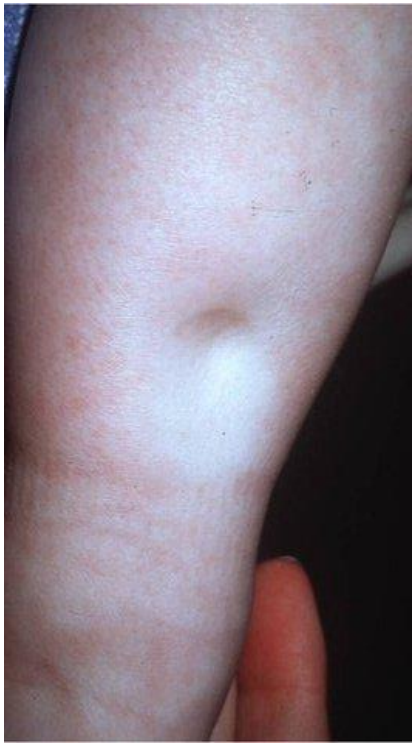
- ❑ **Secondary** MCD
  - Drugs (NSAID, lithium, D-penicillamine, tyrosine kinase inhibitors)
  - Infections (EBV, HIV, syphilis, parasites)
  - Malignancies (Hodgkin lymphoma, lymphohyperplastic diseases, solid organ malignancies)
  - IgA nephropathy, SLE nephritis

Vivarelli M. Clin J Am Soc Nephrol. 2017 Feb 7;12(2):332-345
Ahn W. Am J Kidney Dis. 2020 Jun;75(6):955-964

Clinical presentation of MCD

❑ **Sudden onset nephrotic syndrome**

- periorbital oedema, lower limbs oedema, ascites, anasarca oedema
- hypoalbuminemia
- hyperlipidemia



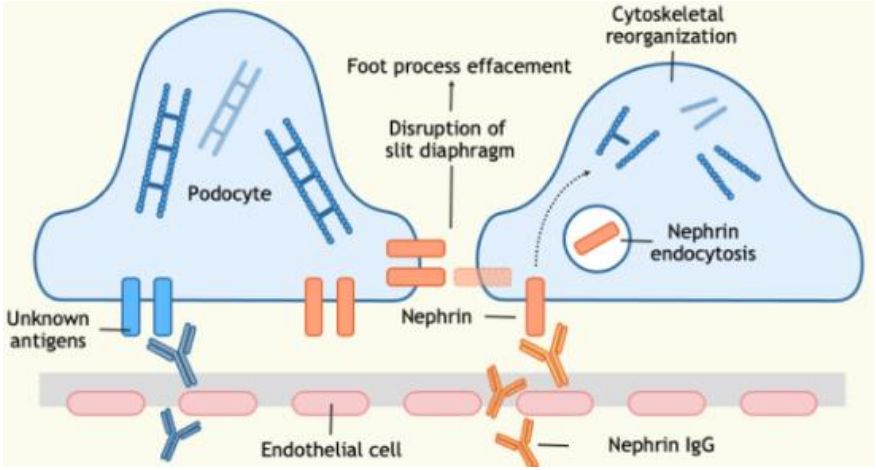
❑ **Microscopic haematuria** (20-30%)

❑ **Acute renal injury** (30%)

Vivarelli M. Clin J Am Soc Nephrol. 2017 Feb 7;12(2):332-345

Pathogenesis of MCD

- Unclear
- Indications of a **circulating glomerular permeability factor** secreted **by T lymphocytes**
- **Anti-nephrin auto-antibodies**
  - 44% of adults with MCD
  - 9% of adults with FSGS
  - 52% of children with idiopathic nephrotic syndrome



Lai KW. J Am Soc Nephrol. 2007 May;18(5):1476-85
Kemper MJ. Am J Nephrol. 2005 Mar-Apr;25(2):132-7
Watts AJB. J Am Soc Nephrol. 2022 Jan;33(1):238-252
Zhao C. Nature 2024

Histological findings in MCD

Light microscopy

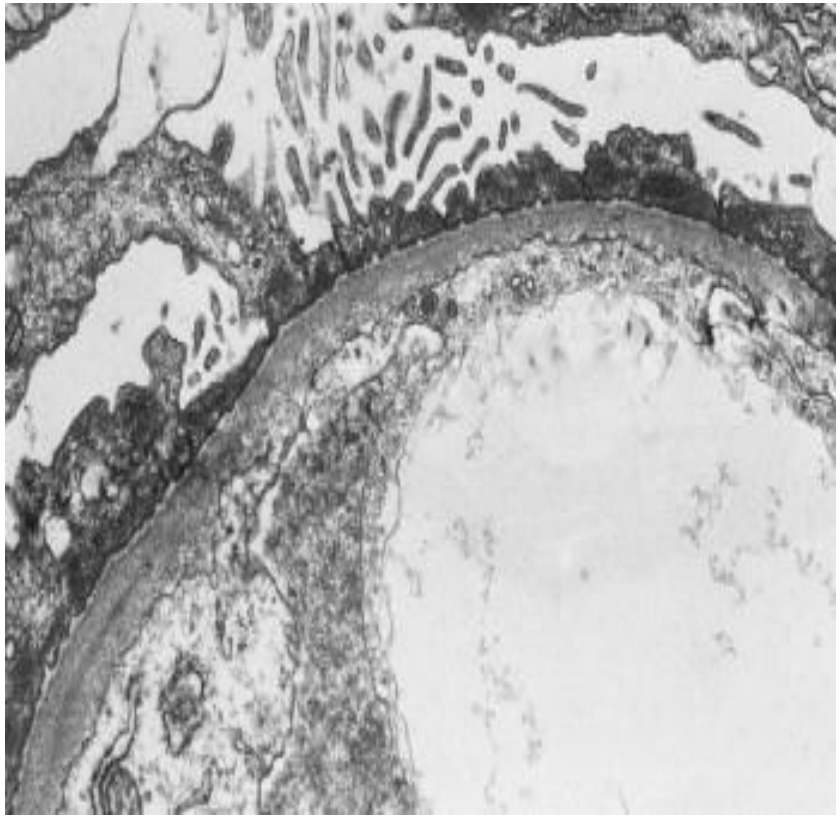
- No specific lesions

IF

- No deposits

Electron microscopy

- Diffuse foot process effacement



Fogo AB. Am J Kidney Dis. 2015 Aug;66(2):376-7

Treatment of MCD

- Treatment of choice →**high-dose corticosteroids**
- Disease **remission in >80%** of patients
- Disease **relapse in 60-85%** of adult patients, mainly in the first 3-6 months after treatment withdrawal
- **Frequently relapsing or steroid-dependent disease in 10-30%** of adult patients → cyclophosphamide, rituximab, calcineurin inhibitors, mycophenolate mofetil

KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276
Korbet. Clin J Am Soc Nephrol. 2019 Jun 7;14(6):911-913
Watts AJB. J Am Soc Nephrol. 2022 Jan;33(1):238-252

Prognosis of MCD

- Excellent long-term prognosis in patients who responded to corticosteroid treatment

- In **<10%** of patients the nephrotic syndrome is **resistant to corticosteroids** → a repeat renal biopsy usually reveals **FSGS** lesions

Korbet. Clin J Am Soc Nephrol. 2019 Jun 7;14(6):911-913
KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276
Waldman M. Clin J Am Soc Nephrol. 2007 May;2(3):445-53

Focal Segmental Glomerulosclerosis

Focal Segmental Glomerulosclerosis (FSGS)

- **Primary** FSGS

- **Genetic/familial** FSGS
  - Positive family history
  - Syndromic characteristics
  - Resistance to corticosteroids

- **Secondary** FSGS
  - Infections (HIV, CMV, Parvovirus B19, EBV, HCV, SARS-COV-2)
  - Drugs (Interferon, mTORi, calcineurin inhibitors, NSAID, heroin, lithium, pamidronate, anabolic steroids)
  - Glomerular hyperfiltration (hypertension, diabetes, obesity, renal dysplasia, solitary kidney, sickle cell anemia)

- FSGS of **undetermined cause**

Clinical presentation of FSGS

- Cause of **nephrotic syndrome** in **35%** of adult cases
- **5-20%** results in **ESRD**
- Primary FSGS
  - Sudden onset of nephrotic syndrome
  - Hematuria in 50%
  - Hypertension in 20%
  - Renal impairment in 25-50%
- Genetic/familial FSGS
  - Early age of onset, depends on the causative mutation
  - Steroid-resistant nephrotic syndrome in children
  - Gradual deterioration of proteinuria and renal function in adolescents and aduts
- Secondary FSGS – FSGS of UC
  - Gradual deterioration of proteinuria and renal function

Pathogenesis of FSGS

- Genetic variants/polymorphisms may act as risk factors for FSGS manifestation
  - **APOL1** polymorphisms

- Possible circulating permeability factor which disrupts podocytes' function
  - **suPAR** (soluble urokinase plasminogen activator receptor)
  - cardiotrophin-like cytokine 1
  - anti-CD40 IgG

- **Anti-nephrin auto-antibodies**
  - In **9%** of patients with **primary FSGS**
  - In **100%** of patients with **FSGS recurrence** in the renal allograft

Maas RJ. Nat Rev Nephrol. 2016 Dec;12(12):768-776
Kopp JB. Nat Rev Dis Primers. 2020 Aug 13;6(1):68
Shirai Y. Kidney Int. 2024 Mar;105(3):608-617
Watts AJB. J Am Soc Nephrol. 2022 Jan;33(1):238-252
Hengel FE. N Engl J Med. 2024 Aug 1;391(5):422-433

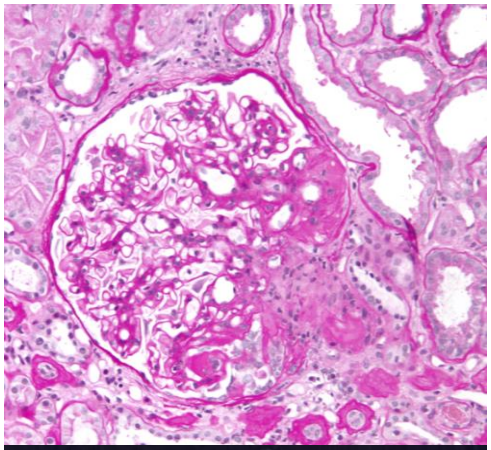
Pathogenesis of FSGS

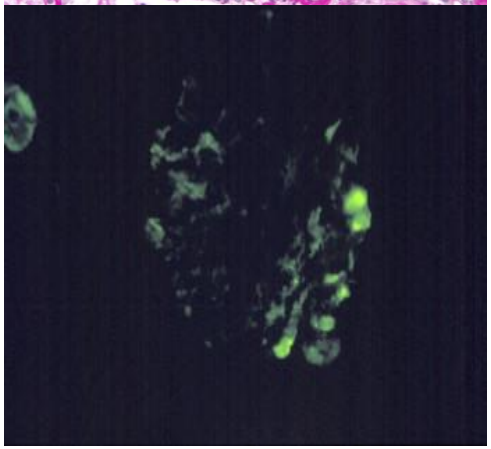
- Genetic/familial FSGS
  - Mutations in genes encoding for **proteins of podocyte cytoskeleton or the slit diaphragm** (i.e. podocin, nephrin)

- Secondary FSGS
  - Adaptive response to nephron loss
  - Nephron loss → hypertrophy and hyperfiltration of the remaining nephrons → increase in intraglomerular pressure → glomerular sclerosis and podocyte loss

Maas RJ. Nat Rev Nephrol. 2016 Dec;12(12):768-776
Kopp JB. Nat Rev Dis Primers. 2020 Aug 13;6(1):68
Shirai Y. Kidney Int. 2024 Mar;105(3):608-617
Watts AJB. J Am Soc Nephrol. 2022 Jan;33(1):238-252
Hengel FE. N Engl J Med. 2024 Aug 1;391(5):422-433

Histological findings of FSGS





Light microscopy

- Focal sclerosis of glomeruli

IF

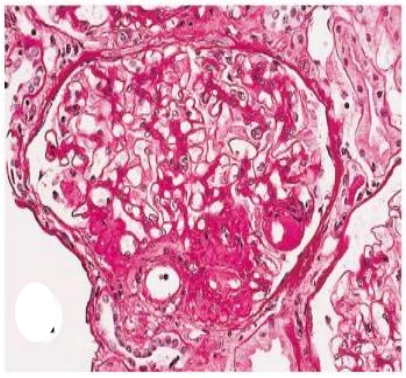
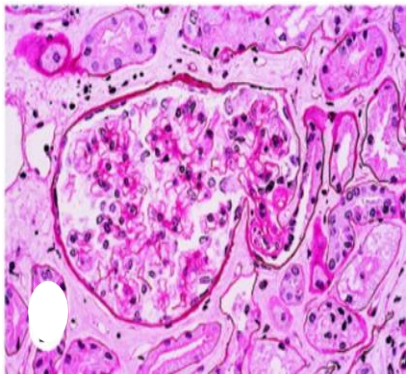
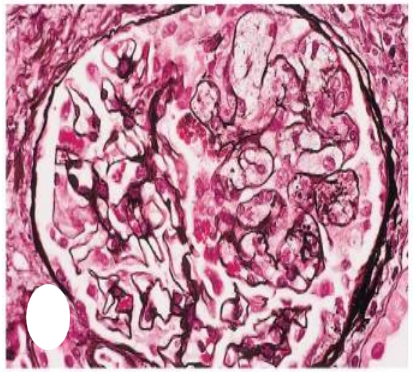
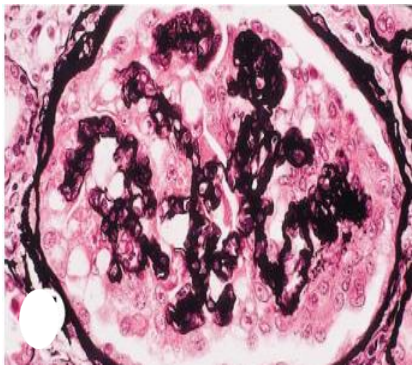
- No immunodeposits
- Rarely IgM and C3 deposits in sclerotic lesions

Electron microscopy

- Segmental or global effacement of podocytes' foot processes

Fogo AB. Am J Kidney Dis. 2015 Aug;66(2):e1-2

Histological types of FSGS
Columbia classification




Perihilar

Περιπυλαία

Tip lesion

Αλλοίωση κορυφής

Cellular

Κυτταρική

Collapsing

Ρικνωτική

D'Agati VD. Am J Kidney Dis. 2004 Feb;43(2):368-82

Histological types of FSGS
Columbia classification

- **Classic (NOS)**

  The most common pattern

- **Perihilar**

  More frequent in **secondary** FSGS – manifested as **proteinuria without nephrotic syndrome**

- **Tip lesion**

  Usually in **primary** FSGS- manifested as **steroid-sensitive nephrotic syndrome**

- **Cellular**

  Less frequent pattern – usually in **primary** FSGS

- **Collapsing**

  More frequent in **black race** – associated with **HIV** – **poor response to steroids**

Shabaka A. Nephron. 2020;144(9):413-427

Treatment of FSGS

- ❑ Lifestyle changes (smoking cessation, weight loss)
- ❑ Salt restriction
- ❑ Blood pressure control
- ❑ RAAS inhibitors
- ❑ SGLT2 inhibitors
- ❑ Diuretics

KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276

Treatment of FSGS

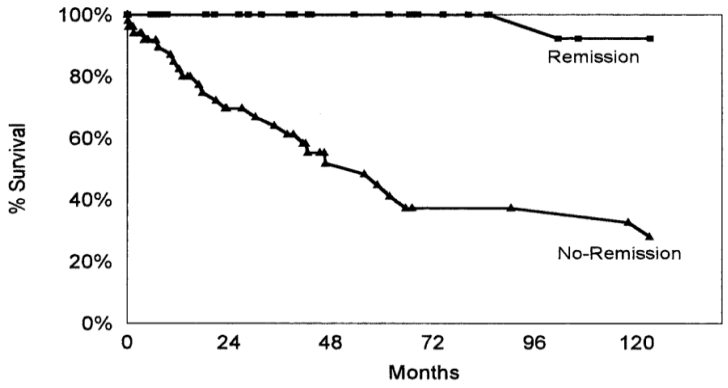
- **Treatment of the underlying disease in secondary FSGS**
  - **No** immunosuppression

- **Immunosuppression in primary FSGS** (nephrotic syndrome + diffuse podocyte effacement)
  - Corticosteroids (about 40% respond)
  - Calcineurin inhibitors
  - Mycophenolate mofetil
  - Rituximab

KDIGO 2021 Kidney Int. 2021 Oct;100(4S):S1-S276

Prognosis of FSGS

- The main prognostic factor for renal survival is the **response to treatment**



- **Prognostic factors at the time of diagnosis**
  - Magnitude of proteinuria
  - Renal impairment
  - Extent of chronic histological lesions
  - Collapsing FSGS

- **Recurrence of primary FSGS in the renal allograft**
  - In 30-40%, soon after kidney transplantation
  - Plasmapheresis ± rituximab are used
  - May lead to allograft loss

Chun MJ. J Am Soc Nephrol. 2004 Aug;15(8):2169-77

Membranous nephropathy

Membranous nephropathy
MN

- The **most frequent cause of nephrotic syndrome** in white adults (**30-50%** of cases)

- Most often **idiopathic** (primary) (75%)

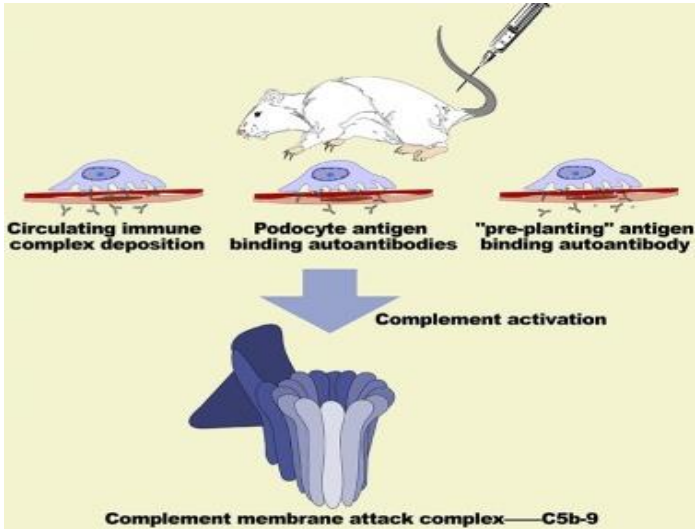
- **Secondary** MN is associated with:
  - Autoimmune diseases (i.e. SLE)
  - Infections (HBV, HCV, syphilis)
  - Malignancies
  - Drugs (NSAID, gold, penicillamine, anti-TNF agents)

Beck LH, N Engl J Med. 2009 Jul 2;361(1):11-21
Debiec H. Semin Immunopathol. 2014 Jul;36(4):381-97

Pathogenesis of MN

- Deposition of immune complexes in the subepithelial space of GBM → thickening of the GBM and complement activation

- Podocyte antigenic targets:
  - NEP
  - **PLA2R in >75%** of patients with primary MN
  - THSD7A in 3-5% of patients with primary MN



Liu W. Front Immunol 2019;10:1809

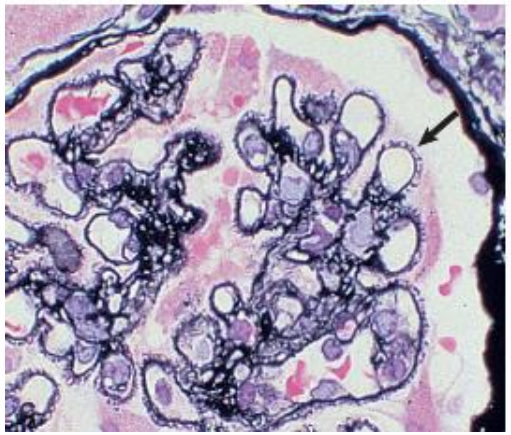
Clinical presentation of MN

- Proteinuria – nephrotic syndrome in 95% of cases
- Microscopic hematuria in 15-30% of cases
- Hypertension
- Edema
- Hypercoagulable state (alb<2)

Histological findings in MN

Light microscopy

- Thickened capillary wall
- Projections of GBM between deposits (spikes)

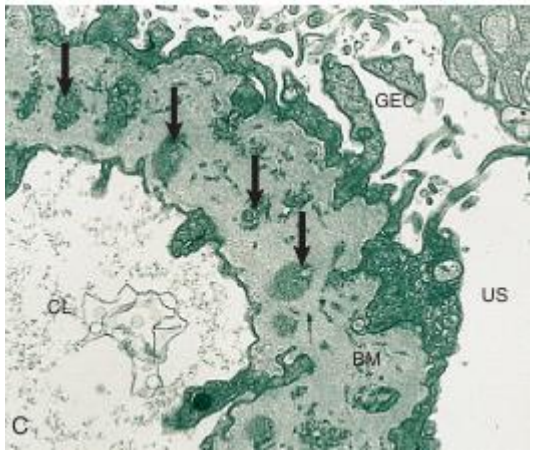


IF

- Positive for IgG ± C3

Electron microscopy

- Subepithelial electron-dense deposits
- Podocyte foot effacement
- spikes



Comprehensive Clinical Nephrology 4th edition

Prognosis of MN

- **Spontaneous** remission in **1/3** of patients
- **1/3** of patients **slowly progress**
- **1/3** of patients reach **ESRD in 10 years**
- **Increased risk of progression**
  - Impaired renal function
  - Proteinuria >3.5g/24h without decrease >50% after 6 months of conservative treatment

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Treatment of MN

- Conservative treatment
  - Blood pressure control
  - Salt restriction
  - RAAS inhibitors
  - SGLT2 inhibitors
  - Diuretics
  - Lipid lowering agents
  - Prophylactic antithrombotic agents

- Immunosuppressive treatment
  - If **no response after 6 months of conservative treatment**
  - If **malignancy has been excluded**
  - Rituximab ± calcineurin inhibitors ± steroids
  - Cyclophosphamide + steroids

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Membranoprilferative glomerulonephritis

Membranoproliferative glomerulonephritis
MPGN

- **Histologic pattern** of glomerular injury characterised by:
  - Glomerular hypercellularity
  - Diffuse thickening of capillary walls
  - Double contour of GBM

- Clinically manifested with
  - Proteinuria, frequently associated with nephrotic syndrome
  - Microscopic or occasionally macroscopic hematuria
  - Renal impairment
  - Hypertension
  - Low levels of C3 or C4

- Due to **immune complex or monoclonal Ig deposition** or **complement activation**

- May be **idiopathic** or **secondary**

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Causes of MPGN

- **Immunoglobulin/immune complex-mediated**
  - Infections (HCV, HBV, endocarditis, visceral abscesses, leprosy, meningococcal meningitis, malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis)
  - Auto-immune diseases (SLE, Sjogren's syndrome, rheumatoid arthritis, mixed connective tissue disease)
  - Monoclonal gammopathy
  - Fibrillary glomerulonephritis
  - Idiopathic

- **Complement-mediated** (C3 glomerulonephritis, C3 Dense Deposit Disease)
  - Mutations in complement regulatory proteins or complement factors
  - Antibodies to complement regulatory proteins or complement factors
  - Very high rate of recurrence in renal allografts

- **No immune complexes or complement**

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Treatment of MPGN

- Treatment of the **underlying cause**
- Supportive care with **RAASi** in:
  - Idiopathic ICGN with proteinuria <3.5g/24h and normal GFR
- Immunosuppressive treatment with **steroids ± MMF ± CYC ± Rituximab** in:
  - Idiopathic ICGN with nephrotic syndrome or/and renal impairment
- Immunosuppressive treatment with **steroids + MMF or eculizumab** in:
  - **C3GN** with moderate-to-severe disease in the absence of monoclonal gammopathy

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