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Childhood nephrotic syndrome: Recommendations for management

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ABSTRACT

These recommendations from the Sociedad Argentina de Pediatría on childhood nephrotic syndrome update the 2014 recommendations with the most recent international evidence, including the 2025 KDIGO guideline. They comprehensively cover diagnosis, classification, immunosuppressive and non-immunosuppressive treatment, complications, indications for genetic testing and renal biopsy, and the vaccination schedule for childhood nephrotic syndrome. The goal is to provide pediatricians with a practical, up-to-date tool to unify diagnostic and therapeutic criteria across variable local clinical practice.

Keywords: *nephrotic syndrome; drug resistance; glucocorticoids, therapeutic use; immunosuppressive agents, therapeutic use.*

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1. What is the goal of these recommendations?

Nephrotic syndrome (NS) is the most common primary glomerulopathy in childhood. It typically follows a relapsing course, requiring prolonged treatment and having a significant impact on the quality of life of patients and their families. In 2014, the Committee on Nephrology of the Sociedad Argentina de Pediatría (SAP) published the *Recommendations for the Treatment of Steroid-Sensitive Nephrotic Syndrome in Childhood*.[1] Since then, evidence regarding the diagnosis, evaluation, and treatment of childhood NS has expanded considerably, with the publication of new international guidelines[2,3] that have led to changes in definitions, corticosteroid regimens, and the use of steroid-sparing agents.

Considering this, and given the variability observed in local clinical practice, the Committee updated the national recommendations with the aim of standardizing diagnostic and therapeutic criteria adapted to the realities of pediatric practice in Argentina.

2. How is nephrotic syndrome defined?

Nephrotic syndrome is defined by the triad of massive proteinuria, hypoalbuminemia and edema (*Table 1).*

- Massive proteinuria: loss ≥50 mg/kg/day or ≥40 mg/m²/hour, or urine protein/creatinine

Table 1. Key definitions

Term	Abbreviation	Definition
Nephrotic-range proteinuria	—	Urinary protein loss ≥50 mg/kg/day or ≥40 mg/m²/hour, or urine protein creatinine ratio (UPC) on a first-morning spot sample ≥2 (expressed in mg/mg).
Hypoalbuminemia	—	Defined as albumin <3 g/dl, generally associated with edema and hypercholesterolemia.
Complete remission	CR	UPC (based on first-morning void or a 24-hour urine sample) ≤0.2 mg/mg or <100 mg/m² per day, respectively, or negative/trace dipstick on three or more consecutive days.
Partial remission	PR	UPC (based on first-morning void or a 24-hour urine sample) >0.2 mg/mg but <2 mg/mg, and serum albumin ≥30 g/L.
Steroid-sensitive NS	SSNS	Complete remission within 4 weeks of PDN at the standard dose (60 mg/m²/day or 2 mg/kg/day, maximum 60 mg/day).
Steroid-resistant NS	SRNS	Failure to achieve complete remission within 4 weeks of standard-dose PDN treatment.
Confirmation period	—	The 4-to-6-week period from the start of PDN during which responses to further oral PDN and/or IV methylprednisolone pulses and RAAS blockade are determined in patients who achieve only partial remission at 4 weeks. A patient who does not achieve complete remission at 6 weeks, despite partial remission at 4 weeks, is defined as SRNS.
Late responder	—	A patient who achieves complete remission during the confirmation period (4 to 6 weeks of PDN therapy).
Relapse	—	Urine dipstick ≥3+ (≥300 mg/dl) or UPC ≥2 mg/mg on a spot urine sample on 3 consecutive days, with or without recurrence of edema, in a child who had previously achieved remission.
Frequent relapser	FRNS	≥2 relapses in the first 6 months after remission of the initial episode, or ≥3 relapses in any 12-month period.
Steroid-dependent nephrotic syndrome	SDNS	A patient with SSNS who experiences 2 consecutive relapses during the PDN therapy recommended for the first presentation or relapse, or within 14 days of its discontinuation.
Late steroid-resistant NS	—	A patient with SSNS who, on a subsequent relapse, does not achieve complete remission within 4 weeks of standard-dose PDN.

Note: *These definitions apply equally to treatment with prednisone (PDN) or meprednisone, the usual equivalence used in Argentina (4 mg of meprednisone = 5 mg of PDN; see Question 5).*
Adapted from Trautmann A, et al. Pediatric Nephrology. *2023;38:877–919.*

ratio (UPC) on a first-morning sample ≥2 mg/mg.
- Hypoalbuminemia: serum albumin <3 g/dl.
- Complete remission: UPC ≤0.2 mg/mg (or <100 mg/m²/day) or negative/trace dipstick on ≥3 consecutive days.
- Partial remission: UPC between 0.2 and 2 mg/mg, with serum albumin ≥3 g/dl.
- Steroid sensitivity (SSNS): complete remission within 4 weeks of treatment with prednisone (PDN) 60 mg/m²/day (or 2 mg/kg/day, max. 60 mg/day).
- Steroid resistance (SRNS): failure to achieve remission after 4 weeks of treatment with PDN 60 mg/m²/day.
- Confirmation period: between weeks 4 and 6 from the start of PDN, during which extending oral PDN, administering IV methylprednisolone pulses and/or starting RAAS blockade is considered in patients with partial remission at 4 weeks.
- Late responder: complete remission achieved during the confirmation period (weeks 4-6).
- Relapse: urine protein dipstick ≥3+ or UPC ≥2 mg/mg on ≥3 consecutive days, in a patient previously in remission.
- Frequent relapser: ≥2 relapses in the first 6 months after the initial episode, or ≥3 relapses in any 12-month period.
- Steroid dependence (SDNS): 2 consecutive relapses during PDN treatment (for the first episode or a relapse), or within 14 days of its discontinuation.

3. How is nephrotic syndrome classified?

Proteinuria results from increased permeability of the glomerular capillary wall due to podocyte dysfunction or injury, of immune cause (cytokines or circulating permeability factors) or due to genetic mutations that alter the structure of the filtration barrier.

- Primary or idiopathic NS: the most common form (>90% of cases between 1 and 10 years; 50% in those over 10 years); histologically corresponds in most cases to minimal change disease.[1]
- Secondary NS (~5% of cases between 0 and 12 years): associated with autoimmune diseases, infections (hepatitis B/C, HIV, EBV, CMV, parvovirus B19), drugs, metabolic or neoplastic causes.
- Congenital NS (<3 months): primary (>85% genetic basis) or secondary to congenital/acquired infections.
- Infantile NS (3-12 months): two-thirds of cases have a genetic basis and an unfavorable prognosis.

4. How is edema managed?

Do all patients with NS present with edema? What are its characteristics? Edema is the most frequent clinical sign at the first episode of NS, although it is not always present during relapses. It is soft and pitting, typically located in dependent areas, and may vary throughout the day. It can progress to anasarca (>30% of body weight), limiting physical activity, and can involve serous membranes (ascites, pleural effusion) and genitalia (scrotum, vulva), especially when albumin is <2 g/dl. Edematous patients frequently present with hyponatremia, secondary to elevated ADH levels and an inability to excrete excess water.

How does edema occur? It is due to primary or secondary retention of sodium and water in the interstitium, from an imbalance between the forces that retain fluid in the intravascular compartment (oncotic pressure) and those that promote its exit (venous pressure, vascular permeability), or from altered lymphatic drainage. It is explained by two complementary theories (*Table 2*): the "underfill" theory, or effective hypovolemia, in which hypoalbuminemia from massive proteinuria reduces oncotic pressure and effective arterial volume, activating the RAAS, the sympathetic system and ADH, and inhibiting atrial natriuretic peptide (ANP); and the "overfill" theory, or effective hypervolemia, in which renal sodium retention is primary and independent of hypoalbuminemia, with an active role for filtered plasminogen —converted to plasmin by urokinase in the distal tubule— which sustainedly activates the epithelial sodium channel (ENaC).[4]

How is intravascular volume status assessed? Physical examination and vital signs (especially blood pressure) should be used to determine whether edema corresponds to underfill or overfill before indicating diuretics or albumin, as management is opposite in each scenario. When in doubt, a chest X-ray to estimate the cardiothoracic index, or the fractional excretion of sodium (FENa), may be useful, although the latter can be influenced by sodium and water intake and by diuretic use or RAAS blockade.

When should pharmacological intervention be considered? In the presence of anasarca, pharmacological intervention is suggested for: respiratory compromise (mechanical difficulty,

Table 2. Pathophysiology of edema: underfill vs. overfill

Underfill	Overfill
Clinical: hypotension, cold extremities, tachycardia, delayed capillary refill	Clinical: normal or elevated BP, no tachycardia
Oliguria	No oliguria
FENa <0.2%	FENa >0.2-0.5%
Albumin <2 g/dl	Albumin >2 g/dl
Increased circulating renin and aldosterone	Decreased circulating renin and aldosterone
Decreased ANP	Increased ANP

Adapted from Kallash M, et al. Pediatric Nephrology.*2021;36:1719-30.*

pleural effusion and/or hypoxia), congestive heart failure, volume-dependent hypertension, oliguria due to acute kidney injury, skin infection/cellulitis, symptomatic ascites, severe scrotal or labial edema, or generalized discomfort (for example, difficulty moving).

Can albumin be used? What about diuretics? In underfill, priority is given to expanding intravascular volume: 20% albumin (0.5-1 g/kg over 4-6 h) combined with furosemide (1-2 mg/kg midway through and/or at the end of the infusion). The initial furosemide dose is 1-2 mg/kg/dose in children <20 kg, or 20-40 mg/dose in older children, every 6-12 h orally; up to 10-40% of patients do not respond to the oral route (due to high sodium intake, decreased glomerular filtration rate, intestinal edema, or hypoalbuminemia, which reduces drug transport), potentially requiring continuous intravenous infusion. In underfill with significant hypoalbuminemia, albumin should always be combined with the diuretic, to avoid exclusive diuretic use worsening intravascular volume contraction.

In overfill, albumin should be avoided, due to the risk of volume overload and pulmonary edema; natriuresis with diuretics alone is prioritized, and in this scenario can be combined with fluid restriction and a low-sodium diet. Diuretics alone may also be used in euvolemic patients with FENa >0.2%, in whom this is safe and effective.

In refractory edema, spironolactone (1-3 mg/kg/day), a thiazide diuretic if there is weight gain >10%, or amiloride combined with loop diuretics and thiazides may be considered; evidence on these last two remains limited in children.

How are fluids and sodium managed? Routine fluid restriction is not recommended, except in hyponatremia (<130 mEq/L), hypervolemia or severe edema; liquid foods at room temperature (milk, juice, yogurt, ice cream, soup) should be accounted for when assessing intake.

In moderate edema with preserved intravascular volume, a low-sodium diet of 2-3 mEq/kg/day of sodium is recommended (maximum 2000 mg/day of sodium in older children, equivalent to approximately 5 g of sodium chloride); a normal-sodium intake is suggested during remission (see *Table 3*, with age-based reference values).

5. What is the initial immunosuppressive treatment?

Steroid treatment (prednisone, PDN) is effective in children older than 1 year with a typical presentation of primary NS; in infants 3-12 months old the evidence is limited, and the decision depends on the feasibility of genetic testing and/or renal biopsy. One of the following oral PDN regimens is recommended:

- 4 weeks at 60 mg/m²/day (or 2 mg/kg/day, max. 60 mg), followed by 4 weeks at 40 mg/m²/day (or 1.5 mg/kg) on alternate days (max. 40 mg).
- 6 weeks at the same daily dose, followed by 6 weeks on alternate days.

It is important to note that in Argentina it is common to use meprednisone instead of PDN (equivalence: 4 mg meprednisone = 5 mg PDN), while international guidelines always refer to PDN. A single morning dose is recommended to favor adherence and reduce suppression of the hypothalamic-pituitary-adrenal axis. Approximately 85% of patients achieve complete remission with the standard regimen. Guidelines such as those from India[5], the Italian Society of Pediatric Nephrology[6] and the German Society[7] recommend 6 daily weeks followed by 6 weeks on alternate days. KDIGO[8] and IPNA[2] propose

Table 3. Sodium and sodium chloride recommendations by age

Age	Sodium	Sodium chloride
0-6 months	120 mg/day or 1-2 mEq/kg	300 mg
7-12 months	370 mg	925 mg
1-3 years	1000 mg	2500 mg
4-8 years	1200 mg	3000 mg
9-18 years	1500 mg	3750 mg

Adequate intake values for the general pediatric population; these are not restriction targets. Sodium chloride calculated as sodium × 2.5. Adapted from Institute of Medicine (US). Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: National Academies Press; 2005.

adapting duration to clinical response: 8 weeks if remission occurs in <7 days, up to 16-24 weeks in younger patients with later remission. The dose can be calculated by weight or by body surface area, but the two methods are not equivalent and can differ significantly, especially if weight is <30 kg and/or the total dose is <60 mg/day; weight and height should both be used to calculate body surface area.[9] The maximum recommended dose is 60 mg/day; some European guidelines recommend up to 80 mg/day.[7]

6. How are relapses treated and steroids discontinued?

For a relapse, recent international guidelines recommend PDN 2 mg/kg/day or 60 mg/m² (max. 60-80 mg) until remission, followed by 1.5 mg/kg/day or 40 mg/m² on alternate days for 4 weeks, with abrupt discontinuation.[2] The 2014 SAP Consensus alternatively proposed continuing the daily dose up to 5 days after remission, followed by the same alternate-day regimen for 4 weeks.

IPNA guidelines recommend abrupt discontinuation after completing the initial regimen.[2] The 2014 SAP Consensus suggests, in frequent relapsers, a gradual 25% reduction every 15 days on alternate days down to less than 0.5 mg/kg on alternate days, maintained for 6 to 12 months[1] — that is, a progressive taper rather than abrupt discontinuation. Separately, according to the SAP guidelines on safe corticosteroid therapy, in treatments longer than 10-15 days the risk of hypothalamic-pituitary-adrenal axis suppression should be estimated: if high, treatment does not move directly to hydrocortisone; instead, the corticosteroid in use is first reduced by 25% every 4-7 days down to a dose equivalent to the physiological replacement dose (10-12 mg/m²/day of hydrocortisone); only then is the taper completed with hydrocortisone, divided every 12 h for 7-10 days, and then at half that dose as a single morning dose for another 7-10 days. Stress-dose precautions should be maintained for 9 to 12 months after discontinuation.[10]

Routine use of steroids during respiratory infections to reduce relapse risk is not recommended,[2,8] although a short, low-dose course may be considered in frequent relapsers or steroid-dependent patients with relapses associated with infections.

7. When to indicate steroid-sparing agents?

These are indicated for frequent relapsers, or in steroid-dependent patients whose relapses are associated with poor general condition, anasarca, toxicity or infections.[2] The choice should be individualized based on age, pubertal status, sex, accessibility, cost and adverse-effect profile. In frequent relapsers, levamisole is suggested as first-line therapy; in steroid-dependent NS, first-line options are mycophenolate or cyclophosphamide, with calcineurin inhibitors as second line; if these fail, rituximab is considered.

- Levamisole: 2-2.5 mg/kg on alternate days (max. 150 mg/dose), with low-dose steroids.[11] If effective, discontinuation is considered at 2 years; response should be assessed at 6-12 months.
- Mycophenolate mofetil (MMF) / mycophenolate sodium (MPS): increasing doses up to 1200 mg/m²/day administered in two divided doses every 12 h (max. 3000 mg/day); 360 mg of MPS is equivalent to 500 mg of MMF.
- Cyclophosphamide (recommended in pre-adolescent patients, as the risk of gonadotoxicity depends on gonadal activity at the time of treatment and on the cumulative dose[2]): 2 mg/kg/day orally (max. 150 mg/day) for 12 weeks, or 3 mg/kg/day (max. 150 mg/day) for 8 weeks, single morning dose preferable; no more than one course (maximum cumulative dose: 168 mg/kg). Give with alternate-day oral PDN, starting at 40 mg/m² (1.5 mg/kg) and tapering to 10 mg/m² (0.3 mg/kg) over treatment. Alternative: a

single course of monthly IV pulses (500 mg/m²/dose, max. single dose 1 g) for 6 months.[12,13]
- Calcineurin inhibitors: tacrolimus 0.1-0.2 mg/kg/day in 2 doses (target trough T0 level 3-7 ng/ml); cyclosporine 3-5 mg/kg/day in 2 doses (target trough T0 level 60-100 ng/ml, or T2 —2 h post-dose— 300-550 ng/ml).
- Rituximab: 375 mg/m²/dose, 1-4 doses (max. 1000 mg/dose), with premedication; the indication depends on the specialist's experience and the type of glomerulopathy.

8. What are the adverse effects of immunosuppressive treatment?

Each immunosuppressive drug has a particular adverse-effect profile that requires specific clinical and laboratory monitoring (see comparative drug *Table 4* and *Figure 1*, with the stepwise treatment algorithm):
- Steroids (low-dose, alternate-day or daily): obesity/weight gain, hypertension, diabetes, behavioral or psychiatric disturbances, sleep disturbances, growth delay, cushingoid features, striae, glaucoma, cataracts, bone pain, and avascular necrosis.
- Levamisole: neutropenia, rash (which usually resolves with discontinuation), vasculitis, gastrointestinal symptoms and hepatotoxicity; rarely, neurological symptoms. In a cohort of 210 children treated for ≥12 months, 18% had positive ANCA (mostly p-ANCA) without clinical symptoms, which resolved on drug discontinuation.[14]
- MMF/MPS: abdominal pain, diarrhea and weight loss (may improve with MPS), leukopenia, anemia, abnormal liver function tests, and warts; more adverse events are seen in children under 6 years. Warn about teratogenicity in individuals of childbearing potential.
- Cyclophosphamide: infections, leukopenia, alopecia, nail discoloration, seizures, infertility, gastrointestinal symptoms, hemorrhagic cystitis (due to acrolein, more common with the IV route), and jaundice; dose-dependent oncogenic potential. Consider GnRH analogs for ovarian preservation in pubertal girls if the total dose will be ≥5 g.
- Calcineurin inhibitors: acute and chronic nephrotoxicity, hypertension, seizures, tremor, posterior reversible encephalopathy syndrome (PRES), and diabetes; risk of toxicity from drug interactions (macrolides, certain antiepileptics, grapefruit juice). Cyclosporine can cause hirsutism and gingival hyperplasia. Consider discontinuation or renal biopsy after 2-3 years of treatment to prevent or detect toxicity.
- Rituximab: infusion reactions, infections, reactivation of latent viruses, and transient or persistent IgG deficiency; possible serious adverse events include tuberculosis, hepatitis B, JC virus infection, and progressive multifocal leukoencephalopathy. Active infections must be ruled out before starting treatment.

9. What non-immunosuppressive measures are recommended?

- Maintain sodium restriction (2-3 mEq/kg/day of sodium, maximum 2000 mg/day of sodium in older children) during periods of edema; normal-sodium intake during remission.
- Protein intake of 1-2 g/kg/day according to age, avoiding high-protein diets that could favor progression of kidney disease.
- Routine supplementation with calcium and vitamin D, gastric protectants (PPIs), or thyroid hormone is not advised without a specific clinical indication; thyroid function should be evaluated in patients with persistent proteinuria.
- Encourage regular physical activity: at least 1 hour daily of moderate-to-vigorous activity, with vigorous activity at least 3 times per week in children over 5 years, and limit screen time to less than 2 hours per day.
- Monitor blood pressure in all patients (between 7% and 34% of patients with steroid-sensitive NS may present with hypertension); avoid RAAS blockers (ACE inhibitors/ARBs) during relapses or in the presence of hypovolemia, due to the risk of acute kidney injury.
- Perform periodic ophthalmologic examinations during steroid treatment, to detect ocular hypertension and posterior subcapsular cataract.
- Use sunscreen (SPF 30-50) and photoprotection measures in all patients on maintenance immunosuppression with steroid-sparing agents.
- Implement structured transition programs to adult nephrology, with progressive education of the patient and family.

10. What vaccines should patients with NS receive?

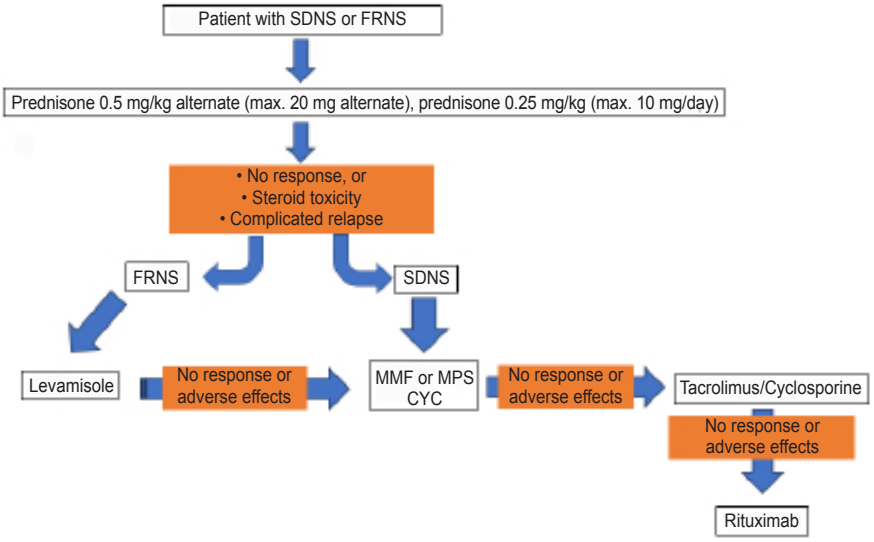
Vaccination status should be reviewed at diagnosis, and inactivated vaccines from the national schedule should be completed without delay, with special attention to encapsulated

Table 4. Comparative table of immunosuppressive drugs: dose, monitoring, adverse effects and cost

Drug / Dose	Monitoring	Adverse effect	Cost
Low-dose alternate-day prednisone (≤0.5 mg/kg/day alternate, max. 20 mg alternate) / Low-dose daily prednisone (≤0.25 mg/kg/day, max. 10 mg/day).	Quarterly: blood pressure, height, weight. Every 6 months: glucose. Annual: eye exam and HbA1c.	Obesity/weight gain, hypertension, diabetes mellitus, behavioral/psychiatric disturbances, sleep disturbances, growth failure, cushingoid features, striae, glaucoma, cataracts, bone pain, avascular necrosis.	Low
High-dose prednisone / induction: 60 mg/m²/day or 2 mg/kg/day (max. 60 mg/day; some European guidelines allow up to 80 mg/day) for 4-6 weeks, followed by the same dose on alternate days for an additional 4-6 weeks (see Question 5).	Baseline glucose and at 4 weeks of treatment; more frequent monitoring (every 1-2 weeks) if risk factors are present (obesity, family history of diabetes, prolonged dose ≥2 mg/kg/day). Every 4 weeks: blood pressure, weight, height.	Same profile as the maintenance dose, with a higher acute risk of hyperglycemia or steroid-induced diabetes, and risk of transient adrenal insufficiency upon discontinuation (see Question 11).	Low
Levamisole: 2-2.5 mg/kg on alternate days (max. 150 mg).	Quarterly: complete blood count, liver function tests. ANCA at baseline and every 6 months.	Neutropenia, vasculitic rash, arthritis, gastrointestinal symptoms and abnomal liver function tests; less frequently, neurological manifestations.	Low
Mycophenolate mofetil (MMF): 1200 mg/m²/day in 2 doses (max. 3000 mg). MPS: 360 mg equivalent to 500 mg MMF.	Quarterly: complete blood count, liver function tests.	Abdominal pain, diarrhea, weight loss (may improve with MPS), leukopenia, anemia, pancytopenia, headache, paresthesia, cramps, abnormal liver tests, warts, and increased risk of skin cancers, (MPS >MMF).	High
Cyclophosphamide: 2 mg/kg/day orally (max. 150 mg) x 12 weeks, or 3 mg/kg/day (max. 150 mg) x 8 weeks, single morning dose preferable; or alternatively, a single course of monthly IV pulses (500 mg/m²/dose, max. single dose 1 g) for 6 months. Give with alternate-day oral PDN (starting 40 mg/m², tapering to 10 mg/m²). No more than one course. Maximum cumulative dose: 168 mg/kg.	Complete blood count every 14 days during treatment.	Leukopenia, serious infections, alopecia, nail discoloration, seizures, infertility, gastrointestinal symptoms, hemorrhagic cystitis, jaundice, and dose-dependent oncogenic risk.	Low
Tacrolimus: 0.1-0.2 mg/kg/day in 2 doses (max. 10 mg). Target trough level: 3-7 ng/ml (aiming for the lowest level that maintains remission).	Quarterly: blood pressure, complete blood count, creatinine, glomerular filtration rate, K+, liver function tests, cholesterol/TG, magnesium, glucose, drug level.	Acute and chronic nephrotoxicity, , hypertension, seizures, tremor, PRES, diabetes mellitus, and risk of toxicity from drug interactions (macrolides, certain antiepileptics, grapefruit juice).	Intermediate
Cyclosporine: 3-5 mg/kg/day in 2 doses (max. 250 mg). Target trough level: 60-100 ng/ml (aiming for the lowest level that maintains remission).	Quarterly: blood pressure, complete blood count, creatinine, creatinine clearance, K+, liver function tests, cholesterol/TG, uric acid, drug level.	Acute and chronic nephrotoxicity, hypertension, seizures, tremor, cramps, hypomagnesemia, PRES, diabetes mellitus, hirsutism, gingival hyperplasia, and risk of toxicity from drug interactions.	Intermediate (less expensive than tacrolimus)
Rituximab: 375 mg/m²/dose, 1-4 doses (max. 1000 mg/dose). Premedicate with IV hydrocortisone, diphenhydramine and paracetamol.	Quarterly: complete blood count, liver function tests, CD19 count and %, IgG (baseline, quarterly during the first year, then annually).	Infusion reactions (including angioedema, bronchospasm and urticaria), neutropenia (including late onset, weeks after the infusion) and pancytopenia, infections, latent virus reactivation, IgG deficiency. Serious: tuberculosis, hepatitis B, JC virus, myocardial, dysfunction risk of progressive multifocal leukoencephalopathy.	High

Note: *The choice and sequence of these drugs is individualized according to age, pubertal status, sex, accessibility, and adverse-effect profile (see Question 7). In pre-adolescent patients, cyclophosphamide is preferred due to its lower risk of gonadotoxicity; in pubertal girls with an expected total dose ≥5 g, GnRH analogs should be considered for ovarian preservation. With levamisole, response should be assessed at 6-12 months, and discontinuation considered at 2 years if effective.*
Adapted from Trautmann A, et al. Pediatric Nephrology. 2023;38:877–919.

Figure 1. Stepwise treatment algorithm in SDNS and FRNS



Algorithm agreed upon by the Committee of Nephrology (SAP) for the stepwise use of steroid-sparing agents in steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS).

bacteria (pneumococcus, meningococcus, H. influenzae), the annual influenza vaccine, and COVID-19. Live attenuated vaccines (MMR, varicella, yellow fever) should also be completed whenever possible, although they require a safety interval relative to immunosuppressive treatment (see *Figure 2*). Household contacts should also be vaccinated against influenza and COVID-19; if live vaccines are contraindicated in the patient, it is recommended that household contacts receive them instead, as an indirect protection (cocooning) strategy.[2]

With high-dose steroids (≥2 mg/kg/day or ≥20 mg/day of prednisone for more than 14 days), live vaccines can be given starting one month after completing steroid therapy, ideally deferred up to 3 months; if starting steroids is planned, live vaccines should be given at least 15 days beforehand.[15] With other immunosuppressants, the interval depends on the drug (one month after levamisole, two months after calcineurin inhibitors or MMF, three months after cyclophosphamide, and six months after rituximab).[16]

All vaccine types are safe in patients with NS, both in terms of relapse and "de novo" onset,[17] and are effective even under immunosuppressive treatment, although seroconversion varies according to vaccine type and timing relative to proteinuria.[16]

11. What are the complications of NS and how are they treated?

Thrombosis: Thromboembolic risk is significantly increased in NS (incidence 2-5%) and decreases in remission; it is higher in the presence of associated complications (difficult-to-control edema, infections, hypovolemia) and lower in steroid-sensitive than in steroid-resistant patients; venous thromboses are more common than arterial ones.[18] Individual risk should be assessed, immobilization and hypovolemia avoided, and referral to Hematology made for patients with a family or laboratory history compatible with thrombotic predisposition.[2] In steroid-resistant NS or with difficult-to-control edema, thrombophilia screening is suggested, along with consideration of prophylaxis with low-molecular-weight heparin.[19] Extreme thrombocytosis (>1 000 000/mm³) during a relapse may require aspirin prophylaxis.

Infections: An estimated 60% of NS-related deaths are due to infectious processes, mainly encapsulated organisms such as *Streptococcus pneumoniae*.[2] Routine antibiotic prophylaxis is not recommended, except for *Pneumocystis jirovecii* chemoprophylaxis in patients on rituximab, up to 6 months after the last infusion.

Abdominal pain and fever during a relapse

should raise suspicion of spontaneous bacterial peritonitis, with blood cultures and empiric antibiotics against *S. pneumoniae*; some guidelines suggest ascitic fluid puncture, although culture yield is low. On exposure to varicella, risk should be assessed according to the immunosuppressant received, history, and vaccination status, and specific immunoglobulin or acyclovir/valganciclovir for 5-7 days should be indicated (ideally between day 7 and 10 post-contact); if varicella develops, IV acyclovir for 7-10 days is indicated and the immunosuppressant dose should be reduced.[20] For COVID-19, management is the same as in the general population, without reducing immunosuppression in mild cases, with relapse being the main possible complication.[21]

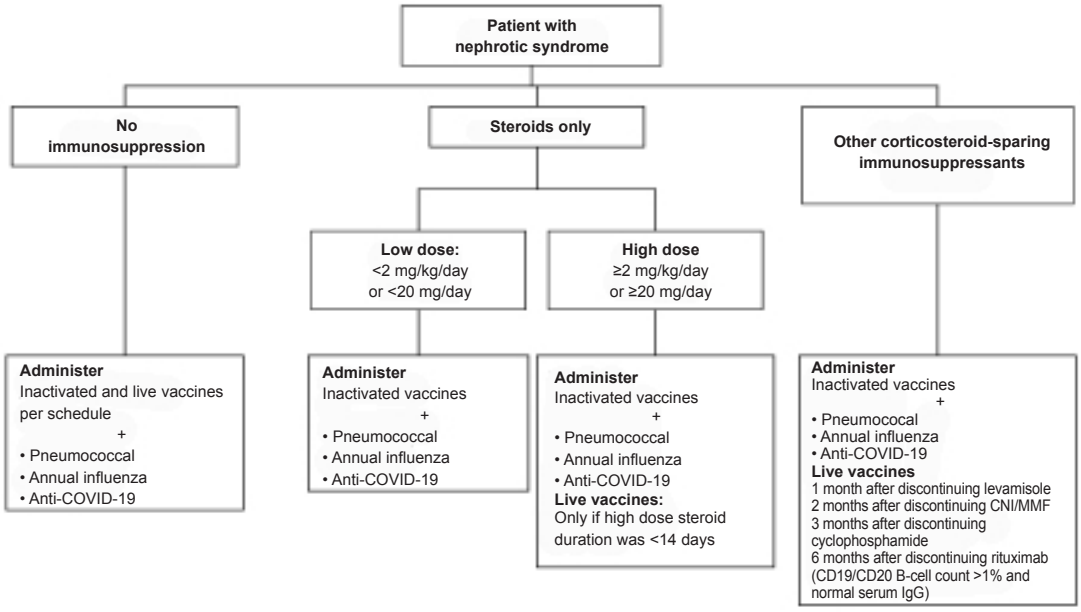
Dyslipidemia: Urinary losses of transport proteins and compensatory hepatic synthesis produce lipid abnormalities that can persist in remission and favor atherosclerosis;[22] elevated LDL levels correlate with higher cumulative steroid doses.[23] Lipid-lowering drugs are not recommended except in severe hypertriglyceridemia. Statins are limited to children over 10 years, with monitoring of liver function and CPK before starting, at 4 weeks, and periodically while receiving them.[24] First-line treatment is non-pharmacological: control of proteinuria and blood pressure, weight reduction, glycemic control, avoiding tobacco, and a healthy diet with lower intake of saturated fat and cholesterol.[24,25]

Adrenal insufficiency: Should be suspected with progressive fatigue, sweating, poor appetite, reduced exercise tolerance, nausea, vomiting, abdominal pain, hypotension, dizziness, or seizures due to hypoglycemia. It is recommended to shorten the duration and reduce the PDN dose as much as possible, and to inform the family about symptoms and emergency management. In patients on corticosteroid therapy for more than 10-15 days exposed to mild stress (fever, pain, minor procedures), consider oral hydrocortisone 20 mg/m² during the process; for severe stress or surgery, hydrocortisone 60 mg/m²/dose IV bolus, continuing 60 mg/m²/day for 48 h and then the mild-stress regimen for another 48 h before returning to the usual dose.[10]

12. Which patients benefit from genetic testing?

Genetic testing is especially indicated for: onset before 2 years of age —including congenital and infantile NS—, a family history of steroid-resistant NS, or the presence of syndromic features. It is also recommended in every patient with steroid-resistant NS, since between 25% and 33% of these present pathogenic variants

Figure 2. Schedule for live vaccine administration according to immunosuppressive treatment



Suggested intervals for administering live attenuated virus vaccines after discontinuation of each immunosuppressant.

in genes of the glomerular filtration barrier.[2,11] It provides an accurate etiological diagnosis, allows personalized treatment by avoiding unnecessary immunosuppression, provides family genetic counseling, and is essential at the time of kidney transplantation to guide management. It is recommended to start with next-generation sequencing (NGS) using a broad nephropathy panel, reserving whole-exome (WES) or whole-genome sequencing (WGS) for cases without a conclusive diagnosis.[26,27]

13. What are the indications for renal biopsy?

It is not routinely indicated in steroid-sensitive NS. It is recommended in the presence of an atypical presentation at onset: low C3, micro- or macrohematuria, nephrotic syndrome associated with nephritic syndrome, unexplained decline in glomerular filtration rate, or extrarenal symptoms (arthritis, rashes) — findings suggestive of secondary etiologies. In children older than 12 years, the indication should be assessed individually based on clinical history, response to initial treatment, and clinical course, considering it especially in the presence of atypical features or steroid resistance. Minimal change disease is the most frequent histological finding; the presence of IgM or C1q on immunofluorescence is associated with a worse prognosis.

14. What are the final recommendations?

- Encourage regular physical activity to prevent thromboembolic events during relapses, counteract steroid-associated weight gain, and reduce muscle and bone mass loss.
- Promote healthy nutrition, with with a low-salt diet (2-3 mEq/kg/day of sodium, max. 2000 mg/day of sodium in older children) during relapse with moderate or severe edema, and normal intake during remission, with protein intake in line with the general pediatric population. Suggest a nutrition consult when available.
- Initial clinical evaluation should include targeted history (edema, fever, pain, secondary causes), complete physical examination (blood pressure, volume status, signs of infection, extrarenal findings), vaccination status, family history, and laboratory studies (UPC, urine sediment, complete blood count, kidney function, electrolytes, albumin, lipid profile, serologies, C3/C4 complement, according to clinical suspicion).
- Renal ultrasound: in all children with NS to rule out malformations and venous thrombosis, especially in cases of impaired kidney function, hematuria, or abdominal pain. Always before renal biopsy.
- Chest X-ray: in indicated cases. ■

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