

IDIOPATHIC NEPHROTIC SYNDROME

Diagnosis

Nephrotic syndrome is a clinical syndrome of massive proteinuria defined by

- oedema
 - proteinuria $> 40 \text{ mg/m}^2/\text{hour}$ ($> 1 \text{ g/m}^2/\text{day}$) or an early morning urine protein creatinine index of $> 200 \text{ mg/mmol}$ ($> 3.5 \text{ mg/mg}$)
- hypoalbuminaemia of $< 25 \text{ g/l}$
hypercholesterolaemia

Aetiology

Primary or idiopathic (of unknown cause) nephrotic syndrome is the commonest type of nephrotic syndrome in children.

Secondary causes of nephrotic syndrome include post-streptococcal glomerulonephritis and systemic lupus erythematosus (SLE). This chapter outlines the management of idiopathic nephrotic syndrome. Management of secondary forms of nephrotic syndrome follows the management of the primary condition.

Investigations at initial presentation

- full blood count
- renal profile
 - urea, electrolyte, creatinine
- quantitative urinary protein excretion (*spot urine protein: creatinine ratio or 24 hour urine protein*)
- serum cholesterol
- liver function tests
 - particularly serum albumin
- urinalysis, urine culture

Other investigations would depend on the age of the patient, associated renal impairment, hematuria, hypertension or features to suggest an underlying *secondary* cause for the nephrotic syndrome.

These tests include:

- antinuclear factor / anti-dsDNA to exclude SLE
- serum complement (C3, C4) level to exclude SLE and post infectious glomerulonephritis
- ASOT titres to exclude post streptococcal glomerulonephritis.
- other tests as indicated.

Renal biopsy

A renal biopsy is not needed prior to starting corticosteroid or cyclophosphamide therapy. This is because 80% of children with idiopathic nephrotic syndrome have minimal change steroid responsive disease.

The main indication for renal biopsy is steroid resistant nephrotic syndrome, defined as *failure to achieve remission despite 4 weeks of adequate corticosteroid therapy*.

Other indications are features that suggest non-minimal change nephrotic syndrome:
- persistent hypertension, renal impairment, and/or gross haematuria.

Management

- confirm that patient has nephrotic syndrome by ensuring that the patient fulfills the criteria above
- exclude other causes of nephrotic syndrome. If none, then the child probably has idiopathic nephrotic syndrome

General management

- a normal protein diet with adequate calories is recommended.
- no added salt to the diet when child has oedema.
- Penicillin V 125 mg BD (1-5 years age), 250 mg BD (6-12 years), 500 mg BD (>12 years) is recommended at diagnosis and during relapses, particularly in the presence of gross oedema
- careful assessment of the haemodynamic status.
 - check for signs and symptoms which may indicate
 - hypovolaemia*: abdominal pain, cold peripheries, poor capillary refill, poor pulse volume with or without low blood pressure; *OR*
 - hypervolaemia*: basal lung crepitations, rhonchi, hepatomegaly, hypertension
 - fluid restriction - not recommended except in chronic oedematous states
- diuretics (e.g. frusemide) is not necessary in steroid responsive nephrotic syndrome but if required, use with caution as it can precipitate hypovolaemia
- human albumin (20-25%) at 0.5 - 1.0 g/kg can be used in symptomatic grossly oedematous states together with IV frusemide at 1-2 mg/kg to produce a diuresis
Caution: fluid overload and pulmonary oedema can occur with albumin infusion especially in those with impaired renal function. Urine output and blood pressure should be closely monitored

General advice

- counsel patient and parents about the disease particularly with regards to the high probability (85-95%) of relapse
- home urine albumin monitoring: once daily dipstick testing of the first morning urine specimen. The patient is advised to consult the doctor if albuminuria > 2+ for 3 consecutive days, or 3 out of 7 days.
- the child is also advised to consult the doctor should he/she become oedematous regardless of the urine dipstick result.
- children on systemic corticosteroids or other immunosuppressive agents should be advised and cautioned about contact with chickenpox and measles, and if exposed should be treated like any immunocompromised child who has come into contact with these diseases.
- immunisation:
 - while the child is on corticosteroid treatment and within 6 weeks after its cessation, only killed vaccines may safely be administered to the child. Live vaccines can be given 6 weeks after cessation of corticosteroid therapy.
 - pneumococcal vaccine should be administered to all children with nephrotic syndrome. If possible, give when the child is in remission.
- *acute adrenal crisis*
this may be seen in children who have been on long term corticosteroid therapy (equivalent to 18 mg/m² of cortisone daily) when they undergo situations of stress. Hydrocortisone at 2-4 mg/kg/dose TDS or prednisolone at 1 mg/kg/day should be given.

Management of the complications of nephrotic syndrome

Hypovolaemia.

- clinical features: abdominal pain, cold peripheries, poor pulse volume, hypotension, and haemoconcentration.
- treatment: infuse human albumin at 0.5 to 1.0 g/kg/dose fast.
If human albumin is not available, other volume expanders like human plasma can be used. Do not give frusemide.

Primary Peritonitis

- clinical features: fever, abdominal pain and tenderness in children with newly diagnosed or relapse nephrotic syndrome.
- investigations: Blood culture, peritoneal fluid culture (not usually done)
- treatment: parenteral penicillin and a third generation cephalosporin

Thrombosis

- thorough investigation and adequate treatment with anticoagulation is usually needed. Please consult the paediatric nephrologists.

Corticosteroid therapy

Corticosteroids are effective in inducing remission of idiopathic nephrotic syndrome.

Initial treatment

- once a diagnosis of idiopathic nephrotic syndrome has been established, oral prednisolone should be started at:
 - 60 mg / m² / day (maximum 80 mg / day) for 4 weeks followed by
 - 40 mg / m² / every alternate morning (EOD) (maximum 60 mg) for 4 weeks.then reduce prednisolone dose by 25% monthly over next 4 months.
- with this corticosteroid regime, 80% of children will achieve remission (defined as urine dipstix trace or nil for 3 consecutive days) within 28 days.
- children with *steroid resistant* nephrotic syndrome, defined by failure to achieve response to an initial 4 weeks treatment with prednisolone 60 mg/m²/ day, should be referred to a nephrologist for further management, which usually includes renal biopsy.

Treatment of relapses

- the majority of children with nephrotic syndrome will relapse.
A relapse is defined by *urine albumin excretion > 40 mg/m²/hour or urine dipstix of ≥ 2+ for 3 consecutive days.*
- these children do not need admission unless they are grossly oedematous or have any of the complications of nephrotic syndrome.
- induction of relapse is with oral prednisolone as follows:
 - 60 mg / m² / day (maximum 80 mg / day) *until remission* followed by
 - 40 mg / m² / EOD (maximum 60 mg) for 4 weeks only

Breakthrough proteinuria may occur with intercurrent infection and usually does not require corticosteroid induction if the child has no oedema, remains well and the proteinuria remits with resolution of the infection.

However, if proteinuria persists, treat as a relapse.

Treatment of frequent relapses

- defined as ≥ 2 relapses within 6 months of initial diagnosis or ≥ 4 relapses within any 12 month period.

Treatment

- induction of relapse is with oral prednisolone as follows:
 - 60 mg / m² / day (maximum 80 mg / day) until remission followed by
 - 40 mg / m² / EOD (maximum 60 mg) for 4 weeks only
- taper prednisolone dose every 2 weeks and keep on *as low an alternate day dose as possible for 6 months*. Should a child relapse while on low dose alternate day prednisolone, the child should be re-induced with prednisolone as for relapse.

Treatment of steroid dependent nephrotic syndrome

- defined as ≥ 2 consecutive relapses occurring during steroid taper or within 14 days of the cessation of steroids.

Treatment

- if the child is not steroid toxic, re-induce with steroids and maintain on *as low a dose of alternate day prednisolone as possible*. If the child is steroid toxic (short stature, striae, cataracts, glaucoma, severe cushingoid features) *consider cyclophosphamide therapy*

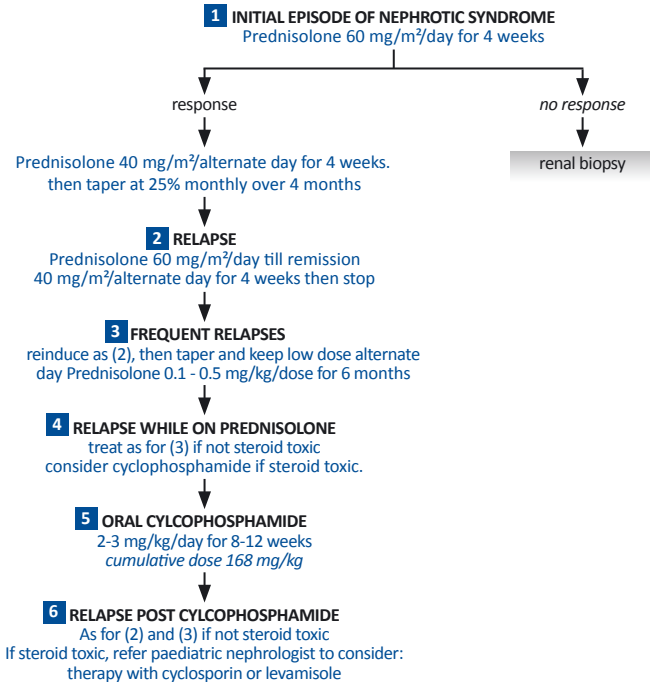
Cyclophosphamide therapy

- indicated for the treatment of steroid dependent nephrotic syndrome with signs of steroid toxicity; begin therapy when in remission after induction with corticosteroids
- parents should be counseled about the effectiveness and side effects of cyclophosphamide therapy (leucopenia, alopecia, haemorrhagic cystitis, gonadal toxicity).
 - dose: 2-3 mg/kg/day for 8-12 weeks (cumulative dose 168 mg/kg)
 - monitor full blood count and urinalysis 2 weekly

Relapses post cyclophosphamide

- relapses after a course of cyclophosphamide are treated as for relapses following the initial diagnosis of nephrotic syndrome, if the child does not have signs of steroid toxicity
- should the relapse occur soon after a course of cyclophosphamide when the child is still steroid toxic, or if the child again becomes steroid toxic after multiple relapses, then a paediatric nephrology opinion should be sought. The treatment options available include cyclosporine and levamisole.

Figure 1. Summary of treatment of nephrotic



Steroid resistant nephrotic syndrome

Refer for renal biopsy. Specific treatment will depend on the histopathology.

General management of the nephrotic state

- control of edema:
 - restriction of dietary sodium.
 - diuretics e.g. frusemide, spironolactone.
- ACE inhibitor e.g. captopril or angiotensin II receptor blocker (AII RB) e.g. losartan, irbesartan, to reduce proteinuria
monitor BP and renal profile 1-2 weeks after initiation of ACE inhibitor or AII RB
- control of hypertension – antihypertensive of choice – ACE inhibitor/AII RB
- penicillin prophylaxis.
- monitor renal function.
- nutrition: normal dietary protein content, salt-restricted diet
- evaluate calcium and phosphate metabolism.