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# Evaluation and Management of Proteinuria and Nephrotic Syndrome in Children: Recommendations From a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE)

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# Evaluation and Management of Proteinuria and Nephrotic Syndrome in Children: Recommendations From a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE)

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**ABSTRACT.** *Objective.* **The development of this review article evolved from a National Kidney Foundation consensus conference on recent advances in the importance of evaluating and treating proteinuria. From this conference, a series of recommendations for the evaluation of adults with proteinuria was published. Because specific pediatric aspects of the problem were outside the scope of the original National Kidney Foundation publication, an ad hoc committee of 6 pediatric nephrologists who were active participants in the National Kidney Foundation conference was established to provide primary care physicians with a concise, up-to-date reference on this subject.**

*Methods.* **The recommendations that are given represent the consensus opinions of the authors. These are based on data from controlled studies in children when available, but many of the opinions are, by necessity, based on uncontrolled series in children or controlled trials performed in adults, because controlled trials in children have not been performed to evaluate many of the treatments described.**

*Results and Conclusions.* **These recommendations are intended to provide primary care physicians with a useful reference when they are faced with a young child or teenager who presents with proteinuria, whether this is mild and asymptomatic or more severe, leading to nephrotic syndrome.** ***Pediatrics*** **2000;105:1242–1249;** ***proteinuria, children, adolescents, nephrotic, nephrosis.***

ABBREVIATIONS. LMW, low molecular weight; IV, intravenous; Pr/Cr, protein/creatinine; NS, nephrotic syndrome; ACEi, angiotensin converting enzyme inhibitors; IDDM, insulin-dependent diabetes mellitus.

The fact that proteinuria is associated with progressive renal disease is well-established.[1,2] Recent reports have further implicated proteinuria as an effector mechanism in the development of renal injury[3–5] and as a risk factor for cardiovascular disease.[6–8] To review these studies and make the information more available to the public and the medical profession, the National Kidney Foundation held a conference entitled, "Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination" in Nashville, Tennessee, on March 25 to 26, 1998. Recommendations for adults with proteinuria were published in the May 1999 issue of the *American Journal of Kidney Disease*.[9] The current article provides some specific comments and recommendations regarding risks associated with proteinuria in children and adolescents and the evaluation of such patients. A more detailed description of the subject and a comprehensive bibliography is available on request (telephone: 1-800-345-4426; e-mail: info@spnsg.org)

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## CLINICAL TESTING FOR PROTEINURIA

The most frequently used screening method for proteinuria is the urinary dipstick, which primarily detects albumin, leaving low molecular weight (LMW) proteins undetected (Table 1). A color reaction between urinary albumin and tetrabromphenol blue produces various green hues based on the concentration of albumin in the sample, eg, trace (≈15 mg/dL); 1+ (≈30 mg/dL); 2+ (≈100 mg/dL); 3+ (≈300 mg/dL); and 4+ (≥2000 mg/dL). Because it is the concentration of urine protein that is measured, false-negative results may occur with very dilute urine. Conversely, false-positive results may occur with very alkaline or concentrated urine specimens in the presence of contaminating antiseptics, such as chlorhexidine and benzalkonium chloride, or after the administration of radiographic contrast, eg, after an intravenous (IV) pyelogram. An alternative office procedure to measure urinary protein in patients with questionable proteinuria by dipstick uses protein precipitation with sulfosalicylic acid. This technique provides a more quantitative estimate of all the urinary proteins including LMW proteins.

Urinary protein excretion in adults is usually measured in 24-hour urine collections. However, in young children, accurately timed urine collections are difficult to obtain. 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. The urine Pr/Cr ratio has been shown to reflect 24-hour urine protein excretion

**TABLE 1.** Methods Available to Test for Proteinuria

| Method | Indications | Normal Range | Comments |
|---|---|---|---|
| Dipstick testing | Routine screening for proteinuria performed in the office | Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020) | False–positive test can occur if urine is very alkaline (pH >8.0) or very concentrated (specific gravity: >1.025) |
| 24-h urine for protein and creatinine excretion | Quantitation of proteinuria (as well as creatinine clearances) | <100 mg/m$^2$/24 h in a documented 24-h collection* | More accurate than spot urine analysis. Inconvenient for patient. Limited use in pediatric practice |
| Spot urine for protein/creatinine ratio—preferably on first morning urine specimen | Semiquantitative assessment of proteinuria | <.2 mg protein/mg creatinine in children >2 y old<br><.5 mg protein/mg creatinine in those 6–24 mo old | Simplest method to quantitate proteinuria. Less accurate than measuring 24-h proteinuria |
| Microalbuminuria | Assess risk of progressive glomerulopathy in patients with diabetes mellitus | <30 mg urine albumin/g creatinine on first morning urine | Therapy should be intensified in diabetics with microalbuminuria |

* Note that in a 24-hour urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24-hour collection. The amount of creatinine in a 24-hour specimen can be estimated as follows: females, 15 to 20 mg/kg ideal body weight; males, 20 to 25 mg/kg ideal body weight.

quite accurately, particularly since first morning specimens eliminate the possibility of postural proteinuria.[10,11]

## PROTEIN HANDLING BY THE KIDNEYS IN NORMAL CHILDREN

The normal rate of protein excretion in the urine is <4 mg/m$^2$/hour or <100 mg/m$^2$/day throughout childhood in both boys and girls (Table 1). Approximately 50% of this small amount of protein consists of Tamm-Horsfall protein, a glycoprotein secreted by the ascending limb of the loop of Henle. The rest is comprised of small quantities of plasma proteins filtered by the glomeruli, eg, albumin, immunoglobulins, transferrin, and $\beta_2$-microglobulin, with albumin comprising <30% of the total urinary protein in normal individuals. The low excretion rate of protein occurs because: 1) the glomeruli restrict filtration of large serum proteins such as albumin and immunoglobulins, and 2) the proximal tubules reabsorb most of the LMW proteins, such as insulin or $\beta_2$-microglobulin, which are filtered across the glomeruli. The resultant modest proteinuria that is present in normal individuals is usually not detected on routine dipstick testing.

## PROTEIN HANDLING BY THE KIDNEYS IN CHILDREN WITH RENAL DISORDERS

Excess urinary protein losses may be caused by either: 1) increased permeability of the glomeruli to the passage of serum proteins (glomerular proteinuria), or 2) decreased reabsorption of LMW proteins by the renal tubules (tubular proteinuria). The finding of proteinuria in a single urine specimen in children and adolescents is relatively common. The prevalence varies in different studies but is generally between 5% and 15%. However, the finding of persistent proteinuria on repeated testing is much less common. In 1 study, which involved nearly 9000 school-aged children, proteinuria by dipstick was found in 1 of 4 samples in 10.7% of the children; however, only .1% had proteinuria in all 4 urine specimens tested.[12]

When proteinuria is detected, it is important to determine whether it is transient, orthostatic, or persistent in type. Transient proteinuria, which is most often associated with fever, stress, dehydration, or exercise, is not considered to be indicative of underlying renal disease. Orthostatic proteinuria, defined as elevated protein excretion when the subject is upright but normal protein excretion during recumbency, occurs most commonly in school-aged children and rarely exceeds 1 g/m$^2$/day. Long-term follow-up studies have documented the benign nature of orthostatic proteinuria in such individuals, although rare cases of glomerulosclerosis have been identified later in life in patients who were initially found to have proteinuria with an orthostatic component.[13,14] Persistent proteinuria, defined as proteinuria of ≥1+ by dipstick on multiple occasions, is abnormal and should be further investigated.

## ASSOCIATION BETWEEN PROTEINURIA AND PROGRESSIVE RENAL DAMAGE

Recent studies have shown that increasing levels of proteinuria provide the best predictor of progressive renal damage in both adults and children with proteinuric renal disease.[15,16] Over the past decade, there has been mounting evidence that persistent proteinuria should be viewed not only as a marker of renal disease, but also as a cause of progressive renal injury.[3–5] Some of the mechanisms whereby proteinuria seems to induce renal injury are listed in Table 2.

## ASSOCIATION BETWEEN PROTEINURIA AND CARDIOVASCULAR DISEASE

Proteinuria of any magnitude has been identified as a risk factor for cardiovascular disease in adults.[6–8] Severe persistent proteinuria may also be a long-term risk factor for atherosclerosis in children.[17] 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.

**TABLE 2.** Mechanisms by Which Proteinuria May Induce Renal Injury

- Renal tubules may be obstructed by proteinaceous casts.
- Damage may occur after the release of lysosomal enzymes into the cytoplasm of protein-reabsorbing tubules.
- Iron that is filtered into the tubular fluid bound to transferrin may be directly cytotoxic or may have indirect effects as a consequence of iron-catalyzed synthesis of reactive oxygen metabolites.
- Activation of the alternative complement cascade by proximal tubules may be harmful.
- Ischemic tubular injury may follow the release of vasoconstricting molecules.
- Release of fibrosis-promoting factors from renal cells activated/injured by proteinuria may result in interstitial fibrosis.
- Filtration of lipoproteins and absorption by proximal tubules may activate inflammatory pathways causing cell injury.
- Filtration of cytokines/chemokines may provoke cell proliferation, inflammatory cell infiltration, and activation of infiltrating cells.
- Filtration/generation of novel antigens may function as antigen-presenting cells and initiate a cellular immune response.

## EVALUATING CHILDREN WITH PROTEINURIA

The first step in the evaluation of a child with persistent dipstick proteinuria (≥1+) should be to obtain a complete urinalysis and a first morning spot urine specimen to determine the Pr/Cr ratio (Fig 1). It is important to have the child void before going to bed and remain recumbent until just before obtaining this specimen. If the urinalysis is normal and the urine Pr/Cr ratio on the first morning urine sample is <.2, a diagnosis of orthostatic proteinuria may be made and no additional studies are necessary. However, if the urinalysis shows other abnormalities and/or the first morning urine Pr/Cr ratio is >.2, the complete history and physical examination, including blood pressure, should be reviewed, and the blood level of 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.

## NONSPECIFIC TREATMENT OPTIONS FOR PERSISTENT PROTEINURIA

### Dietary Recommendations

Although some benefit from dietary protein restriction has been described in a small series of children with chronic renal insufficiency,[18] a recent controlled study has not demonstrated a significant impact of protein restriction on the rate of progression of renal disease.[16] However, it seems reasonable to avoid an excess of dietary protein in children with proteinuric renal diseases, because high dietary protein intake may actually worsen proteinuria, at least in some patients with nephrotic syndrome (NS), and does not result in a higher serum albumin. Thus, it is recommended that children with proteinuria receive the recommended daily allowance of protein for age.[16,19]

### Blood Pressure Control/Inhibition of Angiotensin Effects

Renal function is better preserved in children with chronic renal disease when lower systolic blood pres-

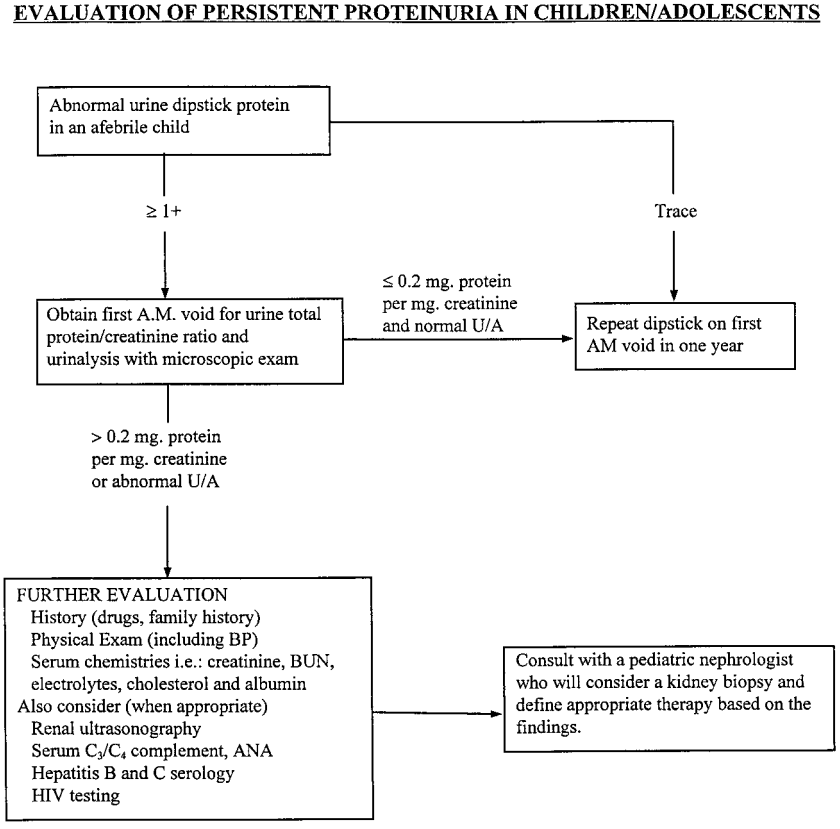


**Fig 1.** Algorithm describing the evaluation of asymptomatic proteinuria in children.

sures are achieved. The choice of antihypertensive agent for such patients should be individualized and determined in consultation with a pediatric nephrologist. Certain classes of antihypertensive agents, eg, the angiotensin converting enzyme inhibitors (ACEi) and the angiotensin II receptor blockers may, in addition to reducing systemic blood pressure, exert other beneficial effects, such as reducing urinary protein excretion and decreasing the risk of renal fibrosis.[20] However, the long-term benefit of ACEi in children and adolescents with proteinuria remains to be established definitively, and there are some concerns with the use of these agents in infants.[21–23] It is known that infants born to mothers receiving ACEi during the second and third trimesters of pregnancy may develop oligohydramnios, pulmonary hypoplasia, hypocalvaria, postnatal hypertension, and anemia. In several such neonates who died, postmortem examination revealed severe glomerular and tubular malformations in the kidneys.[23] It is clear, therefore, that ACEi are contraindicated during pregnancy. Risks of ACEi and angiotensin II receptor blockers in young infants are unknown.

## APPROACH TO PROTEINURIA IN ADOLESCENTS WITH INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

Good glycemic control remains the first goal in preventing renal injury in IDDM, the first sign of which is usually microalbuminuria.[24] However, a consensus is developing to treat young patients with IDDM who have persistent microalbuminuria or proteinuria with low doses of an ACEi.[25–27] Microalbuminuria may be defined as 20 to 200 $\mu$g/minute/1.73 m$^2$, or 30 to 300 mg albumin/g creatinine, on a first morning urine specimen. Overt proteinuria is associated with albuminuria >200 $\mu$g/minute/1.73 m$^2$. Although there are currently no controlled studies in children indicating exactly when ACEi therapy should be started, a reasonable approach in children with IDDM is to begin such treatment when urinary albumin excretion exceeds the normal range.

## EVALUATION AND TREATMENT OF PATIENTS WITH NS

NS may be defined as heavy proteinuria, that is severe enough to cause hypoalbuminemia, hypercholesterolemia, and usually edema. The prevalence of NS in childhood is low—approximately 2 to 3 cases per 100 000 children. 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. Long-term and day-to-day management of a child with NS should be a collaborative effort between the primary care physician and pediatric nephrologist.

In clinical practice, most children with NS are treated initially without undergoing a kidney biopsy, because the majority will have steroid-responsive minimal change NS.[28] However, a pretreatment biopsy should be considered for patients who develop NS in the first year of life or during adolescence[29] 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.

### Clinical Problems Associated With Childhood NS

*Edema*

Edema is usually the first clinical feature that brings a child with NS to the attention of a physician. Initially, the edema is often mild and variable in distribution—being periorbital in the early morning hours and more generalized after the patient has been ambulatory. This gravity-dependent movement of fluid frequently results in a patient with NS being misdiagnosed as having an allergic disorder until the edema becomes more severe (and persistent) or until a urinalysis is obtained. More severe degrees of edema may result in clinically significant problems with ascites, pleural effusions, scrotal or vulvar edema, and skin breakdown. Mild degrees of edema do not require specific measures, whereas more severe edema may require diuretic therapy (as discussed in "Approaches to Treatment in Children and Adolescents With NS").

*Electrolyte Disturbances in NS*

Although NS is usually associated with avid sodium retention, serum sodium concentrations are low in some patients. In many instances, this hyponatremia results from even more avid water retention, secondary to high antidiuretic hormone levels. It should be appreciated, however, that total body sodium is almost always increased in children with NS, especially those who are edematous, despite low serum sodium concentrations and, in some patients, reduced intravascular volume. In other patients with NS, apparent hyponatremia may result from very high lipid levels. This condition, known as pseudohyponatremia, is dependent on the methodology by which sodium is measured. In some laboratories, the technology used to assay serum sodium levels excludes the lipid phase, in which case pseudohyponatremia does not occur.

Although the total serum calcium in patients with NS is often low, the level of free ionized calcium is usually normal. This apparent discrepancy results from the low level of protein-bound calcium that is found in patients with NS. For practical purposes, the total serum calcium should be adjusted upwards by 1 mg/dL for each 1 g/dL decrease in serum albumin below 4 g/dL. Example: the adjusted serum calcium in a child with a measured total serum calcium of 7.5 mg/dL and serum albumin 2.5 g/dL would be $7.5 + (4.0 - 2.5) = 7.5 + 1.5 = 9.0$ mg/dL. Some pediatric nephrologists prescribe a calcium supplement (eg, chewable Tums) for children with NS, because this provides both an increase in calcium intake and an antacid. Occasionally, however, it may be necessary to prescribe an $H_2$-blocker for patients with significant steroid-induced gastric irritation. With respect to the concern about calcium levels, it is noteworthy that a recent preliminary report indicates

that most children with NS do not show any significant deficiency of bone mineral density.[30]

*Infections*

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. If a susceptible child on steroids is exposed to a patient with chickenpox, varicella-zoster immunoglobulin should be given within 72 hours of exposure to prevent or lessen the severity of the disease. In such a patient, the dose of glucocorticoid should be tapered to no more than 1 mg/kg/day until the incubation period has passed. Acyclovir or valacylovir should be given if varicella does develop. In severe cases, consultation with an infectious disease specialist is recommended.

Children with NS are also prone to develop cellulitis and spontaneous (ie, primary) bacterial peritonitis, with pneumococcus being the most common organism.[31] However, it should be noted that not all primary peritonitis is pneumococcal in origin. Gram-negative bacilli, such as *Escherichia coli*, may also be found in such patients, although published reports differ with regards to the frequency of such infections in patients with NS.[31] It is not uncommon for children with NS and primary peritonitis to be misdiagnosed as having acute appendicitis if they present with an acute abdomen and the possibility of primary peritonitis is not considered. Some patients have been given prophylactic antibodies during relapses; however, there are no studies showing this approach to be efficacious in preventing peritonitis.

*Immunizations*

Immunization practices and recommendations from pediatric nephrologists have been published in detail previously.[32,33] This section will provide only a brief update. Although the risk of precipitating a relapse is often stated as a reason for not giving immunizations to children with NS, there are no data to support this stance. In general, the benefits conferred by a standard vaccination program seem to outweigh the potential risks, but the advantages and disadvantages of each vaccine should be considered on an individual basis with the parents of each child. 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,[33] 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.

The safety and efficacy of varicella vaccine in children with NS is currently under investigation. Preliminary results show a 2 dose regimen of Varivax (Merck and Co, Inc, West Point, PA) to be both safe and efficacious.[34] However, a specific recommendation regarding the use of this vaccine in children with NS cannot be made at this time.

*Hyperlipidemia*

Transient hypercholesterolemia in patients with steroid-responsive NS can be quite severe (eg, serum cholesterol levels 300–500 mg/dL or more) but usually resolves when the NS has been treated successfully. In contrast, persistent hypercholesterolemia and hypertriglyceridemia are common in patients who have treatment-resistant NS. The potential implications of this hyperlipidemia are of concern because preliminary data indicate that atherosclerosis may develop at a relatively young age in children with persistent nephrotic range proteinuria.[17] However, the treatment of hyperlipidemia is not well-studied in children, and dietary modification is usually of limited benefit. Cholestyramine is currently the only drug approved for children but small uncontrolled studies suggest that hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors may be safe and effective in children with hypercholesterolemia associated with refractory NS.[35,36]

*Thromboembolism*

Patients with NS usually demonstrate laboratory features of a hypercoagulable state. Venous or, much less commonly, arterial thrombosis represents a particular problem and may be associated with pulmonary embolism. Reduced intravascular volume predisposes to thrombotic events. Hence, it is important to recognize and treat such patients. The use of diuretics must be judicious and must be avoided in patients known to have sustained a thromboembolic event. Antiplatelet drugs and/or anticoagulants are recommended for patients with thrombo-embolic events. Whether prophylactic use of these agents is beneficial for the prevention of thrombotic episodes in children with NS has not been studied carefully. We recommend that such measures only be considered after pediatric nephrology consultation.

## APPROACHES TO TREATMENT IN CHILDREN AND ADOLESCENTS WITH NS

### Specific Treatment Options

We recommend that, whenever possible, the specific treatments listed in this section, particularly those described in the subsections entitled "IV Pulse Steroids" to "Levamisole," only be given after referral to a pediatric nephrologist (Fig 2). Note that a number of the terms used in this section to define responses to treatment in childhood NS are provided in Table 3.

*Prednisone/Prednisolone*

Prednisone and prednisolone represent the mainstay of treatment in children with idiopathic NS. Liquid preparations of prednisolone (eg, Prelone [Muro Pharmaceutical, Inc, Tewksbury, MA] and Pediapred [prednisolone sodium phosphate; Fisons Corporation, Rochester, NY]) allow for accurate dos-

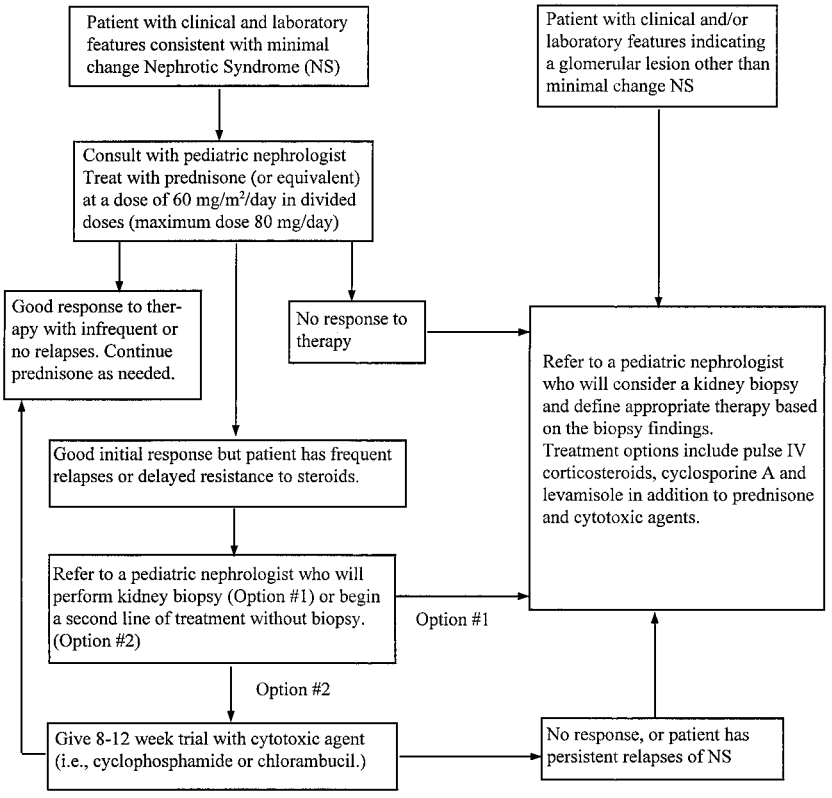


**Fig 2.** Algorithm describing the management of NS in children/adolescents.

**TABLE 3.** Terms Used to Define Response to Treatment in Children With NS

| | |
|---|---|
| Remission | Dipstick negative or trace proteinuria for 3 d or urinary protein excretion <4 mg/m²/h |
| Relapse | Dipstick shows 2+ proteinuria or more for 3 d; or patient found to have 3–4+ proteinuria plus edema |
| Frequent relapses | 2 or more relapses within first 6 mo after initial response, or 4 or more relapses within any 12-mo period |
| Steroid dependency | 2 consecutive relapses during tapering of glucocorticoid therapy, or within 14 d of its cessation |
| 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) |

ing and increased palatability in young children. A typical protocol is to start with high-dose prednisone or prednisolone (2 mg/kg/day or 60 mg/m²/day; maximum: 80 mg/day) in 1 to 3 divided doses. This treatment is continued until the patient becomes free of proteinuria or for a period of 4 to 6 weeks. The patient is then converted to a maintenance dose of alternate-day treatment, ie, 2 mg/kg or 40 mg/m² every other day in the morning, and this dose is gradually tapered and stopped after an additional 4 to 6 weeks. Some recent studies suggest that 6 weeks of daily therapy followed by 6 weeks of alternate day therapy (6 + 6 weeks) induce a higher rate of long remissions than the standard 4 + 4 weeks of treatment. However, the frequency of adverse events is higher with the longer courses, and the degree of benefit has been variable. Hence, there is currently no consensus on the optimal duration of the initial course of therapy.

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 (Fig 2).

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 lability), 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 essen-

tial to discuss measures to control steroid side effects as part of parent and patient education about NS.

*IV Pulse Steroids*

Infusions of high-dose methylprednisolone (eg, 30 mg/kg of body weight, up to 1 g/infusion) have been used recently with success in some patients with steroid-resistant NS.[37] The first 6 infusions are usually given every other day, followed by a tapering regimen for periods up to 18 months. The decision to use such treatment regimens in children should only be made by a pediatric nephrologist. Side effects of IV steroids are essentially the same as the problems noted above with oral prednisone. Additionally, the patient may become hypertensive during the infusions, and cardiac arrhythmias have been described rarely in adults receiving such therapy.

*Cytotoxic Drugs*

When steroid side effects become troublesome after multiple courses of steroids, or when there is failure to respond to steroid therapy, other strategies should be considered. Many pediatric reports indicate that cyclophosphamide or chlorambucil, each given over a period of 8 to 12 weeks, can achieve long periods of remission and reduce the need for steroids.[38]

Bone marrow suppression is a general problem with cytotoxic drugs. The peripheral white blood cell count should be monitored regularly during therapy with these agents, and the future possibility of malignancy must be considered. Other long-term risks of cyclophosphamide in children include oligospermia, azoospermia, and ovarian fibrosis; the risk is highest in children close to or in puberty and in those given large doses over many months. The total cumulative dose of cyclophosphamide should be restricted to <170 mg/kg in most cases. Hemorrhagic cystitis may occur with cyclophosphamide but not with chlorambucil. Seizures may occur with chlorambucil, albeit rarely, but not with cyclophosphamide.

*Cyclosporine A*

An alternative treatment for patients with steroid-dependent or -resistant NS is cyclosporine A.[39,40] However, patients who respond to cyclosporine A tend to relapse once the medication is withdrawn. Cyclosporine A may increase blood pressure or aggravate preexisting hypertension. Some patients demonstrate nephrotoxicity, as evidenced by an increase in serum creatinine. Increase in serum potassium and occasionally a decrease in serum magnesium may also be seen. Hypertrichosis and gingival hyperplasia are common. A pediatric nephrologist should manage all children with renal disease who are on cyclosporine A.

*Levamisole*

Levamisole, which has been used for treating frequently relapsing NS in children outside the United States, has been reported to be effective and well-tolerated in such patients. Early side effects that may occur with Levamisole, such as neutropenia, rash, gastrointestinal disturbances, and, rarely, seizures, were not seen in the patients reported.[41,42] Levamisole therapy must be continued for relatively long periods in most patients to maintain them in remission. Such patients must be monitored for long-term side effects.[41,42]

**Other Practical Aspects of the Management of Children With NS**

Each child should have an individual assessment for any changes that might be needed in day care, schooling, activities, and diet. Most children can and do limit their own activities when nephrotic. Recommendations about sports participation while on high-dose steroids should be considered on an individual basis. Age-appropriate explanations about the appetite-stimulating effects of steroids, and recommendations for a nutritious, relatively low-fat diet with age-adjusted recommended daily allowance of protein, carbohydrates, and other components will help children avoid large weight gains.[43] Salt intake should be limited to control edema and reduce the risk of hypertension especially when daily glucocorticoids are given. Setting a fluid intake limit of about twice the rate of insensible water loss may be helpful in an edematous child. This restriction should be discontinued when the urine output increases in response to specific treatment.

In practice, most patients with NS are monitored closely at home by their parents (or themselves when old enough). Frequent monitoring of body weight and urine dipstick protein levels are undertaken, and the records of these findings are very important in the clinic evaluations of the patients. Such records also often provide the first indication of a relapse—leading the parents to call the health care provider to ask for therapy modification before edema is apparent. Specific approaches of individual pediatric nephrologists to the management of such events vary, but the important role of parents in identifying relapses and treatment complications should be stressed. Waiting for edema to herald a relapse of NS often results in much higher patient morbidity.

Adjunctive therapy with ACEi in patients with steroid-resistant NS is now being prescribed more frequently. This therapy may decrease the rate of urinary protein excretion by as much as 50%. However, the long-term benefit of ACEi in childhood NS is unproven with regards to progression of disease; and these agents should only be given under the direction of a pediatric nephrologist. ACEi should not be given to children with NS during the time they are receiving their initial course of prednisone because they could become hypotensive and have an increased risk of thrombosis, particularly if they have a rapid diuresis.

Diuretics should not be used to treat mild degrees of edema in children with NS. Judicious use of diuretics, such as furosemide (1–2 mg/kg/day) may be used under the direction of a pediatric nephrologist if the child has severe edema. The combined use of IV albumin and furosemide to raise serum albumin and induce a diuresis should be undertaken with caution, because it carries significant inherent risks

for hypertension and even pulmonary edema. Hypertension may also be a serious problem when patients with NS receive over-the-counter decongestants, especially while they are on daily steroids.

## CONCLUSION

It is evident that in recent years proteinuria has become increasingly recognized as a marker and mediator of progressive renal insufficiency and a risk factor for cardiovascular disease. It is important, therefore, that the management of children with persistent proteinuria or NS should be conducted or supervised by physicians who are experienced in treating patients with these problems. Hence, a pediatric nephrologist should be consulted regularly even if the patient resides in an area where there is no pediatric nephrologist in close proximity. In all cases, optimal therapy of children with persistent proteinuria or NS will be achieved by the combined efforts of a primary care physician and a pediatric nephrologist.

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