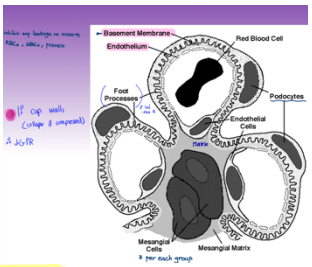
First Part: Basic Concepts



- **Glomerulonephritis is inflammation of the glomeruli**

🔷 The glomeruli are the kidney's little "filters" ,Glomerulonephritis = when those filters get inflamed(angry, swollen, malfunctioning)

- **Glomerulopathy is a disease of the glomeruli when there is no evidence of inflammation.**

🔷 filters are damaged, but no signs of inflammation (no redness, no swelling). They're just... broken.

- **Glomerular Injury: impairment of selective filtering properties of kidney leading to decrease GFR**

🔷 Kidneys normally allow only *tiny good stuff* (water, electrolytes) through. Injury →lets the wrong people (big molecules) through. GFR drops= kidneys get lazy.

- **Molecules normally not filtered such as constituents of the blood and protein pass into the urine and are excreted ,, Glomerular disease**

🔷 Blood parts and proteins are supposed to stay IN the body, not pee out. In glomerular disease, you literally lose these your urine.

Briefly : GN→ inflammation (kidney itself (↑ size) or external (sth invade kidney)) of glomerular↑ = #cell
Glomerulopathy → no inf signs (hypercellularity , fibrosis , thicken BM)
G injury : if blood , protien , glu → in urine (NO NORMAL)

Glomerular Diseases

- **Glomerular disease are classified → urine changes that manifest predominantly with**

🔷 How do we categorize these diseases? Look at what's leaking into the pee. **< URINALYSIS = IMP>**

- **Nephrotic range proteinuria and nephrotic urine sediment (fatty cast, oval bodies, few cell no casts)**

🔷 *Nephrotic:* LOTS of protein leaking out (>3.5 g/day). Sediment = when you spin urine in the lab, you see fatty casts (fat-globs shaped like tubes) and oval fat bodies.
Few cells = inflammation isn't crazy.

- **Haematuria, usually combination with proteinuria (which may be nephrotic range) with dysmorphic RBCs mixed with RBCs cast nephritic urine sediment**

imp

🔷 *Nephritic:* Bloody pee + proteinuria (sometimes heavy) + weird-shaped red blood cells (dysmorphic = damaged from squeezing through broken glomeruli) and red blood cell casts (clumps stuck together).

Briefly : classified ?based on urine changes
Nephrotic → frothy urine (protien in urine (> 3.5g/d)
may be combination (protienuria + hematuria → dysmorphic + RBCS cast)
ps: dysmorphic = prob : proximal

🔴 **remember this: Huge difference**

- **Nephrotic:** Protein protein protein
- **Nephritic:** Blood blood blood

💡 **Top Concept**

- **Proteinuria + Hematuria = Always Significant → Glomerular Origin**
- **Dysmorphic RBCs or RBC casts = Glomerular source**
- **Nephritic = Inflammation** (enough damage to cause leakage of RBC)
- **Nephrotic = Permeability problem (massive protein loss)**

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1. Asymptomatic

- **Proteinuria:150mg–3 g/day (low grade)**

- Hematuria: >2 RBCs/high-power field
- ⚠️ Indicates underlying glomerular disease even if silent

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2. Macroscopic Hematuria (usually painless, no blood clots , post infx)
   - Visible brown/red urine
   - Often post-infection (e.g., URI, pharyngitis)
   - Can be recurrent, especially in IgA nephropathy
   - كل ما ارشح واروح عالحمام بلاقي دم بالبول
   - Mc underlying causes : renal stones , mass , malignancy , liver diseases
   - ⚠️ asymp. Hematuria +/- proteinuria b2wn attacks

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3. Nephritic Syndrome 🔥🚨 (Inflammation) >> collapsed capillaries ↓GFR
   - Oliguria
   - Hematuria + RBC casts (pepsi color)
   - Proteinuria <3 g/day
   - Hypertension
   - Edema (mild to moderate)
   - Sudden , self-limiting (if assosciated with sysdiseases → needs tx)
   - ⚠️ Seen in post-strep GN, lupus nephritis

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4. Nephrotic Syndrome 💧 (Leaky filter) (glomerulopathy)
   - Proteinuria >3.5 g/day
   - Hypoalbuminemia <3.5 g/dL
   - Edema (often severe, generalized) → M/C
   - لما اصحى بلاقي عيوني منفخة او رجلي منفخة ، بلاقي رغوة بالبول
   - Hyperlipidemia, lipiduria
   - ⚠️ immunedeficiency , hypercoagular state →Prone to thrombosis and infections

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5. Rapidly Progressive GN (RPGN) 🚨
   - Renal failure over days–weeks
   - Hematuria : RBC casts
   - Proteinuria usually <3g/d (usually associated with nephritic syndrome).
   - BP often NL
   - ⚠️ may have feautures of vasculitis (e.g., ANCA, Goodpasture)
   - Medical emergency – biopsy + immunosuppression

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6. Chronic Glomerulonephritis
   - Longstanding kidney damage
   - Shrunken smooth kidneys imp
   - Hypertension
   - Proteinuria >3 g/day
   - Other systemic manifestation (ex: blood 8.5)

🔑 KEY EXAM PEARLS:
- 🧠 RBC casts = pathognomonic for glomerulonephritis
- 👁️ Proteinuria >3.5 g/day = Nephrotic range
- ⏱️ RPGN = acute, needs urgent attention
- 🔪 Nephrotic = hypoalbuminemia, hyperlipidemia, edema
- 💡 Asymptomatic + isolated findings still = disease!
- RBCs intact + large → source of blood is urinary tract : pelvis , ureter , bladder

- **Dysmporphic RBSs / cast → blood? From glomeular : destructed RBCS**

🌟 **Definitions of Nephrotic and Nephritic**

• Nephrotic syndrome:

🔷 *Clinical picture:*

- Nephrotic urine sediment (fatty casts, no big inflammation)
- Edema (swelling, thanks to low albumin)
- Hypoalbuminemia
- Hypercholesterolemia and hypertriglyceridemia (body tries to fix the low protein ?make too much fat)

• Nephritic syndrome

🔷 *Clinical picture:*

- Nephritic urine sediment (bloody pee with RBC casts)
- +/- HTN
- +/- high serum creatinine and oliguria

Combined : HTN / AKI / edema / RBCs casts / dysmorphic RBCs / protienuria >> kidney bx →تحدد النوع

• Several glomerular disease typically manifest with both features of both nephritic and nephrotic syndrome for example: MPGN, Lupus nephritis imp : they have nephrotic range but nephritic features.

🔷 Sometimes diseases show *both* blood and protein in urine (ex:MPGN, Lupus nephritis).

• Pathogenesis of nephrotic and nephritic syndrome → differs

• There is clinical overlap, Eg, several disorders may manifest with same clinical picture and presence haematuria and proteinuria does not predict response to treatment or prognosis

🔷 *Translation:* Just because someone has blood and protein in the urine doesn't tell you automatically if they'll get better or worse. Clinical detective work is needed.

🧠 **Diagnosis of Glomerular Diseases**

• It can be Primary or Secondary

🔷 Meaning:

- **Primary:** the problem *starts* in the kidney.
- **Secondary:** (most pt = lupus nephritis)

• Clinical Presentation:

-Asymptomatic proteinuria
-Asymptomatic haematuria
- Macroscopic haematuria → you can **see with your eyes**
- Nephrotic syndrome
🔷 Major proteinuria + edema + low albumin + high cholesterol. Diagnostic criteria.
- Nephritic syndrome
🔷 Hematuria + some protein + hypertension + low urine output maybe.
- Rapidly progressive GN
- Chronic glomerulonephritis

🔍 **How We Suspect Glomerular Disease**

• Usually suspected when screening or diagnostic testing reveals:

🔷 *When you see:*

- **High serum creatinine** (bad kidney function)
- **Abnormal urinalysis** (blood, +/-protein, both)

- Pt with nephritic or RPGN → needs to be admit

- **identifying likely causes by patient's age and associated illness**
- Old diabetic? Think secondary causes. (Diabetic neuropathy)
- Young kid? Think primary GN. (Minimal disease)
- Lupus? Think secondary GN. (Lupus nephritis)

DX of Glomerular Diseases

- **History**
  - Hematuria (tea-colored urine?)
  - Foamy / frothy urine (sign of proteinuria)
  - Swelling (periorbital or leg swelling)
  - High blood pressure
- **Multisystem disease associated with GN (Diabetes (commenst cause of protienuria), Hypertension, Amyloid, Hepatitis, Lupus, Vasculitis, Malignancy)**
- **Positive family history of renal disease or ESRD**
- **Family history of Alport's (hearing loss + kidney disease), Focal Segmental Glomerulosclerosis, Haemolytic Uremic Syndrome,, IgA nephropathy , HIV**

- **Morbid obesity associated with FSGS**
- *Fat overload = stress on kidneys*

- **Medications use** (imp)
  - **NSAIDs, Interferon → Minimal change disease**
  - **Penicillamine, Mercury → Membranous nephropathy**
  - **Pamidronate, Heroin → FSGS**
  - **Cyclosporine, Tacrolimus , ocp → with HUS**

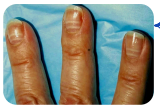
Hx of recent or persistent infection (as streptococcal,infective endocarditis and viral infection) (1)
Hx of malignancy (solid as lung ,breast and GI with **membranous nephropathy** OR Hodgkin's Lymphoma in **minimal change** and Non HL in **membranoproliferative GN**) (2) (3)

- nephrotic s. >> can be 2nd to malignancy

Physical Examination

- **Vital signs — check BP!**
- Hypertension is super common. (especially nephritic >> nephrotic).
- **Dependent pitting edema (lower limb or sacral edema)** →classic for nephrotic syndrome.
- **Periorbital edema** →Puffy eyes, especially mornings. (nephrotic)
- **Genital edema, abdominal wall edema, ascites, pleural effusion** →if severe nephrotic syndrome.

Edema: very imp in nephrotic.

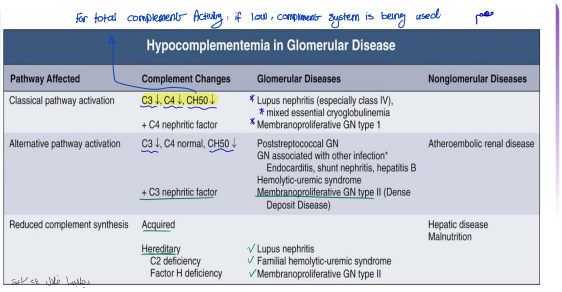


- **Xanthelasma in nephrotic syndrome** →cholesterol is crazy high.
- **Muehrcke's bands (white lines in nails)** → Seen in hypoalbuminemia (low albumin) → NEPHROTIC
- **Pulmonary signs in pulmonary-renal syndrome**
- **Palpable purpura in vasculitis, SLE, cryoglobulinemia or endocarditis**
- Non-blanching, raised red-purple spots — red flag for vasculitis.

Investigations:

- **Renal function (Creatinine, Urea, Electrolytes).**
- **Urine analysis (protein, blood)**
- **Urine microscopy (dysmorphic RBCs, RBC casts)**
- **Serum albumin**
- **24hr urine protein or spot urine protein:creatinine ratio** →How much protein is leaking per day
- **Serology :**

You start with this test in diagnostic approach to differentiate btw nephrotic and nephritic Syndrome



for total complement Activity, if low, complement system is being used

Hypocomplementemia in Glomerular Disease

Pathway Affected	Complement Changes	Glomerular Diseases	Nonglomerular Diseases
Classical pathway activation	C3 ↓, C4 ↓, CH50 ↓ + C4 nephritic factor	* Lupus nephritis (especially class IV), * mixed essential cryoglobulinemia * Membranoproliferative GN type 1	
Alternative pathway activation	C3 ↓, C4 normal, CH50 ↓ + C3 nephritic factor	Poststreptococcal GN GN associated with other infection* Endocarditis, shunt nephritis, hepatitis B Hemolytic-uremic syndrome Membranoproliferative GN type II (Dense Deposit Disease)	Atheroembolic renal disease
Reduced complement synthesis	Acquired		Hepatic disease Malnutrition
	Hereditary C2 deficiency Factor H deficiency	✓ Lupus nephritis ✓ Familial hemolytic-uremic syndrome ✓ Membranoproliferative GN type II	

Ex: ↓C3 ↓C4 → could be lupus nephritis
↓C4 → membr. type I
↓C3 → most likely post infx or Hemolytic uremic synd. / Thrombomicroangiopathic / post. infx nephritis

Interpretation of Hypocomplementemia in Glomerular Diseases

Finding	Think of
↓ C3 + ↓ C4	Lupus nephritis, Cryoglobulinemia, MPGN type I
↓ C4 only	Membranoproliferative GN type I
↓ C3 only	Post-streptococcal GN, HUS, MPGN type II
↓ Complement (production defect)	Liver disease, Malnutrition

🔷 To find autoimmune causes:
- ANA/Anti-DNA = lupus
- RF/Cryoglobulins = vasculitis
- Anti-GBM = Goodpasture's
- ANCA = vasculitis
- ASO = post-strep GN

- **Urine electrophoresis for heavy or monoclonal light chains (myeloma)**

🔷 Look for cancer causing amyloidosis/light chain disease.

- **Hepatitis B, C, HIV testing** → (imp in membranous and MPGN type I)
- **Complement levels (C3, C4, CH50)**

🔷 Low complement = classic in lupus, MPGN.

- **Renal Ultrasound**

🔷 Check size:
- Small = chronic damage
- Large = DM, amyloid, HIV

- **Renal biopsy**

🧠 **Nephritic Syndrome**

= Haematuria with variable degree of proteinuria usually dysmorphic or often RBCs cast

- **Often >= of the following elements are present:**
  - Oedema
  - Hypertension
  - Elevated serum creatinine
  - Oliguria

🔷 Short version: bloody pee + swelling + high BP + low urine.

- **It can be primary or secondary**
  - **Primary**
  - **Secondary:** (in jordann → mc = lupus).
- **dx is based on History, physical examination and sometimes renal biopsy**
- **Treatment and prognosis varies by cause**
- **The syndrome can be:**
  - Acute (serum creatinine rises over days-weeks)
  - Chronic (progress over years)

🔷 Acute = emergency, fast kidney failure.
Chronic = slow, sneaky kidney failure.

- **Or can be:**
  - Primary (like IgA nephropathy)
  - Secondary (like Lupus nephritis)

* Prognosis depends on:
1. Fam Hx
2. Severity of proteinuria
3. Initial presentation → Serum creatinine levels.

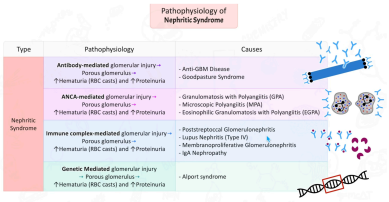
📚 **Types of Nephritic Syndrome**

Acute glomerulonephritis:

1. **Post-infectious GN**
2. **Rapidly progressive glomerulonephritis (RPGN) → ANKA vasculitis / anti - gpm**
3. **Membranoproliferative GN (MPGN) → rapid renal dysfx**

Chronic glomerulonephritis (Hereditary causes).

1. **IgA nephropathy**
2. **Hereditary nephritis (Alport syndrome)**
3. **Thin basement membrane disease**



Extra:

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1 Postinfectious / Diffuse Proliferative GN → immune complex mediated (so we have C3).

- **Occurs after infection, usually with a nephrogenic strain of group A beta-haemolytic streptococcus**
  - 🔷 After strep throat or skin infection (impetigo).
- **Onset 1–4 weeks after upper respiratory or skin infection** → Delay = immune system reaction.
- **Symptoms and signs range from:**
  - **Asymptomatic haematuria** (50%)
  - **Mild proteinuria**
  - **Full-blown nephritis** (gross hematuria, proteinuria, edema, hypertension, renal failure)
- **Fever is unusual and suggests persistent infection**
  - 🔷 *If fever persists,* think: infection is *still active*, not just post-infectious immune reaction.

أي حدا بيجي AKI مع بروتين ودم بالبول لازم اسال اذا رشح قبل ٢-٤ اسابيع

- **Renal failure that causes fluid overload with HF and severe HTN requiring dialysis affects 1 to 2% of patients**

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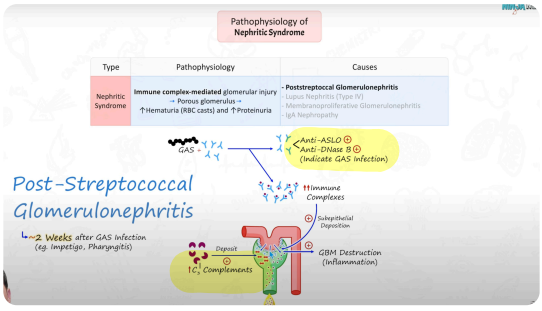


🧪 Lab Investigations in Postinfectious GN

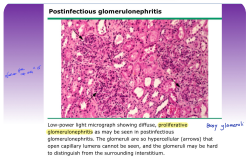
- **Antistreptolysin O level (ASO) → M/C**
  - 🔷 Shows recent **strep infection**.

Elevated in 75% of pharyngitis, 50% impetigo → For several months **BUT NOT SPECIFIC.**

- **Urinalysis**
  - 🔷 Shows:
    - Proteinuria (0.5 – 2)
    - Dysmorphic RBCs
    - WBCs
    - Tubular cells
    - RBC/WBC/granular casts
  - 🔷 Classic for nephritic syndrome.

- **Complement C3 and CH50**
  - 🔷 **Decreased** during active disease (important clue) then return normal within 6 to 8 weeks in 80% of PIGN cases
    - Pt with decreased C3 needs further inv

🔬 Biopsy Findings in Postinfectious GN



- **(LM): Diffuse glomerular proliferation and cellular infiltration** → Swollen, crowded glomeruli.
- **(IF): Granular BM IgG, IgM, C3 deposits** → Starry sky pattern ✨.
- **(EM): Dome-shaped subepithelial deposits ("humps")** imp

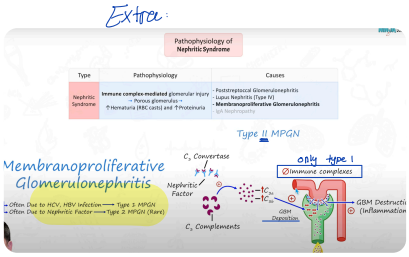
📈 Prognosis and Treatment — Postinfectious GN

- **Good prognosis** → 95% of kids recover fully.

- **Treatment**
  - 🔷 Supportive:
    - Restrict dietary protein, salt, fluid
    - Manage edema, hypertension
    - Rarely dialysis needed
    - **Antibiotics don't help AFTER nephritis develops!** (only preventive if given early during infection (within 36h))

📚 Glomerular Diseases Associated with Nephritic Syndrome

Primary	Secondary
Postinfectious / Diffuse Proliferative GN	HSP (Henoch-Schonlein Purpura)
Membranoproliferative GN	Systemic vasculitis
IgA nephropathy (Mesangioproliferative GN)	SLE
Crescentic GN	Systemic sclerosis



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🧠 Membranoproliferative Glomerulonephritis (MPGN) → immune complex mediated.

(aka: the "double trouble" disease)

• A group of immune-mediated disorders characterized histologically by GBM thickening and proliferative changes on light microscopy.

🔷 Basement membrane = thickened (inflamed and rugged).

🔷 Cells inside the glomeruli = proliferating (too many cells).

• There are 3 types, each of which may have primary (idiopathic) or secondary causes.

• Primary forms → children and young adults between ages 8 and 30 and account for 10% of cases of nephrotic syndrome in children.

• Secondary forms → adults >30.

• M=F

• Many factors contribute to hypocomplementemia.

🔷 Complement system is often consumed (used up) → **low C3 and/or C4**.-->*Big diagnostic clue!*

🚨 Symptoms and Signs of MPGN

• Nephrotic syndrome in 60–80% of cases.

• Nephritic syndrome (acute glomerulonephritis) are presenting features in 15–20% of cases of type I and III disease and in a higher percentage of type II disease.

• At diagnosis, 30% → hypertension and 20% → renal insufficiency.

• Hypertension often develops even before (GFR) declines.

🔬 Classification based on Electron Microscopy

Type I MPGN:

- Immune complex disorder. (C4)↓
- Associated with:
  - SLE
  - Mixed cryoglobulinemia
  - Sjögren's syndrome
  - Chronic infections (endocarditis, hepatitis B/C, HIV, visceral abscess, ventriculoatrial shunt infection)
  - Cancer (leukemia, lymphoma, melanoma)
  - - Other disorders (eg, partial lipodystrophy, C2 or C3 deficiencies, sarcoidosis , thrombotic microangiopathies)

🔷 Basically, anything causing circulating immune complexes.

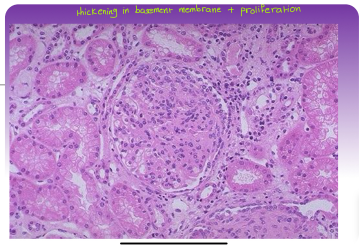
Type II MPGN (Dense Deposit Disease): C3↓

- **Complement activation problem** (not immune complexes!)
- Dense ribbon-like deposits inside GBM.

Type III MPGN:

- Similar to Type I but deposits are found both *below* and *inside* the basement membrane. ↓ C3 and C4.

🛑 Quick **pro-tip:**
👉 MPGN = think **immune complex or complement issue** causing basement membrane thickening AND cell proliferation.
👉 Compliments always low? Think dense deposit disease (type II).



📈 **Prognosis of MPGN**
- **Good if → secondary MPGN is successfully treated.**
- **ESRD occurs in 50% of patients at 10 years and in 90% at 20 years.**

- **Type I MPGN recurs in 30% of kidney transplants.**
- **Type II MPGN recurs in 90% but often doesn't kill the graft fast→** very high recurrence but slower destruction.
- **Outcome worse if proteinuria is nephrotic range.**

🛡️ **Treatment of MPGN**

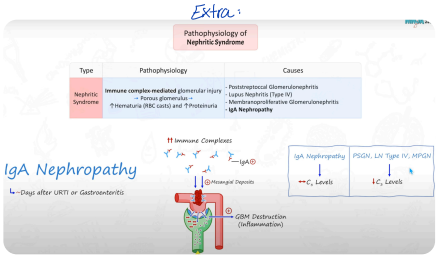
- **Corticosteroids for children with nephrotic-range proteinuria →**stop immune damage in kids.
- **Dipyridamole and aspirin for adults →**protect kidneys a little (not curative though).
- **Kidney transplantation for patients with ESRD →**if kidneys are dead.
- **Treat underlying disorders when possible.**
- **Specific therapy not indicated if proteinuria is non-nephrotic range.**
🔷 If little proteinuria only → no need to go nuclear with treatment.

🛑 **Quick summary checkpoint before moving on:**
MPGN =
- Thick basement membrane + cell proliferation.
- 3 types: immune complex, complement, both.
- Low complement levels clue.
- Half go to ESRD.
- Treat underlying cause if possible.

🧠 **IgA Nephropathy (aka Mesangioproliferative GN)** ⟶ immune-complex.

- **IgA nephropathy → nephritic syndrome, a form of chronic glomerulonephritis characterized by the deposition of IgA immune complexes in glomeruli.**
🔷 The body makes **too much IgA antibody**, or wrong IgA → they deposit in glomeruli → inflammation → bloody pee!
- **M/C primary glomerulonephritis.** IMP
- **It occurs at all ages, with a peak onset in the teens and 20s.**
- **x2-6 M >F.**
- **M/C in whites and Asians than in blacks.**

Extra:



🧬 **Pathogenesis :**

- **Cause is unknown, but :**
  - Increased IgA1 production. ①
  - ② Defective IgA1 glycosylation → makes it sticky → deposits in mesangium.
  - ③ Decreased IgA1 clearance.

4. • Mucosal immune system defects
5. • Overproduction of cytokines (messenger chemicals that cause cell proliferation).
6. • Familial clustering = genetics may play a role.

🔷 *In short:*
Bad IgA + immune overreaction = kidney injury.

🚑 **Clinical Features**

• The M/C are:

- **Persistent or recurrent macroscopic haematuria** = visible blood after infections.
- **Asymptomatic microscopic haematuria with mild proteinuria**

• Gross haematuria usually begins 1 or 2 days after a febrile mucosal illness (upper respiratory, sinus, enteral).
🔷 (This is different from post-streptococcal GN, which happens weeks later.)

• Mimicking acute postinfectious glomerulonephritis, except the onset of haematuria is earlier.
🔷 Remember: **immediate** after illness = IgA.
🔷 **2–3 weeks delay** = post-strep GN.

• RPGN (Rapidly Progressive GN) with crescentic IgA nephropathy <10%.

📉 **Progression**

• IgA nephropathy usually progresses slowly.
• Renal insufficiency and hypertension develop within 10 years in 15–20% of patients.
• Progression to ESRD occurs in 25% of patients after 20 years.
• If diagnosed in childhood, prognosis is usually good.
• Recurs in 20–60% of transplants.
🔷 *Annoying:* even after kidney transplant, IgA nephropathy often comes back.

⚡ **Risk Factors for Bad Prognosis**

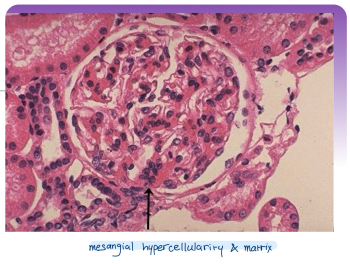
• Proteinuria > 1 g/day
• Elevated serum creatinine
• Uncontrolled hypertension
• Persistent microscopic hematuria
• Extensive fibrosis on biopsy
• Crescents on biopsy (RPGN)
🔷 Basically:
More proteinuria, worse kidney function, high BP, fibrosis = worse outcome.

Prognostic Markers at Presentation in IgA Nephropathy

Clinical	Histopathologic
Poor Prognosis	
Hypertension	Mesangial hypercellularity
Renal impairment	Endocapillary proliferation
Severity of proteinuria	Segmental glomerulosclerosis
Hyperuricemia	Tubular atrophy
Gross obesity	Interstitial fibrosis
Duration of preceding symptoms	Capillary loop IgA deposits
Increasing age	Crescents (controversial)
Good Prognosis	
Recurrent macroscopic hematuria	
No Impact on Prognosis	
Gender	Intensity of IgA deposits
Serum IgA level	

🔬 **Kidney Biopsy Findings**

• (LM): Increased mesangial matrix, mesangial proliferation, sometimes focal sclerosis (FSGS).
• (IF): Mesangial IgA deposits.
🔷 Diagnostic hallmark: IgA lighting up the mesangium under UV microscope.
• (EM): Mesangial deposits. (sticky)


mesangial hypercellularity & matrix

🛡️ **Treatment — IgA Nephropathy**

• ACE inhibitors or ARBs → Control BP and reduce protein loss.

- Indications:
  - Hypertension
  - Serum creatinine >1.2 mg/dL
  - Proteinuria >300 mg/day (macroalbuminuria)
- Goal:
  - Lower urine protein to <500 mg/day.

• **Corticosteroids for progressive disease→** If proteinuria increasing or cr rising despite ACEi/ARB.

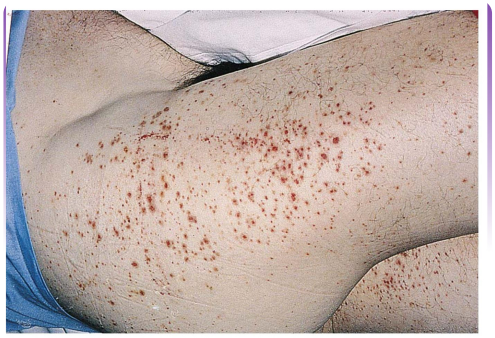
• **Normotensive patients with mild disease:**
- (Creatinine <1.2, Protein <0.5 g/day)
- Only angiotensin inhibition + fish oil (omega-3).

🛑 **Recap :**
- IgA nephropathy = after mucosal infection → blood in urine.
- Biopsy shows mesangial IgA.
- Slow progression usually.
- Treat with ACEi/ARB +/- steroids if bad.

🧠 **Henoch-Schönlein Purpura (HSP)**
(same IgA problem but everywhere in the body, not just kidneys.)

• **Small vessel vasculitis affecting the skin, joints, gut, with kidney involvement.**
• **characterized by mesangial IgA deposition.**

🧯 **Clinical Presentation**



• **Purpuric skin rash →**they do **NOT** blanch when pressed.
• **Arthritis →**usually knees and ankles.
• **Gastrointestinal symptoms (abdominal pain) , rectal bleeding**

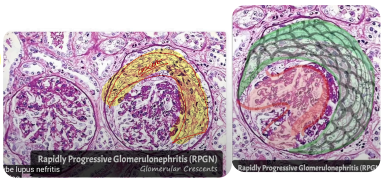
• **Self-limiting illness**
• **Confirm diagnosis by skin or kidney biopsy.**

🛑 Quick tip:
👉 HSP = Purpura + belly pain + joint pain + maybe kidney involvement.
👉 If only kidneys are affected → it's just IgA nephropathy.
👉 If skin/joints/belly + kidneys → it's HSP.

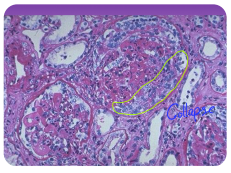
🧠 **Crescentic GN / Rapidly Progressive GN (RPGN) →** *SUPER dangerous, fast kidney failure.)* → *EMERGENCY*

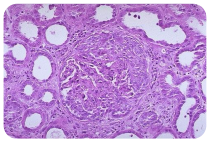
• **Nephritic syndrome →**Blood + protein in urine, swelling, hypertension.
• **Damage to glomerular vessels, egress of inflammatory cells and fibrin into Bowman's space, proliferation of epithelial cells.**

• **Pathologic diagnosis = extensive glomerular crescent formation (>50% of glomeruli).**
🔷 In biopsy, if more than half the glomeruli have crescents → BAD news = RPGN.



• **If untreated, progresses to ESRD over weeks to months.**
• **It is relatively uncommon, affecting 10–15% of patients with glomerulonephritis.**





- **Occurs predominantly in patients 20–50 years.**

🚨 **RPGN Clinical Presentation**

- **Insidious symptoms:**
  - Weakness
  - Fatigue
  - Fever
  - Nausea, vomiting
  - Anorexia
  - Arthralgia (joint pain)
  - Skin rash
  - Abdominal pain

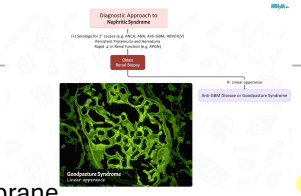
Decreased GFR due to crescentic sheepe compression

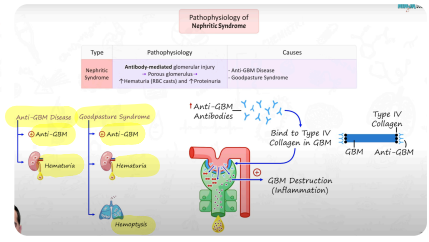
- **50% have edema and a history of acute flu-like illness within 4 weeks of onset.**
- **Severe oliguria follows.**
- **Nephrotic syndrome is present in 10–30%.**
- **Hypertension is uncommon and rarely severe.**
- **pt with anti-GBM antibody → may have pulmonary hemorrhage, (hemoptysis or finding diffuse alveolar infiltrates on chest x-ray (pulmonary-renal syndrome or diffuse alveolar hemorrhage syndrome**

Hemoptysis with Goodpasture Syndrome.

- **Progression to ESRD in most untreated patients within weeks to months.**

🔷 RPGN = EMERGENCY.





🧬 **RPGN Pathogenesis (Causes)**

- **Type I – Anti-GBM antibodies**

🔷 The immune system attacks the basement membrane.

  - **Linear IgG** staining on biopsy. (IF)
  - If it hits lungs too → **Goodpasture's syndrome**.

if not Anti-GBM

- **Type II – Immune complexes**

🔷 Idiopathic or secondary to autoimmune disease or other GN

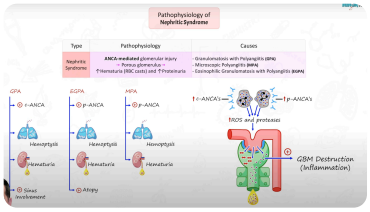
Examples:

  - SLE Lupus nephritis
  - Post-infectious GN
  - HSP
  - IgA nephropathy → 10%

- **Type III – Pauci-immune (no immune deposits visible)**

🔷 idiopathic or with ANCA-positive vasculitis:

  - Granulomatosis with polyangiitis (GPA) (c-ANCA)
  - Microscopic polyangiitis MPA (p-ANCA).



RPGN Treatment

- **Corticosteroids**
- **Cyclophosphamide**
- **Rituximab** → not used if theres pulmonary involvement
- **Plasma exchange (plasmapheresis)** → if severe

🔬 **Biopsy Findings in Crescentic GN**

- **(LM):**
  - Cellular crescents
  - Fibrotic crescents if chronic

- **Immunofluorescence (IF):**
  - **Type I:** Linear IgG
  - **Type II:** Granular IgG
  - **Type III:** No deposits no immune complexes.

- **Electron Microscopy (EM):**
  - **Type II:** Subendothelial, mesangial, subepithelial deposits

🛑👉 **Checkpoint so far:**
- **IgA Nephropathy:** isolated kidneys → after mucosal illness
- **HSP:** skin + joints + belly + kidneys (IgA everywhere)
- **RPGN:** catastrophic crescent formation → needs urgent aggressive therapy!

🧠 **Nephrotic Syndrome**

What defines Nephrotic Syndrome?

- **Proteinuria > 3.5g/day**

🔷 *Massive* protein loss in urine.

- **Hypoalbuminemia (<3.5g/dL)**

🔷 *Low blood albumin* because you're peeing it all out.

- **Edema**

🔷 No albumin = no oncotic pressure = water leaks into tissues = SWOLLEN like a balloon 🎈.

- **Hypercholesterolemia, Lipiduria**

🔷 Liver tries to fix low proteins by making extra fats → blood full of cholesterol and triglycerides → fats spill into urine too.

🩺 **Glomerular diseases associated with Nephrotic Syndrome**

Primary	Secondary
Minimal Change Disease (MCD)	Diabetic nephropathy
Membranous Glomerulonephritis (GN)	Amyloidosis
Focal Segmental Glomerulosclerosis (FSGS)	

🔷 *Remember:*
- Primary = kidney problem only.
- Secondary = systemic disease ruining the kidneys.

🧬 **Pathophysiology – Nephrotic Syndrome**

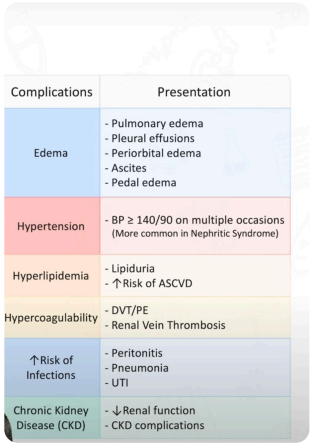
- **Proteinuria occurs because of changes to:**
  - Capillary endothelial cells
  - GBM (Glomerular basement membrane) → loss of -ve charge
  - Podocytes → fusion.

🔷 These structures **normally filter by size and charge** — if damaged, *big proteins like albumin leak through*.

⚡ **Complications of Nephrotic Syndrome**

Because you lose important proteins in the urine, **you get a ton of complications:**

- **Edema**



Complications	Presentation
Edema	- Pulmonary edema - Pleural effusions - Periorbital edema - Ascites - Pedal edema
Hypertension	- BP ≥ 140/90 on multiple occasions (More common in Nephritic Syndrome)
Hyperlipidemia	- Lipiduria - ↑Risk of ASCVD
Hypercoagulability	- DVT/PE - Renal Vein Thrombosis
↑Risk of Infections	- Peritonitis - Pneumonia - UTI
Chronic Kidney Disease (CKD)	- ↓Renal function - CKD complications

  - Including ascites and pleural effusions.
- **Anemia**
  - Loss of transferrin and erythropoietin.
- **Thyroid dysfunction**
  - Loss of thyroid-binding proteins.
- **Dyslipidemia**
  - Fat levels skyrocket.
- **Chronic kidney disease (CKD)**
  - Ongoing glomerular damage.
- **Hypercoagulability**
  - *Very important*.
  - You lose antithrombin III = blood clots form easily.
  - **Renal vein thrombosis and pulmonary embolism** — classic dangers.
- **Protein undernutrition (especially in children)**
  - Growth retardation, brittle hair, brittle nails.
- **Fanconi syndrome** (proximal tubule dysfunction)
  - Kidney tubules get injured by reabsorbing too much protein.

Involved mostly with membraneous type.

📋 Diagnosis — Nephrotic Syndrome

- **Urine protein/creatinine ratio ≥3 or 24-hour proteinuria >3.5g**

🔷 Quick tests for heavy protein loss.

- **Blood urea nitrogen (BUN) and creatinine concentrations**

🔷 To assess kidney function.

- **Serum albumin <2.5g/dL**

🔷 Confirm low blood protein.

- **Total cholesterol and triglyceride levels increased**

🔷 Always check lipids!

- **Tests for secondary causes:**
  - Serum glucose, HbA1c — Diabetic type.
  - ANA (for SLE) — membraneous
  - Hepatitis B and C serologies — membraneous
  - HIV antibody test — FSC
  - Complement levels (C3, C4) — membraneous
  - Rheumatoid factor — "
  - Cryoglobulins
  - Syphilis testing

📈 Prognosis of Nephrotic Syndrome

- **Depends on the cause.**

🔷 Good if:

  - Corticosteroid-responsive disease (like minimal change).

🔷 Bad if:

  - Infection
  - Severe hypertension
  - Azotemia (high BUN/creatinine)
  - Hematuria
  - Thrombosis

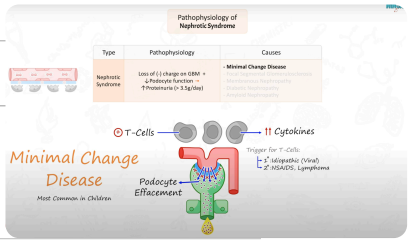
- **FSGS has a high recurrence after kidney transplant!** Poor PX.

(30–50% recurrence rate.)

🫀 Treatment of Nephrotic Syndrome

- **Treat underlying cause**
  - 🔷 Duh — fix the root problem if possible.
- **ACE inhibitors or ARBs**
  - 🔷 Reduce protein loss.
- **Sodium restriction**
  - 🔷 To fight edema.
- **Statins**
  - 🔷 To treat dyslipidemia.
- **Diuretics**
  - 🔷 Help pee out the extra water.
- **Rarely nephrectomy (kidney removal)**
  - 🔷 Only if the protein loss is catastrophic and out of control.

🧠 Now... Primary Nephrotic Syndromes (one by one)



Minimal Change Disease (MCD)

- **Commonest cause of nephrotic syndrome in children aged 4–8 years (80–90%).**
  - 🔷 Kids mainly.
- **Also occurs in adults (10–20% of adult nephrotic syndrome).**

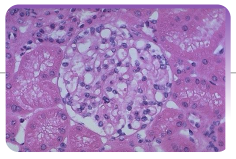
- **Most cases are idiopathic.**
  - 🔷 No clear cause found.

- **Secondary causes:**
  - NSAIDs
  - Hodgkin lymphoma (very famous association)

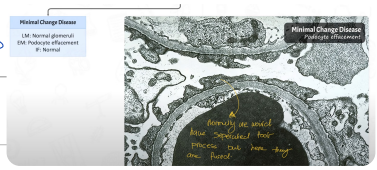
🔬 Diagnosis of MCD

- **Sudden onset of unexplained nephrotic-range proteinuria (mostly albumin).**
- **Normal renal function.** (Minimal)
- **Non-nephritic urine sediment.** (No WBC / no RBC / only protein).

- **In adults: renal biopsy needed.**
- **In kids: diagnose clinically, treat directly without biopsy.**



- **Kidney Biopsy (if done):**
  - **Light Microscopy:** Normal glomeruli (nothing obvious)
  - **Immunofluorescence:** Negative (no Antibodies)
  - **Electron Microscopy:** *Fusion of podocyte foot processes* (signature finding)

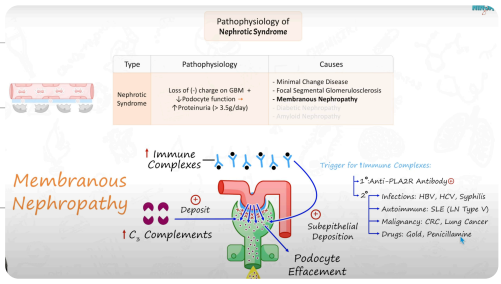


🫀 Treatment of MCD

- **Corticosteroids (mainstay).**
  - 🔷 Most kids go into remission quickly.
- **Relapses are common.**
  - 🔷 But still responsive usually.

- **Steroid-sparing options for frequent relapsers:**
  - Cyclophosphamide
  - Rituximab
  - Mycophenolate
  - Tacrolimus

Membranous GN



- **Most common cause of nephrotic syndrome in adults.**

🔷 Very high-yield fact.

PLA2R Antibody

- **85% idiopathic, 15% secondary to:**
  - Drugs (gold, penicillamine, NSAIDs)
  - Infections (Hepatitis B/C, syphilis, HIV)
  - Autoimmune (SLE)
  - Thyroiditis
  - Cancers

Clinical Features of Membranous Nephropathy

Rare in children – <5% of total cases of nephrotic syndrome
Common in adults – 15% to 50% of total cases of nephrotic syndrome, depending on age. Increasing frequency after age 40 years.
Males > females in all adults groups
Caucasians > Asians > African-Americans > Hispanics
Nephrotic syndrome in 60% to 70%
Normal or mildly elevated BP at presentation
"Benign" urinary sediment
Non-selective proteinuria
Tendency to thromboembolic disease (DVT, RVT, PE)
Secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

Major causes of membranous nephropathy

Idiopathic - may represent autoantibody against a podocyte antigen such as PLA2R
Systemic lupus erythematosus (WHO Class V)
Drugs:
Penicillamine
Bucillamine
Gold salts
Anti-TNF therapy
Tiopronin
NSAIDs
Hepatitis B virus
Hepatitis C virus (rare)
Malignancy (may not be causative)
Hematopoietic cell transplant / GVHD
Status post renal transplantation
Sarcoidosis (uncommon)

🧬 Pathogenesis — Membranous GN

- **Subepithelial immune deposits**

🔷 Immune complexes get stuck under the podocytes.

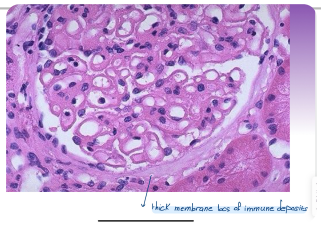
- **Thickened basement membrane seen on silver stain ("spike and dome" appearance).**

🔬 Diagnosis of Membranous GN

- **Anti-PLA2R antibody (70–80% in idiopathic cases).**

🔷 Blood test!

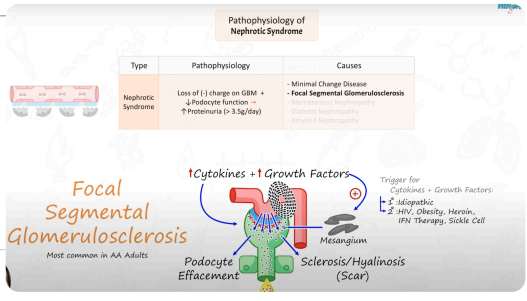
- **Kidney Biopsy:**
  - Light Microscopy: Thickened capillary walls.
  - Immunofluorescence: Granular IgG and C3 deposits.
  - Electron Microscopy: Subepithelial deposits.



🛡️ Treatment of Membranous GN

- **Treat secondary causes (infections, cancer, etc.) first.**
- **ACEi/ARB for proteinuria.**
- **Immunosuppressives for high-risk patients:**
  - Steroids
  - Cyclophosphamide
  - Calcineurin inhibitors (tacrolimus)

Focal Segmental Glomerulosclerosis (FSGS)

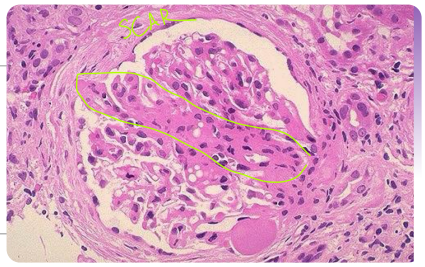


- **Most common cause of nephrotic syndrome in adults (especially Black populations in the US).** AA

- **Idiopathic or secondary to:**
  - Drugs (heroin, lithium, interferon)
  - HIV infection (HIVAN)
  - Obesity

- Sickle cell disease
- Loss of nephrons (reflux nephropathy)

🔬 Diagnosis of FSGS



- **Renal biopsy:**
  - Light Microscopy: Segmental sclerosis (scarring) of some glomeruli.
  - Immunofluorescence: IgM and C3 trapped in scarred areas.
  - Electron Microscopy: Podocyte foot process fusion.

⚡ Clinical Presentation of FSGS

poor

- Heavy proteinuria.
- Hypertension.
- Progressive renal dysfunction.
- Microscopic hematuria (sometimes).

Morphologic Variants of Focal Segmental Glomerulosclerosis

1. FSGS, not otherwise specified (also known as classic FSGS)
2. FSGS, perihilar variant
3. FSGS, cellular variant
4. FSGS, collapsing variant (also known as collapsing glomerulopathy)
5. FSGS, tip variant

🛡️ Treatment of FSGS

- **ACEi/ARB (first).**
- **Corticosteroids for idiopathic primary FSGS.**
- **Immunosuppressive agents if steroid-resistant.**
- **Kidney transplant if ESRD — but recurrence common!** 50%

⚡ Complications of Nephrotic Syndrome

When you lose **lots of proteins** in the urine, several *dominoes* fall:

- **Edema**

🔷 Low albumin → low oncotic pressure → fluid leaks out → swelling everywhere (face, legs, lungs, abdomen).

- **Anemia**

🔷 Loss of transferrin (iron transporter) and erythropoietin (stimulates red blood cell production) → anemia.

- **Changes in thyroid function tests**

🔷 Loss of thyroid hormone binding proteins → falsely low T4 levels → if hypothyroid, they need higher doses of thyroid hormone.

- **Dyslipidemia**

🔷 Liver overproduces cholesterol and triglycerides to "compensate" for low albumin → blood becomes greasy.

- **Chronic Kidney Disease (CKD)**

🔷 Ongoing glomerular damage slowly progresses to full-blown kidney failure.

• **Hypercoagulability and thromboembolism**

🔷 Loss of antithrombin III = blood becomes sticky → clots form easily:

- Renal vein thrombosis
- Pulmonary embolism
- DVTs

(*In adults with nephrotic syndrome, 40% develop some thromboembolism! Serious stuff.*)

• **Protein undernutrition**

🔷 Children especially get poor growth, brittle hair, stunted height.

• **Proximal tubular dysfunction (Acquired Fanconi Syndrome)**

🔷 Tubules get poisoned by absorbing all the extra proteins → glucose, phosphate, bicarbonate wasting.

🧪 **Diagnosis Summary — Nephrotic Syndrome**

When you suspect nephrotic syndrome (patient with edema, foamy urine):

✅ Urine random protein/creatinine ratio ≥3

✅ 24h urine collection showing >3.5g protein loss

✅ Serum albumin <2.5g/dL

✅ Lipid profile = high cholesterol, high triglycerides

✅ Rule out secondary causes: diabetes, lupus, infections (Hep B, C, HIV)

(*ALWAYS think about what's CAUSING the protein loss before you blame the kidneys alone!*)

📋 **Key Points — Treatment Summary**

---

1. Causative disorder:

🔷 Treat underlying disease if found (e.g., control diabetes, treat hepatitis).

---

2. Reduce proteinuria and protect kidneys:

🔷 ACE inhibitors / ARBs.

---

3. Control edema:

🔷 Sodium restriction, diuretics.

---

4. Fix lipids:

🔷 Statins for dyslipidemia.

---

5. Manage hypercoagulability:

🔷 Anticoagulation sometimes needed if clot risk is high.

---

6. Immunosuppressive therapy:

🔷 Given in primary nephrotic syndromes (like minimal change, membranous, FSGS).

🧠 **FINAL BIG PICTURE MIND MAP**

✅ **Glomerular diseases can present as:**

- **Nephritic syndrome:**
  - Blood in urine.
  - Hypertension.

- Some proteinuria.
- ↓ GFR (kidney failure).

- **Nephrotic syndrome:**
  - Massive proteinuria.
  - Edema.
  - Hypoalbuminemia.
  - Hyperlipidemia.

✅ **Nephritic causes:**

- Postinfectious GN
- IgA nephropathy
- HSP
- RPGN (anti-GBM, ANCA vasculitis)

✅ **Nephrotic causes:**

- Minimal Change Disease (kids)
- Membranous GN (adults)
- FSGS (common, bad prognosis)
- Secondary (diabetes, amyloidosis)

✅ **Complications to remember:**

- Edema
- Infections
- Thrombosis
- CKD
- Dyslipidemia
- Malnutrition

✅ **Gold Standard Diagnosis:**

- Renal biopsy (+ serologies depending on suspected cause)

✅ **Key Treatments:**

- Supportive (ACEi/ARB, diuretics, statins)
- Specific (steroids, cyclophosphamide, rituximab if indicated)

🔥 **Quick Final Tip for Exam:**

If you are asked a case:

- Pee looks bloody? → *Nephritic thinking*.
- Pee looks frothy? → *Nephrotic thinking*.
- Fever? Look for infection.
- Systemic symptoms? Think lupus/vasculitis.

Feature \ Disease	Nephritic Syndrome (General)	Postinfectious GN	MPGN	IgA Nephropathy	HSP	RPGN
Definition	Glomerular inf with hematuria and variable proteinuria	Post-strep immune complex GN	Immune complex or complement-mediated GBM thickening + proliferation	IgA deposition in mesangium	IgA vasculitis affecting skin, gut, kidneys	Rapid crescentic glomerulonephritis with renal failure
Cause	Primary or secondary (e.g., lupus)	Group A Strep (1-4 weeks after infection)	Primary or secondary (SLE, Hep B/C, cryoglobulins)	Idiopathic, post-mucosal infection	Post-infection (common in children)	Type I: Anti-GBM; Type II: Immune complex; Type III: ANCA vasculitis
Clinical Features	Hematuria, mild edema, HTN, oliguria	Hematuria, edema, HTN, mild AKI	Nephrotic (60-80%), nephritic (20%), HTN, renal insufficiency	Gross hematuria 1-2 days after infection	Purpura, abdominal pain, arthritis, hematuria	Severe oliguria, edema, weakness, hematuria, possible pulmonary hemorrhage
Labs & Diagnosis	UA: hematuria, RBC casts, mild proteinuria	Elevated ASO, Low C3, Normal C4, RBC casts	Low C3 (sometimes C4), UA: proteinuria, hematuria	UA: persistent hematuria, mild proteinuria	UA: hematuria, proteinuria; clinical rash	UA: hematuria, RBC casts; ANCA, Anti-GBM serologies
Biopsy Findings	Depends on underlying cause	LM: Diffuse proliferation; IF: Starry sky; EM: humps	LM: GBM thickening + proliferation; IF/EM varies	LM: Mesangial proliferation; IF: Mesangial IgA deposits	Skin biopsy: IgA deposits	LM: Crescents >50%; IF: Linear (Type I), Granular (Type II), None (Type III)
Treatment	Treat cause, BP control	Supportive care, manage HTN, dialysis if needed	Steroids (children), treat underlying cause, transplant if ESRD	ACEi/ARB, steroids if progressive	Supportive, steroids if severe	Urgent steroids, cyclophosphamide, plasmapheresis if pulmonary hemorrhage
Prognosis	Varies (acute emergency or slow CKD)	Excellent in children (>95% recovery)	Poor; 50% ESRD in 10 years; Type II recurs 90%	Slow progression; 25% ESRD in 20 years; recurrence common	Good; most recover fully	Poor if untreated; rapid ESRD in weeks to months