Nephrotic Syndrome

Nephrotic syndrome implies a fundamental distortion to the filtration barrier in the glomerulus allowing proteins that would normally not enter the urinary filtrate to enter the Bowman's space.

Definition of nephrotic syndrome

- Proteinuria >3.5 g day
- Hypoalbunimaemia
- Oedema
- As well as but not always:
    - Hyperlipidaemia: Low oncotic pressure is a driver for increased lipid synthesis (mainly LDL and cholesterol for a yet undetermined reason)
    - Lipiduria: As above
    - Thrombotic tendency : Loss of anti-thrombotic proteins (Antithrombin III/plasminogen)in the filtrate coupled with a increased liver production of clotting factors

Causes of nephrotic syndrome

- Primary glomerular disorders:
    - Membranous (most common in adults)
    - Minimal change disease (most common in children)
    - Focal and segmental glomerulosclerosis
    - Mesangiocapillary
    - IgA nephropathy

- Secondary causes
    - Diabetic nephropathy
    - SLE (class V)
    - Amyloidosis
    - Hepatitis B/C (tends to be membranous)
    - HIV: classically looks like FSGS on biopsy
    - Paraneoplastic
    - Drugs: NSAIDs, penicillamine, anti-TNF, gold

Differential of nephrotic syndrome:

- Heart failure: History of heart disease, S3 on exam, little Proteinuria and echocardiogram findings (or positive BNP)
- Cirrhosis: No Proteinuria and history of causative agent

History in nephrotic syndrome

- Presenting complaint
    - Oedema
    - Foaming urine
    - Thrombotic complication: PE/DVT etc
- History of presenting complaint
    - Look for a secondary cause:
        - Recent infections? Jaundice? Tattoos? Risky sexual practice? IVDU? (Hepatitis)
        - New medications: causes as above
        - Systemic symptoms of malignancy or autoimmune condition (Type B symptoms, rash, fatigue etc)
        - Known or new diagnosis of diabetes
        - Chronic infective/inflammatory disease or plasma cell dyscrasia (amyloidosis)

- Nephrotic history:
  - Frothy urine
  - Increasing oedema (face, legs, abdomen etc)
  - Thrombotic event?
  - Infections (increase loss of immunoglobulins increases infection rate)
  - Cardiac history: cholesterol
- Past medical history
  - Diabetes
  - Hepatitis or HIV
  - Autoimmune disease or malignancy
  - Rheumatological disease requiring treatment now or in the past
  - SLE
  - Disease known to cause amyloidosis
- Medications
  - NSAIDs, penicillamine, anti-TNF, gold
- Allergies
- Family history
  - There are inherited versions of most nephrotic glomerulonephrities
- Social history
  - Smoking or other risk factors for malignancy
  - Ideas; concerns; expectations

Examination in nephrotic syndrome

- Assessment of oedema and sequelae of renal disease
- Full set of observations especially looking for hypertension (a rare but poor prognostic marker in nephrotic syndrome)
- Oedema (may be periorbital – least tissue resistance, but don't forget sacrum and legs)
- Look for
  - Ascites
    - Other signs of chronic liver disease as part of differential
  - Cardiac examination
    - Third heart sound as both a sign of fluid overload as well as investigating CCF as part of the differential
  - Lymphadenopathy (infection or malignancy)
  - Nails
    - Meuhrcke's lines
      - Transverse lines across nail bed which do not move with nail growth (just hypopigmentation underneath)
    - Mee's lines affect the matrix so move with nail growth
      - Hodgkins, chemotherapy and periods of being unwell
    - Leukonychia
      - All chronic diseases can give this
  - Pleural effusions/pulmonary oedema
  - Testicular/labia oedema
- Clinical signs of aetiology and risk of disease
  - Fundoscopy in patients with diabetes: Nephropathy is nearly always present in those with retinopathy

- Systemic disease signs: cachexia, wasting, rashes, other skin changes etc.

Investigations in nephrotic syndrome

- Confirm the diagnosis:
  - Urine dip: +++ Protein (blood is rare, keep eye out for glucosuria)
  - Do a formal 24 hour urine collection (>3.5g/day) or spot urine protein:creatinie ratio (>2g/g which is equivalent to 3g protein/day)
  - Serum albumin (less then 20g confers greater thromboembolic risk)
- Bloods
  - Serum urea and electrolytes, FBC, LFTS, bone profile, total serum protein.
    - It is rare for there to be renal function impairment
  - Fasting lipid profile
  - Immune screen and infective screen
    - Immunoglobulins, HIV, Hepatitis B+C, ANA, anti-ds DNA, complement
  - Phospholipase A2 – idiopathic membranous nephropathy – correlates with disease activity
- Urine
  - Urine microscopy for casts
  - In children urinary selectivity index allows one to look into the size of proteins lost and hence assess the degree of glomerular damage (biopsies tend not to be done in the 1st instance in children)
- Imaging
  - USS renal tract
- Renal biopsy (not necessarily in children or if an adult has a very obvious cause such as poorly controlled diabetes)
- Genetic testing in infants may be considered (See Renal Genetics section):
  - NPHS1 and NPHS2 mutations – encode mutated forms of nephrin and podocin
  - NPHS1 is found in Finnish type nephrotic syndrome
  - NPHS2 is found in steroid resistant nephrotic syndrome

Initial management of nephrotic syndrome

- Oedema:
  - Careful monitoring using weight
  - Salt restrict to less than 2g/day
  - Diuretics such as furosemide – if very oedematous (implicating gut oedema) then IV may be considered. Start at 40mg/day Furosemide
  - Thiazide diuretics as an adjunct – needs U+Es monitoring
  - Albumin is sometimes given alongside this but its efficacy has not been proven

- Proteinuria
  - Causes infection and malnutrition
  - ACE-I or ARBs are 1st line
  - Evidence does not support dual administration of an ACE-I and ARB
  - Supplementary protein diets are of no proven value (ensure adequate protein intake)

- Hypercoagulability
  - If deemed to be high risk (albumin <20g/L, long duration of illness, significant proteinuria, membranous nephropathy) then prophylactic subcut heparin may be indicated
  - If known previous thrombotic disease warfarinisation may be indicated (INR 2-3)

- Infection

- Vaccinate persistently nephrotic patients – some advocate low dose prophylactic penicillin
- Treat any infection promptly (cover for encapsulated organisms)

- Hyperlipidaemia
  - Statins are of use, but if patient remains nephrotic the hyperlipidaemia will persist.

Further management of nephrotic syndrome

- Please see section of glomerulonephritis for specific primary causes
- Secondary causes need to have the underlying disease process treated