Glomerular Disease

No.19

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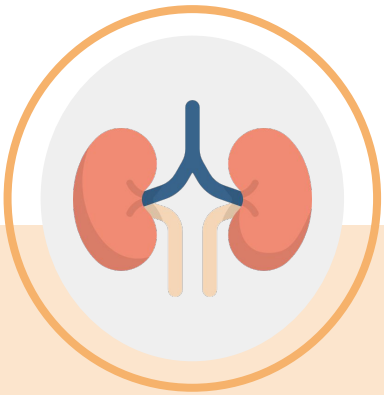

Objectives :

- ★ Understand the physiology / pathophysiology of Glomerular structure.
- ★ Recognize Normal & abnormal urine analysis in making diagnosis of Glomerular Disease vs Non-Glomerular disease
- ★ Recognize the differences between Nephritic & Nephrotic Glomerular diseases.
- ★ To recognize the early features of Glomerular diseases before it is too late! Early Dx & Rx makes a huge difference
- ★ To learn the common causes of Nephrotic & Nephritic renal diseases.

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Glomerular Diseases[1]

◄ Normal Glomerular structure is needed to:

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

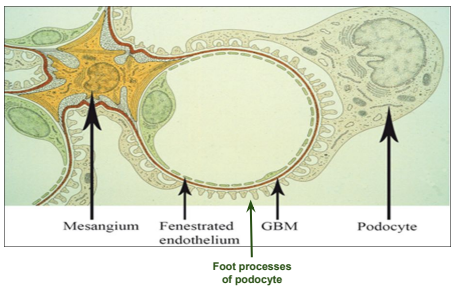
02 Maintain urine volume and hence, preventing fluid retention in the body which causes edema and high blood pressure.

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. Patients with a disease that causes nephron (glomerular or tubular) problem → Cortex Atrophy

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



◄ How glomerular diseases start?

- The insult to the glomeruli is either due to an autoimmune attack (autoantibodies) or is the result of deposition of antibody-antigen complex (immune complex) in the kidney which will attack/get stuck in 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, endothelium, podocytes, etc.)
- 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:

Nephrotic	Nephritic
If **Podocytes** were the main target of the disease process this leads mainly to **proteinuria**[2] (at large amount) due to **foot process effacement;** thus **Nephrotic Syndrome** will be the main finding. If there was only a podocyte problem, the only manifestation that would be seen would be the leakage of proteins into the urine (since the main function of podocytes is to keep albumin and other proteins from leaking out).(proteins+something else in the urine). So, **anything related to podocytes is nephrotic.**	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**)

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.
2. **The podocyte is outside the blood component.** Everything else (epithelium, mesangial cells, BM) is close to the blood compartment. So, destruction to these structures results in the recruitment of blood components and will result in more destruction (destruction to the podocytes does not result in the recruitment of blood components=less destruction).

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

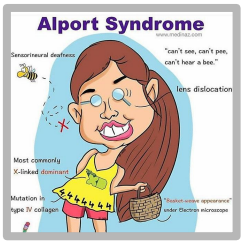
- Focal segmental glomerulosclerosis
- Minimal change disease
- Membranous nephropathy

secondary causes

- IgA nephropathy
- membranoproliferative glomerulonephritis (MPGN)
- ★ **Diabetic nephropathy**[3]
- Amyloidosis[4]

Nephritic syndrome

- IgA nephropathy
- Poststreptococcal glomerulonephritis (PSGN)
- Lupus nephritis
- Rapidly progressive glomerulonephritis
- Anti-GBM (Goodpasture's disease)
- ANCA vasculitis (e.g. Wegner's Granulomatosis)
- Membranoproliferative GN (MPGN)
- Alport's syndrome[2]

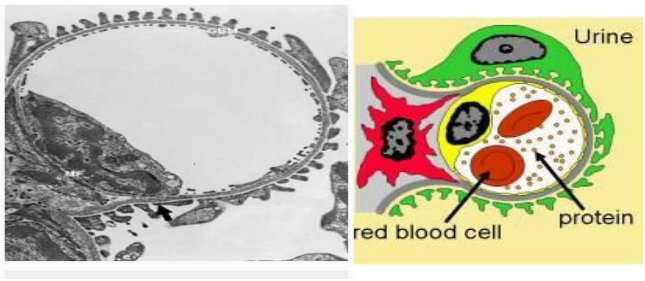


1. The degree or amount of proteinuria is the main difference between glomerulonephritis and nephrotic syndrome.
2. Alport's syndrome (hereditary nephritis): X-linked or autosomal dominant inheritance with variable penetrance. It is a congenital defect of type IV collagen. Features include hematuria, pyuria, proteinuria, high-frequency hearing loss without deafness, visual disturbance, progressive renal failure. No effective treatment.
3. **Commonest cause of secondary Nephrotic syndrome in KSA** (especially in T1D)
4. Second most common cause of Nephrotic syndrome
5. Note : the impairment of renal function is more common in nephritic syndrome

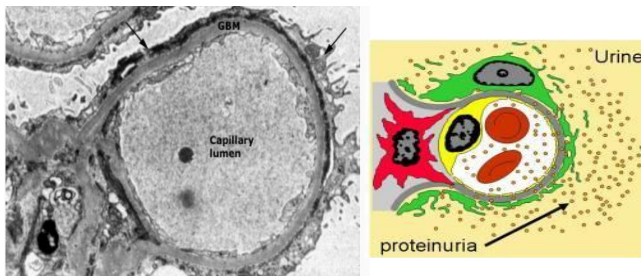
Nephrotic syndrome

◀ Pathophysiology

Normal foot processes



Diffuse Foot Processes Effacement



- The main pathology in NS: is **Podocytes problem** **Foot processes** are very important for the function of podocytes.
- When Podocytes sustain a structural dysfunction; it makes 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**, how? Podocytes are negatively charged 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.
- This will lead to significant amount of protein appearing in the urine (Nephrotic range proteinuria).

◀ Main clinical manifestations

We call it nephrotic **syndrome** because it has these 4 important features:

- **Hypoalbuminemia** (Serum albumin drops to <30g/L; because it is wasted in the urine)
- **Nephrotic range proteinuria** (secretion of >3.5g = > 3500 mg of Albumin in the urine per day by doing 24h urine collection.
- **Peripheral or generalized edema (anasarca)**
- **Hyperlipidemia**[3]

Normal serum Albumin level: 35-55 g/L

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 usually made of Albumin in Glomerular diseases. why? because it's the most abundant molecule of all the proteins
- If Albumin urinary secretion : **30-300 mg/day** is called Microalbuminuria (indicates early renal disease)
  - **> 300 to < 3500 mg/ Day :** overt proteinuria
  - **> 3500 mg/ Day :** Nephrotic range Proteinuria Or Heavy Proteinuria

Any degree of persistent proteinuria that is significant (>500 mg/day), is bad for the kidney because it results in fibrosis of the tubules which can result in the death of the glomerulus. The inverse is also true (if the glomerulus is inflamed and destroyed, the tubules will not be functional and will become fibrotic).

1- We can only detect it when it reaches 30 mg/day
2- Some people extend the range to 15 mg
3- The liver normally makes a maximum 10g of albumin per day. To compensate for albumin loss, the liver is overworking and producing proteins . 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 → hyperlipidemia.

Nephrotic syndrome

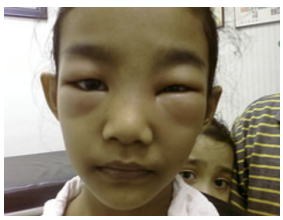
◀ Urine Analysis: the best initial test.

- **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)

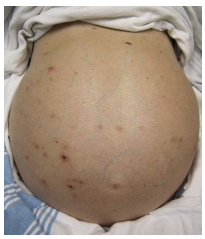
◀ Blood Analysis:

- **Hypoalbuminemia (<30 g/L)** the Normal serum Albumin level : 35-55g/L
- **Hyperlipidemia**

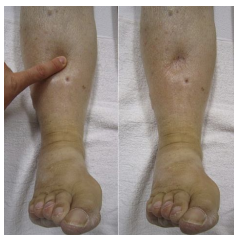
◀ Clinical presentation:



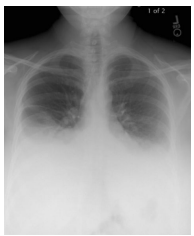
Periorbital edema[1]



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]
- Nausea & vomiting[4]
- Frothy (foamy) urine[5] (froth **persists** for long time after voiding)
- Abdominal pain due to bowel edema
- Weight gain due to fluid retention
- Signs & symptoms of DVT, PE as complications
- Shortness of breath If having **pleural effusion**
- 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? because cardio-pulmonary circulation doesn't depend on oncotic pressure (it is hydrostatic dependent. negative pressure protects them from pulmonary edema).
3- The stomach and bowel is edematous → no feeling of hunger.
4- Peristalsis is impaired due to edema.
5- Due to the presence of Albumin in the urine

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.
- Any patient with proteinuria is given ACEi or ARB. Why? They dilate the efferent arteriole → decreased pressure on the capillary → decreased albumin leakage → albumin remains in the blood, doesn't go into tubules and damage them
- ACEi or ARBS should NEVER be given with NSAIDS. Why? NSAIDs cause afferent vasoconstriction → no blood flow to kidney → 0 GFR → AKI, hyperkalemia

◄ specific measures:

- treat the underlying cause of any protein leak

Nephrotic syndrome

◀ Complications:

1. **Infection and sepsis** (loss of Immunoglobulins)
2. **Thrombosis (3)** (Loss of antithrombotic in urine)
3. **Acute kidney injury**[2]
4. **End stage renal disease**[1] **(ESRD) if proteinuria does not resolve**
5. **Hyperlipidemia(4) (Atherosclerosis)**

◀ Glomerular Diseases that may present as Nephrotic Syndrome:

There are different causes but those are what we see quite often in SA:

01 Focal Segmental Glomerulosclerosis (FSGS)

02 Minimal Change Disease

03 Membranous Nephropathy

An area for your notes

1- Too much protein is damaging renal tubules , because : the proteins when they are passing the tubules they'll cause fibrosis (in long-term proteinuria)

2- due to loss of oncotic pressure the kidney will be less perfused (just like pre-renal AKI). Rarely happens

3- especially DVT , PE and Renal veins thrombosis.

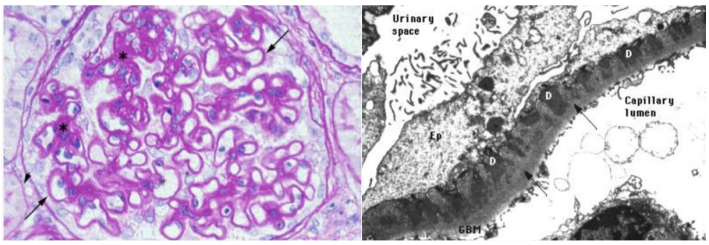
4- Due to Hypoalbuminemia , the liver starts to produce many types of proteins to compensate for the loss and increase the oncotic pressure , one of these proteins is lipoproteins which is in turn serves as a carrier for cholesterol.

- Extra : nephrotic syndrome causes pleural effusion but not pulmonary edema , why ? Because the cardio-pulmonary circulation is hydrostatic not oncotic

Membranous nephropathy[4]

- **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:



LM: - Notice the **Diffuse thickening of the glomerular capillary** throughout all glomeruli, due to IgG and C3 deposition

EM: - Arrows show subepithelial immunoglobulin deposits (IgG and C3) with **spike and dome appearance**
- Foot process effacement

◀ Types:

	Primary	Secondary
Clinical features	Accounts for **75%** of cases in adults.	——
Possible causes	**idiopathic** Anti PLA2R antibodies can be detected in 80% of primary MN cases, useful test.	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, lung, or GI, breast and lymphoma. (This why age appropriate screening for cancer should be done for adults with MN)
Treatment	**-Corticosteroids** plus Cyclophosphamide or cyclosporine -May be Rituximab	Mainly **target the primary disease** that caused membranous nephropathy and treat the Nephrotic syndrome manifestations

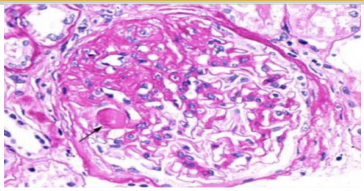
1- It might be idiopathic but it is sometimes caused by cancer e.g. **If someone is old or in his 50s and has risk factors for cancer and he presented with membranous nephropathy we will screen them for cancer (CXR, abdominal CT and colonoscopy is important) cuz it may be their only manifestation.** If a 60 year man who doesn't have diabetes comes in with nephrotic syndrome (you do urinalysis and find a lot of albumin), the logical next stop is to perform a biopsy. You see that he has MN. Do you go straight to treating the MN? No. You have to do age-appropriate cancer screening because MN might be the only indication of an underlying malignancy.
2- Very common in Saudi Arabia. Part of SLE's presentation can present as MN (we refer to it as "Lupus Nephritis") . the most imp cause of 2ndary MN
3- the 2nd most imp cause of 2ndary MN , don't give immunosuppressants before treating the tumour , because when we suppress the immunity , the malignant cells will proliferate
4- Like MCD but for adults

Focal Segmental Glomerulosclerosis (FSGS) [1]

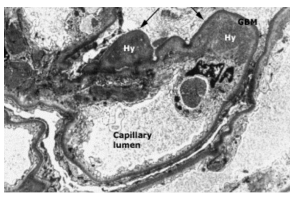
- A common cause of Nephrotic syndrome in **adults**.
- If a child presented to you with FSGS it will be usually secondary to other causes.
- Causes 12 – 35 % of the cases in adults.
- Could be Primary Or Secondary Or Genetic
- **Focal:** some glomeruli are affected by sclerosis (the rest of them look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

	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 < 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 that are affected by sclerosis and the ones that are not affected) will have **a diffuse foot processes effacement** (thus nephrotic syndrome appears)	**Possible causes[3]**
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.	**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
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. secondary FSGS are steroid resistant, and that, a higher IgG/IgM may be associated with a better clinical prognosis Long term proteinuria is > 0.5 gram / day by itself can cause permanent damage of renal tubules (this causes of CKD then maybe ESRD)

Microscopic findings



EM: like minimal change disease, diffuse foot process effacement
LM: segmental sclerosis with hyalinosis
IF: rarely, focal deposits of **IgM**, C1, and C3 inside sclerotic lesion



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). Proteinuria isn't as severe as in primary; however, renal function starts to decline faster and patients present late.
3- Secondary FSGS with similar glomerular changes is seen as a secondary phenomenon when the number of functioning nephrons is reduced for any reason. Secondary FSGS is thought to be a compensatory mechanism. The kidneys hypertrophy to meet increased demand, but anything that hypertrophies declines eventually, and that's how they develop sclerosis.
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.

Minimal Change Disease (MCD)

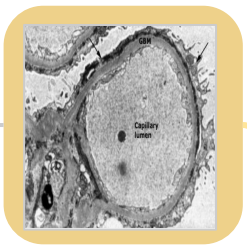
- **The most important difference between MCD and the FSGS is the presence of glomerular sclerosis in FSGS (there's no sclerosis in MCD[1])**
- **MCD is the main cause of Nephrotic syndrome in children[2]:**
  - The cause in 90 % of cases in children < 10 years old.
  - > 50% of cases in older children
- 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.

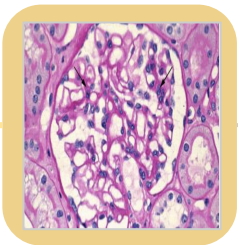
◀ Types[3]:

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 diffuse foot processes effacement.





LM:
Is typically showing **normal glomeruli**
So also 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) "selective proteinuria"
- **Lipiduria** (if can possibly find fat bodies in some proximal tubular cells on LM)
- Hypoalbuminemia (usually very low serum Albumin)
- Hyperlipidemia
- Creatinine is always within the normal range or slightly elevated and normalizes with remission

1- No sclerosis in MCD. If there is sclerosis even in one glomeruli it will be a different disease(FSGS). This is important because MCD responds very well to steroids, GS is a different disease.
2- Any child present with Nephrotic syndrome it's considered minimal change disease until proven otherwise, to the point where biopsy is not indicated, and we treat immediately with corticosteroids and see there response to it.
3- MCD is mainly primary, especially in children, but in Adults it can be secondary.

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[1]:

- 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.

Summary	Focal Segmental Glomerulosclerosis	Membranous Nephropathy	Minimal Change Disease
Pathology	Sclerosis of the glomeruli -> damage + loss of podocyte	Anti phospholipase A2 receptor antibodies binds to phospholipase A2 receptor in glomerular podocyte	Cytokines mediated damage of podocyte
EM	Effacement of the foot process of podocyte	Spike and dome appearance	Effacement of the foot processes of podocytes
LM	Segmental sclerosis and hyalinosis	Thickening of the glomerular capillary	No changes in glomeruli (possibly fat bodies in some proximal tubular cells (Nil disease)
IF	—	Granular subepithelial deposits of immune complexes and complement (IgG and C3)	—

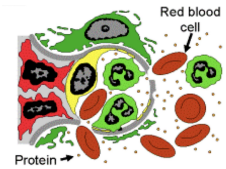
1- Why not let them recover on their own and not intervene? While it is true that some people might recover on their own, we fear the complications that can result in the meantime (thrombosis infection)

Nephritic syndrome

◄ introduction:

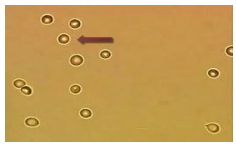
- When we say **Nephritic**, it means a clinical pattern of presentation for a group of glomerulonephritis, and not a syndrome like what we saw in Nephrotic causes.
- **The Nephritic pattern is always indicative of underlying inflammatory process in the glomeruli**; causing inflammatory modulators attraction, 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:



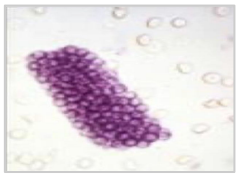
- **RBCs** In renal cell carcinoma, stone in the renal pelvis, the bladder or prostate → when they bleed there will be no change in the shape of RBCs.

★ **Dysmorphic RBCs**[2]
  - (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).



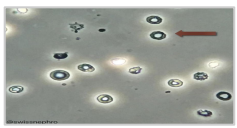
Normal looking RBCs in microscopy

- **RBC casts or cellular casts**[3]
  - 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)



RBCs casts

- 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 (so inactive urinary sediments are <=5 RBCs/HPF)



Dysmorphic RBCs

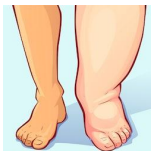
- **Proteinuria** (at variable amounts from subnephrotic to nephrotic range)

◄ 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**

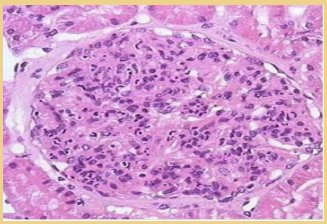
5. **Systemic vasculitis**
   May have other manifestations of systemic vasculitis since some glomerulonephritis types are actually vasculitis (e.g. skin rash, pulmonary hemorrhage , etc)

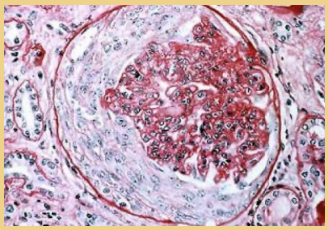
6. **Positive immune markers**
   ANA, Anti-DNA, low complements, +ve ANCA (depends on the cause)

1- Filtration barrier disrupted → decrease in GFR → RAAS activation → Fluid retention.
2- Blood components will squeeze themselves to pass through the damaged capillary wall → Dysmorphic shaped RBCs (lose their smooth surface).
So, when you see a Dysmorphic RBC you're dealing with Glomerular disease not urinary system disease/cancer/stone
If the RBCs are smooth then its NOT from the glomerulus and hence no need for a biopsy (look for cancer, stone and source of blood loss)
3- When RBCs pass the glomeruli and enter the tubules, they will pass through the thick ascending loop of henle which contains a mucus layer. The RBC's will stick to the wall of the thick ascending loop of henle, as RBC's accumulate in this area it increase in weight until it get flushed out

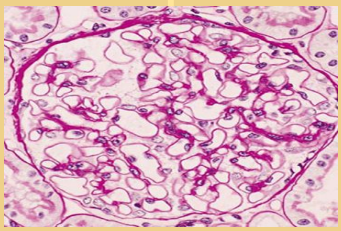
Nephritic syndrome

◀ Microscopic findings:





Normal glomerulus

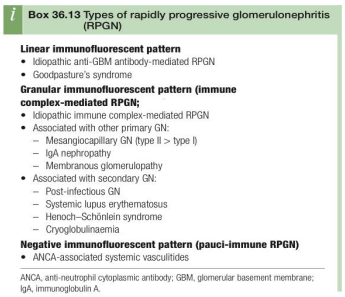


LM: Glomeruli with proliferation (inflammatory) GN

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

glomerulonephritis may present as:

- asymptomatic urinary abnormalities
- acute nephritis (nephritic syndrome)
- rapidly progressive glomerulonephritis



Box 36.13 Types of rapidly progressive glomerulonephritis (RPGN)

Linear immunofluorescent pattern
- Idiopathic anti-GBM antibody-mediated RPGN
- Goodpasture's syndrome

Granular immunofluorescent pattern (immune complex-mediated RPGN;
- Idiopathic immune complex-mediated RPGN
- Associated with other primary GN:
  - Mesangiocapillary GN (type II > type I)
  - IgA nephropathy
  - Membranous glomerulopathy
- Associated with secondary GN:
  - Post-infectious GN
  - Systemic lupus erythematosus
  - Henoch–Schönlein syndrome
  - Cryoglobulinaemia

Negative immunofluorescent pattern (pauci-immune RPGN)
- ANCA-associated systemic vasculitides

ANCA, anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; IgA, immunoglobulin A.

- Rapidly progressive glomerulonephritis (RPGN) is a syndrome with glomerular haematuria (red blood cell casts or dysmorphic red blood cells), rapidly developing acute kidney failure over weeks to months and focal glomerular necrosis with or without glomerular crescent development on renal biopsy.
- It can be classified based on the pattern of immune complex deposition in glomeruli (seen on immunofluorescence): that is, linear, granular and negative immunofluorescence patterns

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)
- Alport's syndrome

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 heavy immunosuppression, if you don't treat him, patient will develop ESRD within days or weeks.

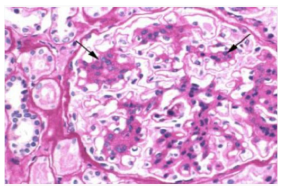
IgA Nephropathy (Berger's disease)/ HSP (Henoch-Schönlein purpura)[4]

◀ General characteristics:

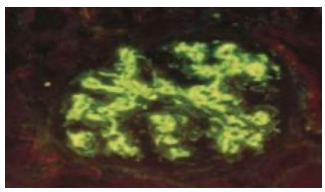
- **Most common type** of Primary GN in developed countries (Very common in East of asia)
- IgA nephropathy tends to occur in children and young males
- Can present actively and can be silent. asymptomatic microscopic haematuria or recurrent macroscopic haematuria following an upper respiratory or gastrointestinal viral infection or strenuous exercise.
- 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. While IgA nephropathy only affects the kidneys.

◀ Microscopic findings:

LM:
IgA deposits in mesangium



IF:
IgA deposits



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

O1

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

O2

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

1- IgA is in the frontlines of the body (it interacts with the environment). IgA is found in the mucus membranes and the gut. 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/ IgA secretion increases (ex: infection) → more IgA in blood → more IgA filtered by the kidney → trapped in the glomerulus → inflammation. Why don't all people develop IgA nephropathy? People who develop IgA nephropathy have abnormally structured IgA molecules (glycated). When this abnormal IgA reaches the kidney to be filtered, it gets deposited in the kidney and results in 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. mainly in pediatrics, presents as skin rash abdominal pain and hematuria→Henoch-schonlein purpura (HSP) Abnormal IGA .
The presentation: after every URT infection accompanied with hematoureia In kids the IGA deposits in skin leading to vasclitis and rash , abdomen pain , joint pain

IgA Nephropathy (Berger's disease[4])/ 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
- ↑ Serum IgA
- Normal C3 complement levels

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.

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.[2]
- 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 [3] (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.

Treatment

- **Lupus Nephritis treatment[1] depends on the findings in renal biopsy**
- **It usually involves high degree of immunosuppressive medications.**

1-Treated aggressively because it can lead to loss of kidney function and renal failure in weeks if not treated.
2- 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.
3- low complement in blood is due to deposition in the kidney
4- Previous name

Post streptococcal glomerulonephritis (PSGN)

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

◀ Clinical features:

Patients present with frank hematuria usually **after one week and up to 3 weeks**[1] from the start of infection (Pharynx or skin 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

- **Treatment is usually supportive = wait and see.**
- Children have better and faster recovery than adults. (Age affects prognosis)

◀ Microscopic findings

LM	Glomeruli appear enlarged and hypercellular
IF	IgG, IgM and C3 deposites along the GBM and mesangium --> Starry sky "lumpy bumpy" appearance
EM	dome-shaped, subepithelial immune complex deposits **(humps)**

1- How is PSGN different from IgA? PSGN is **more severe** and mostly resolves by itself (**self-limited**). IgA usually follows a chronic, lifelong course. More severe and acute than IgA and can cause renal shutdown. PSGN is non synpharyngitic (**develops after a few weeks**), while in IgA it may happen within 3 days.
Bacteria not viral, it's one hit either no effect or a major effect

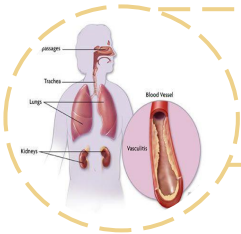
ANCA Vasculitis
(e.g. Wegener's Granulomatosis)

- Autoimmune disease that **involves the presence of Neutrophils adhesion enhancing molecule called** ANCA= anti-neutrophil cytoplasmic antibody[1], This molecule establishes vasculitis 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**[3]

◀ 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 severe Glomerulonephritis; maybe RPGN; but all staining with immunofluorescence for immunoglobulins is **NEGATIVE**; hence the name Pauci-Immune vasculitis or GN (Pauci = little or non deposition of immunoglobulins that caused GN so most likely **diagnosis is ANCA)**
- The best indicators of adverse prognosis are pulmonary haemorrhage and severity of renal failure at presentation.

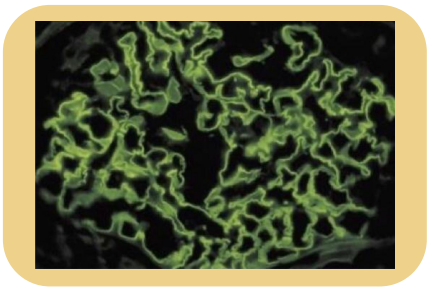
Treatment

- 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 attack/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 (peri-nuclear) it's called P-ANCA. These tests are no longer used and have been replaced with ELIZA, MPO, PR3.
3- Churg-Strauss syndrome is a disorder marked by blood vessel inflammation. This inflammation can restrict blood flow to organs and tissues, sometimes permanently damaging them. Granulomatous inflammation, eosinophilia and asthma distinguish churg-strauss from microscopic polyangitis

Anti-GBM glomerulonephritis

◀ Microscopic findings:



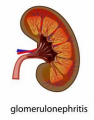
1 **Linear Anti-GBM staining in the Glomerulus by Immunofluorescence is a Diagnostic test** In ANCA , IF will be negative (black) or little

Possible causes

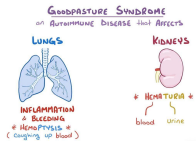
Due to autoantibody **against (alpha-3 chain) of type IV Collagen that is found in Glomerular and alveolar (lungs) basement membrane.**

◀ Clinical features:

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



02 **Pulmonary hemorrhage** (disease is called **Goodpasture's**[1] disease if Lung vasculitis + GN)



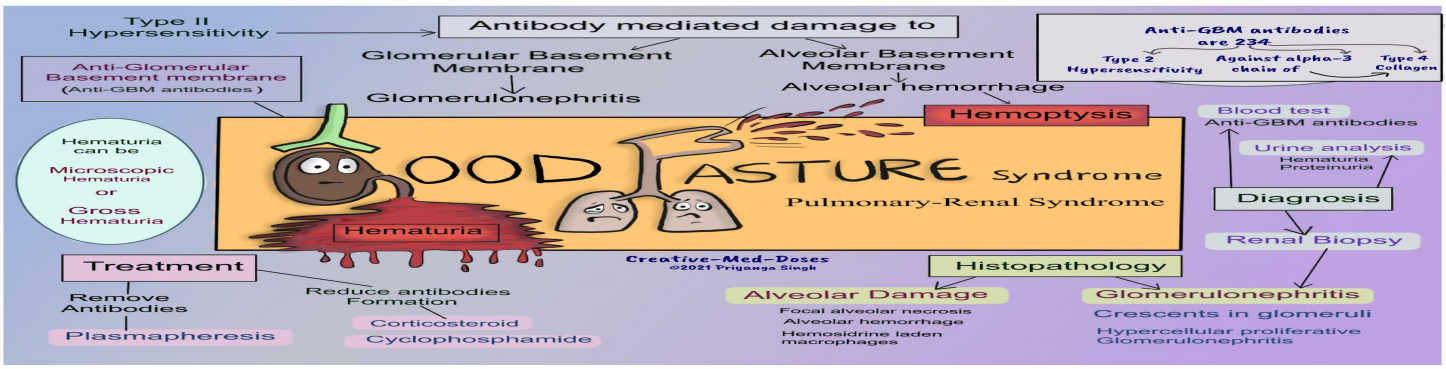
Diagnosis

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

Treatment

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

Extra



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

Membranoproliferative GN (MPGN)

439 slide

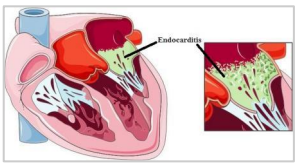
- It is a pathological description & has multiple causes.
- It may present with Nephritic picture or Nephrotic syndrome

◀ Types:

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

Possible causes

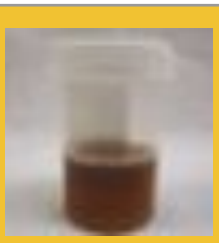
- Hepatitis B and C
- Lupus and Sjogren's syndrome
- Complement deficiency
- Endocarditis
- Cancer



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[2] - + 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
2- Except in diabetes, as it can cause Hematuria. Cellular casts are only seen in Nephritic but granular casts may be seen in a dehydrated person.

Summary from DR slide 442

				
Normal color	Normal color	Bright Red (frank hematuria)	Cola color	Turbid yellow with foam (frothy)
Findings: *No RBCs *No Protein *Normal Creatinine	Findings: *+ RBCs *+ RBCs casts (so why it's not red ? Because they are microscopic RBCs *+ +Protein *Slight high Crt	Findings: *++++ RBCs ***NO casts** (No casts, so it's not from the glomerulus) *++ Protein (because of RBCs) *Normal Creatinine	Findings: *++ RBCs *+++ Casts *+++ Protein *High Creatinine	Findings: *No RBCs *NO Casts ***++++ Protein** *Normal Crt
Normal Healthy kidneys	**Chronic IgA (Usually we detect them incidentally**	Bladder / kidney **cancer or stone** or prostate **(Not GN)**	Post Infectious **GN , or RPGN** or severe IgA (	**Nephrotic syndrome** : MCD FSGS MN

How to approach a patient with glomerulonephritis?

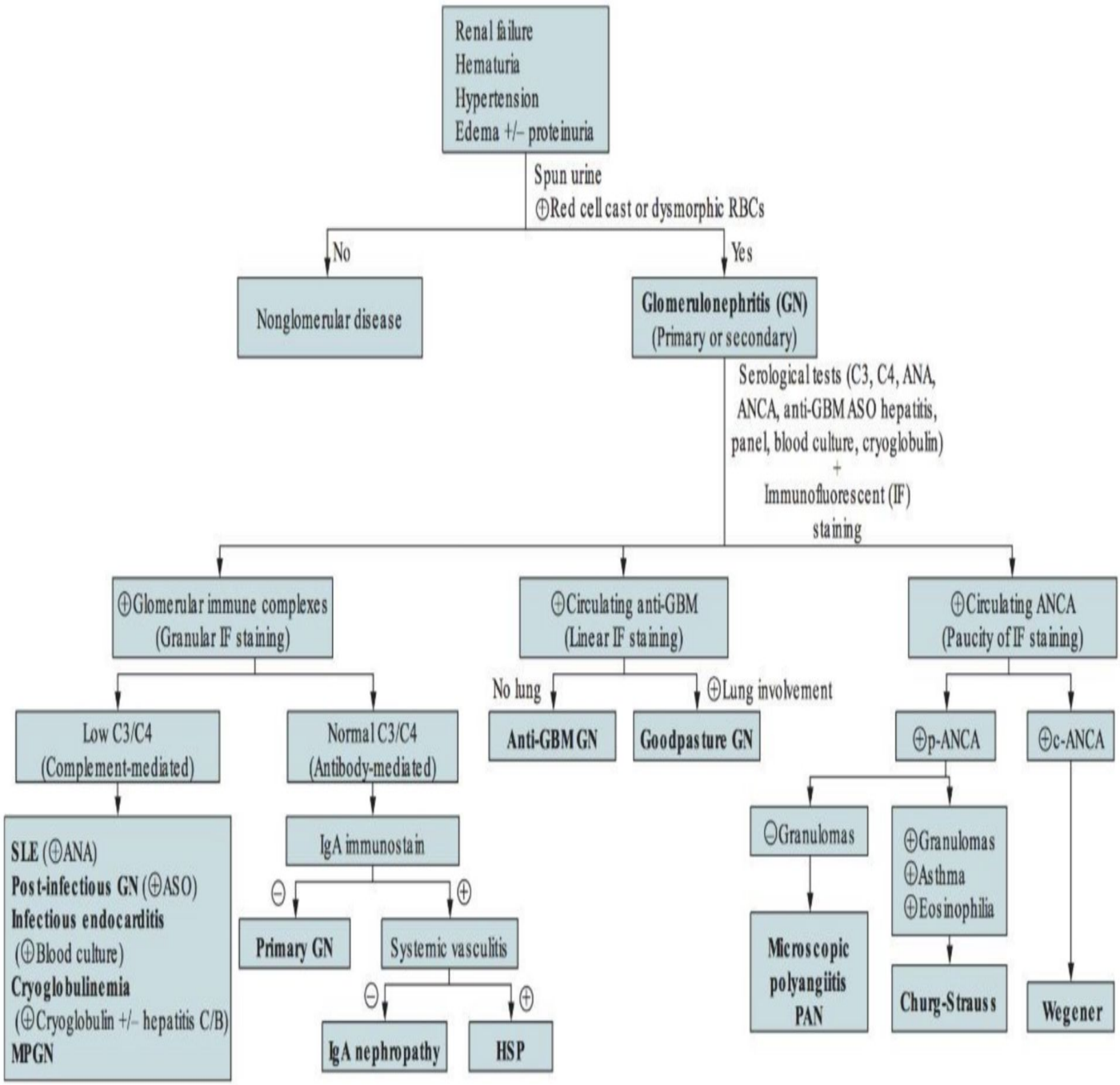


Figure 28–1. Algorithm of approach to the patient with acute glomerulonephritis. Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin-O; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HSP, Henoch–Schönlein purpura; MPGN, membranoproliferative glomerulonephritis; PAN, periarteritis nodosa; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SLE, systemic lupus erythematosus.

TABLE 7-5 Nephritic Versus Nephrotic Syndrome

	Nephritic Syndrome	Nephrotic Syndrome
Pathogenesis	Inflammation of glomeruli due to any of the causes of glomerulonephritis	Abnormal glomerular permeability due to a number of conditions
Causes	Poststreptococcal glomerulonephritis is the most common cause, but may be due to any of the causes of glomerulonephritis	Many conditions. Membranous glomerulonephritis is the most common cause in adults. Other causes include diabetes, SLE, drugs, infection, glomerulonephritis (focal segmental and others) Minimal change disease is the most common cause in children
Laboratory Findings	Hematuria AKI—azotemia, oliguria Proteinuria, if present, is mild and not in nephrotic range	Urine protein excretion rate >3.5 g/24 hr Hypoalbuminemia Hyperlipidemia, fatty casts in urine
Clinical Findings	HTN Edema	Edema Hypercoagulable state Increased risk of infection

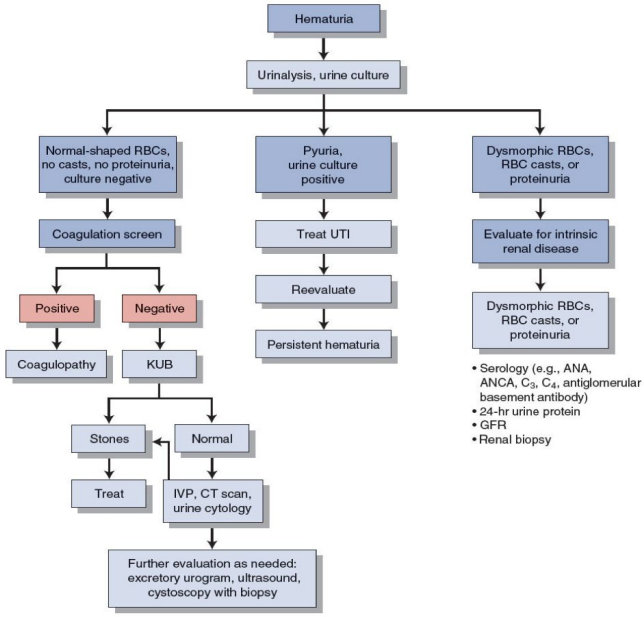


FIGURE 7.3 Evaluation of hematuria.

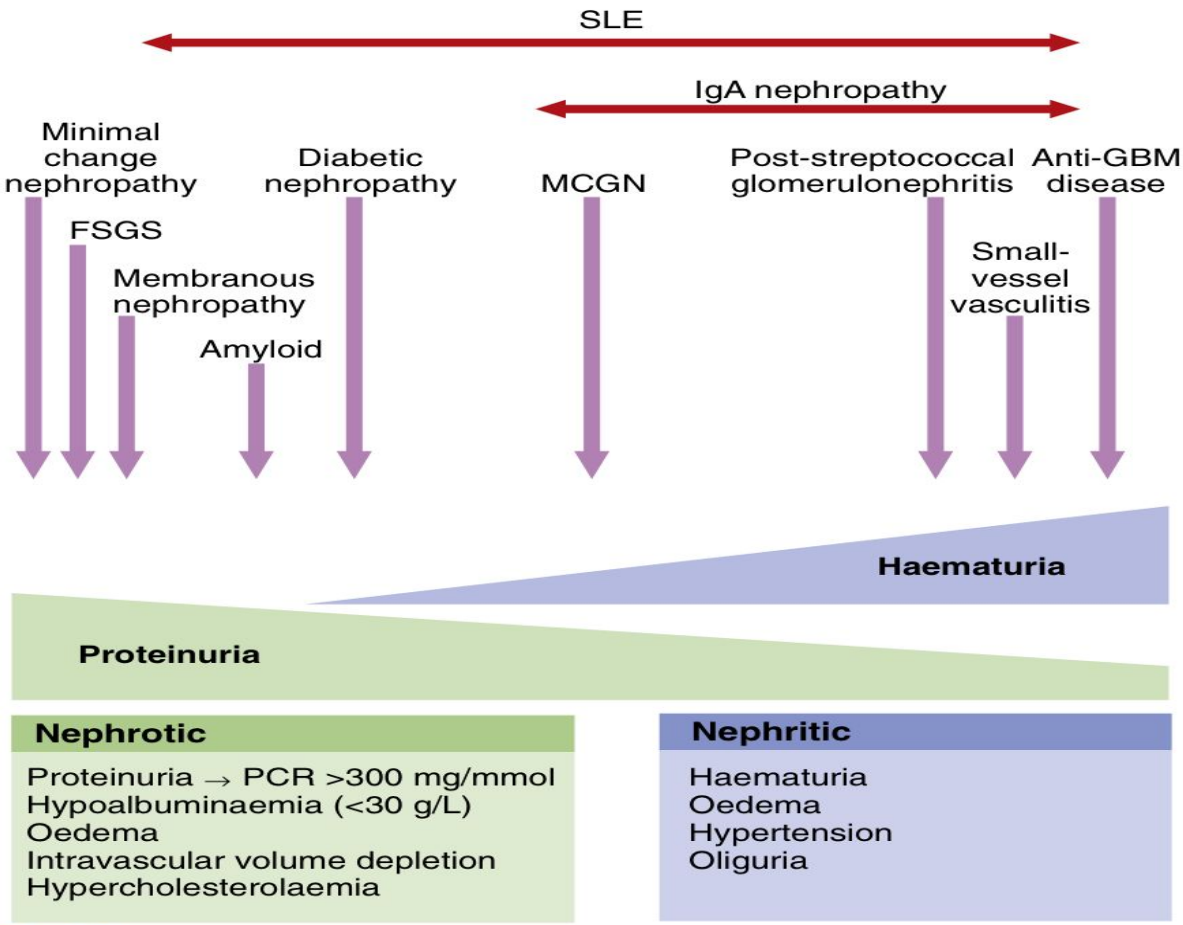


Fig. 7.3 Spectrum of glomerular diseases. *FSGS*, Focal segmental glomerulosclerosis; *GBM*, glomerular basement membrane; *IgA*, immunoglobulin A; *MCGN*, mesangiocapillary glomerulonephritis; *SLE*, systemic lupus erythematosus; *PCR*, protein:creatinine ratio = urine protein (mg/L)/urine creatinine (mmol/L).

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)

Lecture Quiz

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

Answers: Q1:C | Q2:D | Q3:B | Q4:D | Q5:A |

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