**Idiopathic nephrotic syndrome in children**

Idiopathic nephrotic syndrome is the most frequent pediatric glomerular disease, affecting from 1.15 to 16.9 per 100,000 children per year globally. It is characterized by massive proteinuria, hypoalbuminemia, and/or concomitant edema. The majority of affected children (ca. 85%) show complete remission of proteinuria within 4–6 weeks with daily prednisolone/prednisone (PDN) and have steroid-sensitive NS (SSNS). However, about 70–80% of patients will experience at least one relapse during follow-up. About 50% of patients have frequent relapses or are steroid-dependent.

**Definitions.**The current definition of NS requires both nephrotic-range proteinuria (urinary protein/creatinine ratio (UPCR) 2 mg/mg (≥ 200 mg/mmol)) and a serum albumin of < 30 g/L, edema.

**Classification**

It is classified based on the underlying cause: primary NS, secondary NS, and congenital and infantile NS.

## Pathophysiology

### Immune dysregulation and the identification of anti-nephrin autoantibodies

Immune dysregulation is the primary mechanism in the majority of cases with INS, which leads to the production of a circulating glomerular permeability factor. This alters the structure of the podocyte slit-diaphragm, where the main component is nephrin. INS arising from immune dysregulation is mostly steroid-sensitive. However, a subset of children is steroid-resistant and may respond to intensive immunosuppression, or rarely presenting as multi-drug-resistant NS with a high risk of post-transplant recurrence. There is mounting evidence to support the roles of both T and B cell dysregulation in the disease pathogenesis.

The identification of anti-nephrin autoantibodies as a potential candidate for circulatory factor in 2022 is the major breakthrough in the understanding of disease pathogenesis.

**History and physical examination** — In patients with NS, the history and physical examination should focus on potential complications and causes of NS. In particular, a comprehensive history and examination should include evaluation for the following:

●Potential complications, which may include the following:

•Pleural or pericardial effusion, ascites, or anasarca, which are complications of edema

•Thromboembolic events (ie, pulmonary embolism, deep vein thrombosis, cerebral veinous thrombosis, renal vein thrombosis)

•Peritonitis, cellulitis, or another serious bacterial infection

•Tachycardia, suggesting hypovolemia

•Hypertension

•Pancreatitis

**Clinical Features**

 Oedema:

• Most children with nephrotic syndrome present with oedema. However, it doesn’t occur in every patient.

• Commonly affected areas at presentation are periorbital, sacral, lower extremities and genital (i.e. scrotal or labial) areas.

• The oedematous areas are soft and pitting with no erythema.

• Oedema can progress into anasarca (i.e. generalized and massive oedema), which may present as any of the following:

- Marked peripheral oedema

- Abdominal distension resulting from ascites

- Pleural and/or pericardial effusions

- Marked scrotal or vulvar oedema

- Severe periorbital oedema resulting in swollen shut eyelids.

 Extrarenal causes of edema should be considered including hepatic (hepatocellular insufficiency, cirrhosis, Budd-Chiari syndrome), digestive (exudative enteropathy, coeliac disease, lymphangiectasis), severe malnutrition, heart failure, hereditary angioneurotic edema, capillary leak syndrome, and thyroid abnormalities.

# Diagnosis

**Confirming the diagnosis** — The diagnosis of NS is made when **both** nephrotic range proteinuria and hypoalbuminemia are present:

●**Nephrotic range proteinuria** – Nephrotic range proteinuria is usually defined as >50 mg/kg/day or 40 mg/hr/m2 in a 24-hour urine collection.

●**Hypoalbuminemia** – The plasma albumin level in NS is less than 3 g/dL (30 g/L).

**Additional laboratory evaluation**

**•Urinalysis with microscopy**

**•Blood urea nitrogen (BUN) and creatinine**

**•Complement studies**

**•Complete blood**

**•Serum lipids**

**•Serum electrolytes**

**Subsequent evaluation** — Options for the next steps in the evaluation of NS include:

●Genetic testing to evaluate for an inherited form of NS.

 ●Kidney biopsy to establish a histologic diagnosis.

**Indication of Kidney biopsy**

* patients with atypical features including macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash
* patients with infantile onset NS if genetic screening is not available (age 3–12 months)
* patients > 12 years of age on a case-by-case basis
* in patients with persistent microscopic hematuria in specific populations with a high incidence of glomerular diseases such as IgA nephropathy
* in patients diagnosed with SRNS.

**Simptomatic treatment**

**Salt restriction** — Edema is treated by salt restriction because renal retention of sodium is one of two principal mechanisms that lead to edema in the NS. Dietary salt intake should be restricted to less than 2 to 3 mEq/kg per day.

**Diuretics**

[**Furosemide**](https://www.uptodate.com/contents/furosemide-pediatric-drug-information?search=tratament%20simptomatic%20nephrotic%20sindrom%20children%20uptodate&topicRef=6113&source=see_link) – We give furosemide orally or intravenously (IV), in the following doses:

•Orally – We start with 2 mg/kg once or twice daily

•IV – We start with 1 to 2 mg/kg/dose and give a second dose after six hours, if needed, to a maximum dose of 6 mg/kg

**Patients with edema and intravascular hypovolemia** — For patients with any degree of edema (including anasarca, or generalized and massive edema) and evidence of intravascular hypovolemia (ie, tachycardia, peripheral vasoconstriction, oliguria, FENa <0.2 percent), we give IV albumin **and [furosemide](https://www.uptodate.com/contents/furosemide-pediatric-drug-information?search=tratament%20simptomatic%20nephrotic%20sindrom%20children%20uptodate&topicRef=6113&source=see_link)**, as follows:

●We start with an IV infusion of salt-poor albumin, 0.5 to 1 g/kg given over four hours

●We give IV **[furosemide](https://www.uptodate.com/contents/furosemide-pediatric-drug-information?search=tratament%20simptomatic%20nephrotic%20sindrom%20children%20uptodate&topicRef=6113&source=see_link)** at 1 mg/kg per dose in the middle and/or at the end of the albumin perfusion.

**Fluid restriction** — Although there is debate on the role of fluid restriction, initial restriction of fluid intake to an equivalent volume of the patient's insensible losses plus his/her urine output will result in stabilizing the patient's weight without further accumulation of edema.

●**Reducing thromboembolic risk**

●**Reducing infectious risk**

●**Dyslipidemia**

●**Hypothyroidism**

●**Hypertension**

* **Initial treatment of NS in children** We recommend that oral glucocorticoids be given for 8 weeks (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) or 12 weeks (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) (1B).
* The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m2 per day or 2 mg/kg per day (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40 mg/m2 or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60

mg/m2 per day (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m2 or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.

**Treatment of relapses of NS in children**

* The initial approach to relapse should include oral prednisone or prednisolone as a single daily dose of 60 mg/m2 per day or 2 mg/kg per day (maximum 60 mg per day) until the child remits completely for ≥3 days.
* After achieving complete remission in steroid-sensitive nephrotic syndrome patients treated for relapse, reduce oral prednisone/prednisolone to 40 mg/m2 or 1.5 mg/kg (maximum 50 mg) on alternate days for ≥4 weeks.
* For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.
* For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day oral prednisone/prednisolone (optimally ≤0.5 mg/kg per day) can be prescribed to prevent relapse.

Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.

**Complications of NS** may be the presenting symptoms or signs of the disease (e.g., abdominal pain related to severe hypovolemia, ascites, peritonitis, or pneumonia, dyspnea as a consequence of pleural effusion, ascites, pneumonia, or pulmonary embolism).

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