

Nephrotic Syndrome

Summary

Nephrotic syndrome is a collection of signs and symptoms indicating damage to the glomerular filtration barrier. It is characterized by massive proteinuria (> 3.5 g/24 hours), hypoalbuminemia, and edema. In adults, the most common causes of nephrotic syndrome include focal segmental glomerulosclerosis (FSGS) and membranous nephropathy. In children, nephrotic syndrome is most commonly caused by minimal change disease (MCD). Nephrotic syndrome can also be a manifestation of advanced renal disease in systemic conditions (e.g., diabetic nephropathy or amyloid nephropathy). Typical laboratory findings of nephrotic syndrome include hyperlipidemia and fatty casts on urinalysis. Treatment for FSGS, membranous nephropathy, and MCD usually includes immunosuppressive therapy. Nephrotic syndrome due to advanced renal disease is associated with a worse prognosis and is more difficult to treat.

Etiology

Nephrotic syndrome may be caused by primary glomerular disorders (80–90% of cases) and/or systemic diseases and toxic exposures (10–20% of cases).^[12]

- **Primary (idiopathic) forms:** The following types of nephrotic syndrome are commonly associated with other conditions. See the "Overview" section.
 - **Minimal change disease**
 - **Focal segmental glomerulosclerosis**
 - **Membranous nephropathy**
 - **Membranoproliferative glomerulonephritis** (can manifest as nephrotic or nephritic syndrome)
- **Secondary forms**
 - Diabetic nephropathy
 - Amyloid nephropathy: can be associated with multiple myeloma (AL amyloidosis) or chronic inflammatory disease such as rheumatoid arthritis (AA amyloidosis)
 - Lupus nephritis (can manifest as nephrotic or nephritic syndrome)

Pathophysiology

Damage of glomerular filtration barrier^{[13][14]}

- **Minimal change disease:** cytokine-mediated damage of podocytes
- **Focal segmental glomerulosclerosis:** sclerosis of glomeruli → damage and loss of podocytes
- **Membranous nephropathy:** Anti-phospholipase A2 receptor antibodies (anti-PLA2R antibodies) bind to PLA2R (an autoantigen in glomerular podocytes) and thereby form immune complexes that activate the complement system, leading to podocyte injury.^[15]
- **Membranoproliferative glomerulonephritis:** See "Pathophysiology" in "Nephritic syndrome."
- **Diabetic glomerulonephropathy:** See "Pathophysiology" in "Diabetic nephropathy."
- **Amyloid nephropathy**
 - Deposition of amyloid (e.g., AL amyloidosis, AA amyloidosis) in various organs (the kidney is the most commonly involved organ)
 - Amyloid deposition in glomeruli → mesangial expansion → nodular sclerosis^[16]
- **Lupus nephritis:** See "Pathophysiology" in "Lupus nephritis."

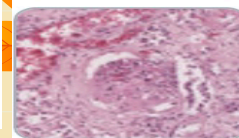
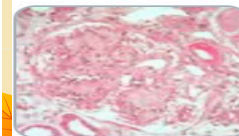
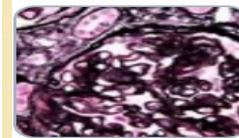
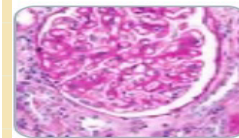
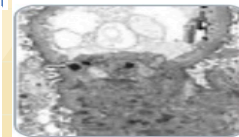
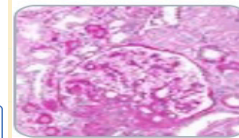
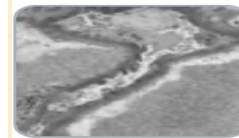
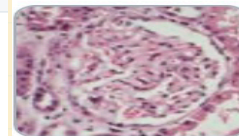
 FSGS is classically **not** associated with immune complex deposition.

Sequelae of glomerular filter damage^{[13][14]}

- Structural damage of glomerular filtration barrier → massive renal loss of protein (**hyperproteinuria**) → reactively increased hepatic protein synthesis
 - **Loss of negative charge of glomerular basement membrane** → **loss of selectivity of barrier** (especially for negatively charged albumin)
 - Podocyte damage and fusion → **nonselective proteinuria** (except in minimal change disease, which manifests with **selective glomerular proteinuria**)^[7]
- If protein loss exceeds hepatic synthesis (usually with a loss of protein > 3.5 g/24 hours) → hypoproteinemia/**hypoalbuminemia**, initially with both normal GFR and creatinine^{[13][14]}
 - ↓ **Serum albumin** → ↓ **colloid osmotic pressure** → **edema** (especially if albumin levels are < 2.5 g/dL)^[17]
 - **Loss of antithrombin III, protein C, and protein S**, increased synthesis of **fibrinogen**, and loss of fluid into the extravascular space → **hypercoagulability**
 - Loss of transport proteins
 - **Loss of thyroglobulin transport protein** → **thyroxine deficiency**
 - **Vitamin D binding protein** → **vitamin D deficiency**
 - Loss of plasma proteins → ↓ plasma protein binding → increase in free plasma drug concentration, but drug toxicity is usually not increased^{[18][19][20]}
- ↑ **Plasma levels of cholesterol, LDL, triglycerides, and lipoproteins (mainly LPA)** to compensate for the loss of albumin → **lipiduria** (fatty casts)^[21]
- **Loss of immunoglobulins** → increased risk of **infection**, especially *Streptococcus pneumoniae* infection (**pulmonary edema** also increases the risk for *S. pneumoniae* infection)
- **Sodium retention** → possible hypertension

Clinical features

- **Classic manifestations**
 - **Massive proteinuria** > 3.5 g/24 hours
 - **Edema**
 - Typically starts with periorbital edema
 - Peripheral edema (pitting)
 - Pleural effusion
 - Pericardial effusion
 - Ascites
 - In severe cases, anasarca
 - **Hypoalbuminemia**
 - Hyperlipidemia
- **Other clinical features**
 - **Hypercoagulable state** with increased risk of thrombosis and embolic events (e.g., pulmonary embolism, renal vein thrombosis)
 - Increased susceptibility to **infection**
 - Hypertension in some cases
 - Possibly frothy urine
 - Symptoms of hypocalcemia (e.g., tetany, paresthesia, muscle spasms)
 - Symptoms of the underlying disease (e.g., malar rash in lupus nephritis)



First: Minimal change disease (lipoid nephrosis)

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

- **Most common form in children**, although it may account for 15% of adult disease.
- Mesangial nephropathy is likely just a variant of minimal change disease (MCD). Although they are more common in **children**, they still occur in adults, especially in those with **lymphoma (Hodgkin lymphoma)**, leukemia, or **NSAID** use.
- A variety of glomerular diseases may be seen in the setting of malignancy. Overall, membranous glomerulopathy is the most common form of nephrotic syndrome associated with malignancies. However, these are usually solid cancers (lung, colon, prostate, breast). **However, minimal change disease is usually seen in patients with Hodgkin lymphoma.**
- Light microscopy is normal and electron microscopy is needed to see fusion of foot processes.
- **Unlike FSGS**, MCD is a highly steroid-sensitive condition, and the diagnosis of MCD is based on age, clinical presentation, and response to steroids. Empiric steroid therapy should be initiated upon suspicion of the diagnosis. **Approximately 85% of children will respond to their first steroid course.**

3- minimal change disease - mcd of nephrotic \$ in children + occur in 15% of adult...

- has high response to the steroid [785% of cases]

- associated with non-solid malignancy [lymphoma-leukemia] . drugs [MAID] ..

• investigation:- urine analysis [+protein]...

- albumin/cr ratio...

- 24hr urinary protein...

- Biopsy [not seen in light microscope, need electron microscope]...

- There is podocyte in the Bowman's capsule which has -ve charge + has processes which prevent the protein infiltration [the proteins is -ve pressure molecules] { make space occupying [a mass] to prevent the protein excretion in the urine...

- in some cases the podocyte become near to each other so this allow the proteins to be infiltrated (we see fusion of pod processes in e microscope)...

* **+++** :- steroids in 85% of cases response but if the pt not response we should do Biopsy indicated focal segmental glomerulosclerosis is $\uparrow$ in α is $\uparrow$

C. Minimal Change Disease and Mesangial Nephropathy:

- **Most common form in children**, although it may account for 15% of adult disease.

- Mesangial nephropathy is likely just a variant of minimal change disease (MCD). Although they are more common in **children**, they still occur in adults, especially in those with **lymphoma (Hodgkin lymphoma)**, leukemia, or **NSAID** use.

- A variety of glomerular diseases may be seen in the setting of malignancy. Overall, membranous glomerulopathy is the most common form of nephrotic syndrome associated with malignancies. However, these are usually solid cancers (lung, colon, prostate, breast). However, minimal change disease is usually seen in patients with Hodgkin lymphoma.

- A diagnosis other than MCNS should be considered if:
 1. presence of age <1 yr
 2. family history
 3. extrarenal findings (arthritis, rash, anemia)
 4. hypertension or pulmonary edema
 5. acute or chronic renal insufficiency
 6. hematuria.
- More than 95% respond to corticosteroid therapy.

2nd: Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis

- Most common cause of nephrotic syndrome in **adults**, especially in **African American and Hispanic populations**

- Can be idiopathic
- Heroin use
- HIV infection
- Sickle cell disease
- Massive obesity
- Interferon treatment
- Congenital malformations (e.g., Charcot-Marie-Tooth syndrome) [8][9]
- NPHS1 and NPHS2 mutations

- LM: segmental sclerosis and hyalinosis
- IM
 - Most commonly negative
 - Possibly IgM, C1, and C3 deposits inside the sclerotic regions
- EM: effacement of podocyte foot processes (similar to minimal change disease)

- Prednisone** (often shows poor response)
- If necessary, PLUS other immunosuppressants (e.g., cyclosporine, tacrolimus)
- RAAS inhibitors
- Usually leads to ESRD if left untreated

2. Focal Segmental Glomerulosclerosis :- occur in children and adult...

... this dz resist the steroid [glucocorticoid]...

... So we treat them by steroid sparing drugs...

... associated with heroin abuse - HIV - IgA nephropathy when it become nephrotic - [VUR :- vesico ureteric reflux] reflux glomerulonephritis - obesity...

... CKD lead to kidney shrink except in the focal segmental glomerulosclerosis... [has normal kidney size or enlarged]... especially if the cause is HIV...

- Focal segmental glomerulosclerosis (FSGS) and membranous nephropathy are the most common causes of nephrotic syndrome in adults in the absence of a systemic disease.
- FSGS is more common in African American patients and in those with obesity, heroin use, and HIV.
- Testing and treatment are the same as for membranous nephropathy, but the response is usually worse.

3rd: Membranous nephropathy

Membranous nephropathy

- Most common cause of nephrotic syndrome in **adults of European, Middle Eastern, or North African descent**

- Primary: anti-PLA2R antibodies
- Secondary:
 - Infections (HBV, HCV, malaria, syphilis)
 - Autoimmune diseases (e.g., SLE)
 - Tumors (e.g., lung cancer, prostate cancer)
 - Medications (e.g., NSAIDs, penicillamine, gold) [10]

- LM
 - Diffuse thickened glomerular capillary loops and basement membrane
 - Granular subepithelial deposits of IgG and C3 (dense deposits) → spike and dome appearance

- RAAS inhibitors**
- Prednisone** (often shows poor response)
- PLUS other immunosuppressants (e.g., cyclophosphamide) in severe disease
- Usually leads to ESRD if left untreated

A. Membranous Nephropathy:

- Membranous nephropathy is also associated with:
 - Cancer (lung, colon, prostate, breast).
 - Infections: Hepatitis B and C.
 - ACE inhibitors, NSAIDs, penicillamine, and gold.
 - SLE.
- Hepatitis B infection is a significant risk factor for membranous nephropathy. Universal vaccination has dramatically reduced rates of hepatitis B virus-associated membranous nephropathy (HBVMN), and unvaccinated children who have immigrated from endemic areas should be screened for hepatitis B.
- The best initial test is a UA and protein-to-creatinine ratio. There is no way to confirm a diagnosis without renal biopsy.
- Treatment:
 - The best initial therapy is with prednisone. If there is severe proteinuria after prednisone, the next best step in management is cyclophosphamide.
 - When there is no response to steroids and cyclophosphamide, the answer is less clear; cyclosporine, tacrolimus, and mycophenolate can all be correct.

1. Membranous nephropathy :- most nephrotic in adults...

lead to heavy proteinuria [may reach 10-15g/day]...
Bad prognosis...

* associated with malignancy [solid] - infection [HBV, HCV]

... drugs [NSAID - penicillamine - gold - ACEI] - SLE...

... RAAS inhibitors...
... RAAS inhibitors...
... RAAS inhibitors...

* HBV vaccine reduce the risk of nephrotic...

* Investigation:- 1. urine analysis 2. albumin/cr ratio

3. 24hr urinary protein 4. Renal Biopsy...

* Htt :- glucocorticoid - steroid sparing drugs...

4th: Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis

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

5th: Diabetic nephropathy

Diabetic nephropathy

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

- **Diabetes is the most common cause of end-stage renal disease in the United States.**
- Diabetic nephropathy begins with **hyperfiltration** (increased glomerular filtration rate - GFR) and **microalbuminuria** (levels of albumin between 30 and 300 mg per 24 hours).
- If not **treated** adequately, **microalbuminuria** may progress to **macroproteinuria**, defined as urine protein excretion **>300 mg/24 hr**. This increase in **urinary protein** is accompanied by a **progressive decline in GFR**.
- **Patients with DM should be screened annually for microalbuminuria and started on an ACE inhibitor or ARB when it is present.**

- **Intensive blood pressure (BP) control is the primary intervention proven to slow the decline in GFR once azotemia develops.** Most patients with diabetes mellitus should be treated toward a target BP of **140/90 mm Hg**, and patients with diabetic nephropathy may benefit from more intensive BP control. Most guidelines now recommend a target BP of **130/80 mm Hg** for patients who are diabetic with signs of nephropathy.
- **Angiotensin-converting enzyme (ACE) inhibitors, and perhaps angiotensin receptor blockers (ARBs), are the preferred antihypertensive drugs for patients with diabetes mellitus.** These drugs may have actions in addition to BP control, such as **reducing intraglomerular pressure, which may be renoprotective**. However, ACE inhibitors or ARBs in patients with **diabetic nephropathy** must be initiated **carefully** as they may induce **an acute decline in GFR and hyperkalemia**.
- **Several randomized controlled clinical trials have demonstrated the beneficial effects of ACE inhibitors in slowing the progression of diabetic nephropathy.** The use of ACE inhibitors reduces **urinary albumin excretion** and the **decline in creatinine clearance**. Its use is recommended in patients with **microalbuminuria** even if their **blood pressure is normal**, since **microalbuminuria** is a **sensitive marker of renal microvascular damage**.

E. Diabetic Nephropathy:

- Screening for proteinuria in diabetes mellitus should occur annually. If the UA is negative, the "next best step" is testing the urine for microalbumin.
- The most common histologic lesion in diabetic nephropathy is diffuse glomerulosclerosis. **Nodular glomerulosclerosis (with Kimmelstiel-Wilson nodules) is pathognomonic.**
- ACE inhibitors and ARBs are used in all those with any degree of proteinuria in diabetes mellitus.

5. Diabetic nephropathy:-
 • treated by ACE I or ARBs [very effective].
 • in stage I there is ↑ GFR...
 • we screen the microalbuminuria

6th: Amyloid nephropathy

Amyloid nephropathy

- More commonly seen in elderly patients^[11]

- The kidney is the most commonly affected organ in systemic amyloidosis.
- Other organs might be involved simultaneously (e.g., the heart).
- Multiple myeloma (AL amyloidosis)
- Chronic inflammatory disease, e.g., tuberculosis, rheumatoid arthritis (AA amyloidosis)

- LM
 - Mesangial proliferation
 - Subendothelial and/or subepithelial immune complex deposition
 - Thickening of the capillary walls (appear as wire loops)
 - Congo red stain: amyloid deposition in the mesangium showing apple-green birefringence under polarized light
 - Nodular glomerulosclerosis
- IM: positive for AA protein (AA amyloidosis), positive for kappa and lambda light chains (AL amyloidosis)
- EM: amyloid fibrils

- Melphalan, corticosteroids
- Treatment of underlying disease (e.g., bone marrow transplantation may be used for multiple myeloma)

7th: HIV nephropathy

F. HIV Nephropathy:

- HIV causes hyponatremia, thrombotic thrombocytopenic purpura, and nephrotic syndrome.
- If HIV-associated nephrotic syndrome is described, the right answer is antiretroviral therapy. The wrong answer is prednisone.
- When CD4 cells rise with the use of antiretrovirals, there should be prompt improvement in both the nephrotic syndrome and renal function as long as the disease has not progressed to ESRD. ACE inhibitors or ARBs are beneficial.

6. HIV nephropathy:-

↳ lead to focal segmental glomerulosclerosis...

- has nephrotic range proteinuria [heavy]...

- has normal size of kidney...

- has normotension...

* tt:- antiretroviral drugs [improve the immune system → brisk of progression of the kidney disease (end stage kidney dz)]...

8th: Lupus nephritis:

⑩ The lupus nephritis:- pt has SLE which lead to damage in the kidney

- ↳ AKI
- ↳ CKD
- ↳ end stage renal dz
- ↳ glomerular dz
- ↳ nephrotic & nephritic

* There is 6 classes of lupus nephritis:-

• Class I: minimal mesangial GN...

• class II: mesangial proliferative GN...

• class III: focal proliferative GN...

• class IV: diffuse proliferative GN...

↳ the most common and most severe form of lupus nephritis...

• class V: diffuse membranous GN...

• class VI: advanced sclerosis... → not has tt just follow up [irreversible - slowly progressive]...

* any pt has SLE then presented with renal symptom we should do Biopsy to determine the class of lupus nephritis...

Lupus Nephritis

- SLE can give any degree of renal involvement. The kidneys in SLE can be normal or present with mild, asymptomatic proteinuria. Severe disease presents with membranous glomerulonephritis. 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.
- Double-stranded DNA levels go up and complement levels go down as a marker of severity in flare-ups of the disease.
- Biopsy is the most accurate test of lupus nephritis.
- Biopsy is not performed to diagnose lupus, but rather to guide intensity of therapy.
- Biopsy is indispensable in determining therapy based on the stage:
 - Mild inflammatory changes may respond to glucocorticoids.
- Severe, proliferative disease such as membranous nephropathy is treated with glucocorticoids combined with either cyclophosphamide or mycophenolate.
- Treatment is not needed for sclerosis; it is simply scarring of the kidney

Pathology

Classification of nephrotic syndrome is based on the pattern of injury as seen on light microscopy (LM) of a renal biopsy specimen. For a complete assessment, all biopsy specimens should be analyzed using LM, immunofluorescence microscopy (IM), and electron microscopy (EM).

- **Minimal change disease**
 - EM: **effacement** of the **foot processes** of podocytes
 - LM: **no changes in glomeruli** (possibly fat bodies in some proximal tubular cells)
- **Focal segmental glomerulosclerosis**: damage to podocytes
 - EM: **effacement** of the **foot processes** (similar to minimal change disease)
 - LM: segmental sclerosis and **hyalinosis** and loss of podocytes
 - IM: rarely, focal deposits of **IgM, C1, and C3** inside sclerotic lesion
- **Membranous nephropathy**: deposition of antibodies between podocytes and the basal membrane
 - EM: **subepithelial dense deposits** (IgG and C3) with a **spike and dome** appearance
 - LM: diffuse thickening of glomerular capillary loops and basal membrane
 - IM: granular subepithelial deposits of immune complexes and complement
- **Diabetic glomerulonephropathy**: light microscopy shows mesangial matrix expansion, thickening of glomerular membrane, and/or nodular eosinophilic glomerulosclerosis (**Kimmelstiel-Wilson lesions**)
- **Lupus nephritis**: light microscopy shows mesangial proliferation, subendothelial and/or subepithelial immune complex deposition, and thickening of the capillary walls (appear as wire loops)
- **Amyloid nephropathy**
 - EM: amyloid fibrils
 - LM
 - Nodular glomerulosclerosis
 - **Apple-green birefringence** (mesangial amyloid deposition) with Congo red stain under polarized light

Diagnostics

Approach

1. Confirm nephrotic-range proteinuria.
2. Assess for potential concomitant and underlying conditions.
3. Assess for nephrotic syndrome complications.
4. Consider kidney biopsy to determine renal pathology.

Initial evaluation [22][12]

Confirmation of nephrotic-range proteinuria

- **Qualitative assessment by urine dipstick** (commonly used for screening)
 - Usually shows $\geq 3+$ proteins
 - Hematuria may indicate concomitant glomerulonephritis.
- **Quantitative assessment of urine protein excretion**
 - 24-hour urine protein (test of choice): > 3.5 g/24 hours
 - Spot urine protein/creatinine ratio: > 3.5 g/g

Urine sediment microscopy [27]

- **Nephrotic sediment**
 - Lipiduria, **fatty casts** with **Maltese cross** appearance under polarized light
 - Renal tubular epithelial cell casts
- Hematuria with acanthocytes and/or RBC casts may indicate concomitant glomerulonephritis (see "Diagnostics" in "Nephritic syndrome").

Additional laboratory studies

- CBC: ↑ Hb/Hct may indicate hemoconcentration
- BMP: ↑ Cr and/or ↑ BUN may be seen; ↓ Na is commonly seen.
- Serum protein: ↓ total protein, ↓ albumin (< 3 g/dL)
- Coagulation factors: ↓ ATIII, ↓ protein S, ↓ plasminogen; ↑ fibrinogen, ↑ D-dimer
- Lipid profile: Hyperlipidemia (↑ LDL, ↑ triglycerides) may be present.
- Vitamin D levels: ↓ 25-OH Vit-D
- Inflammatory markers: ↑ ESR, ↑ CRP may suggest underlying infection, inflammatory condition, or vasculitis.

Imaging

- Renal ultrasound: to assess kidney size and shape and rule out obstruction

Subsequent evaluation

Additional testing to assess for potential concomitant conditions and underlying causes should be based on clinical suspicion.

Work-up for concomitant conditions and underlying causes of nephrotic syndrome	
Suspected condition	Recommended studies
Diabetic nephropathy	• Serum glucose • HbA1c
Membranous nephropathy	• Anti-PLA₂R antibodies • Age-appropriate cancer screening
Lupus nephritis	• ANA • Anti-dsDNA • C3, C4
Multiple myeloma and other plasma cell dyscrasias	• Serum protein electrophoresis and immune fixation • Urine protein electrophoresis and immune fixation
Chronic viral infection	• HIV Ab • HBsAg • HCV Ab
Syphilis	• RPR • FTA-ABS
Cryoglobulinemia	• Cryoglobulins • C3, C4
Congenital nephrotic syndromes	• Genetic testing

Renal biopsy

- Indication: to confirm the diagnosis when the etiology of nephrotic syndrome is unclear and/or to guide management
 - Often required in adult patients to guide management.
 - Sometimes deferred when a likely cause of nephrotic symptoms is evident
 - Consult nephrology to determine the necessity and timing of biopsy.

Complications

Thrombotic complications

- Venous thromboembolism (e.g., deep vein thrombosis, pulmonary embolism)
- Arterial thromboembolism
- Renal vein thrombosis: thrombus formation in the renal veins or their branches
 - Cause: hypercoagulable state (e.g., malignancies, antiphospholipid syndrome, nephrotic syndrome)
 - Manifestations
 - Flank pain
 - Hematuria
 - ↑ LDH
 - Anuria/renal failure in bilateral thrombosis
 - Scrotal edema
 - Diagnostics
 - CT angiography or MR venography (preferred modality in patients with renal injury or failure)
 - Doppler ultrasonography if no other diagnostic modality is available
 - Treatment
 - Anticoagulation
 - Thrombolysis or thrombectomy in selected patients
 - Complications: rupture of renal capsule, pulmonary embolism, kidney injury

Atherosclerotic complications [45][48]

- Abnormal lipid metabolism in combination with a hypercoagulable state leads to an increased risk of atherosclerotic complications
- Manifestation: myocardial infarction, stroke

Chronic kidney disease

- FSGS and membranous nephropathy in particular may progress to chronic kidney disease and ESRD.

Increased risk of infection [49][50]

- Most likely resulting from hypogammaglobulinemia caused by urinary protein loss
- E.g., respiratory tract infections, peritonitis, urinary tract infections, sepsis
- Especially with encapsulated bacteria (e.g., Streptococcus pneumoniae)

Protein malnutrition

- Loss in lean body mass due to proteinuria may be masked by weight gain caused by concurrent edema.

Vitamin D deficiency

- Due to urinary loss of vitamin D binding protein (DBP) and bound 25-hydroxyvitamin D [51][52][53]
- Can cause hypocalcemia → ↑ serum parathyroid hormone (PTH) → bone disease (see "Secondary and tertiary hyperparathyroidism") [54]

Anemia

- Due to urinary loss or impaired synthesis of transferrin (causing hypochromic microcytic anemia), transcobalamin (causing megaloblastic anemia), copper (causing sideroblastic anemia), erythropoietin, and iron [55]

Nephrotic vs. nephritic syndrome [1][2]

- Nephritic syndrome and nephrotic syndrome are both common clinical manifestations of glomerular diseases.
- Both syndromes are composed of characteristic clinical (e.g., edema, hypertension) and laboratory findings (e.g., glomerular hematuria, massive proteinuria), which result from damage to the glomeruli.
- Glomerular diseases are usually categorized by the syndrome they cause, which is either nephritic or nephrotic.
- Some diseases that manifest with nephritic syndrome can simultaneously cause nephrotic-range proteinuria (> 3.5 g/day), the main feature of nephrotic syndrome. When the criteria for both syndromes are fulfilled, the findings are referred to as mixed **nephritic-nephrotic syndrome**.
- Classifying the patient's presentation as nephritic, nephrotic, or mixed nephritic-nephrotic can help narrow down the list of likely differential diagnoses.

	Nephritic syndrome	Nephrotic syndrome
Presentation	- Proteinuria (< 3.5 g/day) (can be in nephrotic range in severe cases [56]) Hematuria with acanthocytes RBC casts in urine - Mild to moderate <u>edema</u> - Oliguria - Azotemia Hypertension <u>Sterile pyuria</u>	Heavy proteinuria (> 3.5 g/day) - Hypoalbuminemia Generalized edema Hyperlipidemia and fatty casts in urine → frothy urine - Hypertension ↑ Risk of <u>thromboembolism</u>: (via loss of <u>antithrombin III</u>) [57] ↑ Risk of infection (via loss of IgG and tissue edema which compromises the local blood supply and <u>immune response</u>)
Pathophysiology	Inflammatory response within <u>glomeruli</u> → GBM disruption → loss of renally excreted RBCs (acanthocytes) and ↓ GFR → hematuria, oliguria, azotemia, and ↑ <u>renin</u> → <u>edema</u> and <u>hypertension</u>	Damage to <u>podocytes</u> → structural damage of <u>glomerular filtration barrier</u> → massive renal loss of protein
Causes	Poststreptococcal glomerulonephritis IgA nephropathy (Berger disease) <u>Granulomatosis with polyangiitis</u> <u>Microscopic polyangiitis</u> <u>Eosinophilic granulomatosis with polyangiitis</u> Goodpasture syndrome (anti-GBM disease) Alport syndrome (hereditary nephritis) <u>Thin basement membrane disease</u> Rapidly progressive glomerulonephritis (RPGN) <u>Lupus nephritis</u> - Most common causes of nephritic-nephrotic syndrome: <u>Membranoproliferative glomerulonephritis</u> <u>Diffuse proliferative glomerulonephritis</u>	- Due to primary or secondary <u>podocyte damage</u> Minimal change disease Focal segmental glomerulosclerosis Membranous nephropathy - Due to secondary <u>podocyte damage</u> Diabetic nephropathy <u>Amyloid light-chain (AL) amyloidosis</u>, <u>light chain deposition disease</u> <u>Lupus nephritis</u>

