Nephrotic Syndrome Guideline

Definition:

Nephrotic syndrome (NS) is defined as the presence of nephrotic-range proteinuria (at least 3+ on urine dipstick, or >40 mg/m^2/h or >1.0 g/m^2/day in children), hypoalbuminemia (<2.5 g/dL in children), and edema. Hypercholesterolemia is commonly present.

Untreated NS can result in anasarca with pleural effusion, ascites, and acute kidney injury. Untreated patients are also at high risk for sepsis, thrombosis, hyperlipidemia and endocrine abnormalities.[5,8] The syndrome is characterized by episodic relapses in at least 80% of patients, often triggered by systemic insults such as viral or bacterial infections.[6,7]

Childhood nephrotic syndromes are most commonly caused by one of two idiopathic diseases: minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Membranous glomerulonephritis, a third distinct type, is rare in children. Other causes of isolated nephrotic syndrome can be subdivided into two major categories: rare genetic disorders, and secondary diseases associated with drugs, infections, or neoplasia. The cause of idiopathic nephrotic syndrome remains unknown.[10]

Courses of systemic corticosteroids are a mainstay of uncomplicated nephrotic syndrome treatment. However, over time, repeated episodes can result in both chronic kidney disease and the secondary effects of repeated and/or prolonged steroid exposure, such as obesity, insulin resistance, osteoporosis, stunted linear growth, and increased cardiovascular disease risk. Although 80% of new-onset NS are steroid sensitive and respond to initial therapy, patients with steroid resistance are at higher risk for developing chronic kidney disease.

Incidence:

The estimated incidence of pediatric nephrotic syndrome is approximately 2-16 per 100,000 children per year.[7] The overall incidence of childhood idiopathic nephrotic syndrome has been generally stable over the past three decades.

Ethnic origin may affect the histological variant and the response to immunosuppressive treatment. In particular, Hispanic and Black patients are more likely to have steroid unresponsive nephrotic syndrome than are white patients.[11]

MCD is the most common cause of NS in children, accounting for more than 75% of all pediatric cases and for 90% of cases in children under 5 years of age.[15] FSGS accounts for 7–20% of nephrotic syndrome cases in

children. It is observed more frequently in Afro-Caribbean patients than in Caucasians, with prevalence as high as 80% among nephrotic patients.[15]

Etiology/Epidemiology:

In the pediatric population, 90% of nephrotic syndrome is primary (i.e., idiopathic). Diagnosis is usually made prior to six years of age. Males are more commonly affected than females (2:1 predominance). Age at initial presentation has an important impact on the disease distribution frequency. 70% of MCD patients are younger than 5 years; 20–30% of adolescent nephrotic patients have MCD.[12] FSGS develops in children at a median age of 6 years. During the first year of life, congenital (birth to age 3 months) and infantile (3–12 months) genetic disorders and congenital infections are much more common than MCNS and FSGS.

Nephrotic syndrome can occur as a result of various disease processes. The vast majority (>70%) of idiopathic NS is due to minimal change disease, which is typically characterized by a favorable response to corticosteroid treatment. Less common causes of pediatric nephrotic syndrome include membranoproliferative glomerulonephritis (~8%) and focal segmental glomerulosclerosis (~7%). The rarer forms of nephrotic syndrome are more commonly steroid-resistant and may ultimately require modifications to treatment with progressive episodes to achieve remission. Certain forms of nephrotic syndrome are inherited and can be confirmed through genetic testing. Renal pathological findings may sometimes be discordant from the patient's clinical course.[1]

Relapses of nephrotic syndrome are often triggered by infectious insults such as viral or bacterial upper respiratory infections (URI), pneumonia, acute otitis media, or even acute asthma exacerbations.

Effects/Sequelae/Comorbidities: During acute nephrotic "flares" or episodes, due to resultant fluid overload, clinically significant hypertension requiring medical management or dietary changes can be seen in patients with nephrotic syndrome. Multiple comorbidities can also be associated with nephrotic syndrome as a byproduct of the increased glomerular permeability: a hypercoagulable state (due to loss of ATIII), an immunocompromised state (both due to loss of immunoglobulins and patients' frequent reliance on daily systemic corticosteroids during flares), increased risk of cardiovascular disease, or anemia due to loss of transferrin and ferritin.

Differential Diagnosis:

- **Allergic rhinitis**: Children with nephrotic syndrome often present with periorbital edema that can be mistaken for allergic rhinitis. If patients have received systemic corticosteroids prior to presentation, caregivers may have noted mild improvement in symptoms.
- **Cellulitis or large local reactions**: Superficial infections of the skin and soft tissues can often result in uncomfortable edema. Furthermore, a nephrotic syndrome flare can in turn be triggered by insect bites or superficial trauma, with or without bacterial superinfection. The edema in nephrotic syndrome is usually bilateral and diffuse, whereas with cellulitis it tends to be localized near the area of insult, and accompanied by other signs of inflammation such as erythema and warmth.
- **Diseases associated with secondary nephrotic syndrome**: Although primary nephrotic syndrome is more common in the pediatric population, causes of secondary nephrotic syndrome (e.g., underlying diseases such as systemic lupus erythematosus or chronic Hepatitis B infection) should be considered in the differential diagnosis.

- **Heart failure**: Myocarditis, cardiomyopathy, or previously undiagnosed congenital heart disease can be considered in the differential, as it may result in hypoalbuminemia and edema. Echocardiography may be helpful to determine the presence of pericardial effusions and cardiac function if clinical suspicion is high.
- **Other causes of hypoalbuminemia**: Protein-losing enteropathy, severe protein-calorie malnutrition, or cirrhosis can all result in fluid retention and edema.
- **Anaphylaxis/hereditary angioedema**: Lip and facial swelling with nephrotic syndrome can be quite severe, and exposure to potential allergens or toxic substances should be considered in the differential diagnosis. As with cellulitis, however, anaphylactic edema is often focal or limited to one body part, while edema due to nephrotic syndrome is progressively diffuse and dependent.

Guideline Inclusion Criteria:

All patients <18 years of age showing signs/symptoms of nephrotic syndrome including:

- *Generalized edema (anasarca)*
- *Pleural effusion*
- *Ascites*
- *Proteinuria and Hypoalbuminemia*

Guideline Exclusion Criteria:

- Patients with a prior known diagnosis of nephrotic syndrome
- Patients with congenital heart disease
- Patients already taking systemic corticosteroids for another illness (e.g., asthma, chronic lung disease)
- Consider excluding if gross hematuria
- Signs of shock at presentation after initial fluid resuscitation
- Signs of malignant hypertension or thromboembolic disease (i.e., renal vein or cerebral venous thrombosis) at presentation

Terms used to Define Response to Treatment in Children with Nephrotic Syndrome	
Remission	Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens.
Relapse	Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, after having been in remission previously.
Frequent Relapses	Two or more relapses in the initial 6-month period or more than 3 relapses in any 12 months.
Steroid Dependency	Two consecutive relapses when on alternate day steroid therapy, or within 14 days of its discontinuation.
Steroid Resistance	Failure to achieve remission despite full-dose therapy for 8 wk (ie, 4 wk of daily steroids followed by 4 wk of alternate-day therapy)

Nourbakhsh, N., & Mak, R. H. (2017). Steroid-resistant nephrotic syndrome: Past and current perspectives. Pediatric Health, Medicine and Therapeutics, 8, 29–37. https://doi.org/10.2147/PHMT.S100803

Critical Points of Evidence *This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive.*

Evidence Supports

Treatment Options

- Empiric corticosteroids to treat first episode (KDIGO)
  - Corticosteroids represent the mainstay of treatment in children with idiopathic NS. Prednisone and prednisolone are equivalent.
  - Steroid courses of 8-12 weeks (e.g., 4-6 weeks of daily corticosteroids followed by 4-6 weeks of alternate-day corticosteroids) are standard. There is not sufficient evidence demonstrating a benefit of 8 weeks vs 12 weeks of induction treatment. Decisions should be individualized for each patient based on treatment response (e.g., consider 8-week course for those achieving remission within 7 days of steroid initiation) and risk of comorbidities from steroid exposure (e.g., obesity, hypertension, diabetes mellitus, etc.). *(Strong Recommendation, Moderate Quality Evidence)*
- Steroid dosing based on body surface area, rather than weight
  - The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m2/d or 2 mg/kg/d (maximum 60 mg/d) in 1 to 3 divided doses for four or six weeks or until the patient becomes free of proteinuria. *(Strong Recommendation, Moderate Quality Evidence)*
  - After four to six weeks, give alternate-day prednisone/prednisolone, 40 mg/m2, or 1.5 mg/kg/d, for another four to six weeks.[3] Alternate-day corticosteroid dosing is part of the treatment regimen itself, and does not constitute a "taper." Subsequent tapering after the alternate-day dosing is not required. *(Strong Recommendation, Moderate Quality Evidence)*
  - Literature does indicate that dosing by weight, rather than body surface area, may potentially lead to underdosing.[4] *(Strong Recommendation, Weak Quality Evidence)*
  - Evidence does not show a benefit of using methylprednisolone over prednisone/prednisolone for induction but could be considered for patients who have not achieved remission by four weeks.[4] *(Strong Recommendation, Weak Quality Evidence)*
- Daily monitoring for albuminuria until instructed to stop by the nephrology team
- Short-course preventative steroids with mild viral/bacterial infections among patients with known nephrotic syndrome
  - For children with frequently-relapsing and steroid-dependent SSNS who are currently taking alternate-day corticosteroids or are off corticosteroids, daily corticosteroids (0.5 mg/kg/day) be given during episodes of upper respiratory tract and other infections for five to seven days to reduce the risk for relapse.[2] *(Strong Recommendation, Low Quality Evidence)*

Cyclosporin

- Cyclosporin is recommended for children who are steroid-dependent following multiple relapses or who have unacceptable steroid toxicity. Cyclosporine should be used in children who remain steroid-dependent despite a course of cytotoxic therapy.[2,15] *(Strong Recommendation, Moderate Quality Evidence)*
- *Tacrolimus may be used in place of cyclosporine due to more favorable side effect profile*

Renal Biopsy

- Renal biopsy and/or further investigation such as genetic testing, should be considered for patients who have not achieved remission by four weeks[2] *(Strong Recommendation, Moderate Quality Evidence)*

Relapses

- Most children (60%-80%) will have a number of relapses of NS, even if the longer initial course of prednisone is given. Such relapses are usually treated with a short course of high-dose daily steroids until the patient is free of proteinuria for 3 days, followed by a maintenance-tapering course of alternate day therapy for 4 to 6 weeks. Subsequent management will depend on the patient's responsiveness and number of relapses.[13] *(Strong Recommendation, Low Quality Evidence)*

Dietary Recommendations

- A low-sodium diet is recommended for patients with nephrotic syndrome while acutely proteinuric[18] *(Strong Recommendation, Low Quality Evidence)* Low sodium diet is preferred among hospitalized patients at our institution.
- Nonspecific treatment options for persistent proteinuria - It is reasonable to avoid an excess of dietary protein in children with proteinuric renal disease because high dietary protein intake may actually worsen proteinuria. It is recommended that children with proteinuria receive the recommended daily allowance of protein for age. [13] *(Weak Recommendation, Low Quality Evidence)*

Immunizations

- Take a comprehensive vaccination history, with particular attention to receipt of varicella and pneumococcal doses.
- Live viral vaccines should not be given to a child receiving high doses of steroids or other immunosuppressive drugs.
- Pneumococcal vaccine is recommended for all nephrotic children ideally after their NS is in remission and they are off daily prednisone, although there have been no controlled clinical trials demonstrating a direct clinical benefit from such vaccination. It is important to note that not all pneumococcal serotypes are included in the vaccine and that antibody levels in nephrotic patients may fall during a relapse. Consequently, previously vaccinated children may develop pneumococcal peritonitis and pneumococcal sepsis.[13,19] *(Strong Recommendation, Moderate Quality Evidence)*
- A varicella antibody titer should be obtained in all children with NS who have not been vaccinated or have not had chickenpox in the past, because this infection may be very serious in a nephrotic child taking steroids or other immunosuppressive agents.[2,13] *(Strong Recommendation, Weak Quality Evidence)*

Evidence Lacking/Inconclusive

- Checking C3 and C4 complement levels at presentation[20]
- PPI coadministration for gastric stress ulcer prophylaxis. The decision to add a prescription medication during steroid administration (vs. calcium carbonate or no additional medications) can be individualized based on degree of PO intake, and family/patient preferences regarding cost and/or pill burden[2]
- Vitamin D coadministration while taking a steroid course[1]
- Recommendations for diuresis vary widely based on individual patient presentation. There is insufficient evidence to recommend IV vs. PO Lasix following infusion of IV albumin.

Evidence Against

- Kidney biopsy with presenting episode. Response to a standard steroid dosing regimen and the number of relapses in the subsequent year allows classification of the child's NS, and this classification holds more prognostic value than a kidney biopsy, which is therefore not routinely performed at disease onset.[2]

Practice Recommendations and Clinical Management

Clinical Manifestation and Diagnosis:
The first sign of nephrotic syndrome noted by caregivers is often periorbital edema, especially in the morning, that worsens over time and then progresses to anasarca and possible volume overload. Nephrotic syndrome is characterized by the triad of edema, proteinuria and hypoalbuminemia; thus, both clinical and laboratory findings are used to confirm a NS diagnosis.

The diagnosis is confirmed by the presence of both nephrotic range proteinuria and hypoalbuminemia. Nephrotic range proteinuria in children is defined as urinary protein excretion greater than 50 mg/kg per day or 40 mg/m^2 per hour. Quantitative measurement of protein excretion is based upon a timed 24-hour urine collection. However, it is difficult to obtain accurately timed urine collections in young children. An alternative method of quantitative assessment of urine protein excretion is measurement of the total protein/creatinine ratio on a spot urine sample. Accordingly, the protein/creatinine (Pr/Cr) ratio of an untimed (spot) urine specimen (preferably a first morning specimen, because urine protein concentrations can vary significantly during the day) is often used to estimate protein excretion in children.[16]

Hypoalbuminemia is defined as serum albumin <2.5 mg/dL. Thrombotic complications in older patients tend to be exacerbated at serum albumin levels below 2.0 mg/dL.

Assessment of NS Severity and Complications	
Intravascular volume depletion	• dizziness, abdominal cramps • peripheral hypoperfusion (cold hands or feet, mottling, capillary refill time >2 seconds) • tachycardia, reduced urine output, hypotension (late sign)
Severe or symptomatic edema	• discomfort (genital, abdominal), gross scrotal, vulval, and/or flank edema • gross limb edema with potential for skin breakdown/cellulitis • increased work of breathing from pleural effusion • ascites
Infection (increased risk in nephrotic state	• cellulitis • spontaneous bacterial peritonitis – abdominal pain, fever, nausea/vomiting, rebound tenderness
Thrombosis (increased risk in nephrotic state)	• swollen calves (i.e., to suggest deep venous thrombosis) • shortness of breath (i.e., signs/symptoms of pulmonary embolism)

Renal Biopsy:
Most children with NS are treated initially without undergoing a kidney biopsy, because the majority will have steroid-responsive minimal change NS. However, a pretreatment biopsy should be considered for patients who develop NS in the first year of life or during adolescence or for those who have presenting features that make

the possibility of minimal change NS less likely--such as persistent hematuria, hypertension, depressed serum complement levels, or reduced renal function.[13]

The key features in a patient with nephrotic syndrome, which suggest the need for genetic testing, include age <6 years at diagnosis (especially age <2 years), positive family history of nephrotic syndrome, consanguinity, a steroid-resistant course, and histopathologic findings of FSGS or diffuse mesangial sclerosis on renal biopsy.[14]

Labs: Obtain the following labs in children with persistent dipstick proteinuria (≥ 1+).
Initial Labs:

- CBC
- CMP (including albumin and liver function testing)
- Lipid panel
- Complete urinalysis

If urinalysis shows other abnormalities and/or the first morning urine Pr/Cr ratio is >.2, providers should take a complete history and physical examination including blood pressure, serum albumin, creatinine, cholesterol, and electrolytes should be determined. Renal ultrasonography and measurement of serum C3/C4 complement, antinuclear antibody, and serologies for hepatitis B and C and human immunodeficiency virus should also be considered. If any of the studies are abnormal, the child should be referred to a pediatric nephrologist for further evaluation.[13]

Secondary Labs:

- PPD/Quant Gold
- Consider Hep B SAg
- Renal Ultrasound (consider)
- Protein Creatinine Ratio (Random Urine)

Treatment
The main treatment goals of nephrotic syndrome are decreasing proteinuria in order to preserve renal function, and preventing thrombotic and immunocompromise-related complications. See Algorithm for management of nephrotic syndrome.

Consults/Referrals:
The prevalence of NS in childhood is low. Hence, it is common for pediatricians and family physicians to encounter very few children with NS in their practices. In view of the relative rarity and serious nature of the condition, once a child has been found to have NS early referral to a pediatric nephrologist is recommended, especially in cases of steroid resistance, dependency, or frequent relapsing state.

Admission Criteria
Gross anasarca, requiring albumin infusion (serum albumin <2.0 mg/dL), unable to tolerate oral intake (AKI), acute kidney injury.

Discharge Criteria

- Albumin improving (from initial labs)
- Blood pressure < 95%ile for sex/age/height

- Improving edema
- Improving oral intake
- Family has completed education and follow up with nephrology as outpatient has been coordinated
- Tolerating fluid and sodium restriction

Follow-Up Care

Patients with NS should be monitored closely at home by their parents. It is important to monitor body weight and continue to monitor for elevated protein levels. Keeping a record of these are important to clinic evaluations of the patient. These records will often provide the first indication of a relapse. The parents play an important role in identifying relapses and educating them on treatment complications.

Association between proteinuria and cardiovascular disease:

Severe persistent proteinuria may also be a long-term risk factor for atherosclerosis in children. As the severity of proteinuria increases, it is associated with a variety of metabolic disturbances that contribute to cardiovascular disease, eg, hypercholesterolemia, hypertriglyceridemia, and hypercoagulability. In some patients, factors such as hypertension, renal insufficiency, and steroid therapy may also contribute to the risk for cardiovascular disease.[13]

Side effects/ Parent & Patient Education

Glucocorticoids have many side effects, and it is critical to discuss these at length with the family of a nephrotic child, as well as with the child if he/she is old enough to understand. Steroids not only cause cushingoid habitus and ravenous appetite in some children in a relatively short period of time but also may be associated with other well-known short- and long-term side effects, such as behavioral and psychological changes (eg, mood swings), gastric irritation (including ulcer), fluid retention, hypertension, steroid-induced bone disease (such as avascular necrosis and bone demineralization), decreased immune function, growth retardation, night sweats, and cataracts. Pseudotumor cerebri, depression, steroid psychosis, and steroid-related diabetes are rare but are very serious potential side effects. It is essential to discuss measures to control steroid side effects as part of parent and patient education about NS.[13]

Outcome Measures

Time to first relapse (days)
Number of relapses during 24 months follow up
Steroid dosing and exposure
Kidney biopsy
Hospital readmission

Methods

Existing External Guidelines/Clinical Pathways

Existing External Guideline/Clinical Pathway	Organization and Author	Last Update
Protocol for Nephrotic Syndrome	Seattle Children's	2018

Any published clinical guidelines have been evaluated for this review using the **AGREE II criteria**. The comparisons of these guidelines are found at the end of this document. **AGREE II criteria** include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms Used:	Nephrotic Syndrome, Congenital Nephrotic Syndrome
Years Searched - All Questions	1995 - 2021
Language	English
Age of Subjects	0-18 years old
Search Engines	PubMed, Scholar Google
EBP Web Sites	https://childrensnational.org/ https://texaschildrens.org https://chop.edu
Professional Organizations	https://www.kidneyresearchnetwork.org/current-research-trials
Joint Commission	
Government/State Agencies	None
Other	International Pediatric Nephrology Association (IPNA)

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects
Type of Evidence	
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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