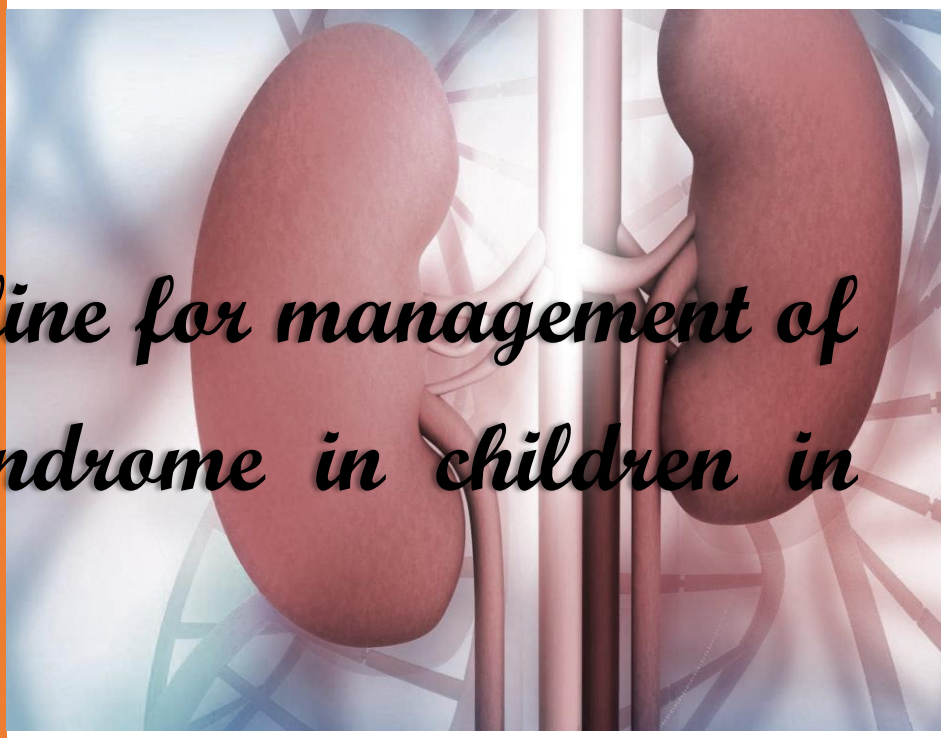
Clinical guideline for management of Nephrotic Syndrome in children in Maldives



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I. Introduction

Nephrotic Syndrome is a common renal disorder in children. It has a greater prevalence among the Asian populations with estimated incidence of 90 to 100 per million population in the Indian Subcontinent. The purpose of this guideline is to provide a comprehensive clinical pathway for management of children presenting with nephrotic syndrome.

II. Objectives

1. **Primary treatment objective** is to achieve remission, alleviate symptoms and prevent/treat acute risks such as hypovolemia infection, and thrombosis
2. **Long- term treatment objective** is to prevent complications like bone disease, hypertension, Cushing syndrome, obesity, growth retardation, cataracts and a variety of psychological, social and behavioral disturbances.

III. Case Definition

Nephrotic Syndrome is the commonest chronic glomerular disorder of childhood, characterized by[i]

1. Heavy protein urea (>40mg/m^2/hr), or ≥ 3+ on dipstick
2. Hypoalbuminima (<2.5g/dL)
3. Edema
4. Hyperlipidemia

IV. Etiological Classification

1. Primary or Idiopathic nephrotic syndrome (90%)

a. Minimal-change disease (MCNS) (85%)
b. Focal segmental glomerulosclerosis (FSGS)
c. Membranoproliferative glomerulonephritis
d. Mesengial proliferative glomerulonephritis
e. Membranous nephropathy

2. Secondary Nephrotic Syndrome related to systemic diseases (10%)

- Viral infections (e.g., hepatitis B and C, HIV, Malaria, Syphilis, Toxoplasmosis
- Immunologic and allergic disorder (e.g., SLE, HSP, IgA nephropathy Bee sting, Food allergens)
- Hematological and malignant diseases (e.g., sickle cell disease, Lymphoma, Leukemia)
- Diabetes mellitus
- Drug related (e.g., penicilamine, gold, NSAID, Mercury)

3. Congenital nephrotic syndrome

V. Clinical Assessment

1. Detailed history

- Edema is the primary presenting feature. Onset is insidious with swelling around eyes and facial puffiness and involving extremities.
- Enquire about recent weight gain, urine output, dizziness, or discomfort/pain due to edema
- Enquire about Immunizations history, and secondary causes

2. Focused examination

- Height, weight, estimated body surface area
- Blood pressure
- Assessment of edema (lower limb, sacral, ascites, scrotal, pleural effusions
- Cardiovascular status and perfusion (volume status)
  - Indicators of fluid overload: tachycardia, hypertension, respiratory distress, warm peripheries, hepatomegaly, raised JVP

- Indicators of hypovolaemia: tachycardia, hyportension, cool peripheries, delayed capillary refill time

Body surface area (m^2) = $\sqrt{\frac{\text{Height (cm) x Weight (kg)}}{3600}}$

Table 1. Degree of edema

Mild	subtle peri-orbital region, scrotum or labia
Moderate	peripheral pitting edema of the limbs and sacrum
Severe	gross limb edema, ascites and pleural effusions

Exclude other causes of generalized edema include liver disease or protein losing enteropathy and congestive cardiac failure.

Keynote 1. Features suggestive of secondary nephrotic syndrome

i. Age <1y or >12y
ii. Fever, rash, joint pains (SLE, HSP).
iii. Persistent hematuria
iv. Persistent hypertension
v. Persistently raised serum creatinine

Table 2. Assess for severity and complications

Complications	Features
Intravascular volume depletion	Dizziness, abdominal cramps Peripheral hypoperfusion (cold hands or feet, mottling, capillary refill time > 2 seconds), tachycardia, oligo/anuria, hypotension (late sign)

Severe/symptomatic oedema	potential skin breakdown/cellulitis, gross scrotal/labial edema, increased work of breathing from pleural effusion
Infection	Cellulitis from gross edema with skin compromise Spontaneous bacterial peritonitis – abdominal pain, fever, nausea/vomiting, rebound tenderness
Deep vein thrombosis, pulmonary embolus	leg pain, chest pain, shortness of breath
Renal vein thrombosis	macroscopic hematuria, palpable kidney, loin tenderness, raised creatinine, hypertension
Cerebral vein thrombosis	headache, vomiting, impaired conscious state or focal neurology

VI. Investigation

Diagnostic studies for nephrotic syndrome should include the following:

Table 3. Urine analysis

Investigation	Clinical interpretation in NS
Single spot collection	3+ or >
Urinary protein and creatinine (P:C) ratio	See table 5
A 24-hour urine collection (7 am to 7am)	See table 5
Quantify any hematuria and red cell casts	> 2 RBCs/hpf (microscopic hematuria) and > 2 granular casts suggest the possibility of significant renal histological lesion

Table 4. Blood investigation

Investigation	Clinical interpretation in NS
Serum albumin	Hypoalbuminaemia (<2.5g/dL)
Serum cholesterol	Elevated
Renal function	normal in uncomplicated nephrotic syndrome
LFT	Essentially normal
CBC/ESR	Essentially normal

1. Screening for infection

- FBC, ESR, CRP, blood culture, Urine routine and Culture, culture of fluid
- Mantoux Skin Test/IGRA to rule out latent tuberculosis infection (prior to starting steroid)

2. Evaluation for secondary causes (in clinically indicated cases only)

1. Immunology
    - C3 and C4 (low in SLE and MPGN)
    - ASOT
    - ANA, anti-dsDNA Anti-Neutrophil Cytoplasmic Antibodies (ANCA)
2. Serologic studies
    - Hep B and C, HIV, syphilis and toxoplasmosis, Malaria
- Varicella serology

3. Renal ultrasonography

- Shows whether a patient has two kidneys (one kidney is a relative contraindication to kidney biopsy).
- Individuals with a single kidney may be prone to developing focal glomerulosclerosis.
- Increased renal echogenicity is consistent with intrarenal fibrosis

Table 5. Quantifying proteinuria

	24hr urine protein excretion(mg/m^2/hr)	Random protein to creatinine (P:C) ratio
Physiologic	<4	<0.5 (<2yrs), <0.2 (> 2yrs)
Pathologic		
Non-nephrotic range	4-40	0.2-2
Nephrotic range	>40	>2

VII. Management of Idiopathic Nephrotic Syndrome (INS)

Majority of the children has primary or INS. Hence, this guideline covers comprehensive management of INS. Corticosteroids is the drug of choice in the initial treatment of INS. Renal biopsy is not mandatorily required for all children before starting steroids in the initial episode.

1. Indications for admission

i. Newly diagnosed, for initial counselling, and social reasons if required.
ii. Severe and symptomatic edema
iii. Associated infection, requiring IV antibiotics
iv. Deranged renal function
v. Hypertension and atypical presentation

2. Treatment of initial episode

a. Edematous state

Edema in nephrotic syndrome is mainly due to hypoalbuminemia causing reduction in plasma oncotic pressure and leakage of intravascular fluid in to the interstitial spaces.

Management

i. **No added salt** diet (overzealous salt restriction should be avoided)

ii. **Strict fluid balance** with close attention to volume status

iii. **Intravenous 20% albumin** (with Furosemide) is indicated for

- Severe or symptomatic edema with serum albumin <1.5g/dL
- Intravascular volume depletion
  - Dose: 20% albumin 0.5-1g/kg over 4-6hrs IV.

iv. **Frusemide**

- Mid infusion, 1-3mg/kg (max 40mg)
- End of infusion, 1mg/kg (max 40mg) can be repeated, if initially given for severe and symptomatic edema
- Larger doses of Frusemide are sometimes given if poor response.
- Close monitoring of blood pressure, pulse rate and peripheral perfusion.

b. Treatment of infection

- Children with severe edema are prone for infection by encapsulated organisms notably Hemophilus influenzae type b, Streptococcus pneumonia, meningococcus, Group B streptococcus, Klebsiella .
- If the child is profoundly ill and or appears to have cellulitis, spontaneous bacterial peritonitis or urosepsis etc., use appropriate IV or oral antibiotics covering the most likely organism, prior to inducing remission with steroid.

c. Induction

- After controlling massive edema and any significant infection and the time admission, corticosteroid therapy should be initiated.
- Prednisolone is the steroid of choice used for induction.
- An ante-acid preparation may be given to reduce gastric irritation.
- Initial episode should be treated for at least 3 months.

d. Dose of prednisolone for induction

- 60 mg/m^2 per day as a single daily dose (max 60 mg/day) for 6 weeks. Then:
- 40 mg/m^2 alternate day as a single daily (max 40mg) for 6 weeks.
- Gradually tapper in 4 weeks

Keynote 3. Optimum duration of initial episode

i.	The Optimum duration of steroid treatment for initial episode of INS is under investigation.
ii.	There is moderate-quality evidence (1B)[ii] that administering prednisone for 12 weeks followed by alternate-day therapy for 2–5 months with tapering of the dose reduces the risk of relapse in children with the first episode of SSNS
iii.	Prolongation of initial therapy is more likely to result in longer reemission and fewer relapses

Table 6. Pattern of response to corticosteroid therapy

Remission	Urine protein negative/trace for 3 consecutive days
Steroid sensitive	show remission of proteinuria following treatment
Relapse	Urine protein 3+ or more for 3 consecutive days
Infrequent relapse	3 or less relapses in 12 months
Frequent relapse	≥2 relapses within 6months of initial episode or ≥4 relapses with any 12-month period
Steroid dependent	Occurrence of 2 consecutive relapses during alternate day steroid therapy or within 2 weeks stopping steroid
Initial resistance	No remission despite 4 weeks of initial steroid therapy
Late response	Patient with initial resistance but responds later
Late resistance	Initial responder who subsequently fails to respond to steroid therapy

3. Treatment of relapses

In a small proportion of children, there may be none or single relapse. Majority of children tend to have multiple relapses of varying period. Prior to commencement of any secondary treatment:

- Assess adherence with steroid therapy
- screen for infection
- RFT, LFT, Bone profile, Magnesium, Lipid profile
- Relapse should prompt re-introduction of full dose prednisolone

a. Infrequent Relapse

- Prednisolone (single morning dose) 60 mg/m2/day (max 60mg) until remission (This usually take 1-2 weeks). Then

  40 mg/m2 alternate day for 4 weeks

  20 mg/m2 alternate day for 1 week

  15 mg/m2 alternate day for 1 week

  10 mg/m2 alternate day for 1 week

  5 mg/m2 alternate day for 1 week
- The total time of weaning regimen can be shortened if responds to treatment quickly

b. Frequently Relapsing

- Require referring to Tertiary care
- Prednisolone 60 mg/m2/day (max 60mg) until remission.
- Then reduce dose to 40mg/m2 (max 40mg) alternate day for 4 weeks
- Wean as above until to a minimum maintenance dose is achieved.
  - keep on this low maintenance dose for at least 6 months
  - If no relapse for 6 months attempts to wean by 5 mg every month.
  - If patient becomes dipstick protein positive (but not relapse) during the weaning, return to previous dose and monitor for a full-blown relapse.

Keynote 4. Response and Relapses in INS

i. Majority of patients encounter relapses and every relapse should be treated early; the patient should not be allowed to develop more than mild edema.
ii. Relapses are often precipitated by URTIs and UTIs.
iii. It is judicious to observe the child for few days and defer institution of standard treatment for relapse.
iv. In case child is receiving alternate day prednisolone while he is having infection related proteinuria, the dose can be doubled and can be given for 1-2 weeks

c. MCNS with initial steroid resistance

- Small proportion of patients with MCNS initially has steroid resistance.
- These patients respond Pulse therapy with Methylprednisolone
- Three-six doses of IV pulses of methylprednisolone 20-30mg/kg given alternate days followed by tapering dose of prednisolone alternate days for 4-12months

4. Monitoring during steroid therapy

a. Induction phase

- Blood pressure, weight, input/output charting, urine albumin, RBS daily
- No added salt and restriction of fatty food

b. Alternate days and maintenance phase

- Cushinoid features (obesity, hirsutism, striae)
- Hypertension
- Impaired glucose tolerance
- Posterior capsular cataracts,
- Growth retardation
- Emotional disturbances
- Vitamin D deficiency (loss in urine)

- Hyperlipidaemia
- Hypothyroidism (loss in urine)

Keynote 5. Steroid Sparing drugs

i. Serious complications of steroid therapy should not be allowed to develop; by close and careful monitoring
ii. Such patients are initially treated with small doses (0.5-0.7mg/kg) of alternate day prednisolone 6-9 months
iii. Prompt institution of alternate regimen should be considered if toxicities not resolving or further relapses

5. Indications for Steroid sparing agents

i. Relapses on a maintenance prednisolone dose of 0.5mg/kg alt days
ii. Steroid dependence
iii. Concerns over linear growth
iv. Intolerable side effects from steroid therapy
v. poor adherence with steroid therapy

Table 7. Steroid Sparing agents

Drug	Dose	Monitoring
Levamisole	2-2.5mg/kg alternate days for 1-2 years (alternate days prednisolone 0.75-1mg/kg is given initially and tapered)	CBC
Cyclophosphamide	2-2.5mg/kg along with alternate day with prednisolone 1-1.5mg/kg for 12 weeks cycles	CBC, RFT
Mycophenolate Mofetil	30mg/kg in 2 divided doses for 1-2 years	CBC, LFT
Cyclosporin A	4-5mg/kg day with alternate days prednisolone for 4-8months	LFT RFT

Tacrolimus	0.1-0.2mg/kg days in 2 divided doses with alternate days prednisolone	RBS
Retuximeb	IV infusion 375mg/m^2 weekly 4 doses	CBC, LFT

When to start steroid sparing agents

- Induce remission with high dose oral prednisolone
- Then introduce first line steroid sparing drugs
- Consider referring to nephrologist before starting second line

6. Indications for referral to nephrology consultation

i. Age at first presentation <12 months or >12 years
ii. Persistent hypertension +/- persistent microscopic hematuria
iii. Elevated creatinine despite correction of any hypovolemia
iv. C3 or 4 below normal range
v. Unclear if nephrotic versus mixed nephritic-nephrotic (e.g. macroscopic hematuria, intravascular fluid overload with hypertension, renal impairment)
vi. Steroid resistance
vii. Steroid toxicity prompting consideration of alternative agent

7. Indications for Renal biopsy

i. Presence of recurrent gross hematuria
ii. Significant nephritic manifestations (persistent hypertension hematuria, persistently elevated Creatinine,)
iii. Low C3/C4 levels
iv. Positive ANA, anti–dsDNA antibody assay
v. Steroid resistance

VIII. Treatment of Complications

1. Infection

- **Chicken pox exposure within 3 months** of high dose steroids or alkylating agents. Give Zoster immunoglobulin within 48 hours of exposure if not immune
- **Measles exposure within 3 months** of high dose steroids or alkylating agents, give normal immunoglobulin if not immune
- **Varicella zoster infection** treat with ACICLOVIR

2. Immunizations

a. Patients receiving prednisolone at dose of 2mg/kg/day or greater or total of 20mg/day for more than 2 weeks are considered immunocompromised.

b. Live vaccines (measles, MMR, oral polio, varicella) is avoided until steroid has been discontinued for at least 4 weeks.

c. Killed vaccines (HIB, Menigococcal C, Influenza) can be given but for best results once the child is taking ≤ 10 mg/m2 alternate days.

d. Children with frequent relapsing or persistent nephrotic syndrome:

i. Should additional booster dose of pneumococcal conjugated vaccine, if under 5years

ii. All children over 5 years of age who have received the conjugate vaccine (PCV) need a single dose of 23valent pneumococcal vaccine (PPV) to provide protection against the serotypes of S. Pneumoniae not covered in the conjugate vaccine.

iii. All children should receive varicella and Influenza vaccine

iv. Vaccination is done while child in remission and off daily prednisolone

v. The siblings of nephrotic children receiving continuous immunosuppression should receive IPV instead of OPV

3. Supportive Medications

- Ranitidine or a proton pump inhibitor as prophylaxis for prednisolone induced gastritis
- Calcium
- Vitamin D

4. Hyperlipidemia

- Lipid abnormalities generally resolve when nephrotic syndrome is in remission.
- Dietary modification is not required
- Chronic hyperlipidemia has been linked to increased risk of atherosclerosis and coronary artery disease
- Simvastatin and Lovastatin are well tolerated and effective in childhood INS.
- Monitor CK level prior to initiating therapy and every 6-12 weeks during treatment (statin associated rhabdomyolysis)
- Families should be instructed to report muscle soreness, tenderness, or pain.

5. Thromboembolism

- Well recognized, but uncommon in children
- Predisposing factors
    i. Hemoconcentraion
    ii. Hypovolemia
    iii. Low level of antithrombin III, and protein S
    iv. Platelet hyperaggregabiltiy
- Treatment
    i. Avoid dehydration and treat infection promptly
    ii. Encourage mobilization and avoid bedrest
    iii. LMW heparine is the drug of choice
    iv. Anticoagulation is maintained with warfarin for 3-6months

6. Hypertension

- Check volume status. If euvolaemic:
- Amlodipine/Nifedipine
- ACEi
- Atenolol

7. Ophthalmology

- Children with frequent relapses, dependency, resistance, should have an annual eye checkup.
- Refer to ophthalmologists if cataracts are suspected

8. Acute kidney failure

Acute kidney failure may rarely result from complications of INS, from the underlying disease, or from drug therapy. In such cases, kidney failure is reversible with remission of nephrotic syndrome

IX. Diet and activity

- The diet should be nutritionally balanced with an emphasis on healthy eating and the avoidance of a high saturated fat intake
- A balanced no added salt diet is recommended while the patient is in relapse. (Avoid the addition of salt in cooking and at the table.
- Reduce the intake of processed foods which contain >0.5 g Na per 100 g weight of food.

- The diet should provide adequate caloric intake and adequate protein (1 g/kg/d). Supplemental dietary protein is of no proven value.
- Fluid restriction *per se* is not needed.
- There are no activity restrictions for patients with nephrotic syndrome.
- Ongoing activity, rather than bedrest, will reduce the risk of blood clots.

X. Family Education

- It is important that parents be well informed that, though their child is likely respond to therapy, they will likely have relapses (80% chance) and remissions over a varying period.
- Educate parents about the course of illness, complications and prognosis
- Inform common side effects of steroid therapy and ask to come back immediately
- Teach to check body weight and test urine protein each morning and keep a dairy (especially during sick days).
- After remission, the urine protein should still be checked and documented daily if feasible or at least weekly (for at least 1-2 years):
    i. To identify a relapse earlier
    ii. Re-institution of prednisolone **prior to the onset of significant edema**
- The most common trigger for relapse is intercurrent infection.
- In patients on weaning, the risk of relapse can be reduced by temporarily increasing the dose from alternate to every day for 3-5 days.

XI. Discharge planning

Children, with significant edema and infection requiring admission, will normally spend several days in hospital following a first presentation with nephrotic syndrome. Even if there is no significant edema, a short admission may sometimes be necessary for some families to teach children and their parents about nephrotic syndrome.

1. During daily ward rounds, patients should have

a. Thorough assessment of their fluid status

b. Blood pressure monitoring
c. Weight check
d. Assessment of edema and signs of hypovolemia.

2. Discharge checklist

Before discharge, parents should know:

a. How to dipstick the child's early morning urine and record this in a daily diary
b. How to recognize a relapse
c. Whom to contact for advice
d. Appropriate fluid and dietary advice
e. Discharge medication advice

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