Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Nephrotic Syndrome

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Nephrotic Syndrome

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Introduction

Nephrotic syndrome is defined by the presence of heavy proteinuria (>1 g/m^2; spot urine protein/creatinine >2 mg/mg), hypoalbuminemia (albumin <3.0 g/dL), and edema. The usual age at onset is between 1 and 12 years. Most cases in childhood are idiopathic, and an underlying systemic illness is seen in <10% of patients. More than 80–85% of children with nephrotic syndrome show remission of proteinuria following therapy with corticosteroids (termed steroid sensitive) and have good outcomes. Approximately 10–15% of patients are not responsive to steroids (steroid-resistant nephrotic syndrome) **(Table 1)**.

TABLE 1: Definitions.

Remission	Urine protein nil or trace (Up/Uc <0.2 mg/mg) for three consecutive early morning specimens
Relapse	Urine protein >3+ (Up/Uc >2 mg/mg) for three consecutive early morning specimens, have been in remission previously
Partial remission	Urine protein 1+/2+ (dipstick), Up/Uc between 0.2 and 2, or 24-hour urine protein 4–40 mg/m^2/day; serum albumin ≥3.0 g/dL; and absence of edema
Frequent relapses	Two or more relapses in 6 months following therapy of the initial episode; more than and equal to three relapses in any 12 months
Steroid dependence	Two consecutive relapses when on alternate day steroids, or within 14 days of its discontinuation
Steroid resistance	Lack of complete remission despite therapy with daily prednisolone at a dose of 2 mg/kg (60 mg/m^2) daily for 6 weeks
Complicated relapse	Relapse associated with life-threatening complications: (i) hypovolemia requiring inpatient care, (ii) severe infection (peritonitis, cellulitis, and meningitis), or (iii) thrombosis
Congenital nephrotic syndrome	Onset of nephrotic syndrome within the first 3 months of life

(Up/Uc: spot urine protein to creatinine ratio)

Evaluation of the First Episode

The goals of evaluation at the onset of disease are to confirm the diagnosis, rule out secondary causes, and screen for complications **(Box 1)**. A kidney biopsy, at onset or during follow-up, is required only in specific circumstances **(Box 2)**. Genetic studies may be needed in selected patients with initial steroid resistance, such as those with onset during infancy, family history of steroid resistance, extrarenal or syndromic features, nonresponse to calcineurin inhibitors (CNIs), and before kidney transplantation.

BOX 1: Investigations at the first episode of nephrotic syndrome.

- ☑ Urinalysis and quantitative estimation of urine protein by spot Up/Uc[a]
- ☑ Complete blood counts
- ☑ Blood urea, creatinine, electrolytes, total protein, albumin, and cholesterol
- ☑ Tuberculin test

Additional evaluation (indications)

- ☑ Complement C3, C4, antinuclear antibody, and antistreptolysin O (gross or persistent microscopic hematuria, sustained hypertension, AKI without hypovolemia, and suspected secondary cause[b])
- ☑ Serum transaminases, hepatitis B surface antigen, and antibody against hepatitis C virus (history of jaundice or liver disease)
- ☑ Chest radiography (positive tuberculin test or history of contact and suspected lower respiratory tract infection)

[a]24-hour protein excretion is seldom necessary

[b]Systemic lupus, immunoglobulin A (IgA) vasculitis, and C3 glomerulopathy

(AKI: acute kidney injury; Up/Uc: spot urine protein to creatinine ratio)

BOX 2: Indications for kidney biopsy in nephrotic syndrome.

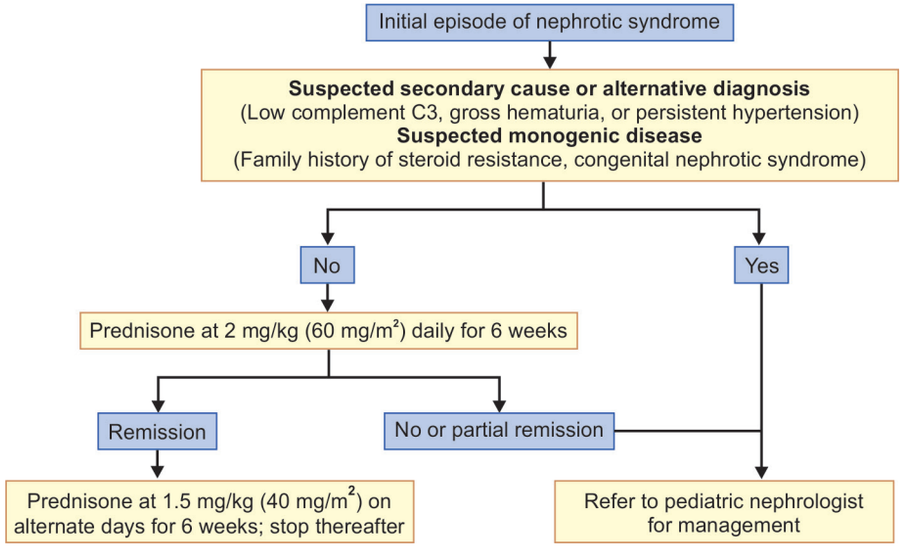
- ☑ Persistent microscopic hematuria and gross hematuria
- ☑ Acute kidney injury despite correction of hypovolemia
- ☑ *Systemic features*: Fever, rash, arthralgia, and suspected secondary cause
- ☑ Low complement C3 level
- ☑ Initial or late corticosteroid resistance
- ☑ Prior to therapy with calcineurin inhibitors, prolonged (>30–36 months) therapy with these agents, and reduced kidney function during their use

Therapy with oral prednisolone is initiated, except in patients with congenital nephrotic syndrome.

First Episode

The approach to treatment of the first episode is given in **Flowchart 1**.

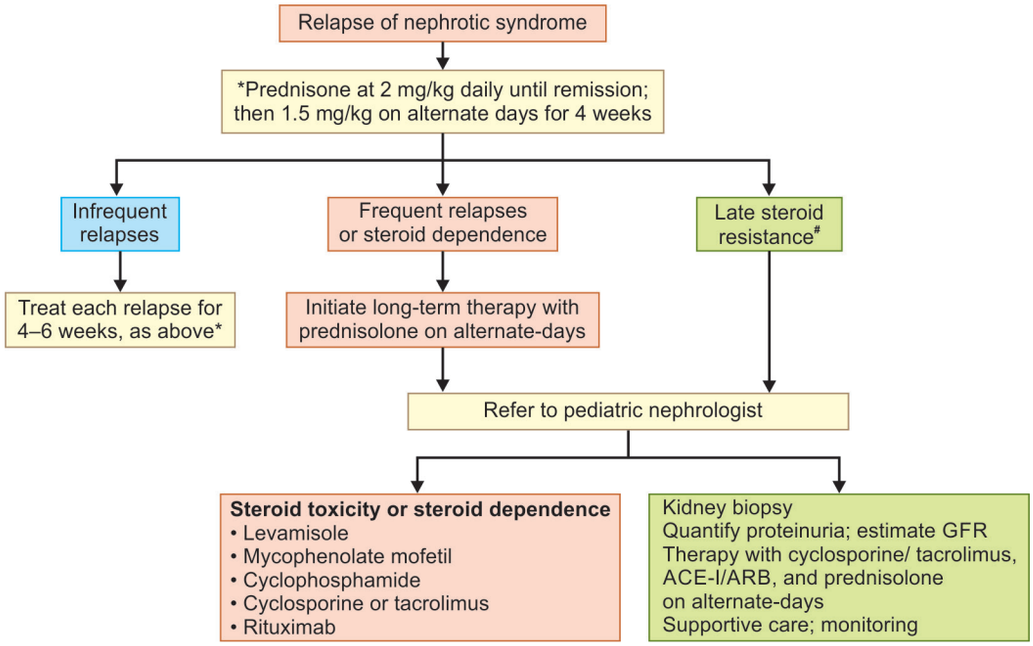
Flowchart 1: Approach to treatment of first episode of nephrotic syndrome.



Treatment of Relapse

Relapse is treated with oral prednisolone, at 2 mg/kg (60 mg/m^2) daily till urine protein is trace or nil for 3 consecutive days, followed by 1.5 mg/kg (40 mg/m^2) on alternate days for 4 weeks. Subsequent treatment is based on the clinical course **(Flowchart 2)**. Infrequent relapses are managed with prednisolone for 4–6 weeks, as described above.

Flowchart 2: Approach to the treatment of relapses. Patients with frequent relapse, steroid dependence, and initial or late steroid resistance should be referred for management by specialists in pediatric nephrology.



#Principles of management are similar for patients with initial and late steroid resistance.
(ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; GFR: glomerular filtration rate)

Frequently Relapsing or Steroid-dependent Disease

Management focuses on reducing the frequency of relapses while avoiding adverse events of immunosuppressive medications. Such cases should be managed in collaboration with a pediatric nephrologist.

Long-term Alternate Day Prednisolone

Therapy is initiated at a dose of 0.5–0.7 mg/kg on alternate days, for a duration of 9–12 months. During episodes of fever or upper respiratory tract infection, prednisolone may be given every day at a dose of 0.5 mg/kg (15 mg/m^2) for 5–7 days, to prevent infection-triggered relapses.

During therapy, patients should be closely monitored for development of steroid toxicity, including obesity, short stature, impaired glucose tolerance, cataract, raised intraocular pressure, and osteoporosis. Repeated courses of prolonged prednisolone therapy are avoided. Patients who continue to relapse while on alternate-day prednisolone and/or show features of steroid toxicity should be considered for steroid-sparing therapy **(Flowchart 2)**.

Steroid-resistant Nephrotic Syndrome

The management of these patients is challenging because of variable response to immunosuppression, therapy- and disease-related adverse effects, and risk of progression to kidney failure. These patients should be managed by pediatric nephrologists.

Supportive Care

Patients with nephrotic syndrome require monitoring, early identification, and prompt treatment of complications resulting from disease or its therapy.

Edema

Patients with mild edema do not require diuretic therapy. Furosemide is effective in patients with moderate edema. Intravenous (IV) albumin (5%) is indicated in patients with hypovolemia and is coadministered with IV furosemide in patients with severe edema that is refractory to furosemide therapy.

Infections

Peritonitis, pneumonia, and cellulitis are the chief infectious complications and account for the majority of hospitalizations. Their management should follow standard guidelines.

Immunization

All children should receive age-appropriate killed, subunit or inactivated vaccines, including those against *Pneumococcus*, influenza, and hepatitis B. Live vaccines are avoided until off immunosuppressive therapy for >1 month (≥3 months for cyclophosphamide and ≥6 months for rituximab). Oral polio vaccine is avoided in immunocompetent siblings and household contacts.

Treatment of Nephrotic Syndrome

Supportive Care

Diet

Foods rich in salt (e.g., bread, cornflakes, processed cheese, sauces, potato chips, salted nuts, papad, pickles, and preserved foods like canned vegetables and soups) should be avoided in the presence of significant edema. There is no need for salt and fluid restriction except in severe edema or during severe acute kidney injury.

Hypertension

Lifestyle measures, restricting salt intake, and avoiding prolonged prednisolone dosing are sufficient in most cases. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are drugs of choice if medication is necessary.

Monitoring

Patients with frequently relapsing, steroid-dependent or steroid-resistant disease require monitoring of anthropometry. Clinical and biochemical evaluations are necessary to detect adverse effects of medications and to monitor estimated glomerular filtration rate (GFR).

Parent and Patient Education

Parents should be counseled about the natural history of nephrotic syndrome, stressing on the relapsing-remitting course of the illness, and the need to ensure normal diet, schooling and activities, while monitoring for relapses by urine dipstick testing. They should be aware of the warning signs for relapse and serious infections, and the need for regular follow-up.

Further Reading

- ☑ Sinha A, Bagga A, Banerjee S, Mishra K, Mehta A, Agarwal I, et al. Steroid sensitive nephrotic syndrome: revised Guidelines. Indian Pediatr. 2021:58:461-81.
- ☑ Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health. 2018;2:880-90.
- ☑ Vasudevan A, Thergaonkar R, Mantan M, Sharma J, Khandelwal P, Hari P, et al. Consensus guidelines on management of steroid-resistant nephrotic syndrome. Indian Pediatr. 2021:58:650-66.