Definition

A clinical syndrome characterised by heavy proteinuria, hypoalbuminaemia (albumin < 25g/l), oedema and hypercholesterolemia. Nephrotic range proteinuria is >40mg/hr/m² or a first morning urine protein to creatinine ratio is >200mg/mmol (normal <20).
Nephrotic syndrome may be primary/ idiopathic (INS):
- minimal change disease (MCD)
- focal segmental glomerulosclerosis (FSGS)
- membranoproliferative glomerulonephritis (MPGN)
- membranous glomerulopathy (MGN)
or secondary to infections, medications or systemic disease (eg lupus or malignancy).

Epidemiology

INS has its peak incidence in early childhood, median age of diagnosis 2.5 years for MCD and 6 for FSGS. Male to female ratio 3:2 in young children. MCD and FSGS may be familial.

Clinical Features

- Proteinuria occurs first, followed by oedema which develops either slowly over a few weeks or rapidly over days.
- Accumulation of fluid in body cavities also occurs.
- Hypertension occurs in 15% at onset of MCD and in 33% of FSGS patients.
- Microscopic haematuria present in 23% of MCD and 48% of FSGS.

Laboratory Features

- Serum albumin < 25g/l
- Haematocrit may be elevated because of intravascular volume contraction.
- Urine microscopy – waxy casts, fat droplets, few red cells.
- Plasma creatinine is usually normal but may be transiently raised in MCD at presentation or in the setting of severe intravascular volume contraction.
- Hypercholesterolaemia.
- If atypical features are present (e.g. age <12 months or >12 years, persistent hypertension, impaired renal function, macroscopic haematuria, signs of systemic illness) measure complement C3, C4 and ANA.
Complications

Hypovolaemia

- Occurs early in relapse as oedema is accumulating.
- May be precipitated by sepsis, aggressive diuretic usage, drainage of ascites.
- May present as acute abdomen, tachycardia, hypertension or hypotension as a late sign. Postural blood pressure change should be assessed.

Infection

Children with INS are at increased risk of infection with encapsulated bacterial organisms (Pneumococcus, H. Influenzae). Infection with gram negative organisms and Varicella zoster may be more severe in those on steroids.

Thrombosis

Deep veins of legs, pulmonary emboli, renal vein thrombosis. Increased risk during relapses, especially in the context of hypovolaemia.

Acute renal failure

Usually due to hypovolaemia. Other causes are renal vein thrombosis and interstitial nephritis secondary to diuretics, and some antibiotics.

Chronic renal failure

Up to 30% FSGS progress to end stage renal failure within 5 years of diagnosis.

Definitions of Response to Treatment

Remission

Urine protein excretion <4mg/hr/m² or albustix is negative/trace for 3 consecutive days.

Relapse

Proteinuria on dipstick 3+ for 3 consecutive days after having been in remission. This is common, occurring in up to 75% of patients.

Frequent Relapse

2 more relapses within 6 months or > 4 relapses in 12 months.

Steroid Dependence

2 consecutive relapses occurring during steroid treatment or within 14 days of its cessation.
NEPHROTIC SYNDROME IN CHILDHOOD

Steroid Resistance
Failure to achieve response after 28 days of steroid at 60mg/m²/day followed by 3 pulses of intravenous methylprednisolone (10mg/kg/dose to maximum 700mg on alternate days).

NOTE – some experts define steroid resistance after 8 weeks of daily high dose prednisone.

Discussion with Nephrology should be made if no response at 28 days to arrange for biopsy within 8 weeks from onset. They will advise re continued steroid therapy whilst awaiting biopsy on a case by case basis.

Management

Diet
Normal protein intake
Salt restriction during relapses

Antibiotics
Oral penicillin should be given during both initial illness and relapses. Pneumococcus is the most common bacteria causing infection. If peritonitis suspected, cover gram negative organisms as well.

Diuretics
Careful use of frusemide only in the absence of hypovolaemia, if fluid restriction (e.g. 70% maintenance) and salt restriction alone not effective in controlling oedema formation

IV Albumin
Only for clinical evidence of hypovolaemia or severe oedema.
Maximum dose 1g/kg of 20%albumin over minimum of 4 hours.
If given for severe oedema, follow infusion with IV frusemide 2-3 mg/kg/dose.
Complications: hypertension, hyponatraemia, hypokalaemia, pulmonary oedema.
If patient has evidence of renal impairment discuss with Nephrology prior to IV albumin use

Steroid Therapy
This is the mainstay of treatment and should be commenced once the diagnosis is established (see below). If concerned re possibility of secondary nephrotic syndrome please discuss with nephrology prior to commencing steroid therapy. Many patients require the addition of gastroprotective medication whilst on high dose steroids.

Steroid therapy for first presentation:
We favour at least 20 weeks of therapy.
- Prednisone or Prednisolone - start at 60mg/m²/day (max 80mg) in a single daily dose to complete a total of 42 days.
- Then switch to alternate day therapy at 40mg/ m²/day (max 60mg) for further 42 days.
- Then wean steroid dose gradually over 8-10 weeks and stop.
- Total treatment duration of first presentation for at least 20 weeks.
Steroid therapy for relapses:

**Infrequent Relapses**
Prednisone or prednisolone - start at 60mg/ m²/day (max 80mg) until in remission. Then give alternate day prednisone or prednisolone at 40mg/ m²/day (max 60mg) for total of 28 days, then stop. Children having <2-3 relapses per year can be managed with repeated courses of prednisone, providing they have a complete response to treatment each time.

**Frequently relapsing or Steroid Dependent**
Consider alternate day prednisone 0.3-0.75mg/kg for 4-6 months, at the lowest dose to avoid side effects. After 4-6 months therapy, slow taper to attempt cessation of steroid therapy.

For patients whose relapses are precipitated by URTI or other infections whilst on alternate day steroid, increasing the alternate day dose to daily at the onset of the illness will reduce the risk of relapse. Seasonal influenza vaccine recommended for these patients.

If relapses continue despite alternate day steroids >1.0mg/kg or steroid related adverse effects develop, referral to Nephrology is indicated for consideration of alternative immunosuppressive therapy.

**Vaccinations**
Recommend updating routine vaccination schedule if not up to date (in particular pneumococcal) and assessment of Varicella serology.

**Pneumococcal:**
Children with nephrotic syndrome under the age of 5 years are currently eligible for funded pneumococcal vaccines PCV13 and 23PPV (high risk condition listed under Ministry of Health Immunisation Schedule 2011). Use of steroids has not been found to alter the serological response to pneumococcal vaccine in these children, therefore there is no reason to delay this or other non-live vaccinations.

**Varicella Zoster:**
If non-immune to Varicella and have a chickenpox contact whilst actively nephrotic and/or on steroid therapy recommend consideration of immunoglobulin. Do not give live vaccinations whilst on long term or high dose corticosteroids (refer to NZ Immunisation Handbook).
Nephrotic Syndrome in Childhood

Indications for referral to Nephrologist for Renal Biopsy

- Steroid resistance.
- Impaired renal function with normal volume status.
- Initial macroscopic haematuria.
- Persistent microscopic haematuria if associated with hypertension.
- Onset less than 12 months of age or greater than 12 years of age.
- Low C3.

Recommended Resources for Patient/Parent Information

http://www.kidneys.co.nz/resources/file/Nephrotic%20syndrome%20in%20children_03.pdf

http://www.medicinesforchildren.org.uk/search-for-a-leaflet/cyclophosphamide-for-nephrotic-syndrome/

http://www.medicinesforchildren.org.uk/search-for-a-leaflet/ciclosporin-for-nephrotic-syndrome/

References


