

Current practice

Managing a child with nephrotic syndrome

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Nephrotic syndrome (NS), which refers to the tetrad of heavy proteinuria, oedema, hypoalbuminaemia and hyperlipidaemia, is the commonest childhood glomerular disorder and the annual incidence is 2-7 per 100, 000¹. It can be classified as secondary, congenital and idiopathic, with idiopathic NS being the most common type in children. NS manifests as the primary disease in the majority while in the remainder it is secondary to systemic disorders such as systemic lupus erythematosus, vasculitis and infections, or may occur following ingestion of drugs and heavy metals². The majority of children show minimal change nephropathy (MCN) or focal and segmental glomerulosclerosis (FSGS) upon histological examination.

While the majority of children with MCN respond to the initial corticosteroid therapy, over 70% of them will subsequently develop relapses. Around 50% of these will have frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS). However, with treatment, most patients will enter long-term remission without progressing to end-stage renal failure^{3,4}. The definitions related to NS are mentioned in table 1. This article will focus on the management of steroid-sensitive nephrotic syndrome (SSNS).

Table 1: Definitions related to childhood nephrotic syndrome

Nephrotic syndrome:	Heavy proteinuria (≥ 300 mg/dL, dipstick urine protein 3+), hypoalbuminaemia (serum albumin < 2.5 g/dl), hyperlipidaemia (serum cholesterol > 200 mg/dl) and oedema
Nephrotic range proteinuria:	Early morning urine protein 3+/4+ (on dipstick or heat test), spot protein/ creatinine ratio > 2 mg/mg, or urine albumin excretion > 40 mg/m ² per hour (on a timed-sample)
Remission :	Urine albumin nil or trace (or proteinuria < 4 mg/m ² /h) on three consecutive early morning specimens
Relapse :	Urine albumin 3+ or 4+ (or proteinuria > 40 mg/m ² /h) on three consecutive early morning specimens, having been in remission previously
Frequent relapses:	Two or more relapses in initial 6 months or more than four relapses in any 12 months
Steroid dependence :	Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.
Steroid resistance :	*Failure to attain remission despite 4 weeks of therapy with daily prednisolone at 60mg/m ²

* Most paediatric nephrologists would give either 6-8 weeks of daily prednisolone⁵ at 60mg/m² or 4 weeks of daily prednisolone at 60mg/m² plus 3 pulses of IV methylprednisolone at 600mg/m² given on alternate days⁶ prior to considering a patient to be steroid resistant.

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Initial evaluation

A complete initial evaluation should be performed. The history should include assessment of complications such as hypovolaemia, thrombosis and sepsis. Features to suggest a secondary cause such as rash and arthropathy are important. Drug history may also reveal a secondary cause. On examination, specific attention should be given to weight, accurate height, volume status (perfusion, capillary refilling time, and blood pressure), evidence of occult infection and evidence of underlying systemic disorders/syndrome.

If NS is suspected at the initial evaluation, the following tests are recommended for confirmation and screen for complications.

- Urine microscopy
- Urinary protein: creatinine ratio
- Urine culture and sensitivity
- Serum electrolytes
- Serum creatinine
- Full blood count

The patient should be referred to a paediatric nephrologist at presentation in the following circumstances:

- Macroscopic haematuria not due to infection
- Renal impairment not due to hypovolaemia
- Intractable oedema
- Sustained severe hypertension
- Failure to respond to 4 weeks of daily steroids
- Thrombotic event
- Age at presentation <1 year or >12 years

Treatment of the initial episode

Specific treatment

After years of intensive research, prednisolone remains the first line agent for treatment of the initial episode. The ideal regimen to treat the initial episode should rapidly induce remission and reduce subsequent relapse rates, while keeping steroid-related side effects to a minimum. Oral prednisolone, prescribed in a dose of 60mg/m² every day for 4 weeks, followed by 40mg/m² every other day (EOD) for another 4 weeks, in accordance with the recommendations of the International Study for Kidney Diseases in Children (ISKDC)⁷, remained the standard therapy for around a quarter of a century. More than 80% of children respond to the initial therapy⁸.

However, a somewhat large and abrupt drop in the steroid concentration in the body is caused by the standard regimen when switching from 60mg/m² daily to 40mg/m² EOD. This significant reduction opens a window for relapses in some patients. Moreover, subsequent published evidence suggests that prolonged tapering of steroids is more effective in maintaining the sustained remission rate than the standard regimen^{9,10,11}. It has also been shown that the time taken to attain remission in the first episode has a bearing on future severity of the disease i.e. those taking longer than 10 to 14 days have more severe disease than those attaining remission quickly¹².

These late responders may benefit from a prolonged course of steroids. We therefore recommend the following treatment for the initial episode.

- *Early responder* (remission induction within 14 days)
Prednisolone 60mg/m² every day for 4 weeks, followed by prednisolone 60mg/m² EOD for 2 weeks, tapered every 2 weeks over a period of 8-12 weeks.
- *Late responder* (remission induction after 14 days)
Prednisolone 60mg/m² every day for 6 weeks, followed by prednisolone 60mg/m² EOD for 2 weeks tapered every 2 weeks over a period of 18 weeks

Treatment of relapse

The standard therapy for relapse according to the modified ISKDC regimen is prednisolone 60mg/m² every day till remission, followed by 40mg/m² EOD for 28 days⁷. However, for the same reasons noted above, switching from 60mg/m² daily to 60mg/m² EOD for 2 weeks and gradually tapering over a variable period of time is more desirable (4-12 weeks). The duration of the taper would be determined by the frequency of relapses and more frequent relapses require a longer duration taper.

Prevention of relapses

Relapse of NS is frequently precipitated by viral upper respiratory tract infection (URTI)¹³. Several studies have demonstrated a reduction in relapse rate by a slight, short term increase in the prednisolone dose at the commencement of an URTI in patients with SDNS who were on EOD corticosteroids^{13,14,15}. Another study recently demonstrated that a 5 day course of prednisolone prescribed at 0.5mg/kg/day during URTI is capable of reducing the relapse frequency in patients who are off steroids¹⁶. Based on these findings we make the following recommendations.

At onset of URTI

- *Patients receiving EOD prednisolone >0.5mg/kg*
Give same EOD dose daily for 5-7 days e.g. For a 20kg patient on 15mg EOD, give 15mg daily for 5-7 days
- *Patients receiving EOD prednisolone <0.5mg/kg*
Give 0.5mg/kg daily for 5-7 days e.g. For a 20kg patient on 5mg EOD, give 10mg daily for 5-7 days
- *Patients not receiving prednisolone*
Give prednisolone 0.5mg/kg daily for 5 days

Steroid dependent and frequently relapsing disease

The first line of treatment for FRNS and SDNS is maintenance therapy with low dose prednisolone 0.1-0.6mg/kg EOD for a period of 6 months followed by slow tapering⁷. In these patients for whom repeated doses of steroids are required, it is necessary to monitor for steroid toxicity with routine check-up of growth and blood pressure⁷.

Steroid-sparing agents such as cyclophosphamide (CYC), cyclosporine A (CyA), levamisole (LEV), mycophenolate mofetil (MMF) and tacrolimus are used if the dose needed to maintain stable remission exceeds 0.6mg/kg EOD or if the child develops steroid toxicity¹⁷. The following table summarises the treatment regimens with different steroid-sparing agents for SSNS patients.

Table 2: Treatment regimens of steroid-sparing agents and monitoring of their side effects

Steroid sparing agent	Dose	Co-treatment with steroids	Side-effects	Monitoring during treatment
Cyclophosphamide (CYC)	3mg/kg/day for 8 weeks orally or 6 IV monthly pulses at 600mg/m ²	1.5 mg/kg on alternate days (EOD) for 4 weeks, followed by 1 mg/kg for 8 weeks. Then tapered and stopped over 2-3 months	Haemorrhagic cystitis, alopecia, nausea and vomiting, gonadal toxicity	Monitoring total leucocyte count every 2 weeks. Discontinue CYC if count falls below 4000/mm ³ .
Levamisole (LEV)	2.5mg EOD up to 5 years	1.5 mg/kg EOD for 2-4 weeks, gradually reduced by 0.15-0.25 mg/kg 4 weekly to maintenance dose of 0.25-0.5 mg/kg that is continued for 6 or more months.	Leucopenia, liver toxicity, convulsions, vasculitis	Monitoring of total leucocyte count every 12-16 weeks.
Cyclosporin A (CyA)	Initial dose 3-5 mg /kg/day in 2 divided doses continued up to 2-3 years. Dose adjustments should be guided by 12 hour trough levels (target level 100µg/l range 50-150 µg/l)	1.5 mg/kg EOD for 2-4 weeks. Then the dose is gradually reduced by 0.15-0.25 mg/kg every 4 weeks to a maintenance dose of 0.25-0.5 mg/kg that is continued for 6 or more months	Hypertension, gum hypertrophy, hypertrichosis, hyperkalaemia, nephrotoxicity	Annual lipid profile and testing serum creatinine 2-3 monthly. If CyA therapy is extended beyond 2 years, a protocol kidney biopsy to check for nephrotoxicity.
Tacrolimus	0.1-0.2 mg/kg daily for 12-24 months		Hyperglycaemia, diarrhoea, nephrotoxicity, neurotoxicity	Blood glucose and serum creatinine estimated every 2-3 months.

The choice of steroid sparing agent should ideally be made following discussion with a paediatric nephrologist to select the most appropriate agent. The flow chart in Figure 1 is a general guide for selection of steroid-sparing agents.

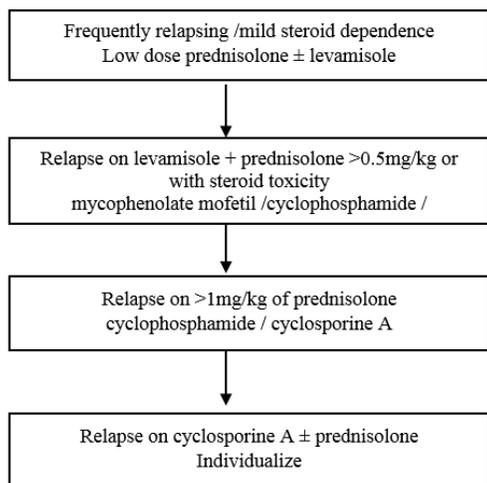


Figure 1: Flow chart for selecting steroid-sparing agents along the treatment course of a nephrotic child

Although not routinely practised in Sri Lanka, it is advisable to screen for tuberculosis using chest X-ray and tuberculin test prior to starting heavy immunosuppressive drugs.

Management of complications of NS

Infections

Infections are the main cause of mortality in patients with NS. Cellulitis and other soft tissue infections, peritonitis, urinary tract infection and pneumonia are the most common infections seen in children with NS^{18,19}. Commonly isolated causative agents include *S. Pneumonia* and *Escherichia coli*²⁰. There is no strong evidence for the use of a prophylactic antibiotic. However, prophylactic penicillin V may be used in the oedematous patient to prevent infection.

Viral infections are also important, with varicella zoster virus being the most significant agent leading to the risk of mortality, especially in children having heavy immunosuppressive therapy²¹. Other important viruses that are likely to trigger relapses include respiratory syncytial virus,

influenza virus, parainfluenza virus and adenovirus²².

Though difficult to carry out in local clinical settings, it is advisable to immunise all children with NS with pneumococcal, varicella, influenza, MMR and hepatitis B vaccines whenever possible²³.

Oedema

Oedema, a primary feature of NS, is usually associated with intravascular hypovolaemia and presents with tachycardia, abdominal pain, hypotension and oliguria. Restriction of dietary sodium to <2 mEq/kg per day and fluid restriction can be employed to manage mild oedema, while monitoring body weight. Oral thiazide diuretic therapy can be considered if the eGFR is normal²⁴.

If severe oedema presents with the above mentioned symptoms and more than 7-10% increase of body weight, pharmacological interventions with loop diuretics would be required. However, it must be stressed that diuretics should be considered only in euvolaemic patients. As a general rule, if in doubt about volume status - **do not use diuretics**. In the suitable patient frusemide can be started at 1-3mg/kg/day and can be increased as necessary up to 4-6mg/kg/day. Due to the pharmacokinetics of frusemide, namely its transport in an albumin bound form, higher doses are usually required for effective diuresis. However, a gradual increase is advisable. Close clinical supervision is needed with electrolyte monitoring and looking for evidence of hypovolaemia. For loop diuretics, intravenous administration is more effective than oral therapy²⁵.

There are 3 primary indications for therapy with human albumin in patients with NS in relapse.

1. Hypovolaemic shock
2. Hypovolaemia without shock
3. Refractory or symptomatic oedema

Note - A low serum albumin **alone** is never an indication for intravenous albumin.

Hypovolaemia usually occurs with the development of oedema. Hypovolaemia and shock can lead to acute renal failure. Injudicious use of diuretics to control oedema is known to precipitate hypovolaemia. Low volume pulse, paradoxical hypertension with narrow pulse pressure, hypotension, cold peripheries and abdominal cramps suggest hypovolaemia and diminished excretion of urinary sodium less than 5mmol/l confirms hypovolaemia and impending shock¹².

For patients in hypovolaemic shock, 10ml per kg of 4.5% albumin should be infused without diuretics. In patients with hypovolaemia without shock or if

the patient has either refractory or symptomatic oedema, 0.5-1g/kg of 20% albumin (2.5-5ml/kg) should be administered over 4-6 hours. Intravenous frusemide should be administered mid-infusion and repeated at the end if diuretic response is poor²⁶. Close monitoring should prevail during albumin infusion.

Dyslipidaemia and obesity

The dyslipidaemia seen in NS is usually transient and resolves once the proteinuria clears. It therefore usually does not warrant treatment with lipid lowering agents. Drug therapy can be considered if fasting low-density lipoprotein cholesterol levels are persistently between 160 and 190 mg/dL (4.1– 4.9 mmol/L)²⁷.

Obesity due to long-term steroid use can be controlled through dietary counselling and exercise. Prolonged corticosteroid therapy can increase the risk of osteoporosis and osteomalacia. Calcium and Vitamin D supplementation might be helpful in managing this condition, although not yet supported by studies.

Hypertension

Persistent hypertension in the normovolaemic patient is unusual in idiopathic NS and warrants consideration of a secondary cause for the NS. This is especially so if the patient continues to be hypertensive once steroids are tapered to lower alternate day doses. There is, however, a higher prevalence of hypertension in NS children with long standing disease²⁸ and hence prevention of cardiovascular disease through early management is advisable. Dietary changes, exercise and weight management would be helpful. Pharmacological intervention with angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers or beta adrenergic antagonists might be required if blood pressure exceeds the 90th percentile for age¹².

Thromboembolic disease

Though NS associated thromboembolic disease (TED) is commoner in adults, TED is the second most frequent cause of death in children with NS. Respiratory compromise is seen in pulmonary embolism while venous thrombosis presents with painful and swollen extremities. Upon suspicion of TED, a computerised tomography pulmonary angiography (CTPA) should be done to confirm the diagnosis. The laboratory tests comprise:

- Platelet count
- Prothrombin time
- Activated partial thromboplastin time
- Thrombin time
- Fibrinogen and quantitative D-dimers

A child with venous thromboembolism would be given an initial 3-6 months of anticoagulation

treatment. If long term anticoagulation is needed, simultaneous warfarin can be started. All patients who have had a thrombotic episode during a relapse should receive anticoagulation with heparin at all subsequent relapses¹².

Psychological support

Both the child and parents needs psychological support throughout the illness.

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