Glomerular disease & Tubulointerstitial diseases

Objectives (regarding the Blueprint) :

1. To understand nephrotic and nephritic range proteinuria.
2. To list common causes of nephritic range proteinuria.
3. To be able to approach patients with nephrotic syndrome.
4. Understand pathophysiology of glomerulonephritis and its common causes and complications and basic management.
5. Understand pathophysiology of Tubulointerstitial diseases and its common causes and complications and basic management.

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Glomerular Diseases[1]

◄ Normal structure is needed to:

01 Keeps the glomerular filtration normal, thus maintains normal kidney function.

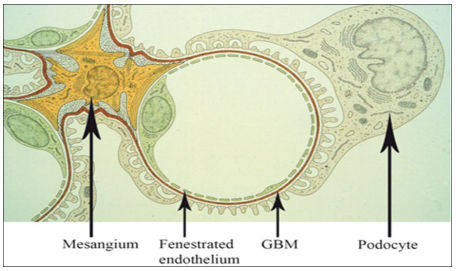
02 Maintain urine volume and hence, preventing fluid retention in the body which causes edema and high blood pressure.

03 Prevents the blood components (cells, proteins) from leaving the bloodstream and appearing in the urine.

★ renal cortex is the most important functional part of the kidney because it has the glomeruli

if the Glomerular structure is <u>intact</u> the urine will show:

- No protein
- No RBCs (Accept: <2 RBCs/high power field)
- No heme
- No cellular casts
- Devoid of fats



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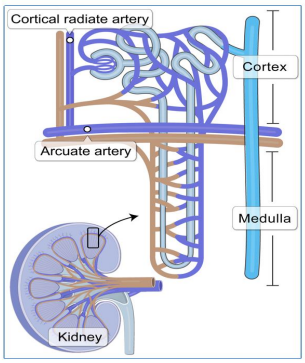

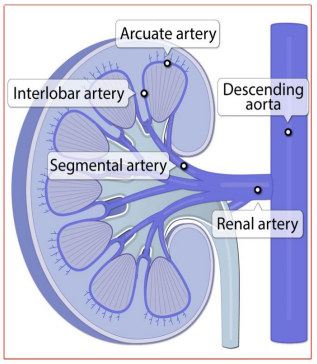

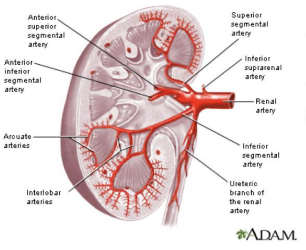

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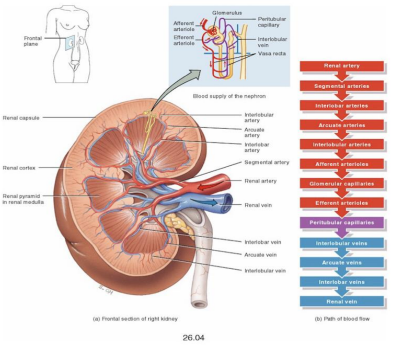

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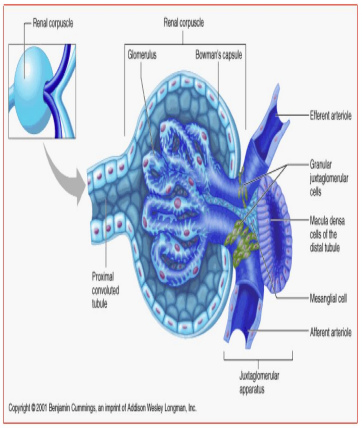
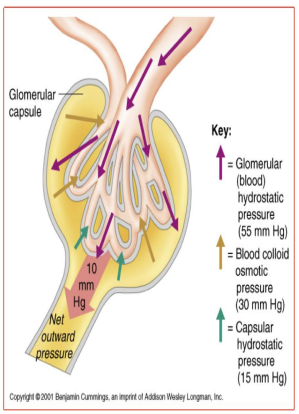
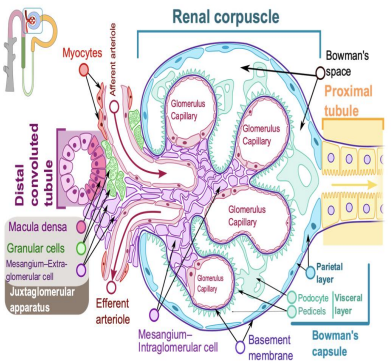
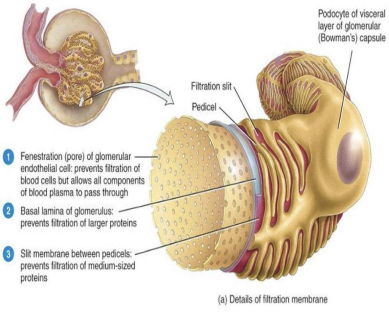








Layers from inside to outside (endothelium > basement membrane > podocyte)

1. Glomerular disorders are characterized by impairment in selective filtration of blood, resulting in excretion of larger substances such as plasma proteins and blood cells. As disease advances, GFR decreases proportionally, leading to renal failure and the possible need for dialysis and/or transplantation. The classic features are proteinuria, hematuria, or both.

- Glomerular diseases are generally chronic and all of them can cause nephrotic syndrome.
- **Biopsy is the most accurate test to establish a diagnosis (though not always needed)**
- Often treated with steroids (several resolve spontaneously)
- Additional immunosuppressive medications (cyclophosphamide, mycophenolate) are frequently used.

Glomerular Diseases classification

◄ Glomerulonephritis Diseases could be primary or secondary to variety of conditions:

- Examples: Membranous nephropathy could be primary (idiopathic) or secondary to HBV or to Lupus.
- Minimal change disease could be primary or secondary to Hodgkin
- lymphoma or NSAID use
- In **primary** we treat them with **immunosuppressive** agents while in **secondary** we **treat the underlying diseases**

◄ Pathological Classification of Glomerulonephritis diseases:

Proliferative:

1-ANCA-associated vasculitis

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)

2-Anti-GBM disease

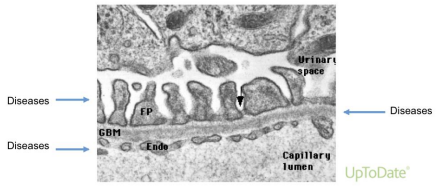
3-Immune-complex disease

- Lupus Nephritis class II, III & IV
- Post-infectious
- IgA nephropathy
- MPGN
- Cryoglobulinemia

Non-proliferative

1. Minimal change disease
2. Focal and segmental glomerulonephritis
3. Membranous nephropathy

◄ Classification based on glomerulus anatomy

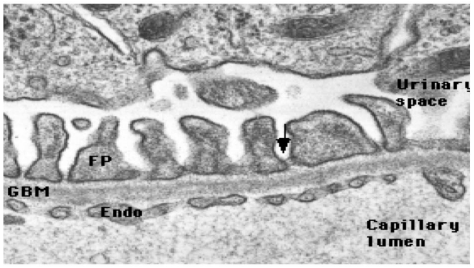


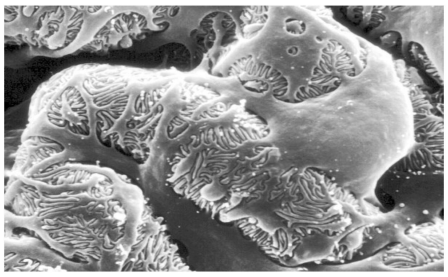
◄ Classification based on general the symptoms and lab result

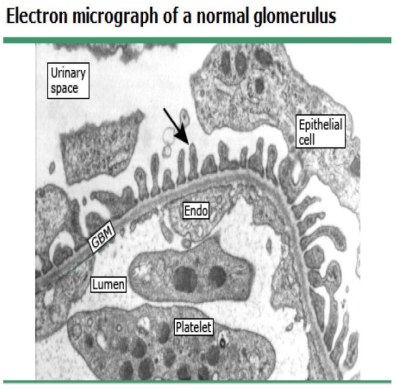
- Nephrotic syndrome
- Nephritic syndrome

Glomerular Diseases[1]

From dr's slide







Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut G Rennke, MD.

UpToDate

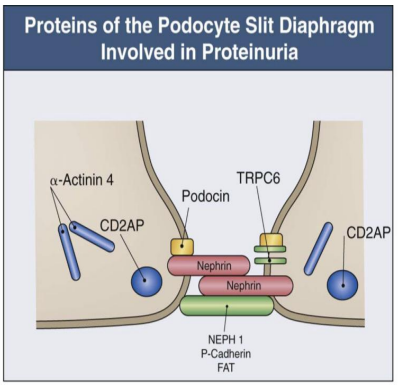


Figure 16.5: Proteins of the podocyte slit diaphragm involved in proteinuria. Several inherited glomerular diseases involve mutations of antigens associated with the slit diaphragm. These include nephrin (congenital nephrotic syndrome of the Finnish type), podocin (autosomal recessive FSGS), and α-actinin and TRPC6 (both associated with autosomal dominant FSGS). In addition, mutation of CD2-associated protein results in nephrotic syndrome in mice.
(Modified from reference 1.)

◄ How glomerular diseases start?

439 medicine team 3rd year

- The insult to the glomeruli is either an autoimmune attack or is the result of deposition of antibody-antigen complex in the kidney which will attack the glomeruli which will lead to a local inflammation there. The pathology depends on the component of the glomeruli that is affected (basement membrane, mesangium…)
- Here we are talking about primary glomerular diseases that are mostly caused by **immune system dysfunction.**
- Auto-antibodies targeting glomerular structure or immune- complexes (antigen-antibody) **depositing and traumatizing the glomerular components.**
- Glomerular diseases are named based on their **histopathological** characteristics seen under the microscope. So, almost always a kidney **biopsy** is needed to diagnose any suspected primary glomerular disease. Urinalysis & blood tests are also used.

The manifestations of a glomerular disease are usually indicative of which components of glomerulus structure was affected mainly by the disease process:

If **Podocytes** were the main target of the disease process this leads **mainly to proteinuria** (at large amount) due to foot process effacement ; thus **Nephrotic** Syndrome will be the main finding.

If **endothelial cells OR Mesangial cells OR GBM OR all of them together** were targeted; then Glom Capillary wall will be damaged by inflammation so **blood components will leak** to the urine space causing: **hematuria, proteinuria and abnormal renal function**; thus **Nephritic** pattern of renal disease will be present **(Clinically called: Glomerulonephritis or GN)**

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Glomerular Diseases

Disease of The Kidney

- Tubular
- Vascular
- **Glomerular**[1]
- Obstructive
- Cysts and tumors

But to make things easier, we can put Glomerular diseases in two main clinical categories

Nephrotic syndrome

Primary causes

- Minimal change disease
- Membranous nephropathy
- Focal segmental glomerulosclerosis

secondary causes

- membranoproliferative glomerulonephritis (MPGN) due to hepatitis for example
- Diabetic nephropathy
- Amyloidosis nephropathy

Nephritic syndrome

- Poststreptococcal glomerulonephritis (PSGN) , { gross hematuria cola colour , RTI 2-3 weeks ago }
- IgA nephropathy {Pt present with hematuria <1 week almost after 4 day of Clinical URT infection }
- Lupus nephritis (female , young age)
- Rapidly progressive glomerulonephritis
- Anti-GBM (Goodpasture's disease)
- Anti-GBM
- ANCA vasculitis (e.g. Wegner's Granulomatosis)
- Membranoproliferative GN (MPGN) like in DM , inherited disease that affect collagen
- Alport's syndrome [2] Weakness thinking of GBM, and it is X linked in 85% of cases
- Familia being hematuria (thin basement membrane)

What is the difference between anti-GBM and goodpasture syndrome ?
-anti-GBM > antibody against GBM only
-goodpasture syndrome > antibody against GBM and alveolar basement membrane they will have pulmonary hemorrhage and acute kidney injuries

What is the different between Albert and familial benign hematuria ? (microscopic hematuria)
-Albert is progressive disease commonly end up with end stage renal disease
-familial benign hematuria , more than 95% they did not progress to ESRD , everything else is Ok in hypertension, no high creatinine

1. The degree or amount of proteinuria is the main difference between glomerulonephritis and nephrotic syndrome.
2. Alport's syndrome (hereditary nephritis): X-linked or autosomal dominant inheritance with variable penetrance. It is a congenital defect of collagen. Features include hematuria, pyuria, proteinuria, high-frequency hearing loss without deafness, visual disturbance, progressive renal failure. No effective treatment.

Nephrotic syndrome

◄ Pathological findings:

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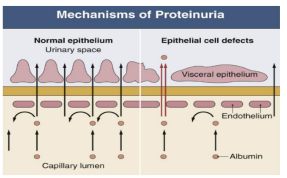
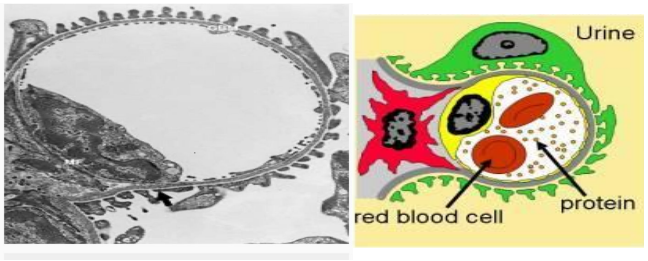
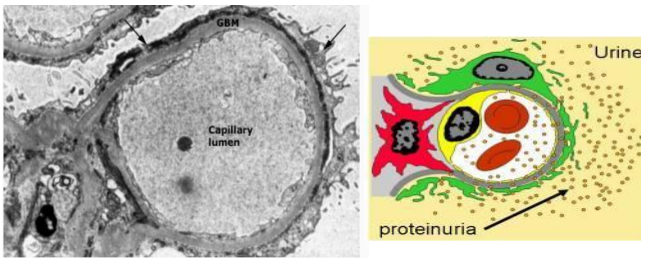


Normal foot processes



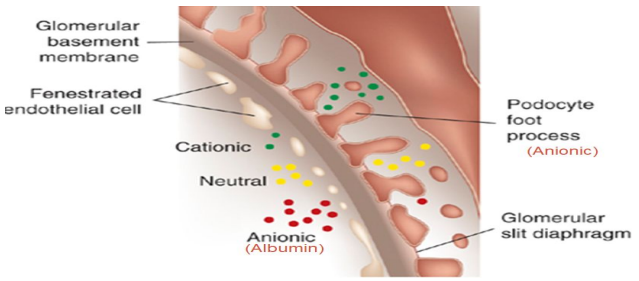
Diffuse Foot Processes Effacement



- **Podocytes** abnormality is the primary finding
- Podocytes will sustain a structural dysfunction; making them **lose their Foot-processes** (called : **foot process effacement**), while their cells bodies remains intact. This pathology makes Glom capillary wall becomes **permeable to Albumin.**
- This will lead to significant amount of protein appearing in the urine (**Proteinuria**).

◄ Pathophysiology:

Podocytes are negatively charged (due to glycoproteins) so they will repel the negatively charged albumin from appearing in the urine ,if they are effaced then albumin will find its way to appear in urine



◄ Important definitions about Proteinuria:

How many milligrams of proteins are **normally** secreted in the urine per-day?

- **< 150 mg/day of all kinds of proteins**. (albumin & non-albumin proteins), on average; **4-7 mg/day[1,2] out the 150mg/Day is Albumin,** the remaining is Non Albumin proteins.
- **Proteinuria > 150 mg/day** is a pathological indicator and is <u>usually made of Albumin in Glomerular diseases</u>
- If Albumin urinary secretion : **30-300 mg/day** is called Microalbuminuria <u>(indicates early renal disease)</u>
  - **> 300 to < 3500 mg/ Day :** overt proteinuria
  - **> 3500 mg/ Day :** Nephrotic range Proteinuria Or Heavy Proteinuria

- In a healthy adult, how many grams of albumin does the liver make everyday? 10 g
- Loss of urinary protein (largely albumin) of the order of 3.5 g or more daily in an adult may lead to hypoalbuminemia. Normal dietary protein intake in the UK is around 70 g daily and the normal liver can synthesize albumin at a rate of 10–12 g daily. **How then does a daily urinary protein loss of 3.5 g result in hypoalbuminemia?** This can be partly explained by increased catabolism of reabsorbed protein, largely albumin, in the proximal tubules, even though the rate of albumin synthesis is increased.

1- We can only detect it when it reaches 30 mg/day
2- Some people extend the range to 15 mg

Nephrotic syndrome

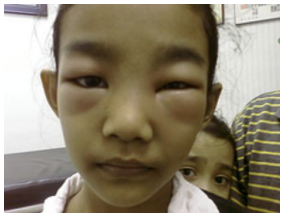
◄ Urine Analysis: the best initial test.

- **Heavy proteinuria (>3.5g = > 3500 mg** "nephrotic range" per 24 hrs. of urine collection)
- **No RBCs** (some times few RBCs are occasionally seen)
- No RBCs casts
- **Fat (Lipiduria):** Fatty casts, oval fat bodies & fat droplets.
- No WBCs (few may be seen)

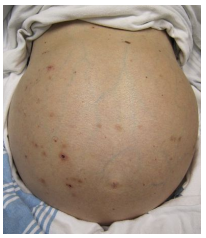
◄ Blood Analysis:

- **Hypoalbuminemia (<30 g/L)** the Normal serum Albumin level : 35-55g/L
- **Hyperlipidemia** Why? The liver is overworking and producing proteins to compensate for albumin loss. One of the proteins that will be manufactured by the liver is lipoprotein which is cholesterol carrier → increased lipoprotein → more cholesterol carried in the blood →

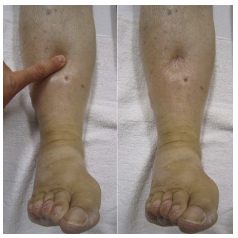
◄ Clinical presentation:



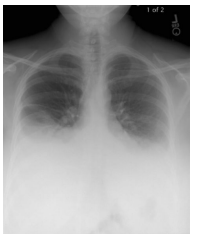
Periorbital edema[1]



Ascites



Pitting edema



Pleural effusion[2]
(Bilateral)

Edema Caused by:

1. **Low** serum **albumin** (↓oncotic pressure)
2. **Increased** renal **sodium** retention. Because of uncontrolled activation of the epithelial sodium channels (ENaC channels in the renal tubules)

Patient may present with:

- Fatigue & Anorexia[3]
- Frothy (foamy) urine (froth **persists** for long time after voiding)
- Weight gain due to fluid retention
- Shortness of breath If having **pleural effusion**
- Nausea & vomiting[4]
- Abdominal pain due to bowel edema
- Signs & symptoms of DVT, PE as complications
- Peripheral or generalized **edema**

1-- Especially in children after waking up. But after walking and playing during the day → gravity will pull the fluid down → it will disappear.
2- Why do patients with nephrotic syndrome get pleural effusion and not pulmonary edema? The cause is that pulmonary cardiac circulation doesn't depend on oncotic pressure (it is hydrostatic dependent).
3 The stomach and bowel is edematous → no feeling of hunger.
4- Peristalsis is impaired due to edema.

Management of nephrotic syndrome

◄ General measures:

Initial management should be with dietary sodium restriction and a loop diuretic

- Initial management should be with dietary sodium restriction and a loop diuretic (e.g. furosemide or bumetanide). Unresponsive patients require furosemide 40–120 mg daily (or more) with the addition of amiloride (5 mg daily; monitor serum potassium concentration regularly).
- Nephrotic patients may malabsorp diuretics (as well as other drugs) owing to gut mucosal oedema, and intravenous administration may be needed initially. Patients are sometimes hypovolaemic, and moderate oedema may have to be accepted in order to avoid postural hypotension.
- Normal protein intake is advisable. A high- protein diet (80–90 g protein daily) increases proteinuria and can be harmful in the long term.

prophylactic anticoagulation

- Hypercoagulable states predispose to venous thrombosis. The hypercoagulable state is due to loss of clotting factors (e.g. antithrombin) in the urine and an increase in hepatic production of fibrinogen. **Prolonged bed rest should be avoided, as thromboembolism is very common** (particularly in membranous nephropathy). Long- term prophylactic anticoagulation may be indicated, and if renal vein thrombosis occurs, permanent anticoagulation is required.

pneumococcal vaccine

- **Sepsis is a major cause of death in nephrotic patients.** The increased susceptibility to infection is partly due to loss of immunoglobulin in the urine. Pneumococcal infections are particularly common and **pneumococcal vaccine should be given**. Early detection and aggressive treatment of infections, rather than long- term antibiotic prophylaxis, constitute the best approach.

HMG- CoA reductase inhibitor

- Lipid abnormalities are responsible for an increase in the risk of cardiovascular disease in patients with proteinuria. Treatment of hypercholesterolaemia starts with an HMG-CoA reductase inhibitor (a **statin**).

ACEI and/or ARB

- Lastly, ACE inhibitors and/or angiotensin II receptor antagonists (AII- RAs) are **indicated for their antiproteinuric properties in all types of glomerulonephropathy, but most especially the nephrotic syndrome.** These drugs reduce proteinuria.

◄ specific measures:

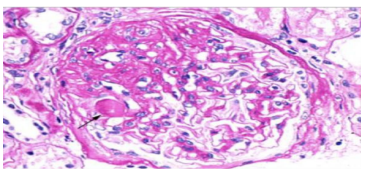
- treat the underlying cause of any protein leak

Focal Segmental Glomerulosclerosis (FSGS) [1]

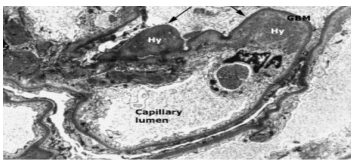
- A common cause of Nephrotic syndrome in **adults**.
- If a child presented to you with FSGS it will be usually secondary to other causes.
- Causes 12 – 35 % of the cases in adults.
- Could be Primary Or Secondary Or Genetic
- **Focal:** some glomeruli are affected by sclerosis (the rest of them look normal)
- **Segmental means:** sclerosis only involves a segment of each glomerulus that is affected by the disease. .

	Primary FSGS	Secondary FSGS[2]
Clinical features	Has sudden onset of heavy proteinuria and other manifestation of nephrotic syndrome	- Proteinuria is less heavy than other causes of nephrotic syndrome,even less < 3.5 gm/Day - Serum Albumin is not very low like the primary type. **- Renal impairment is commonly seen with the secondary FSGS and this is not a good prognostic sign**
Diagnosis	But most importantly, **all glomeruli** (the ones affected be sclerosis and the ones that are not affected) will have **a diffuse foot processes effacement** (thus nephrotic syndrome appears)	**Possible causes[3]** **A number of conditions which include:** 1. Diabetes mellitus. 2. Obesity. [4] 3. Nephron loss (>75% of renal mass e.g renal agenesis). 4. Reflux nephropathy. 5. Healing of prior GN (e.g IgA). 6. Severe preeclampsia. 7. Drugs : Interferon, Bisphosphonates (Pamidronate), Heroin. 8. Anabolic steroid abuse. 9. Infections : HIV 10. Sickle cell anemia
Possible causes	The exact mechanism is unknown Circulating Factor (like autoantibodies) targets podocytes and causes effacement We don't test for it because it's difficult to find.	
Treatment	Immunosuppressive therapy is indicated in most patients with primary FSGS **First line: corticosteroids** Second line: cyclosporine or tacrolimus (CNIs)	Not typically treated with Immunosuppression. treat the primary cause and add supportive measures to protect the kidneys, e.g. keeping blood pressure well controlled with ACE inhibitors.

Microscopic findings



FSGS, like minimal change disease, diffuse foot process effacement **with** segmental sclerosis

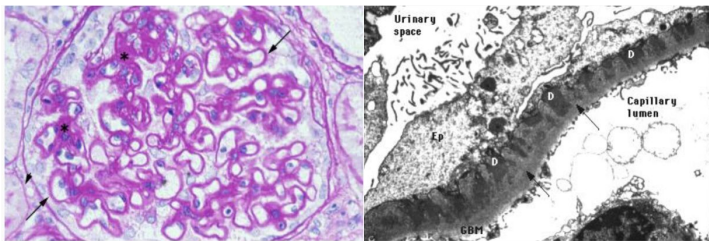


1- It has a fair to poor prognosis. It is generally resistant to steroid therapy—patients develop renal insufficiency within 5-10 years of diagnosis. The course is progressive to ESRD
2- secondary FSGF is more common in Saudi Arabia than primary FSGS while in MCD primary causes are common
3- Secondary FSGS with similar glomerular changes is seen as a secondary phenomenon when the number of functioning nephrons is reduced for any reason.
4-We have a fixed number of glomeruli since birth , when the person is obese the glomeruli will compensate by hypertrophy and will heal by fibrosis leading to sclerosis and ending in renal failure.

Membranous nephropathy

- **Most common cause of Primary nephrotic syndrome in adults** (15% and 33%)
- Mostly **secondary in children** (hepatitis B antigenemia)
- Presentation: slowly developing nephrotic syndrome (few weeks)

◄ Microscopic findings:



1 Notice the **Diffuse thickening of the glomerular capillary** throughout all glomeruli (IgG and C3 deposition)

◄ Types:

	Primary	Secondary
Clinical features	Accounts for **75%** of cases in adults.	——
Possible causes	**idiopathic**	A few conditions: • **Systemic lupus erythematosus (SLE)[2]:** Class V Lupus Nephritis (10-20%) other autoimmune disease (e.g.thyroiditis) • **Drugs:** penicillamine, IV gold salts, high dose Captopril, and NSAIDs, Anti-TNF. • **Infections:** Hepatitis B, Hepatitis C, syphilis, schistosomiasis,Plasmodium malariae) ★ **Malignancies [1,3]: solid tumors** like prostate, carcinoma of the lung, or GI tract,colon, stomach, breast and lymphoma
Treatment	**-Corticosteroids** plus Cyclophosphamide or cyclosporine -May be Rituximab	Mainly **target the primary disease** that caused membranous nephropathy and treat the Nephrotic syndrome manifestations

1- It might be idiopathic but it is sometimes caused by cancer e.g. **If someone is old or in his 50s and has risk factors for cancer and he presented with membranous nephropathy we will screen them for cancer (CXR, abdominal CT and colonoscopy is important) cuz it may be their only manifestation.**
2- the most imp cause of 2ndary MN
3- the 2nd most imp cause of 2ndary MN

Minimal Change Disease (MCD)

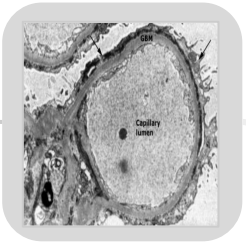
- **The most important difference between MCD and the FSGS is the presence of glomerular sclerosis in FSGS (there's no sclerosis in MCD[1])**
- **MCD is the main cause of Nephrotic syndrome in children :**
  - The cause in 90 % of cases in children < 10 years old.
  - > 50% of cases in older children
- It causes 10-25 % of Nephrotic syndrome cases in adults
- Current evidence points to systemic T-cell dysfunction as the most likely root cause of MCD.

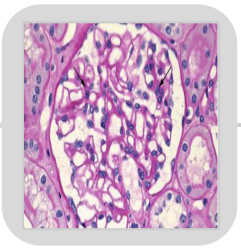
◄ Types:

Primary	Secondary
Idiopathic	• **Drugs (NSAIDs,** lithium, sulphasalazine, pamidronate, D-Penicillamine, some antibiotics) • **Neoplasm (Hodgkin lymphoma**, non-hodgkin lymphoma and leukemia) • **Infections** (TB and syphilis) • Allergies

◄ Microscopic findings:

EM: shows the **diffuse foot process effacement**





basically **no abnormality** is seen in light microscopy called (nil disease) nil =nothing

◄ Clinical features:

- Typically has a sudden onset Edema (few days)
- BP may be normal or slightly elevated
- Heavy proteinuria (Nephrotic range)
- **Lipiduria**
- Hypoalbuminemia (usually very low serum Albumin)
- Hyperlipidemia
- Creatinine is always within the normal range or slightly elevated and normalizes with remission

1- If there is sclerosis even in one glomeruli it will be a different disease. This is important because MCD responds very well to steroids, GS is a different disease.

Minimal Change Disease (MCD)

◄ Diagnosis

Adults: Must do kidney biopsy in adult patients with this presentation, It shows diffuse effacement of foot process ONLY.

Children: In children; **typically is corticosteroid responsive in > 90%, thus kidney biopsy is commonly not done** and treatment is given empirically for such cases. **So, usually nephrotic syndrome in a child < 10 years old is MCD until proven otherwise.**

◄ Treatment:

- First line:
Corticosteroids, given x 3-4 months then taper over 6 months
- Second line:
oral Cyclophosphamide, Cyclosporine

Other important 2ndry causes of nephrotic syndrome in adults

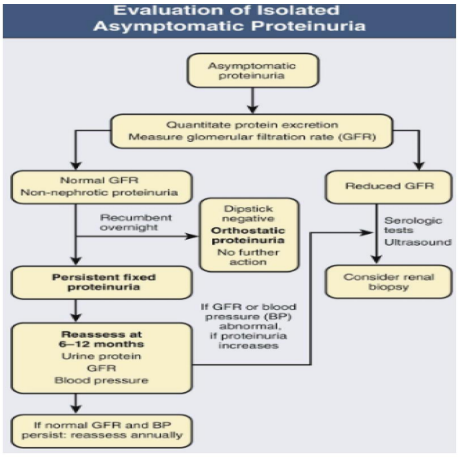
- Diabetes mellitus
- Amyloidosis
- IgA nephropathy
- MPGN

Amyloidosis is a systemic disorder of protein folding, in which normally soluble proteins or fragments are deposited extracellularly as abnormal insoluble fibrils (usually β- pleated sheets that are resistant to proteolysis), causing progressive organ dysfunction and death. The disease may be acquired or inherited. Classification is based on the nature of the precursor plasma proteins (at least 20) that form the fibrillar deposits. The most common forms are AL amyloidosis (where abnormal protein may be derived from light chains or immunoglobulin) and AA amyloidosis (where deposits form from serum amyloid A protein). The renal consequences are similar, even if systemic features differ.

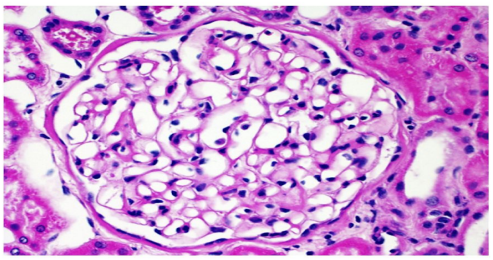
An area for your notes

Glomerular Diseases classification

How would you investigate for GN	Urinalysis : (protein , cast , RBC , WBC) Blood test : (creatinine, BUN) Serological: • ANA, ant DNA • C3 and C4 • Hepatitis B, C and HIV • Cryoglobulin • ANCA serology • Anti- GBM disease • ASO titer Kidney Biopsy

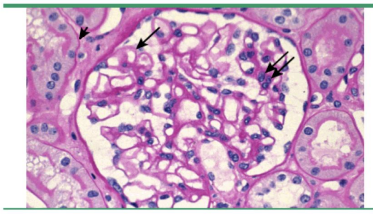


Normal Glomerulus



https://memorang.com/flashcards/257602/Renal+Nephrotic+S

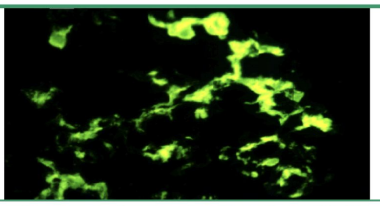
Normal glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).
Courtesy of Helmut G Rennke, MD.

UpToDat

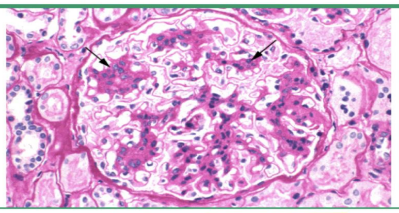
Immunofluorescence microscopy showing mesangial immunoglobulin A (IgA) deposits



Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura (IgA vasculitis). Note that the capillary walls are not outlined since the deposits are primarily limited to the mesangium.
Courtesy of Helmut Rennke, MD.

UpToDate

Light micrograph showing mesangial proliferative glomerulonephritis



Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including IgA nephropathy and lupus nephritis.
Courtesy of Helmut G Rennke, MD.

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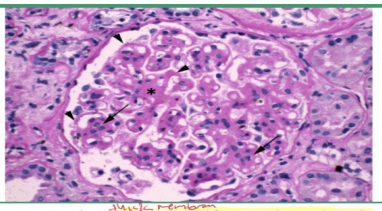
Membranoproliferative glomerulonephritis



Light micrograph in membranoproliferative glomerulonephritis showing a lobular appearance of the glomerular tuft with focal areas of increased glomerular cellularity (large arrows), mesangial expansion (*), narrowing of the capillary lumens, and diffuse thickening of the glomerular capillary walls (small arrows).
Courtesy of Helmut Rennke, MD.

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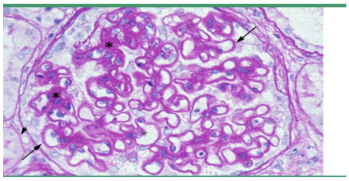
ht micrograph showing membranous nephropathy



t micrograph of membranous nephropathy, showing use thickening of the glomerular basement membrane g arrows) with essentially normal cellularity. Note how the kness of the glomerular capillary walls is much greater that of the adjacent tubular basement membranes ort arrow). There are also areas of mesangial expansion erisks). Immunofluorescence microscopy (showing ular IgG deposition) and electron microscopy (showing epithelial deposits) are generally required to confirm the inosis.
tesy of Helmut Rennke, MD.

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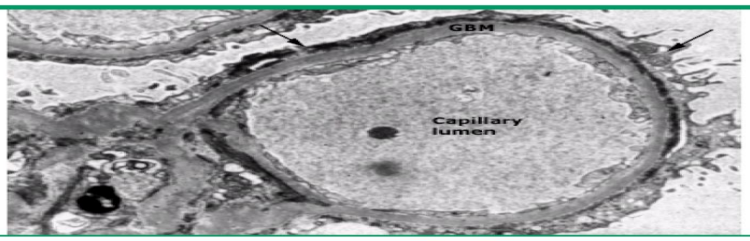
Electron microscopy in minimal change disease



Electron micrograph in minimal change disease showing a normal glomerular basement membrane (GBM), no immune deposits, and the characteristic widespread fusion of the epithelial cell foot processes (arrows).
Courtesy of Helmut Rennke, MD.

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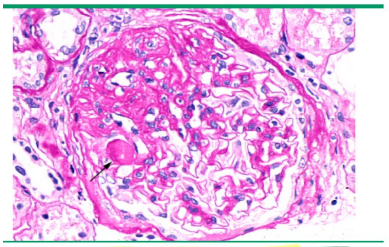
derate FGS



ht micrograph in focal segmental glomerulosclerosis shows noderately large segmental area of sclerosis with capillary lapse on the upper left side of the glomerular tuft; the ver right segment is relatively normal. Focal deposition of aline material (arrow) is also seen.
urtesy of Helmut Rennke, MD.

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Summary from AMBOSS

Differential diagnoses of nephrotic syndrome [2][3][4][5][6]

Disease	Epidemiology	Associations	Findings	Treatment

Minimal change disease (lipoid nephrosis)	• Most common cause of nephrotic syndrome in **children**	• Often idiopathic
		• Secondary causes (rare)
		  ◦ Immune stimulus (e.g., infection, immunization)
		  ◦ Tumors (e.g., Hodgkin lymphoma)
		  ◦ Certain drugs (e.g., NSAIDs)
			• LM: no changes (possibly fat bodies in some proximal tubular cells)
			• IM: negative
			• EM: effacement of podocyte foot processes
			• Selective glomerular proteinuria [7]
				• Responds well to **prednisone**
				• Good prognosis

Focal segmental glomerulosclerosis	• Most common cause of nephrotic syndrome in **adults**, especially in **African American and Hispanic populations**	• Can be idiopathic
		• Heroin use
		• HIV infection
		• Sickle cell disease
		• Massive obesity
		• Interferon treatment
		• Congenital malformations (e.g., Charcot-Marie-Tooth syndrome) [8][9]
		• NPHS1 and NHPS2 mutations
			• LM: segmental sclerosis and hyalinosis
			• IM
			  ◦ Most commonly negative
			  ◦ Possibly **IgM, C1, and C3** deposits inside the sclerotic regions
			• EM: effacement of podocyte foot processes (similar to minimal change disease)
				• **Prednisone** (often shows poor response)
				• If necessary, PLUS other immunosuppressants (e.g., cyclosporine, tacrolimus)
				• RAAS inhibitors
				• Usually leads to ESRD if left untreated

Membranous nephropathy	• Most common cause of nephrotic syndrome in **adults of European, Middle Eastern, or North African descent**	• Primary: anti-PLA2R antibodies
		• Secondary:
		  ◦ Infections (HBV, HCV, malaria, syphilis)
		  ◦ Autoimmune diseases (e.g., SLE)
		  ◦ Tumors (e.g., lung cancer, prostate cancer)
		  ◦ Medications (e.g., NSAIDs, penicillamine, gold) [10]
			• LM
			  ◦ Diffuse thickened glomerular capillary loops and basement membrane
			  ◦ Granular subepithelial deposits of IgG and C3 (dense deposits) → **spike and dome appearance**
				• **RAAS inhibitors**
				• Prednisone (often shows poor response)
				• PLUS other immunosuppressants (e.g., cyclophosphamide) in severe disease
				• Usually leads to ESRD if left untreated

Diabetic nephropathy	• Leading cause of ESRD in high-income countries	• Usually additional signs of other organ system complications (e.g., retinopathy, neuropathy)	• LM
			  ◦ Thickening of the glomerular basement membrane (increased permeability)
			  ◦ Eosinophilic nodular glomerulosclerosis (**Kimmelstiel-Wilson nodules**)
			  ◦ Mesangial matrix expansion
				• Stringent glycemic control
				• RAAS inhibitors

Amyloid nephropathy	• More commonly seen in elderly patients [11]	• The kidney is the most commonly affected organ in systemic amyloidosis.
		• Other organs might be involved simultaneously (e.g., the heart).
		• Multiple myeloma (AL amyloidosis)
		• Chronic inflammatory disease, e.g., tuberculosis, rheumatoid arthritis (AA amyloidosis)
			• LM
			  ◦ Mesangial proliferation
			  ◦ Subendothelial and/or subepithelial immune complex deposition
			  ◦ Thickening of the capillary walls (appear as wire loops)
			  ◦ Congo red stain: amyloid deposition in the mesangium showing **apple-green birefringence** under polarized light
			  ◦ Nodular glomerulosclerosis
			• EM: amyloid fibrils
				• Melphalan, corticosteroids
				• Treatment of underlying disease (e.g., bone marrow transplantation may be used for multiple myeloma)

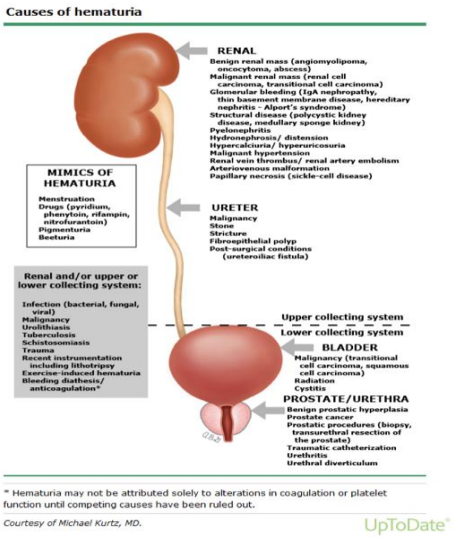
Membranoproliferative glomerulonephritis	• Usually manifests with nephritic sediment, which can indicate:
	  ◦ Nephritic-nephrotic syndrome: if there is concomitant nephrotic-range proteinuria (> 3.5 g/24 hours)
	  ◦ Pure nephritic syndrome: if there is no proteinuria or proteinuria is below nephrotic range (< 3.5 g/24 hours)
	• See "Nephritic syndrome."			

LM = light microscopy, IM = immunofluorescent microscopy, EM = electron microscopy

Nephritic syndrome

◄ Definition of Hematuria:

Presence of at least 3 RBCs per high power field (HPF) in a spun urine
HPF: 400x magnification level



◄ Main causes of Hematuria:

-Glomerular :
-Non- Glomerular :

- Stones
- Tumors
- Infections
- Trauma

◄ Hematuria can present

-Microscopic Hematuria:
Non-visible, detected by microscopy.

-Macroscopic Hematuria:
Gross hematuria

Gross Hematuria: Glomerular vs Extraglomerular

Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	<500 mg/day	May be >500 mg/day
RBC morphology	Normal	Some RBCs are dysmorphic
RBC casts	Absent	May be present

◄ Commonest type of glomerulonephritis that can present with gross hematuria:

-IgA nephropathy
-Post infectious glomerulonephritis
Both can be triggered by URTI Both can cause nephritis: AKI, HTN

- ◄ The onset of hematuria in relation to the URTI is important: In IgA: it is synpharyngitic (within 4 days after URTI symptoms) while in post infectious is usually 1 week– 2 weeks.
- ◄ **The definitive way of differentiation is renal biopsy.**

◄ Commonest Causes of Isolated glomerular microscopic hematuria (without proteinuria or renal impairment):

IgA nephropathy , Thin basement membrane (benign familial hematuria) , Alport's syndrome

◄ Indication for biopsy in microscopic hematuria:

renal impairment or Presence of proteinuria > 1 g/day or HTN

-Not every dark urine means Hematuria: Conditions where the urine becomes dark and positive for heme on dipstick but negative for RBCs on microscopy (+ve dipstick but no hematuria):

- Intravascular hemolysis (Hemoglobin)
- Rhabdomyolysis (Myoglobin).

-Negative dipstick exclude hematuria.

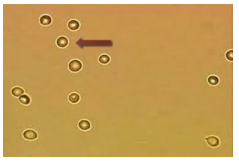
Nephritic syndrome

◄ introduction:

- When we say **Nephritic**, it means a clinical pattern of presentation for a group of glomerulonephritis, and not a syndrome like what we saw in Nephrotic causes.
- **The Nephritic pattern is always indicative of underlying inflammatory process in the glomeruli**; causing inflammatory modulators attraction, cellular proliferation and eventually glomerular permanent dysfunction if left untreated.
- The Glomerular **mesangium**, **endothelium** and Glomerular **basement Membrane** components of the Glomerulus are likely going to be targeted because of their **proximity to blood circulation**

◄ Urine Analysis:

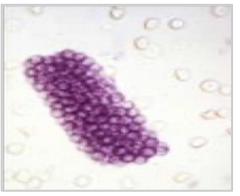
- **RBCs** In renal cell carcinoma, stone in the renal pelvis, the bladder or prostate → when they bleed there will be no change in the shape of RBCs.



Normal looking RBCs in microscopy

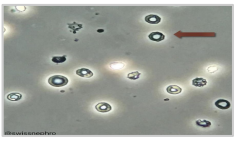
★ **Dysmorphic RBCs**
  - (RBCs lose their smooth surface passing through the cracks in inflamed glomerular capillary wall) considered a red flag for glomerular inflammation that has not manifested yet (critical).

- **RBC casts or cellular casts**
  - formed by naturally occurring **Tamm-Horsfall mucoprotein** in the distal tubules & collecting ducts when they become loaded with RBCs coming from the inflamed Glomerulus (due to GN)
- Dysmorphic RBCs & RBC casts are called **Active Urinary Sediments** when seen under microscope in urine sample (Active = indicative of underlying glomerular inflammatory process; requiring urgent medical attention)



RBCs casts

- **Proteinuria** (at variable amounts from subnephrotic to nephrotic range)
  - Those are called Active Urinary Sediments (Active = is indicative of underlying glomerular inflammatory process; requiring urgent medical attention)



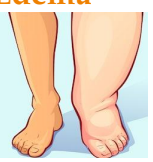
Dysmorphic RBCs

◄ Nephritic clinical manifestations:

1. **AKI**
(Acute Kidney Injury) =Acute Renal impairment or Failure= elevated Creatinine) & electrolytes imbalance.

2. **Decreased Urine output**

3. **Edema** [1]



4. **High Blood Pressure**

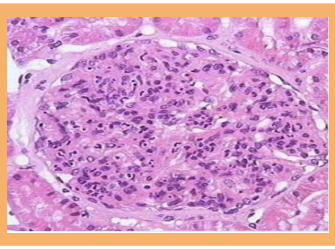
5. **Systemic vasculitis**
May have other manifestations of systemic vasculitis since some glomerulonephritis types are actually vasculitis (e.g. skin rash, pulmonary hemorrhage , etc)

6. **Positive immune markers**
ANA, Anti-DNA, low complements, +ve ANCA (depends on the cause)

1- Filtration barrier disrupted → decrease in GFR → RAAS activation → Fluid retention.

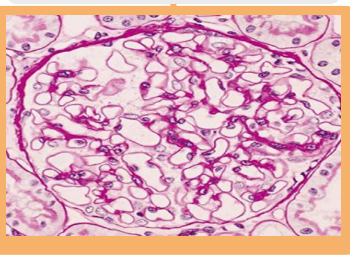
Nephritic syndrome

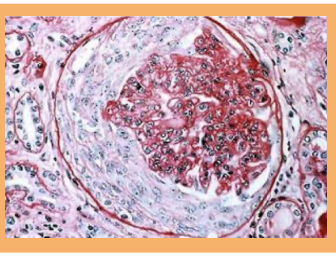
◄ Microscopic findings:



LM:
Glomeruli with proliferation (inflammatory) GN

Normal glomerulus





LM: Glomeruli with crescent[1] (very bad!):
- indicates **severe inflammation** & worse outcome if not treated in a short time from presentation

Renal diseases that can present with nephritic picture:

- IgA Nephropathy / HSP (Henoch-Schönlein purpura)
- Post streptococcal glomerulonephritis (PSGN)
- Lupus Nephritis
- Anti-GBM (Goodpasture's disease)
- ANCA vasculitis (e.g. Wegener's Granulomatosis)
- Membranoproliferative GN (MPGN)

1- Proliferation of parietal cells of bowman's capsule is a MEDICAL EMERGENCY IN NEPHROLOGY. we have to treat the patient in the same night with immunosuppression, if you don't treat him, patient will develop ESKD within days or weeks.

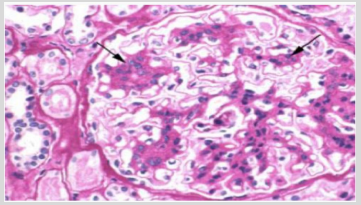
IgA Nephropathy (Berger's disease)/ HSP (Henoch-Schönlein purpura) [4]

◄ General characteristics:

- **Most common type** of Primary GN in developed countries
- IgA nephropathy tends to occur in children and young males
- Can present actively and can be silent.asymptomatic microscopic haematuria or recurrent macroscopic haematuria following an upper respiratory or gastrointestinal viral infection.
- Surprisingly, recurrent macroscopic haematuria is a good prognostic sign, although this may be due to 'lead- time bias' , as patients with overt haematuria come to medical attention at an earlier stage of their illness.
- It has a chronic course that may or may not worsen.
- **HSP** (Henoch-Schönlein purpura) is a **systemic** vasculitis caused by immune deposition of IgA in different organs; typically skin, bowel and kidneys.

◄ Microscopic findings:

LM:



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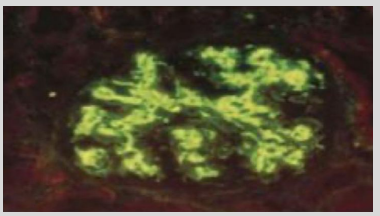


Pathophysiology

It is thought to be secondary to altered mucosal immunity that leads to excessive IgA synthesis[1] followed by deposition in the glomeruli.

Clinical features

01

Can present as dark urine[2] (hematuria) 1-3 days[3] after upper respiratory tract infection. **(< one week of Clinical URT infection)**

02

Commonly picked up **incidentally** by finding abnormal urine analysis (Hematuria +/- Proteinuria) done for other reasons with no symptoms; e.g. pre-employment investigations.

1- We have IgA mainly in the upper respiratory mucosa. If there is an abnormality in IgA synthesis and inflammation occur. abnormal IgA secretion will increase → filtered by the kidney → trapped in the glomerulus → inflammation.
2- Some pt might mention when they have URTI their urine becomes darker or cola like color.
3- Synpharyngitic haematuria: intercurrently with an episode of **pharyngitis**.
4-when IgA affect the **kidney only** this is called IgA nephropathy, while HSP is systemic IgA disorder, in which the skin, kidney and other organs will be affected

IgA Nephropathy (Berger's disease)/ HSP (Henoch-Schönlein purpura)

Diagnosis

- The diagnosis is made by finding abnormal **deposition of IgA** immunoglobulin in the Glomeruli, it elicits a local inflammatory response in the glomerular mesangium (mesangial expansion)
- Needs kidney biopsy to reach the diagnosis

treatment

- There is really no effective immunosuppressive therapy except in severe cases where it can be tried.
- Most important treatment is to control the blood pressure which also decreases the proteinuria. Severe proteinuria is treated with ACEi or ARB.
- All patients, with or without hypertension and proteinuria, should receive an ACE inhibitor or an AII- RA, to reduce proteinuria and preserve renal function.

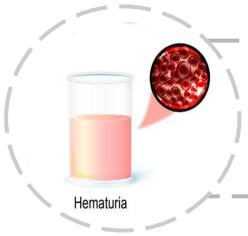
Post streptococcal glomerulonephritis (PSGN)

◄ Possible causes:

1. Typically caused by throat infection with Gram positive cocci (Group A beta-hemolytic Streptococcus (GAS).
2. But also can be caused by Staphylococcus soft tissue or bone infection in adults.
3. Bacterial Antigen cross react with glomerular antigens, or may be an immune complex (Antigen-antibody) response that is responsible.

Post streptococcal glomerulonephritis (PSGN)

◄ Clinical features:



Patients present with frank hematuria usually **after one week and up to 3 weeks**[1] from the start of infection. Patients present with dark (cola-colored) urine, edema that is often periorbital, hypertension, and oliguria.

Diagnosis

- Serum will show **positive Antistreptolysin (ASO) titer.**
- Low C3, Normal or slightly low C4 in the serum.
- May have positive throat culture.

- **Treatment is usually supportive = wait and see.**
- Children have better and faster recovery than adults.

treatment

Lupus Nephritis

- **Lupus (SLE): The Disease with a Thousand Faces.** It can cause membranous nephropathy and lupus nephritis (Nephrotic and nephritis)
- Kidneys can be affected by SLE like other organs.[3]
- The degree of involvement can be from mild (or even not visible to the physician) to a very severe one causing ESRD in few months or few weeks.
- Most important in dealing with these cases is having high suspicion of its presence and to start immediate workup & referral for diagnosis and treatment

Diagnosis

- **Kidney biopsy is mandatory to make the diagnosis**
- Low complements [4] (C3, C4) level along **with the positive Lupus markers (ANA, Anti DNA),** abnormal urine analysis & abnormal renal function should make you think of its presence.

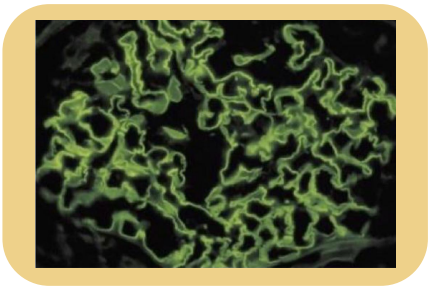
- **Lupus Nephritis treatment[2] depends on the findings in renal biopsy**
- **It usually involves high degree of immunosuppressive medications.**

Treatment

1- More severe and acute than IgA and can cause renal shutdown. Non synpharyngitic (develops after a few weeks), while in IgA it may happen within 3 days.
2-Treated aggressively cuz it can lead to loss of kidney function and renal failure in weeks if not treated.
3- Long-standing SLE may simply "scar" the kidneys and biopsy will show glomerulosclerosis, which has no active inflammatory component but may lead to such damage as to require dialysis.
4- low complement in blood is due to deposition in the kidney

Anti-GBM glomerulonephritis

◄ Microscopic findings:



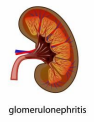
1 **Linear Anti-GBM staining in the Glomerulus by Immunofluorescence is a Diagnostic test** In ANCA , IF will be negative or little

Possible causes

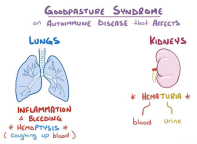
Due to autoantibody **against (alpha-3 chain) of type IV Collagen that is found in Glomerular and alveolar (lungs) basement membrane.** [1]

◄ Clinical features:

01 **GN** (can be the only presenting finding)



02 **Pulmonary hemorrhage** (disease is called **Goodpasture's** disease if Lung vasculitis + GN)



Diagnosis

- **Positive test for Anti-GBM antibodies in the serum**
- **Kidney biopsy shows the diagnostic Immunofluorescence pattern:**
  - **Linear stain of IgG and C3.**

Treatment is always started immediately to remove the antibodies by **Plasmapheresis** and preventing further antibodies production by giving heavy immunosuppression that includes corticosteroids and cyclophosphamide

treatment

1-Specifically targets middle aged smoker women (smoking exposes their lungs collagen as an antigen, so antibodies will be released against it) this collagen is similar to the kidney basement membrane)

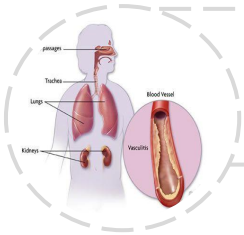
ANCA vasculitis
(e.g. Wegener's Granulomatosis)

- Autoimmune disease that **involves the presence of Neutrophils adhesion enhancing molecule called** ANCA= anti-neutrophil cytoplasmic antibody[1], This molecule establishes vascuilitis cascade

◄ Types [2]:

C-ANCA	P-ANCA
Cytoplasmic type, more commonly causing Granulomatous Polyangiitis = old name **Wegener's Granulomatosis** (so a granuloma forming disease) Angiitis: means small vessels vasculitis	**P**erinuclear type, more commonly associated with **Microscopic Polyangiitis & Churg- Strauss syndrome**

◄ Clinical features:



Upper airways and lung involvement is common and patients can present with renal and pulmonary manifestations (GN + Pulmonary hemorrhage: hemoptysis).

Diagnosis

- **Diagnosis is made by kidney biopsy and positive ANCA titer in the serum.**
- Kidney pathology will show sever Glomerulonephritis; maybe RPGN; but all staining with immunofluorescence for immunoglobulins is **NEGATIVE**; hence the name Pauci-Immune vasculitis or GN (Pauci = little or non)
- The best indicators of adverse prognosis are pulmonary haemorrhage and severity of renal failure at presentation.

Treatment

- The sooner treatment is instituted, the greater chance there is of recovery of renal function.
- It is usually an aggressive disease that should be treated with potent immunosuppressive medications (high dose corticosteroids & cyclophosphamide).
- Rituximab is equally effective in inducing remission in ANCA- associated vasculitides in the short term (6–12 months), with similar adverse event rates. Rituximab may be a therapeutic option in patients who cannot tolerate cyclophosphamide, and in those whose disease is poorly controlled and who relapse while on cyclophosphamide.

1-ANCA is a neutrophil stimulating molecule that causes neutrophils to adhere to blood vessels causing vasculitis
2-P-ANCA and C-ANCA are descriptions of the staining characteristic, so if the stain for ANCA is positive in the cytoplasm it's called C-ANCA, and if the stain is visible around the nucleus it's called P-ANCA

Membranoproliferative GN (MPGN)

Very complicated topic I don't advise you to go through it's details

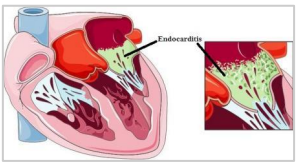
- It is a pathological description & has multiple causes.
- It may present with Nephritic picture or Nephrotic syndrome

◄ Types:

1. The primary (idiopathic) MPGN is mainly seen in children.
2. The secondary type is seen in adults due to:

Possible causes

- Hepatitis B and C
- Lupus and Sjogren's syndrome
- Complement deficiency
- Endocarditis
- Cancer



Syndrome	Nephrotic(NS)	Nephritic (GN)
Pathology	- Mainly a **Podocytes disease** present with Pathology **foot process effacement** +++ - Usually No Glomerular inflammation	Is an **inflammatory** disease involves any or all of Glomerular elements: Base Membrane, Endothelium or mesangium. Foot Processes Effacement ++
Proteinuria	**> 3.5 g/Day**	Variable amount from few 100s mg to grams / day
Urine microscopy	- No hematuria - + Lipids (Lipiduria)	**+ RBCs, + dysmorphic RBCs, + RBC casts (active sediments)**
Labs	- **Low serum** Alb < 30 gm/L - **High Cholesterol**	- Low GFR (Renal impair) - Electrolytes imbalance
Clinical	- **Edema ++++** - BP maybe high	- Edema ++ depends **High BP ++** - Symptoms & signs of renal impairment or vasculitis
Complications (Acute)	- Thrombosis - Infection, AKI	- RPGN (crescentic disease) - AKI
Complication[1] (Chronic)	- Vascular Atherosclerosis -renal Tubular atrophy & Fibrosis then CKD then ESRD	Glomerular sclerosis then CKD (chronic Kidney disease) to ESRD

1- They both have the same outcome but the progression to ESKD is faster in nephritic than nephrotic syndrome

Summary from AMBOSS

Diseases associated with nephritic syndrome			
	Epidemiology	**Clinical features**	**Diagnostics**

Poststreptococcal glomerulonephritis	• Usually affects **children** 3–12 years of age and elderly patients [2]	• Occurs weeks **after group A β-hemolytic streptococcal infections**
		  ○ Pharyngitis/tonsillitis (most common): 1–2 weeks after infection
		  ○ Skin infections: 3–4 weeks after infection
		• Periorbital and peripheral edema
		• Hypertension
		• Tea- or cola-colored urine
		• Usually **self-limiting** in children
		• May lead to rapidly progressive glomerulonephritis (RPGN) → renal insufficiency in adults
			• **Positive antistreptococcal antibodies** (ASO, ADB)
			• ↓ **Serum C3** complement levels (due to consumption)
			• Type III hypersensitivity reaction
			• LM: glomeruli appear enlarged and hypercellular
			• IF
			  ○ Granular subepithelial immune complex **depositions (IgG, IgM, C3)** along the GBM and the mesangium
			  ○ So-called "lumpy bumpy" or "starry sky" appearance
			• Electron microscopy (EM): dome-shaped, subepithelial immune complex deposits **(humps)**

IgA nephropathy (Berger disease)	• Most common type of idiopathic glomerulonephritis worldwide
	• Incidence: ♂ > ♀ [3]
	• Peak incidence: 2nd to 3rd decade of life [4]
		• Asymptomatic microhematuria with intermittent gross hematuria during or directly after one or more of the following:
		  ○ Upper respiratory tract infections
		  ○ Gastrointestinal infections
		  ○ Strenuous exercise
		• 25–30% of patients progress to end-stage renal disease (ESRD) within 20 years of diagnosis. [5]
			• ↑ Serum IgA
			• Normal C3 complement levels
			• Renal pathology findings of IgA vasculitis (IgA vasculitis)
			  ○ LM: mesangial proliferation
			  ○ IF: mesangial IgA immune complex deposits
			  ○ EM: mesangial immune complex deposits

Small vessel vasculitis — **Granulomatosis with polyangiitis**	• Slightly more common in men • Peak incidence: 65–74 years [6]	• Pulmonary and nasopharyngeal involvement is common • May manifest with hemoptysis and nasal ulcers. • Can cause pauci-immune RPGN	• **c-ANCA/PR3-ANCA** • Type IV hypersensitivity reaction • Renal biopsy: segmental necrotizing glomerulonephritis
Small vessel vasculitis — **Microscopic polyangiitis**	• Slightly more common in men • Peak incidence: 50–60 years [7]	• Usually only mild respiratory symptoms • Can cause pauci-immune RPGN	• **p-ANCA/MPO-ANCA**
Small vessel vasculitis — **Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)**	• Least common type of small vessel vasculitides • Peak incidence: 38–54 years [8]	• Asthma • Allergic rhinitis • Purpura • Peripheral neuropathy • Can cause pauci-immune RPGN	• p-ANCA/MPO-ANCA • **Peripheral eosinophilia** • Focal segmental necrotizing glomerulonephritis

Goodpasture syndrome (anti–GBM antibody disease)	• Two peaks of occurrence [9]
	  ○ 20–30 years (♂ > ♀)
	  ○ 60–70 years (♀ > ♂)
		• Pulmonary infiltrates on chest x-ray
		• Pulmonary hemorrhage and hemoptysis
		• Usually presents as RPGN type 1
		• Anti-GBM glomerulonephritis: glomerulonephritis in the presence of anti-GBM antibodies without lung involvement
			• Caused by antibodies against type IV collagen
			• Type II hypersensitivity reaction
			• Hemosiderin-filled macrophages in sputum
			• Iron deficiency anemia
			• IF: linear deposition of immunoglobulin (IgG) along the glomerular basement membrane (and the alveolar basement membrane in the lung)

Thin basement membrane nephropathy (benign familial hematuria)	• Estimated to affect 5–10% of the general population [10]	• Hereditary disorder • Persistent microhematuria and episodic gross hematuria (e.g., following an upper respiratory tract infection or exercise) • Good prognosis	• Abnormalities of type IV collagen • EM: diffuse thinning of glomerular basement membrane
Alport syndrome	• 85% of cases X-linked dominant (♂ > ♀), ~ 15% autosomal recessive [11] • Severe disease typically manifests during adolescence	• Most common type of hereditary nephritis (but rare) • Mutation in gene encoding **type IV collagen** • Associated with sensorineural **hearing loss** • And **abnormalities of the eye** (anterior lenticonus, retinopathy) • Often leads to ESRD	• Persistent microhematuria with intermittent gross hematuria • EM: splitting and alternating thickening and thinning of the glomerular basement membrane (lamellated and basket-weave appearance)

Diffuse proliferative glomerulonephritis (DPGN)	• Most common and severe manifestation of lupus nephritis in systemic lupus erythematosus (SLE)
	• Also seen with IgA nephropathy and with other inflammatory, autoimmune, or infectious diseases
		• Can also be nephritic with nephrotic-range proteinuria (nephritic-nephrotic syndrome)
		• Can lead to immune complex RPGN
			• ↓ Serum **C3 complement** levels
			• ANA, anti-dsDNA antibodies
			• LM
			  ○ Thickening of glomerular capillaries (appear as wire loops)
			  ○ Characterized by increased glomerular cellularity in more than half of the glomeruli
			• IM: granular appearance
			• EM
			  ○ Most commonly subendothelial immune deposits (IgG immune complexes, C3, and C1q)
			  ○ Less commonly subepithelial or intramembranous deposits

Rapidly progressive glomerulonephritis (RPGN)	• Occurrence: ♂ = ♀
	• Peak incidence: 60–85 years [12]
		• Renal function declines rapidly over days to weeks
		• Not a disease entity itself but a possible manifestation of glomerulonephritis
		• Poor prognosis: can progress to ESRD within weeks to months
			• LM, IF, EM
			  ○ **Crescent formation** (moon-shaped) made of plasma proteins (e.g., C3b) and fibrin
			  ○ Monocytes, macrophages, glomerular parietal cells
			• Can be caused by a variety of diseases categorized in three groups according to their IM pattern
			  ○ **Linear**: Goodpasture syndrome (anti-GBM disease)
			  ○ **Granular** (immune complex RPGN)
			  ▪ Poststreptococcal glomerulonephritis
			  ▪ Diffuse proliferative glomerulonephritis (most common with SLE)
			  ○ **Negative** (pauci-immune RPGN)
			  ▪ Granulomatosis with polyangiitis
			  ▪ Microscopic polyangiitis
			  ▪ Eosinophilic granulomatosis with polyangiitis

Membranoproliferative glomerulonephritis (MPGN)	• Primary disease occurs mainly in children	• Most commonly nephritic, but severe forms can also be nephrotic
		• Immunoglobulin (IG)-mediated membranoproliferative glomerulonephritis (type 1 MPGN)
		  ○ Associated with SLE, monoclonal gammopathy
		  ○ Can also be idiopathic
		• Complement-mediated membranoproliferative glomerulonephritis (type 2 MPGN: associated with dense deposit disease (IgG antibodies that stabilize C3 convertase, i.e., C3 nephritic factor, cause a persistent complement activation, leading to a depletion of C3)
		• Both associated with HBV, HCV, and cryoglobulinemia
		  ○ Hereditary diseases (e.g., sickle cell disease, α1-antitrypsin deficiency) [13]
		  ○ Drugs (e.g., heroin, α-interferon)
		  ○ Tumors (e.g., lymphoma)
		  ○ Autoimmune diseases (e.g., SLE)
		• May manifest with concomitant nephrotic-range proteinuria (nephritic-nephrotic syndrome)
			• IG-mediated (type 1)
			  ○ IF: subendothelial and mesangial IgG immune complex deposits with granular appearance
			  ○ ↓ Serum **C3 complement** levels
			• Complement-mediated (type 2)
			  ○ Intramembranous C3 deposits (dense deposit disease) on basement membrane
			  ○ ↓ Serum **C3 complement** levels
			• Both types: LM with H&E or PAS stain shows mesangial ingrowth, which leads to thickening and splitting of the glomerular basement membrane (**tram-track** appearance)

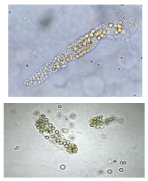
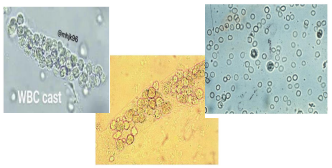
LM = light microscopy, IM = immunofluorescent microscopy, EM = electron microscopy			

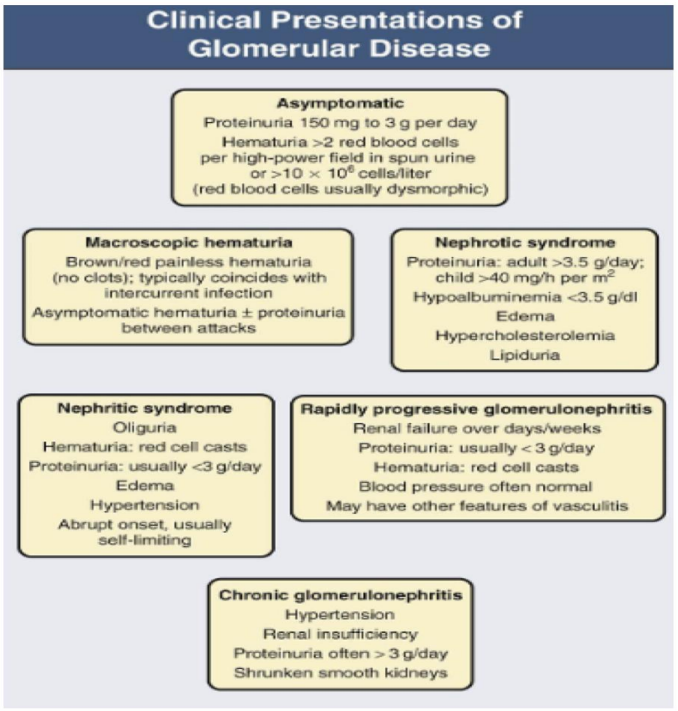
Summary

Nephrotic Syndrome	
FSGS	**Primary (autoimmune)**: sudden onset of heavy proteinuria & other manifestations of nephrotic syndrome. Treatment: corticosteroids **Secondary**: proteinuria is less heavy than other causes of nephrotic syndrome. Associated with sickle cell anemia, steroids & obesity. Treatment: treating the underlying cause. Diagnosis: Focal: some glomeruli are affected by sclerosis (the rest look normal) Segmental: sclerosis only involves a segment of each affected glomerulus but most importantly all glomeruli will have diffuse foot processes effacement (Nephrotic Syndrome)
Minimal Change	Main cause of Nephrotic Syndrome in children. **Primary:** Idiopathic. **Secondary:** Drugs (NSAIDs) Light microscopy: normal glomeruli Electron microscopy: diffuse effacement of the epithelial cells' foot processes only **The most important difference between Minimal Change Disease and FSGS is the presence of glomerular sclerosis in FSGS.** **Nephrotic syndrome in a child < 10 years old is MCD until proven otherwise.** Clinical features: Heavy proteinuria (nephrotic range), Lipiduria, Hypoalbuminemia, Hyperlipidemia. Treatment: corticosteroids
Membranous	Most common cause of primary nephrotic syndrome in adults. **Primary**: Idiopathic Treatment: corticosteroids **Secondary**: SLE, Solid tumors Treatment: treating the underlying cause Diagnosis: Diffuse thickening of the glomerular capillary throughout all glomeruli (IgG and C3 deposition)
Secondary causes of Nephrotic Syndrome: Diabetes Mellitus	

Summary

Nephritic Syndrome VERY BAD CRESCENTIC GLOMERULI	
IgA/Henoch-Schönlein	Most common type of primary glomerulonephritis in developed countries. Can present actively and can be silent. Diagnosis: abnormal deposition of IgA in the glomeruli. Can present as dark urine (hematuria) 1-3 days after upper respiratory tract infection. Henoch-Schönlein Purpura: systemic vasculitis caused by immune deposition of IgA in different organs; typically skin, bowel and kidneys. There's no effective immunosuppressive therapy.
Poststreptococcal	Typically caused by a throat infection with gram positive cocci (Group A Beta-Hemolytic Streptococci) Patients present with frank hematuria usually after one week and up to 3 weeks from the start of the infection. Serum will show positive ASO titer.
Anti-GBM (Goodpasture)	Due to autoantibodies against alpha-3 chain of type IV collagen that is found in glomerular and alveolar basement membrane. Clinical features: glomerulonephritis & pulmonary hemorrhage (collectively known as goodpasture's disease) Diagnosis: Linear stain of IgG and C3 under IF.
ANCA Vasculitis (Wegener's)	Autoimmune disease that involves the presence of neutrophil adhesions enhancing molecule called ANCA (anti-neutrophil cytoplasmic antibodies) **C-ANCA:** Cytoplasmic type, more commonly causes Granulomatous Polyangiitis AKA Wegener's Granulomatosis. **P-ANCA:** Perinuclear type, more commonly associated with Microscopic Polyangiitis & ChurgStrauss Syndrome. Upper airway and lung involvement is common and patients can present with renal and pulmonary manifestations (Glomerulosclerosis & Pulmonary Hemorrhage: hemoptysis). Kidney pathology shows severe glomerulonephritis; maybe RPGN; but all staining with IF for immunoglobulins is NEGATIVE; hence the name Pauci-Immune Vasculitis or Glomerulosclerosis (Pauci = little or none)

types of cast			
Nephritic syndrome	Nephrotic syndrome	In Interstitial nephritis	Acute tubular necrosis
-RBC cast	-fat cast	-Urinalysis typically show WBCs, RBCs and WBC casts.	-Characterized by Heme granular cast (muddy brown cast) on urinalysis -Typically there are no RBCs however presence of some won't exclude the possibility of ATN.
			



Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

Key points

- Hematuria can be benign but might indicate glomerular-based disease or urological malignancy
- Age, gender, smoking, family Hx, PHx are important factors to be considered upon approaching glomerulonephritis
- Glomerulonephritis can be primary or secondary. In Secondary causes treating the underlying disease would improve GN in most of the cases. Screening for secondary causes is worthy in adults
- Nephrotic range proteinuria indicates underlying glomerular-based disease in most of the cases

Lecture Quiz

1:C / 2:D / 3:B / Q4:D / Q5:A

Q1: A 21-year-old man presents with painless haematuria which he has noticed in the last 3 days. He suffers from type 1 diabetes which is well controlled, but is otherwise fit and healthy. The patient has recently recovered from a mild throat infection. Urine dipstick analysis reveals blood and protein in the urine. The most likely diagnosis is:

A- Henoch–Schonlein Purpura
B- Benign Prostatic Hypertrophy
C- IgA Nephropathy
D- Diabetic Nephropathy

Q2: A 64-year-old woman with type 1 diabetes presents to clinic with several months of sinus problem and a 4-day history of oliguria. Her blood pressure is 137/80, serum results show mildly elevated urea and creatinine, absence of anti-GBM antibodies, while a C-ANCA assay is positive. Red blood cell (RBC) casts are present in the urine and her renal biopsy reveals glomerular crescents. The most likely diagnosis is:
A- Post-streptococcal Glomerulonephritis
B- Goodpasture's Syndrome
C- Minimal Change Glomerulonephritis
D- Wegener's Granulomatosis

Q3: A 38-year-old woman presents with newly diagnosed Hodgkin lymphoma associated with bilateral lower extremity edema. Lab workup reveals 10g of proteinuria on a 24-hour urine collection. Which of the following pathological entities most likely explains the presence of proteinuria in this patient?
A- Membranous Nephropathy
B- Minimal Change Disease
C- Focal Segmental Glomerulosclerosis
D- IgA Nephropathy

Q4: A 50-year-old white man presents with mild hypertension, nephrotic syndrome, microscopic hematuria, and venous thromboses (including renal vein thrombosis). Renal biopsy reveals a thickened glomerular basement membrane with subepithelial immunoglobulin deposition. The most likely diagnosis is:
A- IgA Nephropathy
B- Anti-glomerular Basement Membrane Disease
C- Focal Segmental Glomerulosclerosis
D- Membranous Nephropathy

Q5: Patient presents to the clinic complaining of blood in the urine. Patient says I had a sore throat 2 weeks ago after that I felt pain in my joints then this morning I saw blood in my urine. What is the most likely diagnosis?
A- Post-streptococcal Glomerulonephritis
B- Membranous Nephropathy
C- ANCA Vasculitis
D- IgA Nephropathy

Lecture Quiz

1:A,b,c / 2:C / 3:C /4:T /5:F

Q1 : What affect the trans-glomerular passage ?
A.Molecular size
B.Charge
C.Shape

Q2 : Which of the following are typical features of active glomerulonephritis ?
A. high creatinine, hypovolemia and proteinuria
B.High creatinine, hypervolemia, proteinuria & Mg
C.High creatinine, hypervolemia, microscopic hematuria and proteinuria

Q3: What are the layers of the glomerular capillary wall in order from inside to outside?
A.Endothelial cells, podocytes,GBM
B.GBM, endothelial cells, podocytes
C.Endothelial cells, GBM, podocytes

Q4:Is the statement below True or False?
Mesangial cells maintain the structure and the function of the glomerulus

Q5:Is the statement below True or False?
Slit diaphragm is composed of group of proteins that maintain the structure and the alignment of the endothelial cells