Nephrotic Syndrome

Clinical definition:
- Hallmark of syndrome is presence of edema with hypoalbuminemia and severe proteinuria (>3.5 gms/day) with otherwise bland urine sediment.
- Associated with hyperlipidemia, hypercoaguable state (both arterial and venous thromboembolism, commonly renal vein thrombosis (30%) and pulmonary embolism (30%), susceptibility to severe infections, protein malnutrition, iron resistant microcytic anemia, hypocalcemia and thyroid abnormalities

Pathophysiology:
- Edema: primary increased renal salt retention at distal collecting duct.
- Proteinuria: altered permeability of the glomerular basement membrane and epithelial podocytes (both charge selective and size selective barriers) allowing passage of plasma protein molecules >70 kd.
- Hyperlipidemia: reduced oncotic pressure trigger the increase of hepatic lipoprotein synthesis, urinary loss of lipid homeostasis regulators result in net increase levels of VLDL, LDL
- Hypercoaguable state: urinary loss of natural anticoagulants (ATII), altered activity of protein C & S, impaired fibrinolysis, increased levels of fibrinogen and platelet aggregation.
- Susceptibility to infection: urinary loss of immunoglobulins
- Anemia: urinary loss of transferrin
- Hypocalcemia: after correcting for low albumin, there may be urinary loss of cholecalciferol binding protein leading to vit D deficiency, hypocalcemia and secondary hyperparathyroidism
- Thyroid abnormalities: loss of thyroid binding globulin, clinically euthyroid

Etiologies:

Minimal change disease (90% children, 15% adults)
- Clinical: 20% cases with micro hematuria, rare HTN or renal insufficiency
- DDX: primary(majority) or secondary to drugs (NSAIDS, rifampin, interferon alpha) and Hodgkin’s disease
- Mechanism: T-lymphocyte releases cytokines injure epithelial cell, resulting in decrease production of polyanions that maintain the charge selective barrier.
- Pathology: light microscopy may be normal or reveal mild mesangial proliferation, EM reveals diffuse effacement of visceral epithelial cell foot processes, IF negative
- Treatment: highly steroid responsive (50% remission post 8 weeks, 90% post 24 weeks), however, if steroid dependant or frequent relapses, cyclophosphamide or chlorambucil may be used, excellent prognosis.

Focal segmental glomerular sclerosis (33% adults, of these 50% African Americans)
- Clinical: acute nephrotic syndrome except in cases of secondary disease where may be more mild.
- DDX: primary(majority) or secondary due to HIV, heroin use or any condition resulting chronic nephron loss (unilateral renal agenesis, surgical resection, reflux nephropathy, resolving GN or tubular interstitial nephritis), obesity with sleep apnea, post renal transplant
- Mechanism: unclear, possible spectrum of MCD.
- Pathology: light micro reveals sclerosis with hyalinosis of segments of less than 50% glomeruli, EM reveals damage of visceral epithelial cells including effacement of foot processes, detachment, degeneration and necrosis, IF negative
- Treatment: steroids responsive (20-40% remission post 8 weeks, 70% post 24 weeks), cyclophosphamide in frequent relapsers who are steroid responsive, poorer prognosis.

Membranous nephropathy
- Clinical: 30-50 yo, male>female (2:1), acute nephrotic syndrome, hematuria is common
- DDX: primary(majority) and secondary due to systemic autoimmune diseases (SLE, RA, Sjogrens, MCTD, Ankylosing spondylitis, PBS, Graves, Myasthenia gravis), infections (Hep B/C, secondary
**syphilis**, malaria, schistosomiasis, filariasis, enterococcal endocarditis), solid malignancies (breast, lung, colon, gastric, renal cell, melanoma), drugs (NSAID, captopril, gold), and sarcoidosis

- **mechanism:** unclear, autoimmune
- **Pathology:** light micro reveals diffuse thickening of GBM, positive PAS stain, with characteristic spikes, EM reveals subepithelial immune deposits, IF positive for granular deposition of IgG, C3, C5b-9.
- **Treatment:** steroid resistant, 40% spontaneous remission, 40% frequent relapses, 10-20% progressive disease to ESRD. Conservative treatment is indicated unless high-risk patient with renal insufficiency and severe proteinuria may try immunosuppressive agent.

**Membranous proliferative glomerulonephritis**

- **Clinical:** acute nephrotic syndrome with active sediment
- **DDX:** primary or secondary to due infection (hep B/C, HIV endocarditis, visceral abscesses), neoplasm (lymphoma, leukemia), CVD (SLE, sjogrens) and drugs (heroin) or sarcoidosis.
- **Mechanism:** type I immune complex GN, type II autoimmune IgG antibody to C3 convertase
- **Pathology:** light micro reveals diffuse increase of mesangial matrix and thickening GBM, type I on EM reveals subendothelium and mesangial deposits with positive IF for C3, IgG, IgM, and type II on EM reveals GBM deposits positive for C3 but no Ig’s.
- **Treatment:** steroid resistant, type I 70% benign course, type II variable course.

**Amyloidosis**

**AN APPROACH TO INITIAL EVALUATION**

- Confirm clinical syndrome with 24 hour protein
- Assess for secondary causes (MEDS, HIV, HEROIN, HEPATITIS B &C, RPR, ANA)
- If none, get renal biopsy, for appropriate treatment and prognosis.

**MANAGEMENT ISSUES**

- Anti-inflammatory: MCD and FSGS are highly steroid responsive, if not proceed to alkylating and immunosuppressive agents. Membranous and MPGN steroid resistant watch and wait.
- **Ace inhibitors:** decreases proteinuria
- **Diuresis:** high dose of lasix needed for effect because or resistance, may need thiazide added
- **Anticoagulation:** no good trials supporting prophylaxis, but may be considered in highest risk groups (those with membranous, severe proteinuria and alb <2), treatment of known thromboembolism with heparin and coumadin must be continued until nephrotic syndrome resolved.
- **Anti lipid treatment:** Use a statin for cardiac disease prevention.
- **Vaccinations:** pneumococcal vaccination is recommended
- **Drug interactions:** less albumin results in increased free drug levels, seen with prednisilone, warfarin

Harrison’s Text of Internal Medicine, 15th edition, pp. 1585-1600.
Up to Date Nephrotic syndrome 2002.