

# Nephrotic Syndrome

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## EDUCATION GAPS

Pediatricians must be aware of the presentation, complications, and overall long-term implications of nephrotic syndrome and its treatment, with the primary goal of minimizing the impact of this disease on children's growth, development, and quality of life.

## OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize the clinical presentation and laboratory findings associated with nephrotic syndrome.
2. Understand the variable etiologies of nephrotic syndrome and further testing required to differentiate them.
3. Recognize minimal change disease as the most common etiology of nephrotic syndrome.
4. Plan adequate initial treatment for new-onset nephrotic syndrome.
5. Identify the different complications associated with nephrotic syndrome, including those resulting from diuretic therapy.
6. Understand that prognosis of the disease depends on etiology and response to treatment.

## ABSTRACT

Nephrotic syndrome (NS) encompasses a variety of disease processes leading to heavy proteinuria and edema. Minimal change disease (MCD) remains the most common primary cause of NS, as well as the most responsive to pharmacologic treatment with often minimal to no chronic kidney disease. Other causes of NS include focal segmental glomerulosclerosis, which follows MCD, and secondary causes, including extrarenal or systemic diseases, infections, and drugs. Although initial diagnosis relies on clinical findings as well as urine and blood chemistries, renal biopsy and genetic testing are important diagnostic tools, especially when considering non-MCD NS. Moreover, biomarkers in urine and serum have become important areas for research in this disease. NS progression and prognosis are variable and depend on etiology, with corticosteroids being the mainstay of treatment. Other alternative therapies found to be successful in inducing and maintaining remission include calcineurin inhibitors and rituximab. Disease course can

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## ABBREVIATIONS

AKI	acute kidney injury
Angptl4	angiopoietin-like 4
CNI	calcineurin inhibitor
ESKD	end-stage kidney disease
FSGS	focal segmental glomerulosclerosis
GFB	glomerular filtration barrier
IPNA	International Pediatric Nephrology Association
ISKDC	International Study of Kidney Disease in Children
KDIGO	Kidney Disease: Improving Global Outcomes
MCD	minimal change disease
MN	membranous nephropathy
NS	nephrotic syndrome
RAASi	renin-angiotensin-aldosterone system inhibitors
suPAR	soluble urokinase plasminogen activator receptor

range from recurrent disease relapse with or without acute kidney injury to end-stage renal disease in some cases. Given the complex pathogenesis of NS, which remains incompletely understood, complications are numerous and diverse and include infections, electrolyte abnormalities, acute kidney injury, and thrombosis. Pediatricians must be aware of the presentation, complications, and overall long-term implications of NS and its treatment.

## INTRODUCTION

Nephrotic syndrome (NS) is a condition characterized by increased permeability of the glomerular filtration barrier (GFB) leading to proteinuria with consequent hypoalbuminemia, edema, and hyperlipidemia. Nephrotic-range proteinuria in children is defined as a urine protein-to-creatinine ratio of 200 mg/mmol or greater ( $\geq 2$  mg/mg) or 24-hour urine sample of 1,000 mg/m<sup>2</sup> per day or greater, corresponding to 3+ or 4+ by urine dipstick. (1) NS, although primarily a glomerular disorder, can result from multiple different etiologies, including genetic mutations, systemic diseases, vasculitis, infections, toxins, and malignancy. (2) Some examples of extrarenal etiologies include systemic lupus erythematosus, nail-patella syndrome, and Denys-Drash syndrome, among others. With that in mind, NS should be considered a constellation of symptoms arising from heavy proteinuria rather than a disease in and of itself, and its presentation can vary based on its etiology.

## EPIDEMIOLOGY

NS can affect children of any age; worldwide prevalence is approximately 16 cases per 100,000 children, and the reported incidence has ranged from 2 to 7 per 100,000 children. (3)(4) Although the literature suggests that male children are more affected than females at a ratio of 2:1, this male-to-female predominance does not seem to exist in adolescence. In terms of age, NS classically presents in school-age children, although age at presentation can vary depending on the etiology; younger children usually have minimal change disease (MCD), and teenagers with new-onset NS are more likely to have non-MCD causes, such as lupus nephritis.

## PATHOPHYSIOLOGY

### Proteinuria

The pathophysiology of NS, although not completely understood, is thought to be multifactorial, with a common end point leading to disease, which is disruption of the GFB (Fig 1). Mutations of genes encoding structural proteins of the GFB, as well as mitochondrial proteins and nuclear transcription factors, have been identified as causes of NS. (5) The GFB is composed of several layers of

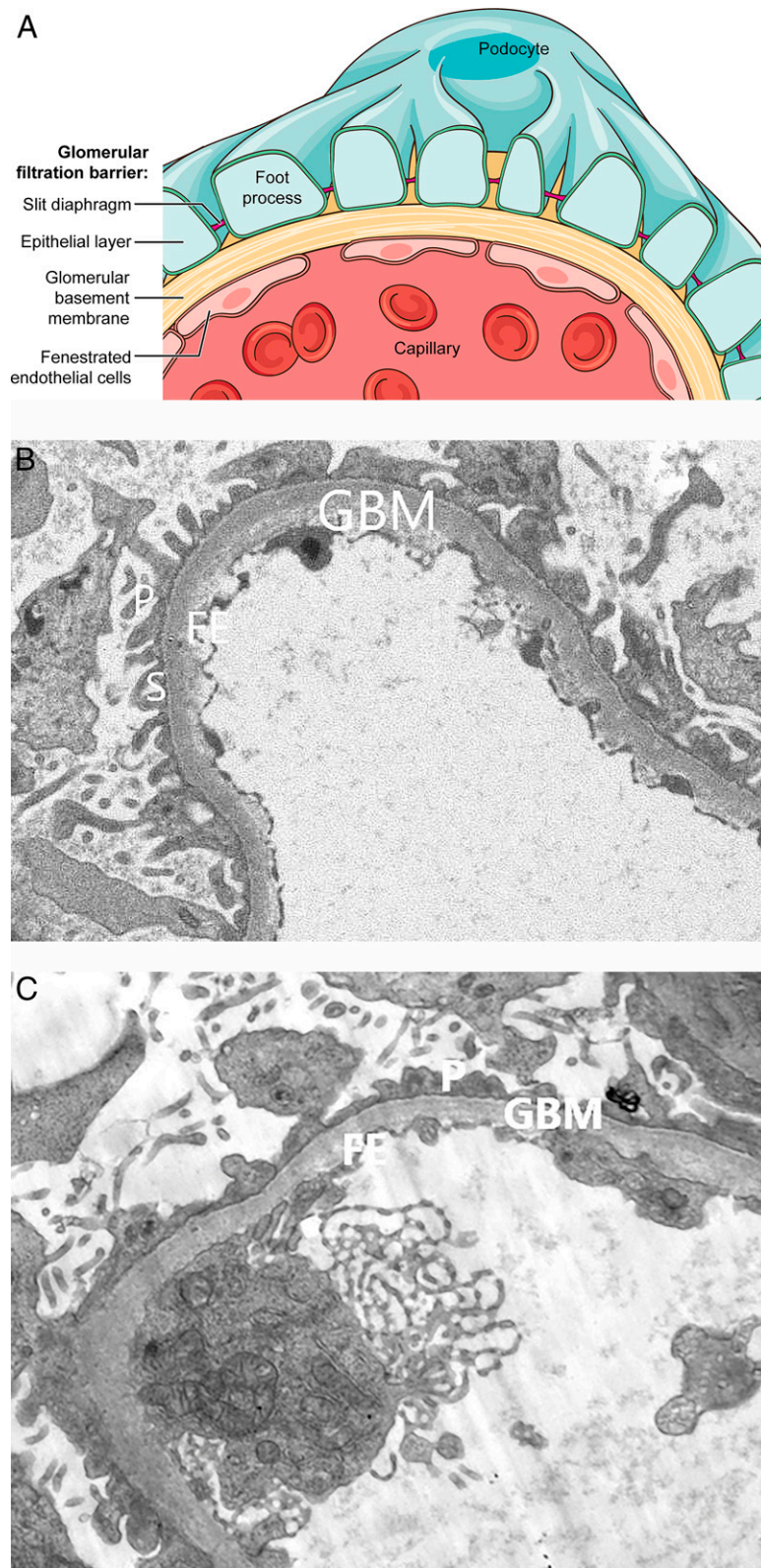
specialized cells that allow water and small solutes to be filtered into the urinary space while retaining large molecules and proteins. The different layers of the GFB, from outermost to innermost, include 1) a podocyte-rich epithelial layer with special cell junctions, or slit diaphragms; 2) the glomerular basement membrane, a noncellular layer composed of matrix proteins; and 3) endothelial cells with interspaced fenestrae. All 3 layers make up a complex filtration system that is charge and size specific; its hallmark sign of disruption is proteinuria.

The epithelial layer of the GFB is mainly formed by podocytes, specialized epithelial cells composed of a cell body and cytoplasmic extensions known as foot processes, which surround the glomerular capillaries. Podocytes play a crucial role in the GFB and filtration process and have limited ability to regenerate. (6)(7) Consequently, excessive podocyte destruction or depletion can lead to irreversible renal damage and impaired function.

Some of the proposed mechanisms of disruption of GFB leading to NS include intrinsic disorders of the glomerulus that can be genetic in origin, dysregulation of cell-mediated immunity leading to cytokine release affecting glomeruli, and production of circulating immune complexes that alter podocyte structure and/or function. (8)(9)(10) These theories have been supported throughout time by the nature of treatment that is typically successful in the various etiologies of NS, for example, immunosuppression considering T-cell dysfunction as the cause or plasmapheresis in renal transplant focal segmental glomerulosclerosis (FSGS) recurrence considering circulating permeability factor as the cause. (11) However, definitive evidence is lacking, with the latter supporting multiple mechanisms of injury and, therefore, varying etiologies rather than 1 pathology.

### Edema

Although it seems intuitive to consider that edema is due to urinary loss of protein leading to a decrease in intravascular oncotic pressure and subsequent fluid shifts, this theory does not always manifest clinically in all patients. This theory, called the “underfill” hypothesis, has been classically thought of as the main pathophysiology behind the edema; however, some patients present with hypertension associated



**Figure 1.** Glomerular filtration barrier (GFB). A. Schematic diagram. B. Normal GFB. C. GFB in nephrotic syndrome. Note the effacement of the podocyte foot processes (P) with poor visualization of the slit diaphragm (S). FE=fenestrated endothelium, GBM=glomerular basement membrane. (Schematic diagram courtesy of Jill K Gregory, CMI, FAMI, Icahn School of Medicine at Mount Sinai, New York, NY. Printed with permission from ©2021 Mount Sinai Health System. Electron microscopy images courtesy of Fadi El Salem, MD, Icahn School of Medicine at Mount Sinai.)

**Table 1.** Causes of Nephrotic Syndrome

Idiopathic	Minimal change disease FSGS Membranous nephropathy
Genetic mutations	Congenital nephrotic syndrome–related gene mutations: <i>NPH1</i> , <i>NPHS2</i> , <i>PDCN</i> , <i>SRN1</i> , <i>ITGA3</i> , <i>WT1</i> FSGS-related gene mutations: <i>APOL1</i> , <i>MYH9</i> , <i>NPHS2</i> , <i>CD151</i> , <i>PTPRO</i> , <i>MYO1E</i> , <i>CD2AP</i> , <i>INF2</i> , <i>TRPC6</i> , <i>FSGS2</i>
Infections	Hepatitis B, hepatitis C Human immunodeficiency virus, syphilis Malaria, toxoplasmosis
Medications/Drugs	Lithium, nonsteroidal anti-inflammatory drugs, pamidronate Penicillamine, interferon- $\gamma$ Gold Heroin
Systemic disorders	IgA nephropathy, membranoproliferative glomerulonephritis, IgA vasculitis Lymphoma, amyloidosis Lupus

FSGS = focal segmental glomerulosclerosis.

with increased intravascular volume. In this case, the “overfill” hypothesis comes into play. Essentially, this theory suggests that the loss of protein through the urine leading to decreased intravascular volume will, in turn, decrease the glomerular filtration rate and activate the renin-angiotensin-aldosterone system. This will lead to sodium and water retention, increasing the intravascular volume and further perpetuating the edema. (12) Considering that both theories can be valid likely explains why some patients present with either increased or decreased intravascular volume.

### Hyperlipidemia

The loss of albumin with a decrease in oncotic pressure along with altered rates of production and degradation of certain products in the cholesterol pathway can cause hyperlipidemia in these patients. More specifically, there is an increase in activity of the enzyme  $\beta$ -hydroxy- $\beta$ -methylglutaryl-coenzyme A reductase (responsible for cholesterol synthesis) and a concomitant decrease in activity of the enzyme  $7\alpha$ -hydroxylase (responsible for cholesterol catabolism). These changes result in elevated levels of cholesterol and low-density lipoprotein. (13) Hypertriglyceridemia results from decreased conversion of circulating triglycerides to free fatty acids due to angiopoietin-like 4 (Angptl4), a circulating glycoprotein. Angptl4 is found in various tissues and causes hypertriglyceridemia through its secretion in response to nephrotic-range proteinuria. (14)

### ETIOLOGY

Based on etiology, NS can be classified based on primary or secondary causes (Table 1), with a third subset classified based on age at presentation. Primary or idiopathic NS

refers to intrinsic glomerular dysfunction without an identifiable extrarenal cause or systemic disease. Primary causes of NS include MCD, FSGS, and membranous nephropathy (MN). These can be distinguished based on histologic results obtained via percutaneous renal biopsy. In addition, multiple genetic mutations have been identified that can present as isolated NS or can be part of a larger syndrome with NS being one of the features. Secondary causes include those that are associated with some external or internal systemic primary event, including systemic diseases, drugs, infections, or malignancies. Some glomerular diseases, mostly secondary in origin, can also present as a nephritic syndrome/NS overlap, including lupus nephritis, IgA nephropathy, and membranoproliferative glomerulonephritis, both complement-mediated and immune complex-mediated. Last, congenital and infantile forms of NS are classified based on age at presentation and usually occur before 1 year of age. Congenital NS presents from birth to age 3 months, whereas infantile NS presents between 3 and 12 months of age. In children younger than 1 year, genetic causes and congenital conditions and infections are more common. Congenital NS in the classical sense is known to originate from a mutation in nephrin, a transmembrane protein that is a component of the slit diaphragm. An autosomal recessive condition, classic congenital NS has been most frequently observed in Finland (incidence of 1 in 8,200 live births, hence the name *Finnish type NS*). In addition, congenital NS can also be caused by gene mutations leading to defects in other proteins of the GFB or congenital infections such as cytomegalovirus, toxoplasmosis, and syphilis. Other, more rare congenital causes of NS can be secondary to maternal lupus or to neonatal



autoantibodies to neutral endopeptidase. Genetic testing should be performed in cases of families with a history of nephrotic-range proteinuria.

Historically, MCD has accounted for most cases of primary NS in school-age children. The histologic evidence of disease lies in the flattened or fused foot processes apparent on electron microscopy. On light microscopy, however, the glomeruli appear normal; this finding on light microscopy led to the designation of *minimal change*. This has been further validated by prospective multicenter studies under the International Study of Kidney Disease in Children (ISKDC), which had their beginnings in the late 1960s. The ISKDC studies consisted of renal histologic evaluation of children from North America, Europe, and Asia, 3 months to 16 years of age, who presented with NS. Approximately 75% of these patients had biopsy-proven MCD, and FSGS was found in approximately 8% of children. (15) FSGS is the second most common primary cause of NS in children, as well as a rising and leading cause of end-stage kidney disease (ESKD) in adults. (16) The name FSGS, as in MCD, refers to specific findings on renal biopsy. It involves scarring (or glomerulosclerosis) of segments of some glomeruli in the setting of surrounding intact normal glomeruli. Because of its histologically patchy nature, it is common to mistake FSGS for MCD initially, mostly due to sampling inadequacy of renal biopsy. In these cases, FSGS may be initially missed, and diagnosis is often achieved on repeated biopsy, motivated by recalcitrant proteinuria. In contrast to the chronic remitting and relapsing nature of NS caused by MCD, FSGS is less likely to remit and more commonly causes chronic kidney disease leading to ESKD. (3) Multiple genetic mutations responsible for FSGS have been identified to date; however, there are still several documented cases for which there is no identified causal mutation (Table 1). (6)(17)(18) MN is characterized by subepithelial immune complex deposits along the GFB, along with diffuse thickening of the glomerular capillary walls. Although more commonly found as a primary disease in the adult population, primary MN is relatively rare in children and is rather more commonly found secondary to systemic disease. For example, disorders such as lupus or systemic infections such as hepatitis B may incite pathologic changes leading to MN.

## CLINICAL PRESENTATION AND COMPLICATIONS

The hallmark clinical feature of NS is gravity-dependent edema, typically starting as periorbital edema noted on awakening that seems to resolve over the course of the day. Edema

may progress to involve the lower extremities, genital area, and/or abdomen, with ascites if severe. Patients can present signs of increased or decreased intravascular volume, including hypertension and/or tachycardia, respectively.

Renal dysfunction can also be identified on presentation. Decreased intravascular volume, especially in the setting of preceding illness and/or diuretic use, results in further decreased renal blood flow and can lead to acute kidney injury (AKI). Remission of the NS along with volume repletion and/or correction of the fluid maldistribution reverses the AKI in most cases.

NS can sometimes follow a recent illness or infection, and on occasion patients present with additional nonspecific symptoms such as nausea, vomiting, and/or malaise.

Patients with NS can present with different complications that stem from the loss of protein itself as well as other contributing factors; although the primary protein excreted in urine is albumin, larger proteins can also be lost, such as immunoglobulins, thyroid-binding globulin, and vitamin D binding protein. Some of these complications include infections, metabolic bone disease, and thrombosis.

The loss of circulating antibodies places patients with NS at higher risk for infections than the general population and at particular risk for infection with encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group B streptococcus. (19) *S pneumoniae*-associated peritonitis is a well-described infection in children with NS; however, there is insufficient data supporting the efficacy of penicillin at prophylactic doses in this population. (20) The loss of vitamin D binding protein and thyroid-binding protein places these children at risk for metabolic bone disease and, less commonly, hypothyroidism. Patients with unremitting, long-standing heavy proteinuria are at higher risk for these complications.

Last, intravascular depletion potentially exacerbated by diuretic use combined with the urinary loss of coagulation cascade regulators such as antithrombin 3 can lead to thrombosis, 1 of the most feared complications. Increased hepatic production of procoagulant factors such as fibrinogen, factor V, and factor VIII is also known to contribute to thrombus formation in NS, as well as underlying risk factors in some patients. (21) Thrombosis presents in 2.8% of children with NS and is more common after age 12 years and in children with MN (25%). (21) Despite the life-threatening nature of thrombosis, data have not been robust enough to support routine prophylaxis in these children. (22)

## EVALUATION AND MANAGEMENT

Assessment of a child with suspected NS includes a thorough medical history focusing on both renal and extrarenal

**Table 2.** Laboratory Evaluation in Suspected Nephrotic Syndrome

Initial evaluation
• Urinalysis and urine protein-to-creatinine ratio
• Blood urea nitrogen and creatinine
• Electrolytes
• Serum albumin level
Additional testing
• Complements C3 and C4
• Antibodies: antinuclear antibodies, anti-double-stranded DNA
• Hepatitis panel, human immunodeficiency virus serology
• Renal biopsy in older children and teenagers

manifestations, as well as pertinent medical and family history. Laboratory tests as well as specific clinical clues will be helpful in determining the etiology and possible differential diagnoses (Table 2). Initial evaluation will include urinalysis and a urine protein-to-creatinine ratio. Besides proteinuria, a urinalysis might also further reveal hematuria or cellular casts. Gross hematuria is uncommon in MCD compared with other diagnoses associated with NS, such as C3 glomerulonephritis, although microscopic hematuria has been described in 10% to 15% of patients. (12)(23)

Renal function tests, electrolytes, and albumin levels should also be included in the initial evaluation. Renal function tests can be altered in the setting of AKI. Serum electrolytes are generally normal in nephrotic patients. Calcium levels can be depressed secondary to hypoalbuminemia, although ionized calcium levels will usually be within normal limits. Hyponatremia can ensue as an expected response to lower effective circulating volume, causing secretion of antidiuretic hormone and subsequent renal retention of water. In addition, aggressive diuretic use to treat the edema can also lead to hyponatremia.

Based on history and the suspected diagnosis, serum complement studies and autoimmune and/or infectious serologic testing should be considered. Decreased complement C3 and C4 levels can suggest membranoproliferative glomerulonephritis, or lupus nephritis, especially in the setting of positive antibodies, such as antinuclear antibodies, and/or anti-double-stranded DNA antibodies. Infectious causes to be considered and tested for include hepatitis B or C and human immunodeficiency virus. Interferon- $\gamma$  release assay or tuberculin skin testing should be performed at the time of diagnosis and before starting therapy if results of tuberculosis testing in the past year are not documented.

### Renal Biopsy

Although most children with NS will not require kidney biopsy given the nature of the most common cause (MCD), this is an important diagnostic tool in patients

with non-MCD NS. Early kidney biopsy should be considered in children falling out of the usual age range for MCD or who present with any clinical features not typical for MCD. (1) Some atypical clinical features include low serum complement levels, rashes, arthralgias, cytopenias, and fever. Additional recommendations from the International Pediatric Nephrology Association (IPNA) include kidney biopsy to be performed in all children with corticosteroid-resistant NS, except in known infection- or malignancy-associated secondary disease, or patients with known genetic and/or familial causes. (24)

### Genetic Testing

Genetic testing has become more widely available in recent years and can be of great importance for treatment, surveillance, and prognosis of patients in whom specific mutations are identified because results can guide therapy by predicting response and risk of recurrence of the disease. (5) NS in children younger than 1 year should raise suspicion for a non-MCD diagnosis; genetic testing of patients in this age group is likely to have a higher yield over kidney biopsy. Moreover, the IPNA recommends genetic testing in all children with primary corticosteroid-resistant NS (moderate recommendation), familial cases and cases with extrarenal features, and those undergoing transplant preparation (weak recommendation). Genetic testing is not recommended in patients with secondary corticosteroid resistance. (24)

### Biomarkers

Serum and urinary biomarkers have been a popular ongoing topic of research in NS; however, none of them are validated for clinical use as of the writing of this article (Table 3).

The study of serum biomarkers has focused mostly on the theory that some forms of NS can be caused by circulating permeability factors, including hemopexin, soluble urokinase plasminogen activator receptor (suPAR), cardiotrophin-like cytokine factor 1, and Angptl4. One of the most widely studied circulating permeability factors is suPAR. Initial promising studies that showed increased expression of suPAR in episodes of nephritis prompted further exploration on the subject, with subsequent studies failing to prove any significant association of suPAR with podocytopathies, proteinuria, or FSGS itself. (25)(26)(27) Serum cardiotrophin-like cytokine factor 1 was found to be elevated in patients with FSGS, and Angptl4 has been associated with increased foot process effacement and proteinuria in animal and human models, suggesting a possible early marker of

**Table 3.** Biomarkers

BIOMARKER	HIGH-LEVEL STATES
Urinary vitamin D binding protein	SRNS
Urinary $\alpha_1$ B-glycoprotein	SRNS
Urinary neutrophil gelatinase-associated lipocalin	SRNS
Urinary CD80	Disease relapse in MCD
Serum soluble urokinase plasminogen activator receptor	FSGS
Serum cardiotrophin-like cytokine factor 1	FSGS recurrence
Serum Angptl4	Nephrotic-range proteinuria and increased foot process effacement
Serum CD40	FSGS recurrence
Serum hemopexin	Disease remission in MCD

Angptl4 = angiotensin-like 4, FSGS = focal segmental glomerulosclerosis, MCD = minimal change disease, SRNS = corticosteroid-resistant nephrotic syndrome.

podocyte injury. (28)(29) Last, CD40 and anti-CD40 antibodies are being studied based on the inflammatory role that CD40 plays in renal cells and its subsequent activation of endothelial cells to synthesize suPAR.

Urinary vitamin D binding protein and  $\alpha_1$ B-glycoprotein have mostly been intended to predict corticosteroid sensitivity in primary NS, obtaining promising results in smaller studies. (30)(31) Neutrophil gelatinase-associated lipocalin is a well-known validated biomarker for chronic kidney disease and was found to be significantly elevated in patients with corticosteroid-resistant NS, although its clinical value and association to proteinuria is yet to be demonstrated. (32)(33) CD80 (B7-1) is one of the most studied biomarkers in NS. It is a trans-membrane protein on the surface of B cells and has been found to be elevated in periods of disease relapse in MCD compared with patients in remission. (34)

Overall evidence on both serum and urinary biomarkers is encouraging, and larger studies are needed to establish a clear use and benefit of these biomarkers in the management of NS. In the interim, their use is not indicated in the diagnosis, management, or prognosis of NS.

## TREATMENT

Therapeutic goals in NS include achieving remission of the disease by decreasing urinary protein spilling and controlling the symptoms arising from ongoing proteinuria and its complications. Treatment options can be viewed as medications that modify the disease and medications aimed at treating the symptoms of NS.

### Immunosuppressive Agents: Corticosteroids

Immunosuppressive medications, which mostly target the immune system, include corticosteroids and corticosteroid-sparing medications. Corticosteroids are considered first-line therapy, and patients can further be classified based on their response (Table 4). Corticosteroid-sensitive classification includes patients who respond to treatment within 4 weeks of initiation of therapy. Most cases of corticosteroid-sensitive idiopathic NS are thought to be secondary to MCD; in fact, in ISKDC studies, control of proteinuria achieved within 8 weeks of corticosteroid therapy was predictive of MCD, with fairly significant sensitivity and specificity. (1)(15) Biopsies are

**Table 4.** Common Definitions of Patients with Nephrotic Syndrome

TERM	DEFINITION
Remission	Urine protein-to-creatinine ratio <0.2 or dipstick negative or trace reading for 3 consecutive days
Relapse	Increase in first-morning urine protein-to-creatinine ratio to $\geq 2$ or dipstick reading of $\geq 2+$ for 3 of 5 consecutive days
Corticosteroid-responsive	Attainment of complete remission with corticosteroid therapy
Corticosteroid-resistant	Inability to induce remission within 4 wk of daily corticosteroid therapy
Confirmation period	Period between 4 and 6 wk from the start of corticosteroid therapy
Late responder	Patient achieving complete remission during the confirmation period or at 6 wk from the start of corticosteroid therapy
Infrequent relapse	1–3 relapses annually
Frequent relapse	$\geq 2$ relapses within 6 mo after initial therapy or $\geq 4$ relapses in any 12-mo period
Corticosteroid-dependent	Relapse during taper or within 2 wk of discontinuation of corticosteroid therapy

Adapted from Gipson et al (20), Tarshish et al, (42) and Trautman et al. (24)

limited to cases in which corticosteroid treatment fails or in which clinical presentation overall is strongly suggestive of a different etiology. Consequently, corticosteroid responsiveness is crucial in guiding treatment and prognosis in NS.

Once the diagnosis of MCD is suspected and in the absence of clinical features suggesting an alternate diagnosis, therapy with corticosteroids should be initiated. Initial therapy dosing based on consensus guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) from 2012 consists of prednisone at 2 mg/kg per day for a total of 4 to 6 weeks. Once initial remission is achieved, therapy is decreased to alternate-day dosing of 1.5 mg/kg per dose for an additional 8 to 20 weeks, with tapering of the dose. Maximum doses are 60 mg for the initial treatment phase and 40 mg for the subsequent remission phase. (35) In contrast, guidelines published by the American Academy of Pediatrics in 2009 suggest similar dosing with different duration of treatment: an initial treatment phase of 6 weeks, followed by a remission treatment phase of 6 weeks with no tapering of dose. (20) Patients who experience relapse are treated with an additional course of prednisone, although in these subsequent courses the prednisone is weaned soon after the patient is in remission, with the goal of minimizing corticosteroid toxicity as much as possible. The same dosing as for initial presentation is used, but the timing of therapy differs; patients are transitioned to alternate-day dosing after a urine dipstick test for protein is negative or trace for 3 consecutive days. Alternate-day therapy is then continued for 1 to 3 months based on frequency of relapses.

The dosing of corticosteroid therapy has remained unchanged throughout the years, although several randomized controlled trials have looked into the effect of the duration of therapy on relapse rates. The results have been very variable, with earlier studies showing significantly reduced relapse rates on longer therapy. In 2007 Hodson et al (36) demonstrated a relapse rate reduction of 30% at 12 to 24 months, with 12 weeks or more of prednisone compared with 8 weeks. (37) Conversely, the more recent 2019 PREDNOS trial in the United Kingdom revealed grossly equal rates of relapse with a 16-week course of prednisolone compared with a standard 8-week course in children with corticosteroid-sensitive NS. (38) Similar results were obtained in 2015 randomized controlled trials by Yoshikawa et al (39) in Japan and Sinha et al (40) in North India. In addition, evidence has suggested that tapering of the prednisone dose for weeks or months can result in a decrease in the rate of relapse. (35) Ongoing reevaluation and studies on duration of therapy are

necessary, especially due to the significant adverse effects caused by long-term therapy with corticosteroids, including, but not limited to, fluid retention, weight gain with redistribution of fat, gastritis, elevated blood pressure, behavioral problems, elevated blood sugar levels, poor wound healing, and bone loss.

### Noncorticosteroid Immunosuppressive Agents

Alternative therapy under the guidance of a pediatric nephrologist is recommended for children with NS who are corticosteroid-sensitive with frequent relapses, corticosteroid-dependent, and/or corticosteroid-resistant. Alternative corticosteroid-sparing medications, including renin-angiotensin-aldosterone system inhibitors (RAASi) and several different immunomodulators, have their own adverse effect profiles and varying success rates (Table 5). The latter include calcineurin inhibitors (CNI), alkylating agents, monoclonal antibodies, mycophenolate mofetil, and others. These therapies act through different pathways in the immune system and ultimately decrease the activity of B cells, T cells, or both, functionally depleting immunocompetent cells.

Although no hierarchy or order of medications has been established for the treatment of corticosteroid-sensitive NS, a clear structured algorithm was recently developed for corticosteroid-resistant NS. This was included in the IPNA guidelines for corticosteroid-resistant NS in 2020, in which RAASi were first officially included as first-line noncorticosteroid therapy in corticosteroid-resistant NS. (24)(41) RAASi are known to reduce proteinuria through an incompletely known mechanism, although thought to primarily occur secondary to vasodilation of the efferent arteriole in the glomerulus, resulting in a decreased glomerular filtration rate. Moreover, the IPNA 2020 guidelines introduced the “confirmation period,” which is the period between 4 and 6 weeks from the start of oral corticosteroid therapy at standard doses. This period is used to ascertain response to corticosteroids and serves as the point in time in which the addition of RAASi is recommended in patients who achieve partial or no remission by the initial 4 weeks of treatment with corticosteroids.

Patients who go on to achieve complete remission after 4 weeks and before 6 weeks are considered to be “late responders.” Further escalation in therapy after 6 weeks and after having started RAASi include CNI. Corticosteroid tapering should be initiated at this stage if patients have not responded by 6 weeks. If partial or



**Table 5.** Alternative Therapies for Nephrotic Syndrome

DRUG	CLASSIFICATION	MECHANISM OF ACTION	ADVERSE EFFECTS	NEED TO KNOW FACTS
Renin-angiotensin-aldosterone system inhibitors	Angiotensin-converting enzyme inhibitors Angiotensin receptor blocker inhibitors	Vasodilation of the efferent arteriole in the glomerulus, leading to decreased glomerular filtration rate Mechanism incompletely known, possibly added direct action on podocyte cytoskeleton and slit diaphragm	Cough, hyperkalemia, hypotension, dizziness, abnormal taste, rash, kidney injury, angioedema	Decrease in proteinuria independent of BP by 4–6 wk of treatment, with complete remission within ~12 mo (48)(49)(50)
Cyclophosphamide	Alkylating agent	Depletes immunocompetent cells by adding an alkyl group to DNA	Alopecia, myelosuppression, gonadal toxicity with infertility, hemorrhagic cystitis, secondary malignant tumor	Decreased risk of relapse at 6–12 mo. Observational studies have found variation in reported remission rates (51)(52)(53)
Cyclosporine (CSA)	Calcineurin inhibitors	Prevent nuclear factor of activated T cells from entering the nucleus. This leads to a decrease in cytokine production, including interleukin-2 and interferon- $\gamma$	Nephrotoxicity, tremor, headache, thrombotic microangiopathy, hyperlipidemia, hypertension, hypomagnesemia, hypokalemia CSA specific: gum hyperplasia, hypertrichosis FK specific: neurotoxicity, hair loss, new-onset diabetes	Effective in inducing and maintaining remission. More effective than MMF in preventing relapse, with a less favorable adverse effect profile (54)(55)
Tacrolimus (FK)				FK is associated with higher efficacy and lower renal toxicity compared with CSA treatment. Similar efficacy to CSA in 1 small trial. (55)(56)
Mycophenolate mofetil (MMF)	T- and B-cell proliferation inhibitor	Purine and DNA synthesis inhibitor in lymphocytes	Myelosuppression, gastrointestinal effects including nausea, diarrhea, abdominal pain, oxalate nephropathy	Small studies showed ~60% response rate (including partial or complete remission). FK found to be superior in maintaining remission compared with MMF (57)(58)(59)
Rituximab	Monoclonal antibody	Antibody specific to CD20 found on B cells, inducing cell lysis	Pulmonary toxicity, myelosuppression, infusion reaction (including headache, fever, dyspnea, diaphoresis, hypotension, nausea, chills)	Decreased risk of relapse after 6–12 mo. Patient relapses often correlate with recovery of B-cell count (60)(61)(62)
Corticotropin	Hormone	Contains peptides related to melanocortin, which binds to melanocortin receptors expressed in podocytes	Hypertension, fluid retention, glucose intolerance, insomnia	Small studies of adult patients with MN and FSGS showed a decrease in proteinuria, with complete remission in ~20%–60% (63)(64)

BP = blood pressure, FSGS = focal segmental glomerulosclerosis, MN = membranous nephropathy.

complete remission is achieved with CNI, mycophenolate mofetil can be added to treatment. If the patient with NS is also found to be CNI-resistant, enrolling the patient in a clinical trial or considering rituximab is the next step.

Last, if remission is not achieved with rituximab, additional therapeutic options such as ofatumumab, plasma exchange, immunoadsorption, or lipid apheresis are considered.

### Adjunctive Therapy and Considerations

Symptomatic treatment aims to limit clinical manifestations of the disease, specifically fluid imbalance, intravascular depletion, and/or hypertension. Depending on the degree of edema, this can usually be achieved with a combination of diuretics, albumin infusions, and antihypertensives. Strict intake and output, although important in the management of these patients, is difficult to perform in the outpatient setting. Caregivers should be counseled on the importance of fluid and sodium restriction. In addition, vitamin D and calcium supplementation should be considered in frequent or long-standing relapsers.

As previously mentioned, patients with NS have an inherent elevated risk of infection. Moreover, these patients can have added risk from immunosuppressive therapy; hence, febrile illnesses in this population require close monitoring, and, accordingly, immunizations are of special importance. Current recommendations call for the timely administration of all required immunizations per American Academy of Pediatrics guidelines, including yearly influenza immunization, with special caution on live vaccines, which should not be administered to patients receiving chronic corticosteroid therapy. Patients taking high-dose systemic corticosteroids (2 mg/kg of body weight or a total of 20 mg daily) for 2 weeks or more should wait for 3 months before administration of live vaccines. In addition, 23-valent pneumococcal polysaccharide vaccine should be administered to all children older than 2 years with NS, followed by a booster dose 5 years later in patients with ongoing disease. Moreover, patients with ongoing proteinuria should also undergo serial monitoring of dyslipidemia, and statin drugs might be considered if necessary.

In considering the potential for viral illness as a trigger for NS relapse, some pediatricians may elect to use short-course prednisone therapy in patients with frequently relapsing NS with upper respiratory infections, as per KDIGO guidelines.

### PROGNOSIS

Remission of proteinuria is seen in approximately 85% of children with NS receiving daily prednisone treatment. (35) In these patients, the natural course of disease is that of variable episodes of relapse and remission, in some cases requiring multiple courses of prednisone plus standing alternative therapy. In the ISKDC cohort, 75% of the initial responders who remained in remission 6 months after initial presentation either continued to be in remission or relapsed infrequently. Most patients who experienced relapse in the first 6 months

achieved a nonrelapsing course by 3 years from initial presentation. Retrospectively, 80% of the entire cohort was found to be in remission 8 years after enrollment. (42)

Despite the high rate of success of corticosteroid treatment for MCD, other causes of NS are less responsive to corticosteroids. Ten percent to 20% of children with NS are corticosteroid-resistant, and most of these children will have diagnoses different than MCD, often being FSGS. (43) These cases require more specialized care and testing, including pediatric nephrology referral and renal biopsy. Prognosis is poor because these children are more likely to progress to ESKD (estimated glomerular filtration rate <15 mL/min or dialysis dependency) and will ultimately require dialysis or renal transplant. (44) Furthermore, although renal transplant is curative in some forms of NS, FSGS has increased risk of recurrence even after transplant, with broad reported recurrence rates ranging from approximately 20% to 55%. (45)(46)(47) These children can often require extensive medication courses, and in some cases, a subsequent renal transplant.

### CONCLUSION

NS is a common and often chronic condition affecting children worldwide. It encompasses a variety of disease processes leading to a common end point: heavy proteinuria, hypoalbuminemia, and edema. The course of patients with NS is variable but in most cases is one of relapse and remission. MCD has remained the most common primary cause of NS and the most responsive to treatment, with a great prognosis with minimal to no long-term renal sequelae. However, there are other less common causes, which have a less desired prognosis and carry increased risk of progression to ESKD. Renal biopsy, although not routinely performed, is an important diagnostic tool in non-MCD NS. Moreover, genetic testing has become an increasingly valuable tool in the identification of mutations associated with NS and is on track to obviate more and more biopsies in the years to come. Urinary and serum biomarkers have been an important ongoing research topic for NS with encouraging results; however, no biomarkers have been validated for clinical use at this time. Despite ongoing research in disease mechanisms and the potential intervening agents, corticosteroids have remained the first-line treatment for decades. Alternative therapies to corticosteroids, such as CNI and rituximab (among others), have been found to be successful in induction or maintenance of remission, although response is dependent on disease etiology and with varying and inconsistent results, warranting further studies comparing these medications. Pediatricians must be aware of the presentation,

complications, and overall long-term implications of NS and its treatment and can partner with pediatric nephrologists to minimize the impact of NS in their patients, allowing for improved growth, development, and quality of life.

## Summary

- On the basis of observational studies, nephrotic syndrome (NS) can affect children of any age, with minimal change disease (MCD) being the most common cause in school-age children. (3)(4)
- On the basis of observational studies, expert opinion, and reasoning from first principles, some of the proposed mechanisms leading to NS include inherent disorders of the glomerulus, dysregulation of cell-mediated immunity, and production of circulating immune complexes that alter podocyte structure/function. (8)(9)(10)
- On the basis of research evidence and consensus, corticosteroids are considered first-line therapy

for the treatment of NS, with remission of proteinuria seen in approximately 85% of patients receiving daily prednisone treatment. (35)

- On the basis of research evidence, consensus, and expert opinion, early kidney biopsy should be considered in patients with corticosteroid-resistant NS, in patients falling outside of the usual age range for MCD, or in patients who present with clinical features not suggestive of MCD. (1)(24)
- On the basis of consensus and expert opinion, it is important to recognize and manage the complications of NS, such as infection, dyslipidemia, metabolic bone disease, and thrombosis. (17)(19)(21)

*References for this article can be found at  
<https://doi.org/10.1542/pir.2020-001230>.*



1. A 7-year-old is evaluated in the emergency department for edema, decreased energy, and decreased urine output. His vital signs include a heart rate of 87 beats/min, a respiratory rate of 14 breaths/min, blood pressure of 132/81 mm Hg, and oxygen saturation of 98% on room air. Laboratory evaluation of his urine reveals proteinuria with a urine-to-creatinine ratio of 270 mg/mmol. Serum laboratory testing is performed. An elevation in which of the following is expected in his laboratory results?
  - A. Albumin.
  - B. Calcium.
  - C. Immunoglobulins.
  - D. Sodium.
  - E. Triglyceride.
2. A 9-year-old is brought to the clinic by his parents for follow-up after being seen in the emergency department because of periorbital edema, proteinuria, and hypertension. An evaluation was initiated and the patient was asked to follow up in the clinic today. You review the laboratory results, etiology, and treatment options with the parents. Which of the following is the most likely diagnosis in this patient?
  - A. Focal segmental glomerulosclerosis.
  - B. Membranoproliferative glomerulonephritis.
  - C. Membranous nephropathy.
  - D. Minimal change disease.
  - E. Rhabdomyolysis.
3. An 8-year-old is being treated with furosemide for nephrotic syndrome and having improvement in his edema. Discussion about medication adverse effects and family guidance regarding potential emergencies is provided. Of the following complications, which is the most important risk factor to discuss?
  - A. *Escherichia coli* infection.
  - B. Encephalopathy.
  - C. Hyperthyroidism.
  - D. Tendon rupture.
  - E. Thrombosis.
4. A 7-year-old girl is brought to the emergency department for evaluation. She is diagnosed as having nephrotic syndrome. You are consulted to initiate treatment and give guidance to her family regarding her expected prognosis. Which of the following is the most appropriate first-line treatment regimen?
  - A. Corticotropin.
  - B. Cyclophosphamide.
  - C. Intravenous immunoglobulin.
  - D. Prednisone.
  - E. Rituximab.

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5. A 10-year-old boy, newly diagnosed as having nephrotic syndrome, returns to the clinic with persistent symptoms despite initial treatment with prednisone, which began 5 weeks earlier. The next steps in treatment and diagnosis are discussed with the family. Which of the following is the best next step in the management of this patient?
- A. Azathioprine.
  - B. Computed tomographic scan of the abdomen.
  - C. Genetic testing.
  - D. High-dose prednisone.
  - E. Renal biopsy.