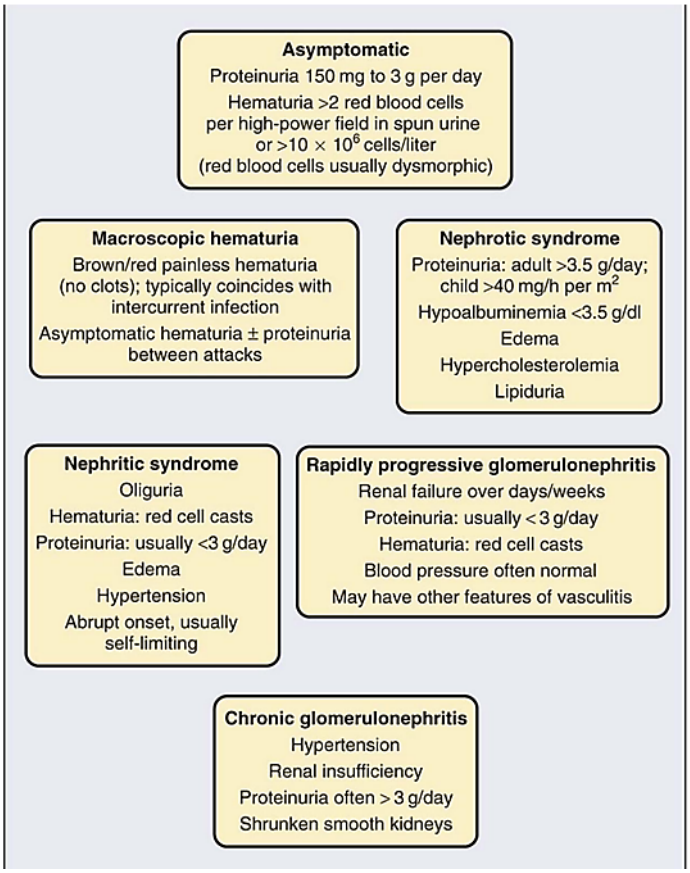
NEPHROLOGY

Clinical presentations of glomerular disease



Glomerular injury:
↓GFR and/or molecules normally not filtered (e.g., blood cells and proteins) are excreted.
Nephrotic urine sediment: fatty casts ("oval fat bodies").
Associated with "Maltese cross" sign.
Nephritic urine sediment: dysmorphic RBCs.
Presence of proteinuria dose not predict response to treatment or prognosis.

Associations:

Morbid obesity → FSGS
Hearing loss → Alport's syndrome
Hemoptysis → Goodpasture syndrome
Xanthelasma →nephrotic syndrome generally
Muehrcke's bands (white nail bands) → nephrotic syndrome generally

NSAIDs and interferon → minimal change disease
Penicillamine, gold, mercury → membranous nephropathy
Pamidronate, heroin, lithium→ FSGS
Cyclosporine, tacrolimus and oral contraceptives → HUS

Solid malignancy (e.g., lung, breast, and GI cancers) → membranous nephropathy
Hodgkin's lymphoma → minimal change disease
Non-Hodgkin's lymphoma → membranous nephropathy

Nephritic syndrome --- hematuria, RBC casts in urine, ↓GFR → oliguria, azotemia, and ↑renin release →HTN
Proteinuria often in the sub-nephrotic range (>3.5 g/day) but in severe cases may be in nephrotic range.

1. **Acute** glomerulonephritis
   Postinfectious glomerulonephritis
   Rapidly progressive glomerulonephritis (RPGN) (crescentic GN)
   Membranoproliferative glomerulonephritis
2. **Chronic** glomerulonephritis
   IgA nephropathy (Mesangioproliferative GN)
   Hereditary nephritis (Alport syndrome)
   Thin basement membrane disease

Postinfectious glomerulonephritis

- Usually with group A beta- hemolytic streptococcus (GAS)
- Onset 1 – 4 weeks after the pharyngitis or impetigo infection.
- Ranges from asymptomatic hematuria with mild proteinuria (50%) to full-blown nephritis with microscopic or gross hematuria (cola-colored, brown, smoky, or frankly bloody urine), proteinuria (sometimes nephrotic-range), HTN, edema, oliguria, and ↓↓GFR. Fluid overload with heart failure and severe hypertension requires dialysis.
- ↑Anti streptolysin O level → recent streptococcal infection (not specific, remains elevated for several months).
- ↓ C3 and total hemolytic complement activity and return to normal within 6 to 8 weeks in 80% of PIGN cases.
- DDx.

Biopsy shows diffuse glomerular proliferation and cellular infiltration. Immunofluorescence (IF) shows granular BM IgG, IgM, C3. Electron microscopy (EM) shows dome shaped subepithelial deposits.

- It has good prognosis and treatment is supportive.
- Antimicrobial therapy is preventive only when given within 36 hours of infection and before PIGN established.

IgA nephropathy (mesangioproliferative GN)

- Deposition of IgA immune complexes in glomeruli.
- **Most common primary glomerulonephritis.**
- It occurs at all ages, with a peak onset in the teens and 20s; affects men 2 to 6 times more frequently than women;
- Familial clustering has also been observed.
- Usually manifested as gross hematuria that begins 1 - 2 days after a febrile mucosal (respiratory, GI) infection. This manifestation carries good prognosis.
- It progresses slowly → 10 years to develop HTN and/or renal insufficiency and 20 years to progress to ESRD.
- Recurs in 20-60% of transplants.
- Risk factors for progressive deterioration in renal function: proteinuria > 1 g/day, elevated serum creatinine, uncontrolled hypertension, persistent microscopic hematuria, extensive fibrotic changes in the glomerulus or interstitium, and crescents on biopsy.
- DDx.
  Biopsy shows IgA mesangial proliferation, focal sclerosis (FSGS).
- Tx.
  ACEI or ARBs for HTN. Corticosteroids for only for progressive disease (creatinine > 1.2 mg/dL and proteinuria >0.5 g/day. Normotensive patients with only mild proteinuria should only take ACEI and omega3.
- ** Honcech-Schonlein Purpura (HSP) vasculitis is characterized by mesangial IgA deposition. Manifested as purpuric skin rash, arthritis, gastrointestinal symptoms (e.g., abdominal pain). It's self-limiting. DDx. by kidney or skin biopsy.

Membranoproliferative glomerulonephritis (MPGN)

- A group of immune-mediated disorders with glomerular basement membrane (GBM) **thickening** and **proliferative** changes on light microscopy.
- Primary variants affect children and young adults (8 – 30 y/o). Secondary variants tend to affect adults (> 30 y/o).
- MOST IMPORTANTLY, it's manifested as nephrotic syndrome in 60 to 80% of cases, and nephritic syndrome (**acute**; especially type II disease).
- **Hypertension develops at first**, followed by renal insufficiency (↓GFR and azotemia).
- Classified based on electron microscopy as follows:
  1) Type I (immune complex mediated; mesangial proliferation with immune subendothelial deposits; granular IF) is seen in (1) **systemic immune disorders** (e.g., SLE, mixed cryoglobulinemia, Sjögren syndrome), (2) **chronic infections** (e.g., endocarditis , HIV, HBV, HCV, visceral abscess, VA shunt infection), (3) **cancers** (e.g., CLL , lymphomas, melanoma), and other systemic disorders, and may also be idiopathic.
  2) Type II (complement mediated (↓C3) **dense deposit disease**) is immune mediated uncontrolled activation of the complement cascade.
  3) Type III is like type I (immune complex mediated) but with subendothelial and subepithelial immune deposits.
- ESRD occurs in 50% of patients at 10 years and in 90% at 20 years
- Type I MPGN recurs in 30% after kidney transplant. Type II MPGN recurs in 90%.
- Outcome tends to be worse if proteinuria is in the nephrotic range.
- Tx.
  Treat the underlying cause. Corticosteroids for children, dipyridamole and aspirin for adults.

Rapidly progressive GN (crescentic GN)

- >50% of sampled glomeruli contain crescents which can be seen in a biopsy specimen.
- If untreated, progresses to ESRD over weeks to months.
- Occurs predominantly in patients **20 to 50 years.**
- Usually insidious, with weakness, fatigue, fever, nausea, vomiting, anorexia, arthralgia, skin rash and abdominal pain.

- About 50% have a history of an acute influenza-like illness within 4 weeks of onset of renal failure, usually followed by severe oliguria.
- Several disease processes may result in RPGN which may be delineated via IF pattern.
    1) Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis; type II hypersensitivity reaction. Treatment: plasmapheresis.
    2) Negative IF/Pauci-immune (no Ig/C3 deposition): granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)—PR3-ANCA/c-ANCA, eosinophilic granulomatosis with polyangiitis, or microscopic polyangiitis—MPO-ANCA/p-ANCA.
    3) **Granular** IF— idiopathic or secondary to autoimmune disease or from another GN (e.g., **SLE**, IgA nephropathy, **postinfectious GN**).

Nephrotic syndrome— proteinuria > 3.5g protein / day, hypoalbuminemia < 3.5 g/dl, edema, hypercholesterolemia, and lipiduria

Minimal change disease (MCD), Membranous nephropathy (MN), and Focal segmental glomerulosclerosis (FSGS)

Factors Associated with the Onset of Nephrotic Syndrome in Minimal Change Disease
Drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Interferon alfa
Lithium: rare (usually causes chronic interstitial nephritis)
Gold: rare (usually causes membranous nephropathy)
Allergy
Pollens
House dust
Insect stings
Immunizations
Malignancy
Hodgkin's disease
Mycosis fungoides
Chronic lymphocytic leukemia: uncommon (usually associated with membranoproliferative glomerulonephritis)

Minimal change disease (MCD)

- Commonest cause of nephrotic syndrome in children 4-8 years.
- Most cases are idiopathic, it can be secondary, see →
- Unexplained nephrotic-range proteinuria with normal renal function.
- DDx.
  In adults, biopsy → Lack of glomerular changes on light microscopy and no immune deposits. Electron microscopy shows effacement (fusion) of podocyte foot processes.
  In children, based on the typical presentation.
- Tx.
  Good response to steroids.
  Recurrence is common, in this case try giving them cyclophosphamide, chlorambucil, mycophenolate, rituximab, and tacrolimus.

Membranous nephropathy (MN)

Clinical Features of Membranous Nephropathy
Rare in children – <5% of total cases of nephrotic syndrome
Common in adults – 15% to 50% of total cases of nephrotic syndrome, depending on age. Increasing frequency after age 40 years.
Males > females in all adults groups
Caucasians > Asians > African-Americans > Hispanics
Nephrotic syndrome in 60% to 70%
Normal or mildly elevated BP at presentation
"Benign" urinary sediment
Non-selective proteinuria
Tendency to thromboembolic disease (DVT, RVT, PE)
Secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

- The most common cause of nephrotic syndrome in adults.
- Idiopathic (85%) or secondary (15%).
- It can be secondary to certain drugs (e.g., penicillamine, gold, mercury), infections (HIV, syphilis, HBV, HCV), autoimmune diseases (e.g., SLE, thyroiditis), solid malignancies, parasitic diseases (e.g., malaria, schistosomiasis, leishmaniasis).
- MN in a child? → think of HBV or SLE.
- Deep vein thrombosis is frequent in MN. Renal vein can occur causing flank pain, hematuria, and HTN.
- Anti-Phospholipase A2 receptor (anti-PLA2R) antibody is usually present. Nephrotic pattern of urinalysis and lab results is usually present too. GFR is normal or decreased.
  ¼ → spontaneous remission, ¼ → persistent, non-nephrotic–range proteinuria, ¼ → persistent nephrotic syndrome, and ¼ → to end-stage renal disease.
- Risk of progression to renal failure is highest among patients with persistent proteinuria ≥ 8 g/day, particularly men age > 50 years, and/or an elevated serum creatinine level at presentation or diagnosis .
- DDx.
  Biopsy → interstitial inflammation, "Spike and dome" appearance of subepithelial immune deposits (IgG, and C3), granular immune fluorescence pattern, and diffusely thickened GBM.
- Tx.

Asymptomatic with non-nephrotic–range proteinuria → monitor renal function only (e.g., twice yearly).
Nephrotic-range proteinuria w or w/out symptoms (e.g., edema, HTN)→ Angiotensin inhibition, sodium restriction, statins, diuretics.

Focal segmental glomerulosclerosis (FSGS)

- The most common cause of idiopathic (or primary) **nephrotic syndrome** among adults is **FSGS**. It can be secondary to certain drugs (e.g., pamidronate, heroin, lithium), atheroembolic disease, morbid obesity, HIV infection, renal hypoplasia (e.g., oligomeganephronia), subtotal nephrectomy, reflux nephropathy, and familial cases.
- It has poor prognosis (especially in adults; it hates large people (adults and obese)) and often progresses to ESRD (CRF then ESRD) which is more likely if the patient has significant tubulointerstitial fibrosis →requiring renal transplant → then it recurs in 25-50% renal transplants.
- Pregnancy may exacerbate FSGS.
- DDx.

  Suspect FSGS in patients with nephrotic syndrome or renal dysfunction with no obvious cause.
  Biopsy is diagnostic; LM shows segmental sclerosis (some glomeruli are sclerotic, others are normal). IF shows IgM, C3 deposits (maybe negative). EM shows effacement of podocyte foot processes (like MCD).
  Tx.
  Angiotensin inhibition, corticosteroids, and sometimes cytotoxic drugs. Treatment often is not effective.
