Team Medicine

Nephrotic Syndrome

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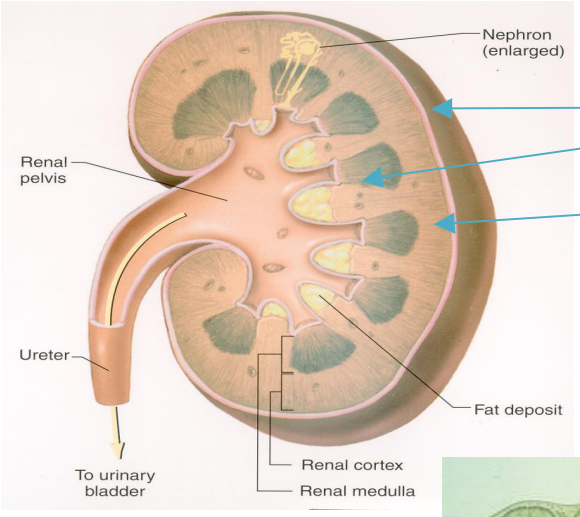
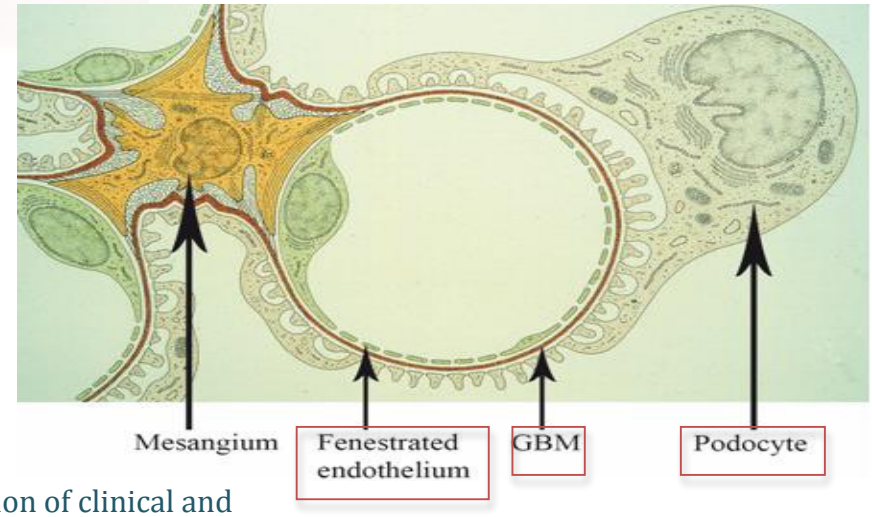
■ Important notes ■ doctor notes ■ extra info

431 Teams
medical students

Kidney is composed of three major components; capsule, medulla and cortex. Cortex is the most important part because it contains the nephrons



Capillary loop has 3 layers



➔ Podocyte and its associated endothelial cell is the site of ultrafiltration

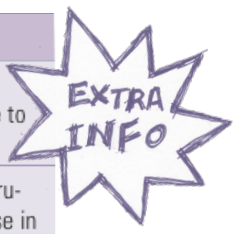
Nephrotic syndrome

It refers to a distinct constellation of clinical and laboratory features of renal disease, of which are:

- **Heavy proteinuria** (> 3.5 g/24 hours)
- **Hypoalbuminemia** <30 g/L (Normal:35-55 g/L)
- Peripheral or generalized **edema**

➔ **These are the most important three features of nephrotic syndrome**

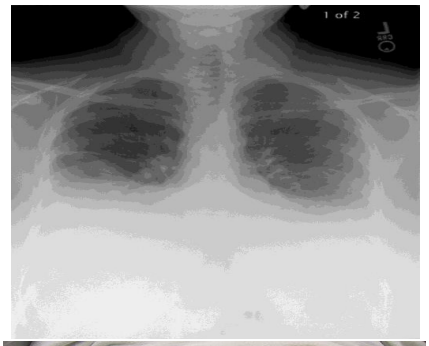
	Nephritic Syndrome	Nephrotic Syndrome
Pathogenesis	Inflammation of glomeruli due to any of the causes of glomerulonephritis	Abnormal glomerular permeability due to a number of conditions
Causes	Poststreptococcal glomerulonephritis is the most common cause, but may be due to any of the causes of glomerulonephritis	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

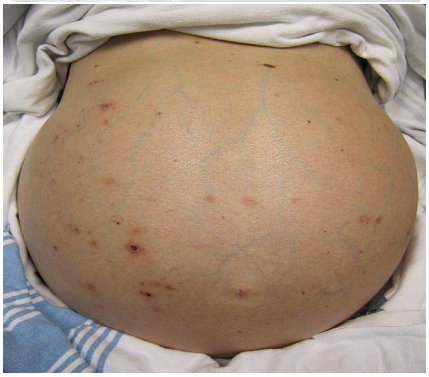


Clinical Presentation:

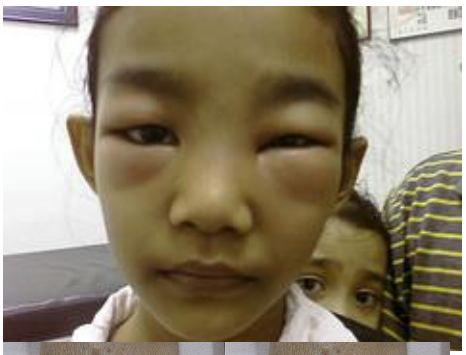
- **Edema**:
  - Low serum albumin.
  - Increase renal sodium retention. uncontrolled activation of the epithelial sodium channels (ENaC)
- Fatigue
- Foamy urine that persists
- Anorexia because of small bowel congestion.
- Nausea & vomiting
- Abdominal pain impaired peristalsis
- Weight gain
- Shortness of breath
- Signs & symptoms of DVT, PE

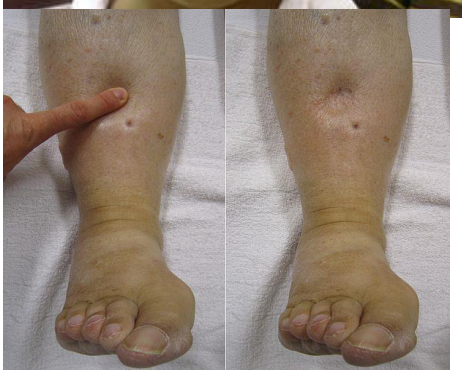
Hyperproteinuria
↓
Hypoproteinemia
↓
Low oncotic pressure
↓
Edema





Generalized symptoms of edema are called anasarca

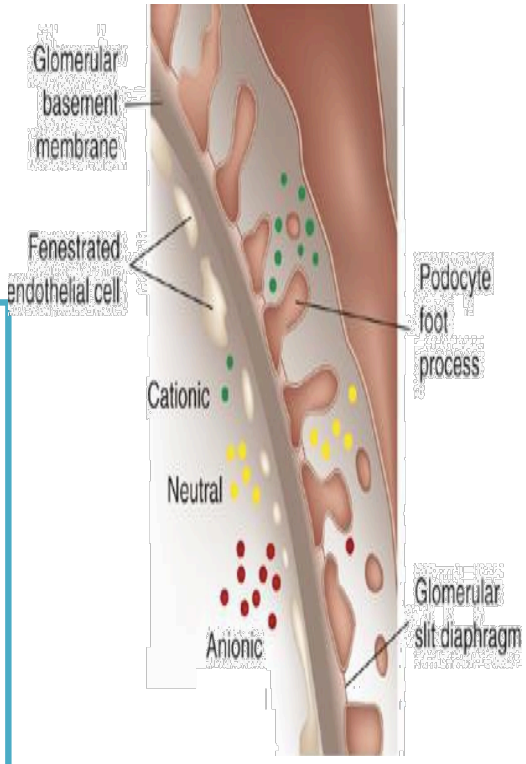




A substantial volume (litres) of extracellular fluid may accumulate without any clinical signs. In adults dependent regions or immobile limbs are usually the first sites of oedema formation, where it is easy to mistake the early signs of generalized oedema for a local problem. Ankle swelling is characteristic, but oedema develops over the sacrum in bed-bound patients. It rises higher up the lower limbs with increasing severity, to affect the genitalia and abdomen. Ascites is common and often an earlier feature in children or young adults, and in liver disease. Pleural effusions are common and can be a feature of any cause of generalized oedema. Facial oedema on waking [in the morning] is common in adults with low oncotic pressure oedema and in young patients. Features of intravascular volume depletion (tachycardia, postural hypotension) may occur when oedema is due to decreased oncotic pressure or increased capillary permeability. If oedema is localized—for example, to one ankle but not the other—then features of venous thrombosis, inflammation and lymphatic disease should be sought. (Davidson; 482)

Albumin

- Synthesized in the liver.
- ½ of the total serum protein is Albumin.
- A major contributor to oncotic pressure (Stabilizing the extracellular fluid volume).
- As a carrier protein for steroids, fatty acids, and thyroid hormones.



What keeps Albumin in?

- Endothelium and the GBM are strongly anionic with the electronegative charges.
- Albumin is negatively charged at neutral pH.
- The negative charge of GBM repulses the negative charge of the Albumin; preventing Albumin leaving the capillary lumen.
- Proteinuria is a manifestation of defected GBMs Albumin repulsion mechanism.

Normal Urine Analysis	Urine Analysis In Nephrotic Syndrome
No protein	**Proteinuria**
No RBCs or heme (accept 1-2 RBCs/hpf)	No RBCs (few are seen occasionally) because GBM and endothelium are fine, the dysfunction is only in the podocytes.
No cellular casts	No RBC casts. Because GBM and endothelium are fine.
	plenty of fat (Lipiduria) (fatty casts, oval fat bodies and fat droplets)
	No WBCs (few are seen occasionally)

EXTRA INFO

17.22 Consequences of the nephrotic syndrome and their management

Feature	Mechanism	Consequence	Management
Hypoalbuminaemia	Urinary protein losses exceed synthetic capacity of liver	Reduced oncotic pressure Oedema	Diuretics and a low-sodium diet*
Avid sodium retention	Secondary hyper-aldosteronism Additional poorly characterised intra-renal mechanisms	Oedema	
Hypercholesterolaemia	Non-specific increase in lipoprotein synthesis by liver in response to low oncotic pressure	High rate of atherosclerosis	Lipid-lowering drugs (e.g. HMG CoA reductase inhibitors, p. 455)
Hypercoagulability	Relative loss of inhibitors of coagulation (e.g. antithrombin III, protein C and S) and increase in liver synthesis of procoagulant factors	Venous thromboembolism	Consider prophylaxis in all patients with chronic or severe nephrotic syndrome
Infection	Hypogammaglobulinaemia (urinary losses)	Pneumococcal infection	Consider vaccination

*Severe nephrotic syndrome may need very large doses of combinations of diuretics acting on different parts of the nephron (e.g. loop diuretic plus thiazide plus amiloride). In occasional patients with hypovolaemia, intravenous salt-poor albumin infusions may help to establish a diuresis, although efficacy is controversial. Over-diuresis risks secondary impairment of renal function through hypovolaemia.

Proteinuria:

How much protein in the urine is considered Normal?

- **< 150 mg/day of all proteins**.
- Albumin in the urine only comes from the Glomerulus.
- < 20 mg/day of Albumin is Normal (average 4-7mg/day).

Detecting Proteinuria:

- Urine dipstick.
- Urine chemical Analysis.
  - True measurement: 24h urine collection
  - Estimated measurement : Urine Albumin Creatinine ratio

Albuminuria: 30-300 mg/day = HIGH ALBUMINURIA (microalbuminuria) •Indicative of renal disease, especially Diabetic Nephropathy in Diabetic patients. • Associated with an increased risk for cardiovascular disease in non-diabetics. • Needs chemical analysis to find, cannot be detected by dipstick.	Albuminuria > 300 mg/day = OVERT PROTEINURIA or VERY HIGH ALBUMINURIA (macroalbuminuria) •Urine dipstick will be positive. •Most of this protein is Albumin.

Sub-Nephrotic proteinuria: **< 3.5 gm**/day

Nephrotic Range Proteinuria: **> 3.5 gm**/day

Complications of Nephrotic Syndrome

If left untreated: potentially fatal complications

A. Thromboembolism:

In 10 to 40% of patients
- Arterial and venous thrombosis (DVT, PE &renal vein thrombosis)
- Membranous Nephropathy ↑Renal vein thrombosis risk
- Mechanism is not clearly understood
- May be renal loss of antithrombin proteins and plasminogen, and platelets activation.

B. Infections & sepsis:

the mechanism is not well understood
- Renal loss of IgG may play a rule
- Impaired ability to make specific antibodies
- Low alternative complement pathway
- Pneumococcal infections are more common; should get pneumococcal vaccine

C. Hyperlipidemia: common

•Hypercholesterolemia; Decreased plasma oncotic pressure stimulates hepatic lipoprotein synthesis to replace the protein that has been lost
•Hypertriglyceridemia; Due to impaired metabolism ↑ risk for atherosclerotic disease. Severe hypertriglyceridemia can lead to acute pancreatitis.
Lipiduriais a common finding in Nephrotic syndrome. The glomerular capillary wall lost its selective permeability, so anything that resembles protein (hydrophobic) will pass.

D. Acute kidney injury: (acute renal failure)

Seen more in adult patients. (Minimal Change Disease, MCD)
Possible causes:
- Hypovolemia
- Interstitial edema of the kidneys
- ATN
- NSAIDs

E. End Stage Renal Disease (ESRD) if heavy proteinuria not going into remission.

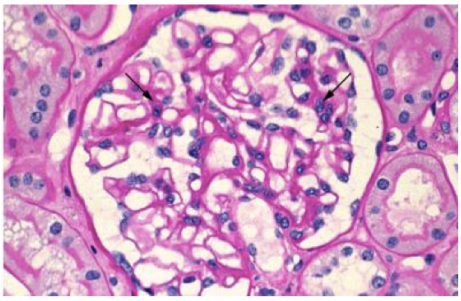
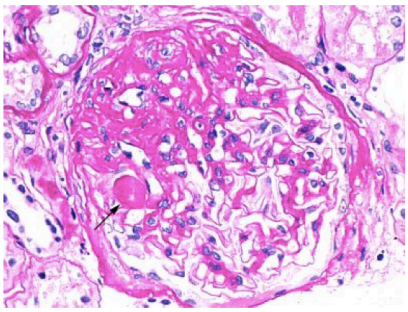
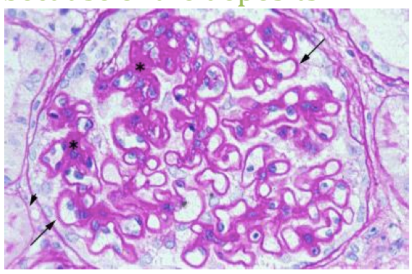
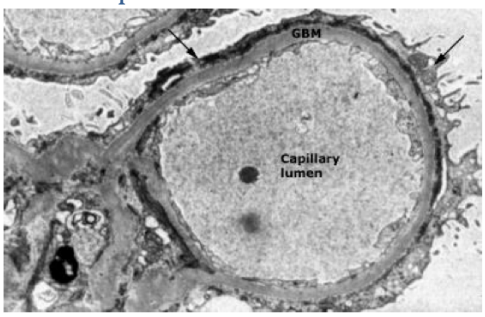
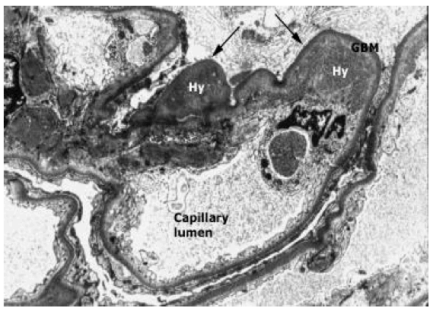
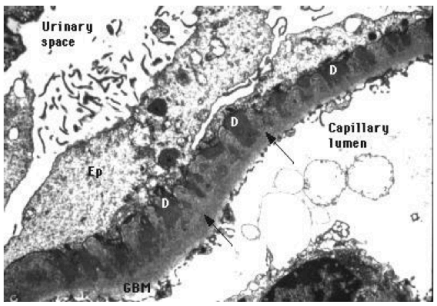
Causes of Nephrotic Syndrome

Approximately 30% is due to systemic diseases (DM, Amyloidosis, SLE)
The rest of NS causes are Primary glomerular diseases:
- Membranous Nephropathy (MN)
- Focal Segmental GlomeruloSclerosis (FSGS)
- Minimal Change Disease (MCD)

Other complications:
- Impaired thyroid function; Low thyroxine-binding globulins
- Vitamin D deficiency
- Proximal Tubular dysfunction
- Protein malnutrition : loss in lean body mass with negative nitrogen balance

Differential Dx:
- Congestive heart failure
- Liver cirrhosis (portal hypertension)
- Protein losing enteropathy
- Protein malnutrition
- Increased capillary permeability due to an allergic reaction

Primary Glomerulopathies:

	Minimal Change Disease	Focal Segmental GlomeruloSclerosis	Membranous Nephropathy
Light Microscopy	is either normal or reveals only mild mesangial cell proliferation So called: nil disease 	Sclerosis 	Diffuse thickening of the glomerular basement membrane (GBM) throughout all glomeruli (IgG and C3 deposits underneath the foot processes causing GBM thickening without inflammation causing podocyte dysfunction and therefore proteins will pass) Capillary loops are thickened because of the deposits 
Electron Microscopy	Diffuse effacement of the epithelial cell foot processes 	foot processes effacement or diffusion and sclerosis 	Thickened GBM 
	Causes Idiopathic Nephrotic syndrome mainly in children: • 90 % of cases in children < 10 years old • > 50 % of cases in older children • typically is corticosteroid responsive in > 90% children, thus kidney biopsy is commonly not done. • 10-25 % of Nephrotic syndrome in adults	• Focal: some glomeruli are affected • Segmental: only a segment of the affected glomerulus is sclerosed. • A more common cause of Nephrotic syndrome in adults (specially African American) • Causes 12 – 35 % of the cases in adults. Depending on the population.	• Most common cause of nephrotic syndrome in adults (15% and 33%) • Mostly secondary in children (hepatitis B antigenemia) from the mother of the child

Presentation	Clinical presentation: • Typically sudden onset Edema • BP may be normal or slightly elevated • Heavy proteinuria, Lipiduria • Hypoalbuminmia • Hyperlipidemia • Creatinine is normal or slightly elevated Diagnosis: Must do kidney biopsy in adult patients with this presentation.	Primary FSGS: • Presents suddenly like MCD with heavy proteinuria and other manifistations of nephrotic syndrome • Typically responds to corticosteroids Secondary FSGS: more common • Proteinuria is less heavy than other causes of nephrotic syndrome. • Albumin is not very low • slowly progressing disease, present late, with high creatinine • Renal impairment is commonly seen	Presentation: slowly developing nephrotic syndrome over a month or two
Etiology	Idiopathic (Primary) or Secondary: • Drugs (NSAIDs, Lithium, Sulfasalazine, Pamidronate, D-penicillamine, some antibiotics) • Neoplasm (Hodgkin Lymphoma, non-Hodgkin lymphoma, and leukemia) • Infections (TB, syphilis) • Allergy	Possible causes of Secondary FSGS: • Massive obesity • Nephron loss (> 75% of renal mass) Hypertension & reflux nephropathy • Renal agenesis • Healing of prior inflammatory injury (IgA, Lupus) • Anabolic steroid abuse • Severe preeclampsia • Drugs: Interferon, Pamidronate, Heroin (IV drug abusers) • Infections: HIV	Idiopathic approximately 75% of cases Secondary: • SLE Class V Lupus Nephritis (10-20%) • Drugs: penicillamine, gold, high dose Captopril, and NSAIDs, Anti-TNF • Infections: Hepatitis B, Hepatitis C, syphilis • Malignancy: solid tumors prostate, lung, or GI track
Treatment	First line: Corticosteroids because it is autoimmune (response 8- 16 weeks) Given x 3-4 months then taper over 6 months Second line: a more potent immunosuppression oral Cyclophosphamide, Cyclosporin or Tacrolimus, Rituximab	**Immunosuppressive therapy is indicated in most patients with primary FSGS** • First line: corticosteroids • Second line: cyclosporine • Third line: MMF (mycophenolate mofetil) Secondary FSGS: not typically treated with Immunosuppression, treat the primary cause and add supportive measures.	Primary MN • Corticosteroids plus • Cyclophosphamide or cyclosporine • Maybe Rituximab Secondary MN • Mainly target the primary disease, and the Nephrotic complications.

Amyloidosis:

Appears in 4 to 17% of idiopathic Nephrotic Syndrome (NS) in adults.

- **Primary amyloidosis: AL**, light chain dyscrasia, fragments of MLC form the amyloid fibrils deposits in kidneys damages GBM and podocytes dysfunction.
- **Secondary amyloidosis: AA**, acute phase reactant serum amyloid A forms the amyloid fibrils due to chronic inflammatory processes, chronic infection TB or osteomyelitis.
- Presentation will be the same in both: Heavy Proteinuria, nephrotic syndrome and renal insufficiency. Fatigue and weight loss.

Glomerulonephritis positive in NS patients:

Nephritic picture with nephrotic symptoms are present in

- Postinfectious glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

General management issues in NS patients

- **Proteinuria**: Heavy proteinuria is toxic to renal tubules must act instead of waiting for the primary treatment to work
    - ❖ lower intra glomerular pressure by angiotensin converting enzyme inhibitor or angiotensin receptor blockers.
- **Edema**; Peripheral edema and ascites is due to primary renal sodium retention
    - ❖ Salt intake restriction
    - ❖ Diuretics (Loop Diuretics, usually high doses)
- **Hyperlipidemia**; Usually resolves with resolution of proteinuria (Accelerate Atherosclerosis)
    - ❖ HMG CoA reductase inhibitor (statin)
    - ❖ Dietary modification
- Prevent infection by vaccination.
- Search for the possible cause of secondary Nephrtic syndrome
    - ❖ ANA to look for underlying SLE
    - ❖ Hepatitis serology Membranous Nephropathy
    - ❖ Protein Electrophoresis Amyloidosis
    - ❖ Complements level Membranous Nephropathy

Summary

- there is no (protein, red blood cells, heme. and cellular casts) in normal urine.
- nephrotic syndrome is characterized by:
  - **Heavy proteinuria**(> 3.5 g/24 hours)
  - **Hypoalbuminemia**<30 g/L (Normal:35-55 g/L)
  - Peripheral or generalized edema
- Nephrotic Syndrome If left untreated will cause potentially fatal complications:
  - Infections & sepsis
  - Thromboembolism
- Hypercoagulability: a venous thrombosis and pulmonary embolism are well known complications of nephrotic syndrome. Hypercoagulability in these cases appears to derive from urinary loss of anticoagulant proteins, such as antithrombin III and plasminogen, along with the simultaneous increase in clotting factors, especially factors I, VII, VIII, and X.
- Malignancy is associated with membranous nephropathy (MN)
- Treatment of primary nephrotic syndrome (MCD, FSGS, MN) immunosuppressive therapy.
- Treatment of secondary nephrotic syndrome: Mainly target the primary disease, and the nephrotic complications.

Extra information: Nephrotic Syndrome can also cause iron, copper and zinc deficiency because of loss of transport proteins. (Kaplan)