MANAGEMENT OF STEROID SENSITIVE NEPHROTIC SYNDROME IN CHILDREN

Contents

GUIDELINES FOR MANAGEMENT OF STEROID SENSITIVE NEPHROTIC SYNDROME IN CHILDREN

AIM

The aim of these guidelines is to provide evidence based recommendations to paediatricians in the management of the initial episode of nephrotic syndrome and subsequent follow up.

INTRODUCTION

It is now evident that the long term outcome of minimal change nephrotic syndrome is dependent on the adequacy/ inadequacy of treatment of the initial episode. A consensus has not yet been reached regarding the best steroid regimen for treatment of the initial episode. These guidelines are based on the evidence currently available.

1. DEFINITIONS

Nephrotic syndrome:
Oedema, hypoalbuminaemia (<25g/l) and proteinuria > 40mg/m^2/hour or protein/ creatinine ratio > 200mg/mmol

Remission:
Urinary protein excretion <4mg/m^2/hour or reagent strip / sulphosalicylic acid test negative or trace for 3 consecutive days

Relapse:
Urinary protein excretion >40mg / m^2/hr or reagent strip / sulphosalicylic acid test ++ or more for 3 consecutive days or recurrence of proteinuria at any level with hypoalbumiaemia <2.5g/dl and/or oedema having previously been in remission.

Frequent relapses:
Two or more relapses during the first 6 months after the initial episode or four or more relapses within any 12 month period.

Steroid responsive:
Remission achieved with steroid therapy alone.

Steroid dependence:
2 consecutive relapses occurring during corticosteroid therapy or within 14 days after its cessation.

Steroid resistance:
Failure to enter remission following 4 weeks of daily prednisolone at 60mg/m^2/day.

2. INITIAL EVALUATION OF THE PATIENT

Clinical Assessment

Once a clinical diagnosis is suspected, a complete examination with specific attention to the following is necessary before commencing treatment.

1. Weight
2. Accurate height
3. Blood pressure
4. Funduscopy
5. Evidence of infection
6. Evidence of underlying systemic disorders/syndrome

Once a clinical diagnosis of nephrotic syndrome is made it is essential to confirm the diagnosis.

Investigations to confirm the diagnosis

1. 24 hour urine protein excretion / urine protein : creatinine ratio
2. Serum albumin
3. Serum cholesterol

Other investigations

1. Urine microscopy for pus cells, pus cell casts, RBC and RBC casts
2. Urine culture and ABST
3. Serum electrolytes
4. Serum creatinine and blood urea
5. Full blood count including Hb and packed cell volume

If the patient has macroscopic haematuria or persistent microscopic haematuria after excluding an infection, and hypertension and evidence of renal impairment (not due to hypovolaemia) the following investigations are recommended.

1. Anti streptolysin O titre
2. ESR
3. C3 and C4
4. Anti nuclear antibody and double stranded DNA
5. Hepatitis B surface antigen
6. HIV screening (optional)

3. RENAL BIOPSY

In clinical practice the renal histology is less important than the response to corticosteroid therapy. As a consequence, a renal biopsy is performed only when there are features that suggest histology other than minimal change disease or later when there is steroid resistance.

Key point

International Study of Kidney Diseases in Children (ISKDC) had found that at the initial presentation of children with minimal change nephrotic syndrome.

- 20.7% had systolic blood pressure above 98th percentile for age.
- 22.7% had microscopic haematuria.
- 32.5% had transiently raised plasma creatinine concentration.

Recommendations for renal biopsy.

1. Onset < 6 months of age
2. Initial macroscopic haematuria (without infection)
3. Persistent microscopic haematuria with hypertension
4. Renal failure not attributable to hypovolaemia
5. Persistently low plasma C3, C4 levels
6. Steroid resistance

Renal biopsy is discretionary if:

1. Onset 6-12 months of age
2. Onset above 12 years
3. Persistent hypertension, persistent microscopic haematuria in isolation
4. Frequently relapsing disease before commencing on second line drugs (especially cyclosporin A)

Key point
In clinical practice the renal histology is less important than the response to corticosteroid therapy.

4. MANAGEMENT

A. Bed rest

This is not required and could be harmful. (Predisposes to thrombosis)

B. Diet

A normal protein diet with adequate calories is recommended. A high protein diet had not been shown to improve serum albumin concentration.

C. Antibiotics

Children with nephrotic syndrome are more prone to primary bacterial peritonitis. Prophylactic oral penicillin is recommended during relapse of proteinuria.

D. Fluid restriction

This is usually not recommended.

E. Diuretics

Diuretics are beneficial to control oedema but should be used cautiously in nephrotic syndrome. (x)

Diuretics should only be used after correction of hypovolaemia. (x)

Frusemide can be administered in a dose of 1-2 mg/kg in divided doses orally or intravenously.

It can also be used along with colloid (albumin or cryo-poor plasma) infusions.

Spironolactone (2mg/kg) can be used as an adjunct provided the renal function is normal.

F. Hypercholesterolaemia

Hypercholesterolaemia in most patients with steroid sensitive nephrotic syndrome is transient and is unlikely to have long term implications and hence lipid lowering drugs are not routinely used.

5. TREATMENT OF THE FIRST EPISODE

Recommendation

Prednisolone at 60 mg/m^2 per day (up to a maximum of 80 mg/day) , preferably given as a single dose in the morning for four weeks **(grade A)** and then 40 mg/m^2 of prednisolone on alternate days for a further four to six weeks **(grade A)** is recommended. There is increasing evidence that a longer tapering regimen up to 5-6 months is beneficial to maintain long-term remission. However, it is not clear whether such therapy will reduce the incidence of steroid dependent disease and the need for second line agents.

6. TREATMENT OF RELAPSE

Recommendation

The majority of children with idiopathic nephrotic syndrome will relapse. For those who relapse after initial treatment, prednisolone should be given at 60 mg/m^2 per day (up to 80 mg/day) until the urine is protein free for three consecutive days; then 40 mg/m^2 should be given every other day for a further four weeks **(grade A)**.

Patient should be carefully assessed for evidence of infection prior to initiating steroid therapy, as infections especially viral upper respiratory tract infections trigger recurrence of proteinuria.

To reduce morbidity and mortality, a relapse must be diagnosed and treated before significant oedema develops.

7. FREQUENT RELAPSES AND STEROID DEPENDENCE

Re-induction of remission of any relapse with steroids is described in section 6 on relapse. The prednisolone is now tapered instead of abrupt cessation at the end of re-induction regimen. The prednisolone is then kept on as low as possible on alternate days for 6 months. This dose preferably should not exceed 0.5mg /kg alternate days.

Figure 1

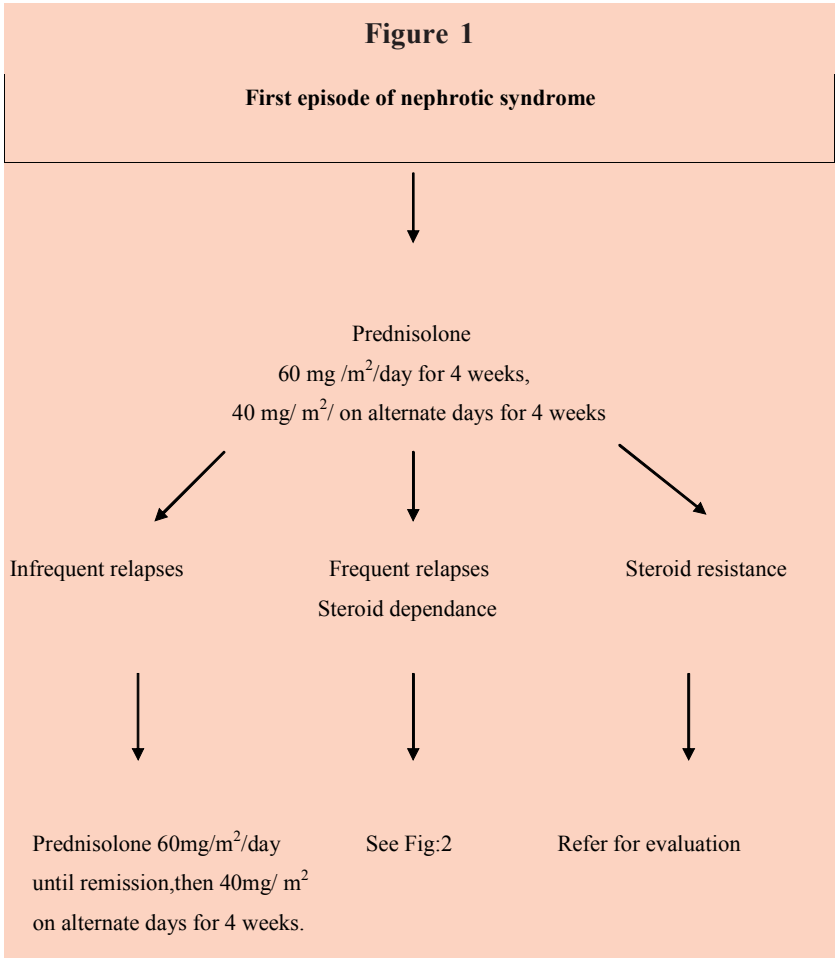
First episode of nephrotic syndrome
Prednisolone
60 mg /m2/day for 4 weeks,
40 mg/ m2/ on alternate days for 4 weeks
Infrequent relapses
Frequent relapses
Steroid dependance
Steroid resistance
Prednisolone 60mg/m2/day
until remission,then 40mg/ m2
on alternate days for 4 weeks.
See Fig:2
Refer for evaluation

Figure 2
Treatment of frequently relapsing steroid sensitive disease

Frequent relapses

1. Maintenance prednisolone 0.1-0.5-mg/kg/alternate days for 6-12 months and taper

↓

2. **Relapse**

Prednisolone 0.6-1mg on alternate days

or

Prednisolone <0.5 mg/kg/alternate days

+

Levamisole 2.5 mg/kg/alternate days for 6-12 months or longer

↓

3. Relapse on prednisolone

>0.5 mg/kg/alternate days + Levamisole

or

Steroid related side effects

or

Relapse on prednisolone >1 mg/kg/alternate days

↓

4. Cyclosphosphamide 3mg/kg/day for 8 weeks

or

2.5 mg/kg/day for 12 weeks

+

tapering regimen of prednisolone

↓

5. Post-cyclosphosphamide relapse

as 2-3 above

May try a second course of cyclophosphamide **after one year** for those who have had a significant response to the first course, but the cumulative dose should not exceed 300mg/kg

↓

6. Relapse on prednisolone

>0.5 mg/kg/alternate days

↓

7. Cyclosporin 3-5 mg/kg/day for one year

↓

8. Relapse post-cyclosporin

↓

Should be decided on an individual patient basis

8. PATIENT AND PARENT EDUCATION

The relapsing, chronic nature of the disease makes it imperative, that both the patient and parents are educated on the nature of the disease and its prognosis. Parental motivation and involvement is essential in the management of a child with nephrotic syndrome. Patients and parents who have a clear understanding of the disease comply better with treatment.

Reassurance that progression to end stage renal failure is extremely rare is important.

Prior to discharge following treatment of the initial episode – the following aspects of management must be emphasized.

a) Urine examination for protein at home. Parent/patient should have a clear understanding of grading proteinuria.

   Examination should be done every morning during a relapse, during intercurrent infection or if the child has even mild periorbital oedema.

   Urine is examined twice / thrice a week during remission.

   The dipstick test is carried out by dipping the marked end of the strip in urine for 3 seconds and comparing the colour change with the code given in the pack.

   To perform the heat test, two thirds of a test tube is filled with urine. It is held at a slant and the lower half of the tube is heated until boiling point. If turbidity appears, two drops of 10% acetic acid are added to exclude the possible presence of phosphates. The degree of turbidity is read against a background of black print. Proteinuria is graded according to the degree of turbidity.

   Grading of proteinuria

Nil	-	no turbidity
Trace	-	slight turbidity with no difficulty in reading the print
+	-	clouding of the print but possible to read the print
++	-	cannot read the print but can notice black
+++	-	cannot notice black
++++	-	cannot notice black and with precipitate

   The sulphosalicylic acid test is performed by adding 2 drops of 30% sulphosalicylic acid to 5 ml of urine in a test tube and observing the resulting turbidity. Grading of proteinuria is similar to the heat test. The sulphosalicylic acid test is recommended by the World Health Organisation to detect proteinuria.

b) Maintain a diary showing proteinuria, medications received and intercurrent infections.

c) Ensure normal activity and school attendance. It is important that the child participates in all activities and sports.

d) Infections are an important cause of morbidity and mortality and parents need to understand the measures needed for preventing frequent infections and the importance of seeking early treatment for infections.

e) Diet
It is important to give clear instructions as most parents have their own views and beliefs regarding dietary restrictions in kidney diseases.

A balanced diet adequate in protein and calories with a protein intake of 1.5-2 g/kg/day is recommended. (The average Sri Lankan diet contains approx. 0.8g/kg/day of proteins) Not more than 30% calories should be derived from fat and saturated fats should be avoided.

Carbohydrates are best given in complex forms. A modest reduction in salt is advised in the presence of oedema. Snacks containing high salt are best avoided during this period. Fruits and fruit juices can be given without restrictions. Corticosteroids stimulate the appetite, and advice should be given about ensuring physical activity and preventing excessive weight gain.

f) All killed vaccines included in EPI programme should be offered to these children preferably while receiving alternate day prednisolone. Parents must be made aware that live vaccines are contraindicated while on treatment with steroids.

Live vaccines are contraindicated in children receiving high dose systemic steroids (prednisolone 2mg/kg/day or 20mg/day in children >10kg body weight) until the steroids have been discontinued for 3 months. (BNF;2006, SLMA guidelines on vaccines:2004)

Hepatitis B vaccine should be given to all the children who were not vaccinated previously.

9. MANAGEMENT OF COMPLICATIONS

9.1 Hypertension

Evaluate hypertension very carefully. It may reflect hypovolaemia, an extreme vasoconstrictive response to hypovolaemia or may be due to the nature of the underlying pathology (mesangio-capillary). The presence of significant oedema with oliguria would necessitate exclusion of hypovolaemia.

If blood pressure exceeds the normal limits a short course of antihypertensives could be prescribed once euvolaemia is established. Recommended antihypertensives are nifedipine, hydralazine and atenolol. Diuretics are useful when hypertension is due to fluid overload.

9.2 Infections

Primary peritonitis
Children with nephrotic syndrome are prone to infections particularly cellulitis and primary peritonitis. Should a child develop primary peritonitis the antibiotics recommended are parenteral penicillin and a third generation cephalosporin. (x)

Pneumococcal infections
Children with nephrotic syndrome have an increased risk of developing infections, especially pneumococcal infections. Prophylactic oral penicillin is recommended during treatment of relapses until proteinuria has cleared. Routine immunization with polysaccharide pneumococcal vaccine is currently not recommended.

Varicella infections
A child who develops overt disease while receiving immunosuppressive medications should be treated with intravenous acyclovir. Patients should be advised to avoid contact and in case of contact advised to seek medical advice immediately. Varicella zoster immunoglobulin, if available, is recommended within 96 hours of exposure, preferably as early as possible.(x)

9.3 Hypovolaemia

Commonly occurs with development of oedema. However, hypovolaemia could precede clinical oedema especially in the presence of diarrhoea, vomiting or sepsis and also with injudicious use of diuretics.

Symptoms and signs

- Dizziness
- Severe central abdominal cramps with or without vomiting or back pain
- Reduced urine output (< 1ml / kg/ hour)
- Cold extremities
- Low blood pressure
- Reactive hypertension

Laboratory manifestations

Urinary sodium <5mmol / L
Rising PCV

If in shock, infuse 4.5% albumin or plasma 10ml/kg body weight as a bolus. Although albumin is preferred to plasma it is not freely available. Intravenous frusemide should not be used in conjunction with plasma/ albumin infusion when correcting hypovolaemia. Vital signs should be monitored as rapid infusions or repeated infusion may result in pulmonary oedema.

Indications for albumin/plasma transfusions

The aim should be to minimise the use of blood products. The only indications for transfusion of albumin/plasma are:

a) Hypovolaemia
a) Control of intractable oedema

9.4 Addisonian crisis

Patients on long-term steroids can rarely have circulatory failure due to adrenal suppression during intercurrent illnesses. They should be managed with intravenous fluids, correction of blood sugar and intravenous hydrocortisone.

9.5 Thromboembolism

Patients with clinical and radiological evidence of thrombosis should be treated with heparin or low molecular weight heparin. Initial therapy with heparin is followed by oral warfarin for 6 months or longer. Prophylactic use of these agents for prevention of thrombosis is currently not recommended.

10. DRUG FORMULARY

10.1 Levamisole

Dosage
2.5mg/kg, given on alternate days

Monitoring during treatment
Check white blood cell count (WBC) 2 weeks after treatment. WBC must be repeated monthly for the next 3 months and once in 3 months thereafter.

Side effects
Reversible neutropenia is a rare complication and if it occurs levamisole should be discontinued. Reintroduction is not recommended. Other rare side effects include an itchy skin rash and vasculitis which is a further indication for discontinuation of therapy. Levamisole is not used to induce remission, but is able to maintain remission in patients with a lesser degree of steroid dependence. It is prescribed initially with alternate day steroids and subsequently as a single agent.

Duration of therapy
1-3 years. Longer duration of therapy in selected patients.

10.2 Cyclophosphamide (CYC)

Dosage:
Oral: 3mg/kg once a day for 8 weeks or 2mg/kg once a day for 12 weeks.
Total recommended cumulative dose is 168mg/kg.

Intravenous pulsed CYC at 600mg/m^2 monthly for six months is being increasingly used with variable success rates for SDNS. Most studies include small number of patients and therefore it is difficult to interpret the advantages over oral therapy. The advantage however is that with intravenous administration the total dose of CYC is less than the oral route and the compliance is not an issue.

Precautions and Monitoring

Patients should be adequately hydrated prior to commencement and during therapy to minimise the risk of haemorrhagic cystitis especially with intravenous administration. Full blood count should be performed weekly during oral therapy and monthly during intravenous therapy to detect leucopenia/neutropenia. Therapy should be discontinued in the event of

neutropenia (<1,500/cumm) or leucopenia (<3,000/cumm). Recommence once the counts recover, to complete the 8 weeks. CYC may also cause nausea and vomiting, alopecia and amenorrhoea during therapy. The risk of occurrence of long term side-effects such as azospermia and future malignancy is remote with a single course of CYC. CYC is prescribed to induce remission in steroid resistant nephrotic syndrome and to induce long lasting remission in steroid dependent nephrotic syndrome.

10.3 Cyclosporin A (Cy A)

Dosage
Initial dose 3-5mg/kg (100-150mg/m^2) daily in 2 divided doses. Dose adjustments should be guided by 12 hour trough levels (target level 100µg/l range 50-150 µg/l).

Precautions and monitoring

Renal function should be monitored closely. If there is any deterioration of renal function an urgent glomerular filtration rate (GFR) should be arranged. If the GFR is diminished CyA dose must be reduced by 20% and a renal biopsy should be carried out.

10.4 Prednisolone

Dosage
As described above.

Precautions and monitoring

Children on long-term use of steroids should have regular eye checks 6 monthly or whenever symptomatic for detection of posterior subcapsular cataract, glaucoma and secondary ocular infections etc.

Regular assessment (3-6 monthly) of height, weight, blood sugar and serum calcium should be done. Hypocalcaemia can result due to hypercalciuric effects of steroids as well as vitamin D deficient states created by nephrotic syndrome itself and most patients will require calcium supplementation.

During minor and major surgical procedures patients need high dose IV steroids while on treatment and until 1 year after discontinuation of steroids.

Members of the Guideline Committee

Dr Chandra Abeysekera (Coordinator)	Senior Lecturer, Head, Dept. of Paediatrics, Faculty of Medicine, Peradeniya.
Dr Sarath de Silva	Former Consultant Paediatrician, Lady Ridgeway Hospital, Colombo.
Dr U K Jayantha	Senior Lecturer, Dept. of Paediatrics, Faculty of Medicine, Galle.
Dr Asiri Abeyagunawardena	Senior Lecturer, Dept. of Paediatrics, Faculty of Medicine, Peradeniya.
Dr Vindya Gunasekera	Senior Registrar in Paediatric Nephrology, Lady Ridgeway Hospital, Colombo.