Glomerular diseases

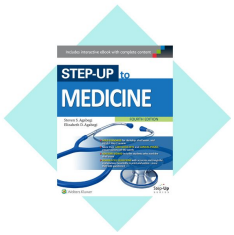
Objectives:

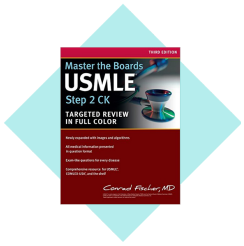
- Classify Glomerular diseases
- Understand the pathophysiology is correlated with the clinical manifestation in Glomerular diseases.
- Recognize the clinical manifestations in Glomerular diseases
- Recognize the most common causes of Nephritic glomerular disease.

[Color index : Important | Notes | Extra]

Resources:

- 435 slides, 435 renal pathology team, Step-Up to medicine, Master the boards and davidson.





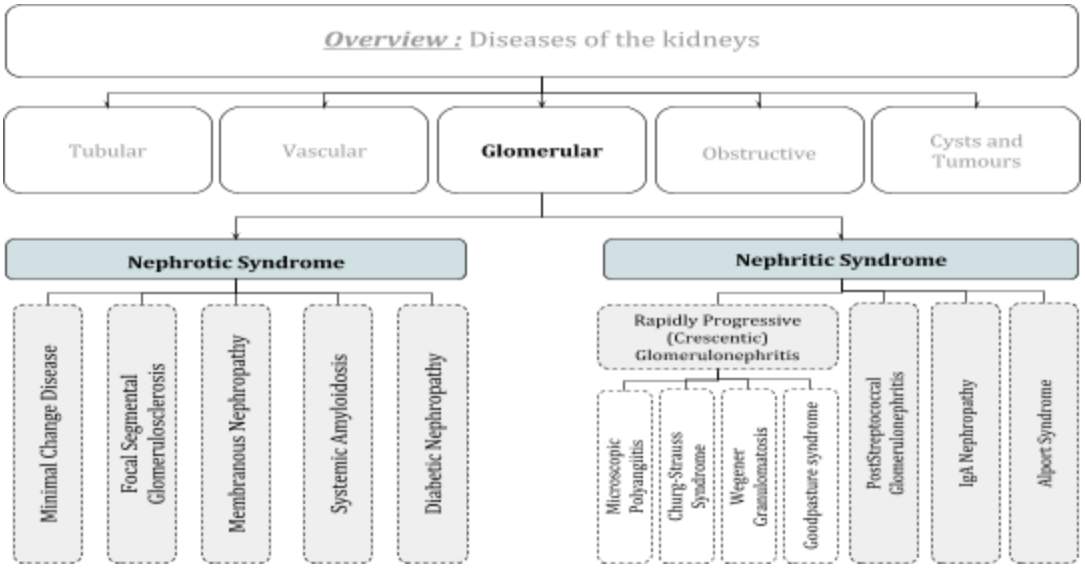
[Editing file | Feedback | Share your notes | Shared notes | Twitter]

★ **Note : click here if you want a quick review from basic sciences**

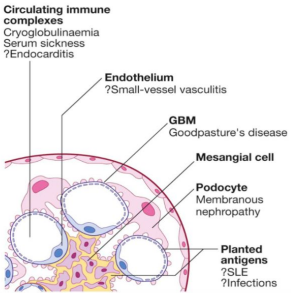
- Done by: Deema AlFaris & Khawla AlAmmari
- Team sub-leader: Shamma Alsaad
- Team leaders: Khawla AlAmmari & Fahad AlAbdullatif
- Revised by: Ahmad Alyahya

"Medicine is an art, nobody can deny it."

Glomerular diseases



Glomerular diseases :



- Glomerular diseases account for a significant proportion of acute and chronic kidney disease. There are many causes of glomerular damage, including immunological injury, inherited diseases such as *Alport's syndrome*, metabolic diseases such as *diabetes mellitus*, and deposition of abnormal proteins such as *amyloid* in the glomeruli.

How do glomerular diseases start ?

- We will be talking about primary glomerular diseases that are mostly caused by immune system dysfunction How? **Autoantibodies** targeting glomerular structure or immune-complexes (antigen-antibody) depositing and traumatizing the glomerular components.
  - ➔ *A lot of times the exact cause is not really clear, but the result of the damage in the glomerulus is telling how immune system is playing an important rule.*
- The manifestations of a glomerular disease are usually indicative of which components of glomerular capillary wall was affected at the most, examples include:
  - ➔ if **Podocytes** are the main target of the disease process → mainly **proteinuria** (at large amount) will manifest; thus **Nephrotic Syndrome** **will be the main finding.**
  - ➔ If **Endothelial cells**, **Mesangial cells** or **GBM** are affected → mainly **hematuria** and abnormal renal function will manifest because of disruption in glomerular filtration wall; thus **Nephritic pattern** of renal disease will manifest. *(Note that **Proteinuria** is always present in this kind of glomerular injury as well).*
- 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.

General points about Glomerular diseases :

- ➔ **Biopsy** is the most accurate test to establish a diagnosis (though not always needed)
- ➔ Glomerular diseases are usually chronic, they are often treated with corticosteroids. Additional immunosuppressive medications (Cyclophosphamide, Mycophenolate) are frequently used.
- ➔ To make things easier, we can put glomerular diseases in two main categories : Nephr**O**tic and Nephr**i**tic.
- ➔ The major difference between "nephritic" and "nephrotic" is *the amount of proteinuria.*
- ➔ Proteinuria levels correspond to severity of disease and likelihood of progression.

Glomerular = **S**low = **S**ample = **S**teroids = Immuno**S**uppressive.

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

- **Normally** < 150 **mg/day** of all kinds of proteins. Including on average 4-7 **mg/day** of *Albumin* that are secreted in the urine normally. In **heavy proteinuria**, more than 3.5 g /24 hrs (gram not milligram) of proteins will be secreted into urine (more than 3.5 g /24 hrs = nephrOtic range).

Clinical categories of glomerular diseases:

	Nephrotic Syndrome[1]	Nephritic Glomerular Disease
Clinical presentation	▵ Urine analysis shows :[2] ➔ **Heavy proteinuria (>3.5g per 24 hrs of urine collection)**[3] ➔ **Hypoalbuminemia** (<30 g/L) "Normal serum Alb: 35-55g/L" low SERUM albumin ➔ **Fat (Lipiduria) :** Fatty casts, oval fat bodies & fat droplets. NOTE : No RBCs, RBCs casts or WBCs are seen here ▵ **Peripheral or generalized edema**[4] **:** ➔ Low serum Albumin (Low oncotic pressure). ➔ Increase Renal sodium retention because of uncontrolled activation of the epithelial sodium channels (ENaC channels in the renal tubules). ▵ **Hyperlipidemia**[5] ▵ **Patients may also get:** Fatigue, frothy urine (froth persists for long time after voiding), anorexia, Nausea & vomiting, abdominal pain, weight gain due to fluid retention, shortness of breath if having pleural effusion and signs & symptoms of DVT, PE.	▵ Urine analysis shows : ➔ **Hematuria** ➔ **RBC 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 (RBCs lose their smooth surface passing through the cracks in inflamed glomerular basement membrane) ➔ **Proteinuria** at variable amounts Those are called ***Active Urinary Sediments*** (Active = is indicative of underlying glomerular inflammatory process; requiring urgent medical attention) ▵ Decreased Urine output ▵ Edema ▵ **High Blood Pressure** ▵ May have other manifestations of systemic vasculitis since some glomerulonephritis types are actually vasculitis (e.g. skin rash, pulmonary hemorrhage, etc) ▵ Positive immune markers: ANA, Anti-DNA, low complements, +ve ANCA (depends on the cause)
Pathological findings	▵ **Podocytes** abnormality is the primary finding ▵ Podocytes will sustain a structural dysfunction; making them **lose their Foot-processes**, but the cells bodies are intact. ▵ This will lead to significant amount of protein appearing in the urine (Proteinuria).	▵ 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 GBM** components of the Glomerulus are likely going to be targeted because of their proximity to blood circulation
Complications	▵ Infections and sepsis (Increased urinary loss of immunoglobulins and complement) ▵ Thrombosis (loss of anticoagulants) Loss of natural anticoagulants: Proteins S and C and antithrombin ▵ Acute Kidney injury. ▵ End Stage Renal Disease (ESRD) if proteinuria does not resolve.	▵ AKI (Acute Kidney Injury) =Acute Renal impairment or Failure= elevated Creatinine). ▵ End Stage Renal Disease (ESRD). ▵ Pulmonary edema

[1] Key findings in nephrotic syndrome (highly recommended video)

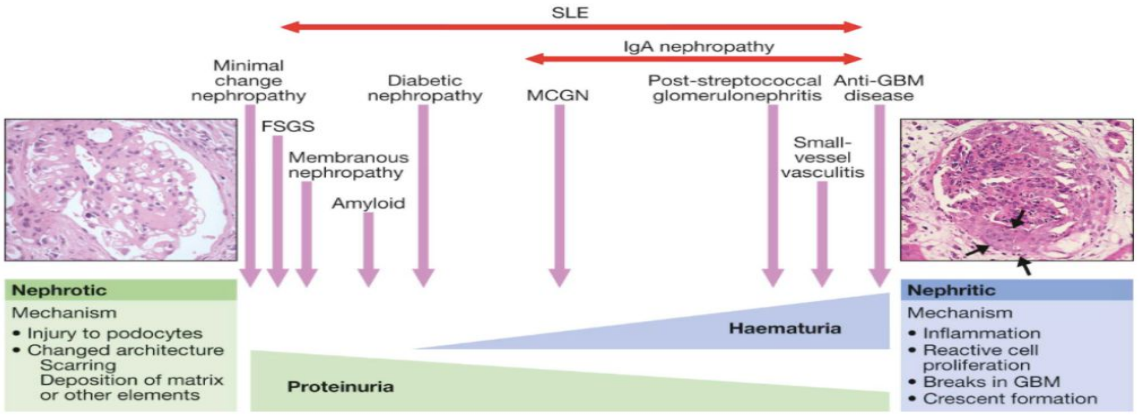
[2] Note that the presence of heavy proteinuria, hypoalbuminemia and peripheral generalized edema is diagnostic

[3] In all diverse causes of the nephrotic syndrome there is a derangement in the capillary walls of the glomeruli that results in increased permeability to plasma proteins → allows protein to escape from the plasma into the glomerular filtrate → **Extremely heavy proteinuria**, serum albumin is decreased→ **hypoalbuminemia** and a drop in plasma colloid osmotic pressure. → Increased release of renin from renal juxtaglomerular cells → Renin in turn stimulates the angiotensin- aldosterone axis→ promotes the **retention of salt and water** by the kidney.

[4] CHF leads to edema of dependent areas like the legs.Nephrotic patients are edematous everywhere.

[5] Hyperlipidemia and hypercholesterolemia are caused by increased hepatic lipoprotein synthesis.

Nephrotic VS. Nephritic :

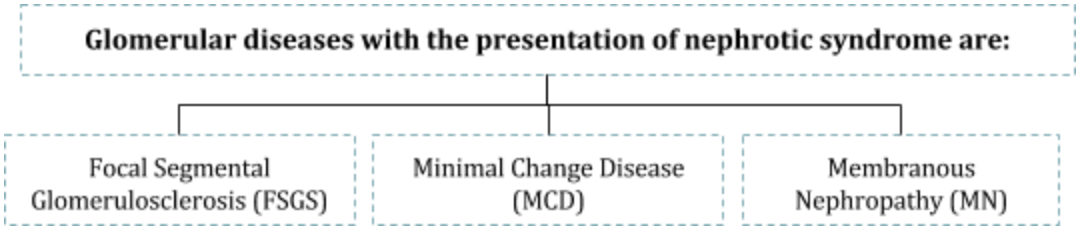


At one extreme, specific injury to podocytes or structural alteration of the glomerulus affecting podocyte function (for example, by scarring or deposition of excess matrix or other material) causes proteinuria and **nephrotic syndrome**.The histology to the left shows diabetic nephropathy. At the other end of the spectrum, inflammation leads to cell damage and proliferation, breaks form in the GBM and blood leaks into urine. In its extreme form, with acute sodium retention and hypertension, such disease is labelled **nephritic syndrome**. The histology to the right shows a glomerulus with many extra nuclei from proliferating intrinsic cells, and influx of inflammatory cells shows crescent formation (arrows) in response to severe post-infectious glomerulonephritis. (FSGS = focal and segmental glomerulosclerosis; MCGN = mesangiocapillary glomerulonephritis).

After the comparison between nephrotic and nephritic, let us discuss them in much more details :

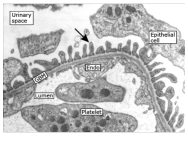
Nephrotic syndrome :

- **Definition :** Nephrotic syndrome is a measure of the severity of proteinuria in association with any form of glomerular disease.It occurs when proteinuria is so massive that the liver can no longer increase the production of albumin to compensate for urinary loss.
- **Diagnosis :** The best **initial** test for nephrotic syndrome is urinalysis but the **most accurate** test is renal biopsy *(although there are certain associations with each form of nephrotic syndrome, only the biopsy can distinguish between them).*
- **Treatment (In general)** :The best initial therapy for nephrotic syndrome is **glucocorticoids**. If there is no response after several weeks of therapy, other immunosuppressive medications such as **cyclophosphamide** are used. **ACEI or ARBs** are used to control *proteinuria*. *Edema* is managed with salt restriction and **diuretics**. *Hyperlipidemia* is managed with **statins**
- **Causes/associations :** Overall, diabetes and hypertension are the most common conditions associated with nephrotic syndrome. In addition to systemic diseases, there are a number of diseases limited to the kidney that produce nephrotic syndrome. It is better to describe “associations” rather than “causes” since we do not know what exactly causes nephrotic syndrome.

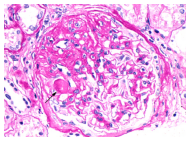


1. Focal Segmental GlomeruloSclerosis (FSGS):

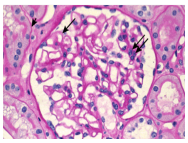
- A common cause of Nephrotic syndrome in **ADULTS**.
- Causes 12 – 35 % of the cases in adults
- More common among people of African descent



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



FSGS

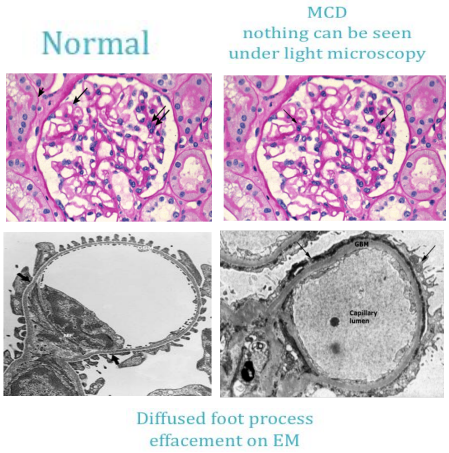


Normal

	Primary FSGS:	**Secondary FSGS:**
Clinical features	◬ Has sudden onset of heavy proteinuria and other manifestations of nephrotic syndrome.	◬ Proteinuria is **less heavy** than other causes of nephrotic syndrome. ◬ 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	◬ Has sudden onset of heavy proteinuria and other manifestations of nephrotic syndrome. ◬ Seen on light microscopy as **focal:** some glomeruli are affected by sclerosis (the rest of them look normal) and **segmental**: sclerosis only involves a segment of each glomerulus that is affected. Less than 50% of the glomerulus is affected may also show positive staining for deposits of C3 and IgM on immunofluorescence. ◬ But most importantly, all glomeruli (the ones affected by sclerosis and the ones that are not affected) will have a diffuse foot processes effacement (thus Nephrotic syndrome appears).	-
Treatment	◬ **First line: corticosteroids** 80% of patients DO NOT respond ◬ Second line: cyclosporine or tacrolimus ◬ ACEIs/ARBs are commonly indicated	◬ 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 ACEI.
Possible causes	The underlying cause is unknown (primary FSGS)	◬ Obesity, anabolic steroid abuse ◬ Nephron loss (>75% of renal mass e.g renal agenesis). ◬ Reflux nephropathy. ◬ Healing of prior GN (e.g IgA). ◬ Severe preeclampsia. ◬ Drugs : Interferon, Pamidronate[6], Heroin. ◬ Anabolic steroid abuse. ◬ Infections : HIV.

[6] Nitrogen-containing bisphosphonate used to prevent osteoporosis.

2. Minimal Change Disease: (MCD = ChilDren)



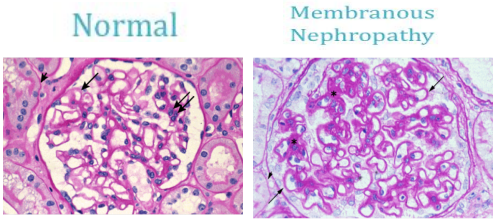
Diffused foot process effacement on EM

- Called minimal change because:
  - Light microscopy: is typically showing normal glomeruli (so called: nil disease).
  - Electron microscopy: shows **diffuse effacement of the epithelial cells' foot processes only.**
- The most important difference between MCD and the FSGS is the presence of glomerular sclerosis in FSGS (there's no sclerosis in MCD)
- Hodgkin disease and non-hodgkin lymphoma have been associated with minimal change disease.
- Current evidence points to systemic T cell dysfunction as the most likely root cause.
- Incidence follows two peaks, one is in young adults, another is in the elderly (60-70 Y/O)
- It 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
  - Child with nephrotic syndrome > think of minimal change, you don't need to biopsy
- It causes 10-25 % of Nephrotic syndrome cases in adults
- Can be:
  - ***Primary (Idiopathic)***
  - ***Secondary (less common) :***

Secondary MCD	
Possible causes	▵ Drugs (NSAIDs, Lithium, Sulphasalazine, Pamidronate, D-Penicillamine, some antibiotics). ▵ Neoplasm (Hodgkin lymphoma, non-hodgkin lymphoma and leukemia). ▵ Infections (TB and syphilis). ▵ Allergies (like asthma and allergic rhinitis)
Clinical features	▵ Typically has a sudden onset Edema ▵ 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
Diagnosis	▵ Must do kidney biopsy in **adult** patients with this presentation, It shows diffuse effacement of foot process. ▵ Kidney biopsy is not done on children, usually nephrotic syndrome in a child < 10 years old is MCD until proven otherwise.
Treatment	▵ In children; typically is corticosteroid responsive in > 90%, treatment is given empirically. ▵ First line: Corticosteroids, given x 3-4 months then taper over 6 months (90%+ responsive) ▵ Second line: oral Cyclophosphamide (for relapsing MCD as it prolongs remission), Cyclosporine (for steroid resistant nephrotic syndrome)

3. Membranous Nephropathy:

- Most common cause of Primary nephrotic syndrome in **adults** (15% and 33%) In caucasians
- **Mostly secondary in children** (hepatitis B antigenemia congenital HBV) Remember: Mem**B**ranous hep**B**
- Slowly developing nephrotic syndrome FSGS can develop within one week but here the onset is very slow
- Can be:



Diffuse thickening of the glomerular capillary wall throughout all glomeruli (IgG and C3 deposition)

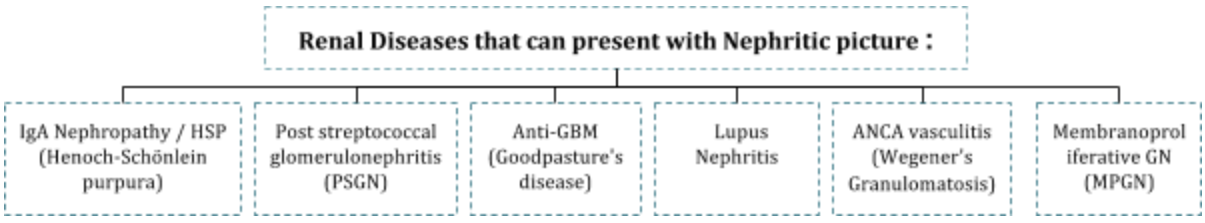
	Primary Accounts for 75% of cases in adults	**Secondary**
Causes	Idiopathic	◬ Systemic lupus erythematosus (SLE): Class V [7] Lupus Nephritis (10-20%) Young females ◬ Drugs: penicillamine, IV gold salts, high dose Captopril, and NSAIDs, Anti-TNF. ◬ Infections: Hepatitis B, Hepatitis C, syphilis ◬ Malignancies: solid tumors prostate, lung, or GI tract Account for 20% in 60+ Y/O
Treatment	◬ Corticosteroids plus Cyclophosphamide or cyclosporine (33% resolve spontaneously) ◬ May be Rituximab	◬ Mainly target the primary disease that caused MN, and treat the Nephrotic syndrome manifestations.

Other important Secondary causes of Nephrotic syndrome in adults:

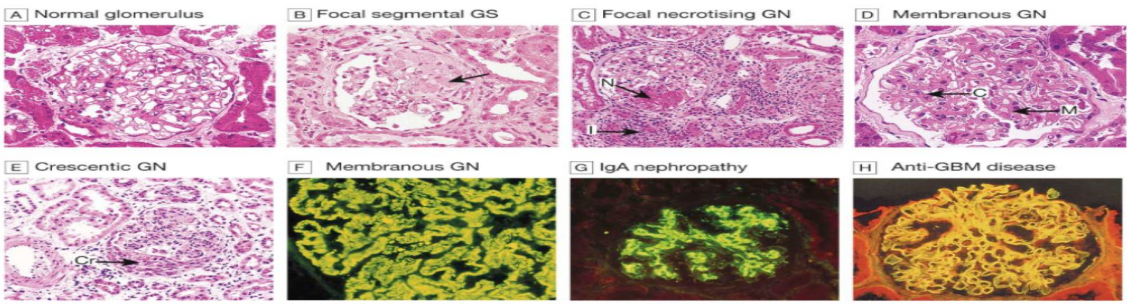
- **Diabetes Mellitus[8].**
- **Amyloidosis** produced in association with myeloma, rheumatoid arthritis, IBDs and chronic infections. Biopsy + Congo Red will show green birefringence. Remember that amyloidosis and DM enlarge the kidneys (along with HIV nephropathy and polycystic kidneys)
- **IgA Nephropathy** Nephrotic syndrome is a rare presentation of IgA nephropathy
- **Membranoproliferative glomerulonephritis (MPGN)** It may present with *Nephrotic or Nephritic picture.*

Nephritic syndrome :

❖ **Definition :** 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. Here; they are called Glomerulonephritis.



[7] Membranous lupus glomerulonephritis. In class 5, the patients have severe nephrotic syndrome and there is thickening of the capillary walls due to deposition of basement membrane like material as well as immune complexes.
[8] Nephrotic syndrome in a patient with diabetes mellitus (DM) first suggests the diagnosis of diabetic nephropathy. However, glomerular diseases other than diabetic nephropathy have been reported in patients with DM.



Picture E : Rapidly progressive glomerulonephritis (crescentic GN)[9] which is a very bad GN. It indicates severe inflammation & worse outcome if not treated rapidly *(Note picture A-E : Light microscopy, pictures F-H EM).*

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

- **Most common type of Primary GN in developed countries**
- It has a chronic course that can progress to ESRD.
- HSP (Henoch-Schönlein purpura) is a systemic vasculitis caused by immune deposition of IgA in different organs; typically **skin, bowel and kidneys.**

Clinical features	◬ Can present as dark urine (hematuria) **1-3 days** after upper respiratory tract infection (**SYNPHARYNGITIC** meaning it occurs with or immediately following pharyngitis). (< one week of URT infection) follows mucosal infections ◬ A lot of times it gets picked up incidentally by finding abnormal urinalysis (Hematuria +/- Proteinuria) done for other reasons with no symptoms. It is the most common cause of glomerular hematuria
Diagnosis	◬ The diagnosis is made by finding abnormal deposition of IgA immunoglobulin in the Glomeruli, it elicit a local inflammatory response in the glomerular mesangium (mesangial expansion) "conclusion : mesangial deposition of **IgA and C3** seen in EM" ◬ Needs **kidney biopsy** to reach the diagnosis as IgA levels are elevated in only 50% of patients. (The most accurate test) ◬ More common among Asians ◬ Look for → **1-2 day** history of an upper respiratory tract infection
Possible causes	◬ It is thought to be secondary to altered mucosal immunity that leads to excessive IgA synthesis followed by deposition in the glomeruli.
Treatment	◬ There is really **no effective immunosuppressive** therapy except in severe cases where it can be tried. 30% will completely resolve ◬ Most important treatment is to control the blood pressure which also decreases the proteinuria. Severe proteinuria is treated with ***ACEi and steroids***. Fish oil is of uncertain benefit.

[9] Rapidly progressive glomerulonephritis (also known as crescentic glomerulonephritis) is characterised by rapid loss of renal function over days to weeks. Renal biopsy shows crescentic lesions, often associated with necrotising lesions within the glomerulus, termed focal segmental (necrotising) glomerulonephritis. It is typically seen in **Goodpasture's disease**, where the underlying cause is the development of antibodies to the glomerular basement membrane (anti-GBM antibodies), and in **small-vessel vasculitides**. It can also be observed in **SLE** and **occasionally IgA and other nephropathies**. Rapid-onset disease may be associated with relatively little proteinuria. Management depends on the underlying cause but immunosuppressive drugs are often required. Patients with anti-GBM disease should be treated with plasma exchange combined with corticosteroids and immunosuppressants. Patients with renal involvement secondary to ANCA-associated vasculitis and SLE should also be treated with corticosteroids and immunosuppressants.

2. Post streptococcal glomerulonephritis (PSGN) :

PSGN follows throat or skin infection (impetigo) by one to three WEEKS in contrast to IgA nephropathy which follows an infection by 1-3 DAYS.

Possible causes	◬ This is a specific subtype of post-infectious glomerulonephritis. It is much more common in children than adults but is now rare in the developed world. The latency is usually about 10 days after a throat infection or longer after skin infection, suggesting an immune mechanism rather than direct infection. ◬ **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 from the start of infection.** ◬ Dark cola coloured urine ◬ Periorbital edema ◬ Hypertension ◬ Oliguria
Diagnosis	◬ **Serum will show positive Antistreptolysin (ASO) titer.** ◬ **Low C3, Normal or slightly low C4 in the serum** (Complement levels are low in PSGN). ◬ May have positive throat culture. ☆ Confirmed by → AntiStreptolysin O (ASO) titers and anti DNAse antibody ☆ Most accurate test → kidney biopsy (not done routinely) ☆ Look for → A history of URTI or skin infection (impetigo) in the last 1-3 weeks
Treatment	◬ Children have better and faster recovery than adults. ◬ Management of PSGN does not reverse the GN, use **supportive therapies** such as : Antibiotics / diuretics (to control fluid overload).

3. Lupus Nephritis :

- Lupus (SLE): The disease with a thousand faces
- **Kidneys can be affected by SLE like other organs**.
- 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.
- 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**. It's needed for accessing the stage of involvement (biopsy is not performed to diagnose lupus, but rather to guide intensity of therapy).Long-standing SLE may simply "scar" the kidneys and biopsy will show glomerulosclerosis which has no active inflammatory components and may lead to such damage as to require dialysis. ◬ **Low complements (C3, C4)** level along with the positive Lupus markers, abnormal urine analysis & abnormal renal function should make you think of its presence.
Treatment	◬ Lupus Nephritis treatment depends on the findings in renal biopsy. ◬ It usually involves high degree of immunosuppressing medications. ◬ Mild inflammatory changes may respond to glucocorticoids.

4. Anti-GBM (Goodpasture's disease) :

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	◬ **GN (can be the only presenting finding) & Pulmonary hemorrhage** (if with GN; is called **Goodpasture's disease** = Lungs + renal involvement). ◬ Unlike Wegener granulomatosis there is NO upper respiratory tract involvement. Goodpasture is limited to the lung and kidney, so signs of systemic vasculitis are **absent**. There is NO skin, joint, GI, eye or neurological involvement. ◬ Anemia is often present from chronic blood loss from hemoptysis.
Diagnosis	◬ Positive test for **Anti-GBM antibodies** in the serum ◬ Kidney biopsy shows the diagnostic Immunofluorescence pattern: **Linear stain of IgG and C3.** ◬ The chest x-ray will be abnormal but it is insufficient to confirm the diagnosis.
Treatment	◬ Treatment is always started immediately to remove the antibodies by **Plasmapheresis** [10] and preventing further antibodies production by giving **heavy immunosuppression** that includes corticosteroids and cyclophosphamide.

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

- Autoimmune disease that involves the presence of **Neutrophils adhesion enhancing molecule** called ANCA = Anti-neutrophil cytoplasmic cytoplasmic antibody.
- Can be:
  1) **C-ANCA**= Cytoplasmic type, more commonly causing Granulomatous Polyangiitis = old name **Wegener's Granulomatosis** (so a granuloma forming disease) "Angiitis: means small vessels vasculitis"
  2) P-ANCA = Perinuclear 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). hemoptysis can cause anemia
Diagnosis	◬ Diagnosis is made by kidney biopsy and positive ANCA titer in the serum.
Treatment	◬ It is usually an aggressive disease that should be treated with potent immunosuppressing medications. (high dose corticosteroids & cyclophosphamide).

6. Membranoproliferative GN (MPGN) :

- It is a pathological description & has multiple causes. The black box, where every peculiar cause fits
- It may present with Nephritic picture or Nephrotic syndrome there is mesangial expansion and GBM thickening
- Can be:
  - Primary (idiopathic): MPGN is mainly seen in **children**.
  - Secondary: You don't need to know them

Possible causes
- ◬ Hepatitis B and C
- ◬ Endocarditis
- ◬ Lupus and Sjogren's syndrome, Cancer or Complement deficiency

[10] Plasmapheresis is a process in which the liquid part of the blood, or plasma, is separated from the blood cells. Typically, the plasma is replaced with another solution such as saline or albumin, or the plasma is treated and then returned to the body.

How to approach a patient with glomerulonephritis?

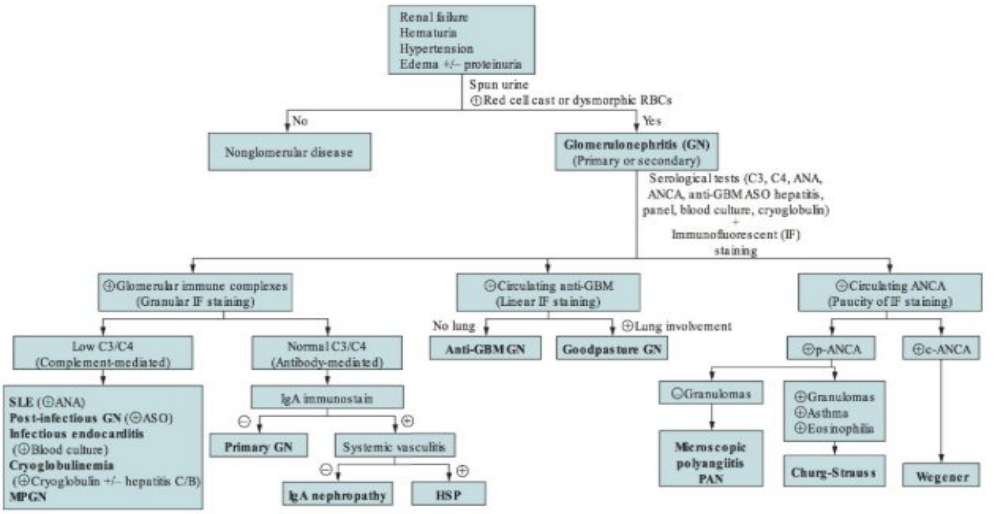


Figure 28–1. Algorithm of approach to the patient with acute glomerulonephritis. Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin-O; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HSP, Henoch–Schönlein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

Cases from the doctor :

Case 1: A **17 year old** male presents with generalized swelling of lower limbs and abdomen for 3 days. He also complains that his urine has bubbles. He has no prior illness. His BP is 110/70 mmHg ,HR is 90, RR is 20 , temp is 36.1. He has puffy eyes, abdominal swelling lower limb pitting edema. Otherwise his exam is normal.

- ➔ Serum creatinine (SCr) : 50 umol/L, Lytes are normal, Urinalysis +3 protein, negative glucose, negative blood, urine microscopy : no casts/cells.
- ➔ 24 hr urine 15 g/day, serum albumin 10 g/L
- ➔ ANA negative, HepB,HepC,HIV negative. CXR and ECG are normal.

Kidney biopsy will most likely show which of the following pathologic features :

A. Minimal change disease.
B. Focal segmental glomerulosclerosis.
C. Membranous nephropathy.
D. IgA nephropathy.
E. Lupus nephritis.

Case 2: A 70 year old man presenting to your clinic with history of lower limb swelling for 3 weeks.

- ➔ PMH : Smoker for 50 years, HTN (on amlodipine).
- ➔ BP : 130/80 mmHg, HR: 90 b.p.m, RR: 18, T: 36.1 C
- ➔ Serum creatinine (SCr) : 80 umol/L, Lytes N, Urinalysis +3 protein, negative blood, urine microscopy : no cells/casts.
- ➔ 24 hr urine 4 g/d, serum albumin 20 g/L
- ➔ ANA negative, HepB,HepC,HIV negative.
- ➔ A kidney biopsy was performed.

Which of the following is the next step in management ? (DDx : FSGS)

A. Start treatment with prednisone
B. Start treatment with cyclosporine
C. Start treatment with rituximab
D. Start treatment with plasmapheresis
E. None of the above

Cases

1) Match the clinical and microscopic presentation with the correct primary glomerular disease. Each lettered option may be used once, more than once, or not at all.

a. Minimal change disease
b. IgA nephropathy
c. Focal and segmental glomerulosclerosis
d. Anti-glomerular basement membrane disease e. Membranous nephropathy
f. Membranoproliferative glomerulonephritis

- 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.
- A 19-year-old white man presents with hypertension, nephrotic syndrome, mild renal insufficiency, RBC casts in urine, and depressed third component of complement (C3). Renal biopsy shows thickened basement membranes and increased cellular elements. Electron microscopy shows dense deposits within the basement membrane.
- A 43-year-old woman complains of fatigue and swelling of her legs. She has been taking several ibuprofen tablets daily for recurrent headaches. She has no history of lymphadenopathy, night sweats, or weight loss. On examination she has a slightly puffy face and her blood pressure is 150/95. She has no adenopathy, her lungs are clear, her heart is normal, and she has 2+ pitting edema to the mid-calf bilaterally. Her creatinine is 0.8 and her urinalysis shows 3+ protein, some amorphous material, and eosinophils. Her 24-hour urine protein is 3.9 g. Renal biopsy results show normal light microscopy and no deposits by immunofluorescence microscopy. Electron microscopy shows effacement of the foot processes.

2) 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 prostate hypertrophy
C. IgA nephropathy
D. Diabetic nephropathy
E. Urinary tract infection (UTI)

3) A 17-year-old patient is referred by his GP after presenting with periorbital oedema. The patient noticed the oedematous eyes 3 days ago, but reports feeling unwell since a throat infection 3 weeks ago with nausea and vomiting in the last week. A urine dipstick is positive for protein and blood while serum creatinine and urea are mildly deranged. The most likely diagnosis is:

A. Nephrotic syndrome
B. Nephritic syndrome
C. Renal failure
D. Glomerulonephritis
E. Von Grawitz tumour

4) A 6-year-old has a sore throat and has been given antibiotics. Three weeks later, he represents feeling feverish with nausea, vomiting and tea-coloured urine. Urine dipstick confirms haematuria and protein. Blood pressure is 100/60mmHg. The most likely diagnosis is:

A. Nephritic syndrome
B. UTI
C. Acute tubulointerstitial nephritis
D. Minimal change glomerulonephritis
E. Post streptococcal glomerulonephritis

5) A 21-year-old man complains his urine has turned a faint red in the last week. He denies any significant changes in his diet or lifestyle and has no other medical problems except for sensorineural deafness diagnosed when he was young. On examination, you notice retinal flecks and urine dipstick confirms protein and blood. The most likely diagnosis is:

A. Alport's syndrome
B. Benign familial haematuria
C. Wolfram syndrome
D. IgA nephropathy
E. Down's syndrome

6) 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. Rapidly progressive glomerulonephritis
E. Wegener's granulomatosis

Answers

1) **The answers are :First case : E , second case : F , third case :A** . Glomerular diseases present with proteinuria and sometimes an active urinary sediment (dysmorphic red cells, white blood cells, and red cell casts). Many patients have the nephrotic syndrome. Patients who present with an active sediment, hypertension, and worsening renal function without nephrotic-range proteinuria and hypoalbuminemia are said to have the nephritic syndrome. Finally, some patients (eg, the usual patient with IgA nephropathy) will have asymptomatic proteinuria or hematuria. Serological studies, complement levels, and, often, renal biopsy will be necessary to establish a definite diagnosis and to adequately plan treatment. Membranous nephropathy is the commonest cause of idiopathic nephrotic syndrome in adults. One-third of cases improve spontaneously, one-third remain stable, and one-third progress to end-stage renal disease if untreated. The condition is fairly responsive to corticosteroid and cytotoxic therapy. Membranoproliferative glomerulonephritis is an uncommon cause of idiopathic nephrotic syndrome in adults. Depressed C3 is caused by an autoantibody that directly activates the third component of complement. A progressive clinical course and erratic response to therapy are typical. Minimal change disease is the cause of nephrotic syndrome in about 15% of adults and 70% to 90% of children. While it often presents as primary renal disease, it is also seen in association with other conditions like NSAID use with concomitant interstitial nephritis and Hodgkin disease. Clinically, patients present as described with sudden onset of edema, nephrotic syndrome, and amorphous urinary sediment on the urinalysis. Most (80%-85%) adults achieve remission of the disease with the use of prednisone, cyclophosphamide, chlorambucil, or mycophenolate mofetil. Relapses can occur but are less common in adults than in children. While children often do not require a biopsy if they respond to high- dose steroids, most adults do undergo biopsy to confirm the etiology. Renal biopsy and electron microscopy are exactly as described in the question. IgA nephropathy is the commonest glomerular disease in adults but rarely causes nephrotic syndrome. Focal and segmental glomerulosclerosis is often associated with drug use or AIDS. Anti-glomerular basement membrane (anti-GBM) disease causes a nephritic picture with hematuria and rapidly progressive renal insufficiency. Light microscopy often reveals crescent formation, and immunofluorescence shows linear IgG staining of the GBM.

2) C : Haematuria may be macroscopic with blood evident in the urine or microscopic requiring urine dipstick testing. The anatomical origin of macroscopic haematuria can often be deduced from its presentation in the urine, although this should not be relied upon. Bleeding from the bladder or above usually presents throughout voiding, terminal bladder or prostatic bleeding occurs at the end of voiding, while urethral sites present at the beginning. Microscopic haematuria identified by urine dipstick requires microscopic analysis to confirm red blood cell presence. Red cell casts are red blood cells that have leaked into renal tubules and clump together forming a cast-like structure which is excreted into the urine. The presence of red cell casts are therefore strongly suggestive of glomerular pathology. False-positive results may arise from haemoglobin or myoglobin in the urine. IgA nephropathy or Berger's disease (C) is the most common cause of glomerulonephritis and may present at any age. Haematuria is usually acroscopic and occurs in intervals corresponding with glomerular attacks, infections such as pharyngitis can exacerbate the condition. Henoch– Schonlein purpura (A) differs from Berger's disease through more systemic involvement, often presenting with arthritis of the large joints, abdominal pain and a characteristic purpuric rash of the extensor skin surfaces. The absence of pain and genital symptoms excludes a UTI (E). Diabetic nephropathy (D) typically presents with proteinuria and not haematuria. Benign prostatic hypertrophy (B) occurs in much older patients often alongside poor urine flow.

3) D : This patient is suffering from post-streptococcal glomerulonephritis (D), which forms part of the nephritic syndrome consisting of haematuria (micro- or macroscopic), hypertension, proteinuria and oedema. In severe cases, oliguria and uraemia can also occur. Patients usually suffer from a streptococcal infection 1–3 weeks prior to presenting with the above symptoms or signs of the nephritic syndrome. During this time, immune complexes are formed and deposited in the glomeruli causing damage. The nephrotic syndrome (A) involves albuminuria usually in the order of ≥3.5 g/d in adults causing oedema and is also associated with hyperlipidaemia (increased LDL/HDL ratio). Nephritic syndrome (B) involves haematuria (micro- or macroscopic) alongside hypertension and proteinuria. Renal failure (C) is an abrupt reduction in kidney function, usually ≤48 hours, with an increase in serum creatinine of ≥26.4 μmol/L or reduction in urine output. A Von Grawitz tumour (E), otherwise known as renal cell cancer, typically occur in males (2:1 male to female ratio) originating from the proximal tubular epithelium. The average age of presentation is 50 years with symptoms including pain, haematuria and usually a mass in the flank alongside other symptoms of malignancy such as weight loss.
4) E : This patient has the typical findings that manifest in a case of post- streptococcal glomerulonephritis (E). The group A streptococcus infection causes deposition of immune complex in the glomeruli. Within this period, the streptococcal organisms themselves are destroyed, hence a UTI (B) coinciding this presentation is not likely. Also, other symptoms suggestive of a UTI are absent, such as dysuria. This patient does not fulfil the triad required for nephritic syndrome (A) since there is no hypertension despite the presence of haematuria and proteinuria. An acute tubulointerstitial nephritis (C) is usually accompanied by fever, skin rashes and painful joints. Minimal change nephropathy (D) is the most common cause of the nephrotic syndrome in children. In this case, haematuria is not a feature of minimal change glomerulonephritis, although proteinuria are present but there is no oedema, which does not fulfil the criteria present in the nephrotic syndrome.

5) A : Alport syndrome (A) is caused by a genetic defect in type IV collagen synthesis causing the triad of hereditary nephritis, sensorineural deafness and ocular abnormalities which can include cataracts and macular retinal flecks. Renal abnormalities are progressive in such patients and include proteinuria, haematuria and eventually renal failure. Thin basement membrane nephropathy or benign familial haematuria (B) is a common cause of asymptomatic haematuria. Apart from glomerular basement membrane thinning, there are no other associated abnormalities and patients have an excellent prognosis. IgA nephropathy (D) is the most common cause of glomerulonephritis and one of the most common causes for asymptomatic haematuria. Glomerular attacks occur episodically and, during these, haematuria presents. Features such as retinal flecks are not present. Wolfram syndrome (C) is a rare genetic disease that causes diabetes insipidus, diabetes mellitus, optic atrophy and deafness. This is not likely given the absence of glucose on urine dipstick. Patients suffering from Down's syndrome (E) have a range of abnormalities and are often recognized from their characteristic facial appearance. The kidney, however, tends to be spared in such patients. Brushfield spots may be mistaken for retinal flecks in such patients and while sensorineural deafness can occur in Down's syndrome, this is not congenital as occurs in Alport's syndrome.

6) E : Wegener's granulomatosis (E) is part of the small vasculitides that also includes other diseases such as Churg–Strauss syndrome. Wegener's typically affects the lungs and kidneys although other body systems can be involved. The pathology of Wegener's is autoimmune in nature. Antineutrophil cytoplasmic antibodies (ANCAs) attack small to medium-sized blood vessels resulting in necrotizing granulomatous inflammation. There is a broad spectrum of symptoms but specific to the renal system patients can be asymptomatic to presenting with renal failure on presentation. Patients characteristically have a crescentic necrotizing glomerulonephritis with the presence of RBC casts. Minimal change nephropathy (C) most commonly occurs in young children causing the nephrotic syndrome. There is also a high association with asthma and eczema. Rapidly progressive glomerulonephritis (D) is characterized by the presence of RBC casts (dysmorphic RBCs damaged as they pass into the renal tubules) which are present in the haematuria. Patients rapidly develop renal failure over weeks and may have glomerular crescents on histology. There are several common causes of rapidly progressive glomerulonephritis, such as ANCA- associated glomerulonephritis, including Wegener's granulomatosis, Goodpasture's disease and a severe form of lupus nephritis. Goodpasture's disease (B) is due to a type 2 autoimmune reaction with antibodies attacking the glomerular basement membrane and lung membrane. Patients often present with upper respiratory tract complaints such as haemoptysis with renal manifestations, such as anaemia and glomerulonephritis, occurring later. ANCA may be positive but are not a dominant feature. Post-streptococcal glomerulonephritis (A) is usually associated with haematuria and hypertension following a streptococcal infection which leads to an acute nephritis due to deposition of immune complex.