

# Nephrotic Syndrome

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## Practice Gap

Pediatricians must be aware of the updated treatment recommendations and the various complications associated with nephrotic syndrome, a common childhood renal disorder.

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

1. Understand the natural history of minimal change nephrotic syndrome.
2. Recognize the clinical and laboratory findings associated with minimal change nephrotic syndrome.
3. Plan the appropriate initial management of the first episode of minimal change nephrotic syndrome.
4. Formulate a differential diagnosis of nephrotic syndrome with and without hematuria.
5. Identify the cause of hyponatremia in nephrotic syndrome.
6. Recognize complications associated with nephrotic syndrome, including those resulting from diuretic therapy.
7. Understand the various factors that affect the prognosis of nephrotic syndrome.

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### ABBREVIATIONS

CNF	congenital nephrotic syndrome Finnish type
CNS	congenital nephrotic syndrome
FSGS	focal segmental glomerular sclerosis
ISKDC	International Study of Kidney Disease in Children
KDIGO	Kidney Disease Improving Global Outcomes
MCNS	minimal change nephrotic syndrome
MN	membranous nephropathy
MPGN	membranoproliferative glomerular nephritis

Nephrotic syndrome is a disorder of the kidneys that results from increased permeability of the glomerular filtration barrier. It is characterized by 4 major clinical characteristics that are used in establishing the diagnosis: proteinuria, hypoalbuminemia, edema, and hyperlipidemia. This article reviews nephrotic syndrome in the pediatric population, with special attention paid to minimal change nephrotic syndrome (MCNS).

### EPIDEMIOLOGY

Nephrotic syndrome can affect children of any age, from infancy to adolescence, and is most commonly seen among school-aged children and adolescents. The prevalence worldwide is approximately 16 cases per 100,000 children with an incidence of 2 to 7 per 100,000 children. (1) Males appear to be more affected than females at a ratio of 2:1 in children, but this predominance fails to persist in adolescence.

## PATHOPHYSIOLOGY

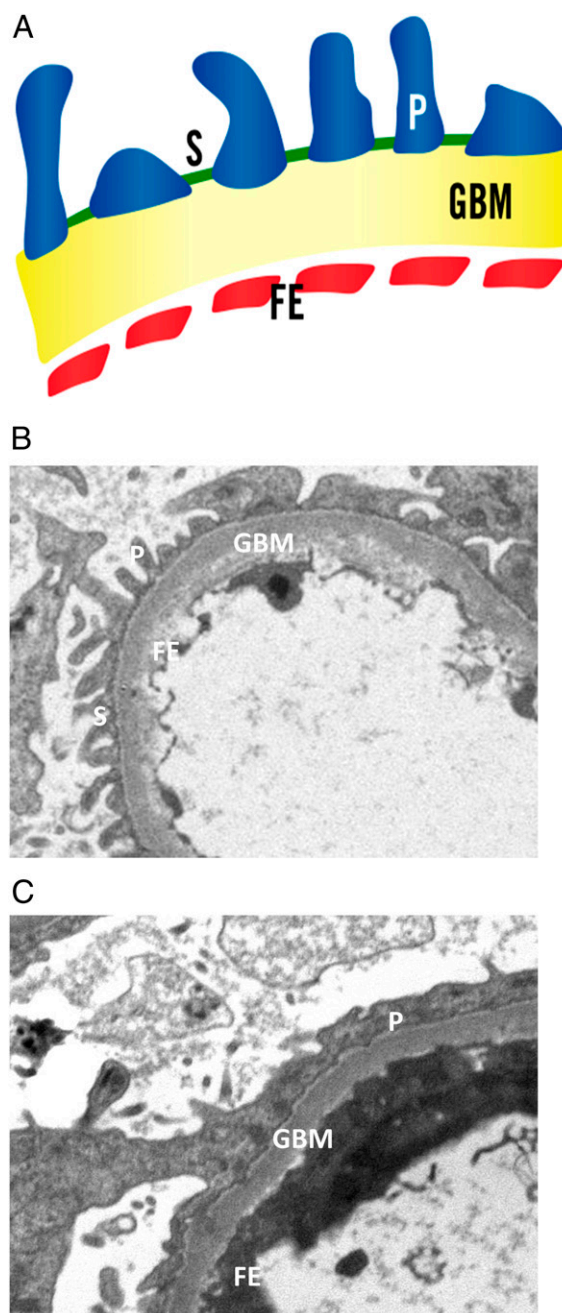
The kidney uses a complex filtration system known as the glomerular filtration barrier (GFB). It is composed of a glomerular basement membrane sandwiched between a fenestrated endothelium and an epithelial layer made up of podocytes and their foot processes, with interspersed filtration slits and slit diaphragm (Figure 1). As part of the system's intrinsic design, it is charge and size specific, allowing water and small solutes to pass through its pores into the urinary space. In nephrotic syndrome, there is an effacement of the podocyte foot processes that can be seen on electron microscopy. Disruption of this barrier leads to the proteinuria seen in nephrotic syndrome.

Nephrotic syndrome can be inherited from a number of genetic mutations that lead to defects in various regions of the glomerular filtration barrier; presentation can vary from isolated nephrotic syndrome seen in corticosteroid-resistant nephrotic syndrome or focal segmental glomerular sclerosis (FSGS) to more involved syndromes, such as nail-patella or Denys-Drash syndromes (Table 1). Congenital nephrotic syndrome (CNS) is usually seen within the first 3 months after birth. The classic form of CNS is the Finnish type (CNF), which is most frequently seen in Finland and has an incidence of 1 in 8,200 live births, although this autosomal recessive condition has been described in many other populations. CNF results from a mutation in the gene encoding the protein nephrin, a key component of the slit diaphragm. CNS is also caused by mutations of genes encoding other proteins of the glomerular basement membrane, slit diaphragm, and podocyte (Table 1). CNS can also be secondary to underlying processes such as maternal lupus, neonatal autoantibodies to neutral endopeptidase, and infections such as syphilis, toxoplasmosis, and cytomegalovirus.

Most ongoing research into mechanisms of pathogenesis of idiopathic nephrotic syndrome explores the roles of the immune system and the podocyte in disease. Proposed theories include (1) T-cell dysfunction that leads to cytokine release that affects glomeruli and causes increased permeability and (2) immune system dysfunction that leads to the production of circulating factors (soluble urokinase plasminogen activator receptor is one example) that alter podocyte structure and/or function, resulting in proteinuria. (2)(3)(4) B-cell involvement is also suggested by reports of remission after administration of rituximab, an anti-CD20 antibody. (5) However, definitive evidence of the underlying mechanism of action is lacking at this time.

## CLASSIFICATION

Nephrotic syndrome can be divided into primary (idiopathic) and secondary causes (Table 2). Idiopathic nephrotic



**Figure 1.** Glomerular filtration barrier (GFB). A. Schematic diagram; B. normal GFB; and 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. Electron microscopy images courtesy of Fadi El Salem, MD, Icahn School of Medicine at Mount Sinai, New York, NY.

syndrome refers to that which is not associated with another identifiable systemic disease. Outside these 2 major groupings, there are 2 subsets that are based on age of presentation: CNS and infantile nephrotic syndrome. Patients with the latter condition typically present between ages 3 months and 1 year. Some prenatal signs that are nonspecific but may

TABLE 1. Genetic Forms of Nephrotic Syndrome

PROTEIN	LOCATION	GENE	INHERITANCE PATTERN	ASSOCIATED DISEASE
Nephrin	Slit diaphragm	<i>NPHS1</i>	AR	CNF, FSGS
Podocin	Podocyte foot process	<i>NPHS2</i>	AR	CNS, FSGS, SRNS
CD2-associated protein	Slit diaphragm	<i>CD2AP</i>	AR, AD	FSGS, SRNS
$\alpha$ -Actinin-4	Podocyte cytoskeleton	<i>ACTN2</i>	AD	FSGS, SRNS
Nonmuscle myosin heavy chain IIA	Podocyte cytoskeleton	<i>MYH9</i>	Polymorphisms associated with increased risk for ESRD in blacks	FSGS, SRNS
LIM homeobox transcription factor 1 $\beta$	Podocyte cytoskeleton	<i>LMX1B</i>	AD	Nail-patella syndrome, FSGS, SRNS
Apolipoprotein L1	Podocyte cytoskeleton	<i>APOL1</i>	Polymorphisms associated with increased risk for ESRD in blacks	FSGS, SRNS
Inverted formin 2	Podocyte cytoskeleton	<i>INF2</i>	AD	FSGS, SRNS
Transient receptor potential cation channel 6	Podocyte cell membrane	<i>TRPC6</i>	AD	FSGS, SRNS
Laminin $\beta$ 2	Glomerular basement membrane	<i>LAMB2</i>	AR	Pierson syndrome, DMS, CNS
Tetraspanin CD151	Podocyte cell membrane	<i>CD151</i>	AR	FSGS
Phospholipase C $\epsilon$ 1	Podocyte cytoplasm	<i>PLCE1/NPHS3</i>	AR	FSGS, DMS, CNS
Wilms tumor 1	Podocyte nucleus or cytoplasm	<i>WT1</i>	AD	Frasier syndrome, Denys-Drash syndrome, FSGS, DMS, CNS

AD=autosomal dominant; AR=autosomal recessive; CNF=congenital nephrotic syndrome Finnish type; CNS=congenital nephrotic syndrome; DMS=diffuse mesangial sclerosis; ESRD=end-stage renal disease; FSGS=focal segmental glomerulosclerosis; SRNS=(cortico)steroid-resistant nephrotic syndrome.

suggest CNF are an enlarged placenta apparent on ultrasoundogram in addition to elevated maternal serum and amniotic fluid  $\alpha$ -fetoprotein levels. If CNF is suspected in families with known risk factors, genetic testing can be performed.

Idiopathic nephrotic syndrome can be further subdivided based on histologic information gathered via percutaneous renal biopsy. The 3 major subgroups are MCNS (also known as minimal change disease), FSGS, and membranous nephropathy (MN). MCNS is the most common form of nephrotic syndrome in school-aged children. On light microscopy, the glomeruli appear histologically normal, hence the name minimal change disease. Although light microscopy findings are normal, inspection by electron microscopy reveals fusion of the foot processes. FSGS describes what is found histologically: some glomeruli can be normal, whereas others exhibit segmental areas of sclerosis or scarring. Diffuse thickening of the capillary walls of the glomeruli are histologically characteristic of MN. There

are other glomerulopathies that can present with nephrotic syndrome, including IgA nephropathy, lupus nephritis, and membranoproliferative glomerulonephritis (MPGN), and often present with a nephritic/nephrotic picture, with hematuria in addition to proteinuria. Aside from histologic features, children with nephrotic syndrome can be further classified by their response to corticosteroid therapy (discussed in detail below).

Because of the patchy nature of FSGS histologically, it is common to mistake FSGS for MCNS because of a sampling inadequacy at the time of renal biopsy; thus, an additional biopsy may be required at a future date to make the diagnosis. The incidence of FSGS has increased since the original studies examined nephrotic syndrome in children. There are ongoing discoveries of genetic mutations responsible for FSGS, although these do not account for all documented cases (Table 1). Several reports suggest that MN in children is more commonly secondary in nature, with causes such as hepatitis B and lupus inciting the pathologic changes.

**TABLE 2. Secondary Causes of Nephrotic Syndrome**

INFECTIONS	
Hepatitis B	Hepatitis C
Human immunodeficiency virus	Toxoplasmosis
Syphilis	Malaria
DISEASES OR CONDITIONS	
Amyloidosis	Lupus
Henoch-Schönlein purpura	IgA nephropathy
Lymphoma	Membranoproliferative glomerulonephritis
MEDICATIONS/DRUGS	
Lithium	Nonsteroidal anti-inflammatory drugs
Heroin	Penicillamine
Gold	Interferon $\gamma$
Pamidronate	

Idiopathic MN is more common in adults than in children, with the exact incidence difficult to ascertain. Within the past 5 years, studies of MN revealed the presence of an autoantibody to the M-type phospholipase A2 receptor that is increased in adults with idiopathic MN; although anti-phospholipase A2 receptor has been also observed in children, the exact prevalence among pediatric patients with MN is unknown at this time. (6)

## CLINICAL FEATURES

Initial presentation of patients with nephrotic syndrome can vary. The classic presentation is a child between the ages of 3 and 9 years with sudden-onset gravity-dependent edema. Patients tend to have periorbital edema that is often mistaken as sequelae from seasonal allergies. Other children can present without any classic signs of edema but have nephrotic range proteinuria (protein level  $>50$  mg/kg/d or a spot urine protein:creatinine ratio of  $>2,000$  mg/g) on urinalysis. The onset of nephrotic syndrome may sometimes follow a recent illness, such as a upper respiratory tract infection. There are 2 dominant theories regarding the pathogenesis of edema in nephrotic syndrome. Classically, it is thought to be a result of decreased intravascular oncotic pressure that results in movement of fluid into the

interstitial spaces (the underfill hypothesis). The hypovolemia that results from this fluid shift eventually leads to sodium retention to compensate for the low intravascular volume. This finding is not apparent across the board among nephrotic patients (who may present with higher plasma volumes), leading to an opposing theory of overfill in which primary sodium retention leads to the edema formation. One proposed mechanism is that proteinuria leads to increased sodium retention in the distal tubule through increased activation of epithelial sodium channels. (7)

Further laboratory evaluation of patients with nephrotic syndrome may reveal other abnormalities. Urinalysis can reveal hematuria, which can be either macroscopic or microscopic ( $>3$  red blood cells per high-power field). The percentage of patients in whom hematuria is found is lower in patients with MCNS compared with other diagnoses associated with nephrotic syndrome, such as FSGS and MPGN. (8) Although microscopic hematuria is known to occur in 20% of children with MCNS, gross hematuria is relatively uncommon and should prompt the physician to consider diagnoses other than MCNS. The proteins lost in the urine primarily consist of albumin but also include larger proteins, such as immunoglobulins. These losses correlate with the aforementioned hypoalbuminemia and contribute to hyperlipidemia. Hyperlipidemia results from a variety of factors in nephrotic syndrome, including the decrease in oncotic pressure through loss of albumin and changes in the rate of production and degradation of various products along the cholesterol pathway. More specifically, there is an increase in  $\beta$ -hydroxy- $\beta$ -methylglutaryl-coenzyme A reductase activity (responsible for cholesterol synthesis) with a decrease in  $7\alpha$ -hydroxylase activity (enzyme responsible for cholesterol catabolism), leading to resultant elevated cholesterol and low-density lipoprotein cholesterol levels. (9) Hypertriglyceridemia is a result of decreased conversion of circulating triglycerides to free fatty acids due to a circulating glycoprotein, angiopoietin-like 4. This glycoprotein is found in various tissues and is secreted in response to nephrotic range proteinuria and causes hypertriglyceridemia. (10)

Serum electrolytes are generally normal in nephrotic patients. Calcium levels can be low secondary to hypoalbuminemia, but the ionized calcium will be within normal limits. In addition, sodium levels can be decreased secondary to lower effective circulating volume coupled with inappropriate secretion of antidiuretic hormone, causing renal retention of water. Hyponatremia can also be iatrogenic in the setting of diuretic use for edema.

## COMPLICATIONS

Patients with nephrotic syndrome are at risk for the development of a variety of complications, which include thrombosis, infections, dyslipidemia (explored in the previous section), and renal dysfunction. Venous thrombosis is more common in patients with nephrotic syndrome compared with arterial thrombosis; thrombosis, when present, may occur in the renal vein, sagittal sinus, or pulmonary artery. Thrombosis in this patient population is multifactorial. Patients may have a hereditary risk factor (such as Factor V Leiden mutation) that predisposes them to clot formation. They may be intravascularly depleted as a result of nephrotic syndrome that may be exacerbated by diuretic use to control edema. When combined with the urinary loss of coagulation cascade regulators (such as anti-thrombin III) and an increase in hepatic production of procoagulant factors (such as fibrinogen, factor V, and factor VIII), conditions that favor thrombus formation result. Thrombocytosis and platelet aggregation also occur in nephrotic syndrome and may play a role in thrombosis. (11)

In addition to urinary loss of hematologic factors, there is also loss of immunoglobulins. This loss of circulating antibodies puts nephrotic children at risk for bacterial infections, particularly those with encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Group B streptococcus). Peritonitis caused by *S pneumoniae* is a well-described infection in children with nephrotic syndrome. Patients may also experience serious infections like cellulitis and pneumonia, and can develop sepsis. These children must be vaccinated against these bacteria because of waning immunity over time as a result of their underlying diagnosis. Current recommendations call for administration of the 23-valent pneumococcal polysaccharide vaccine for all children older than 2 years with nephrotic syndrome. The vaccine should be administered at least 8 weeks after the last dose of the 13-valent pneumococcal conjugate vaccine, with an additional dose of the 23-valent pneumococcal polysaccharide vaccine 5 years after the first dose in patients who have ongoing disease. Patients undergoing treatment for nephrotic syndrome with immunosuppressants are also at continued risk of infections, and febrile illnesses in this population require close follow-up.

Beyond the urinary loss of albumin and immunoglobulins, nephrotic syndrome also causes the loss of other important proteins, including vitamin D-binding protein and thyroid-binding globulin. This loss may cause vitamin D deficiency and increase the potential for metabolic bone

disease. Although hypothyroidism is more of a frequent problem in patients with CNS, in whom proteinuria is heavy and long-standing, general practitioners should recognize this as a potential issue in children who are resistant to corticosteroids or who have frequent relapses.

Renal dysfunction can occur in the setting of nephrotic syndrome, especially with patients presenting with hypovolemia. Preceding illness, aggressive diuretic use, or sepsis with hypotension may result in decreased renal blood flow, causing a decrease in the glomerular filtration rate. Acute kidney injury in most of these cases is reversible with remission of the nephrotic syndrome and adequate volume repletion.

## MANAGEMENT AND PROGNOSIS

Initial workup of a child with suspected nephrotic syndrome includes urinalysis and a urine protein:creatinine ratio to establish the heavy proteinuria (usually, a urine protein:creatinine ratio  $\geq 2$ ); serum chemical analyses, including creatinine, electrolytes, and albumin; and a cholesterol and lipid panel. Serum complement component C3 and antinuclear antibody titer may be indicated if there are abnormalities within the initial aforementioned laboratory analyses or if the clinical presentation indicates a process other than MCNS (hematuria, elevated creatinine, or clinical features suggestive of autoimmune disease [eg, rashes, arthralgias, and unexplained fevers]). On the basis of history, the practitioner may also consider infectious causes, including hepatitis B or C or human immunodeficiency virus. A tuberculin skin test should be performed at the time of diagnosis and before the start of therapy if results of a tuberculin skin test within the past year are not documented.

Standardization of management of patients with nephrotic syndrome came from prospective multicenter trials under the International Study of Kidney Disease in Children (ISKDC) that began in the late 1960s. Through their work and others, the clinical course and prognosis were described, and definitions of subgroups with indications for renal biopsy were established. The cohort involved children with nephrotic syndrome ages 3 months to 16 years from North America, Europe, and Asia, and all children underwent renal biopsy on entry into the study. Approximately 75% of patients had biopsy-proven MCNS. (8) Corticosteroids became the hallmark of treatment for nephrotic syndrome and continue to be today. Patients are primarily classified by their response to corticosteroid therapy.



Once the diagnosis of MCNS is suspected in a child presenting in the classic age range for MCNS and with classic features and active or latent infections are ruled out, therapy with corticosteroids should be initiated. Consultation with a pediatric nephrologist and biopsy before initiation of corticosteroid therapy should be strongly considered for patients who fall outside the typical age range (age older than 10–12 years is often used as a cutoff) or who have features atypical of MCNS (such as gross hematuria, hypertension, low complement levels, or markedly elevated creatinine level). Although most children respond to prednisone, the importance of genetic testing is highlighted by the fact that certain mutations result in nephrotic syndrome that is not responsive to corticosteroid therapy. For children younger than 1 year, there should be high suspicion for a non-MCNS diagnosis; although these patients may also require biopsy, genetic testing is likely to have a higher yield in this group and should be strongly considered. Prednisone and prednisolone dosing based on evidence and consensus is highlighted in guidelines from the Children's Nephrotic Syndrome Consensus Conference (12) and, most recently, Kidney Disease: Improving Global Outcomes (KDIGO). (13) Dosing strategy in both guidelines is similar, although recommendations regarding length of treatment differ somewhat. KDIGO recommends an initial dose of 60 mg/m<sup>2</sup> per day (2 mg/kg per day), with a maximum dose of 60 mg/d administered for 4 to 6 weeks. This is then followed by a dose of 40 mg/m<sup>2</sup> per dose (1.5 mg/kg) every other day for 2 to 5 months, with tapering of the dose. This is in contrast to the consensus guidelines published by the American Academy of Pediatrics, which call for daily corticosteroids for 6 weeks followed by alternate-day corticosteroids for another 6 weeks, with no taper of dose. (12)(13) Initial studies comparing a total of 8 weeks of corticosteroid therapy to a 12-week course revealed fewer relapses of nephrotic syndrome in patients with the longer course. (14) Although there are recommendations that corticosteroid therapy stop at the end of 12 weeks, there is evidence that suggests that subsequent tapering of the prednisone dose for weeks or months results in a decrease in rate of relapse. (13) Most children with nephrotic syndrome will respond in the first few weeks of therapy and are labeled as corticosteroid responsive (Table 3).

The natural course of disease for most patients will be that of relapse and remission; the number of relapses is variable and person dependent. In the ISKDC cohort, 75% of the initial responders who remained in remission at 6 months after initial presentation either continued to be in remission or infrequently relapsed (one-third of the total cohort). Patients who relapsed in the first 6 months on

**TABLE 3. Common Definitions of Patients With Nephrotic Syndrome<sup>a</sup>**

TERM	DEFINITION
Remission	Urine protein:creatinine ratio <0.2 or dipstick negative or trace reading for 3 consecutive days
Relapse	Increase in first morning urine protein:creatinine ratio to ≥2 or dipstick reading of ≥2+ for 3 of 5 consecutive days
Corticosteroid responsive	Attainment of complete remission with corticosteroid therapy
Corticosteroid resistant	Inability to induce a remission within 4 weeks of daily corticosteroid therapy
Infrequent relapser	1–3 Relapses annually
Frequent relapser	≥2 Relapses within 6 months after initial therapy or ≥4 relapses in any 12-month period
Corticosteroid dependent	Relapse during taper or within 2 weeks of discontinuation of corticosteroid therapy

<sup>a</sup>Adapted from Gipson et al (12) and Tarshish et al (15).

average were able to achieve a nonrelapsing course by 3 years from initial presentation. Eighty percent of the entire cohort was found retrospectively to be in remission 8 years after enrollment in the study. (15) Most of these children were noted to have MCNS as opposed to FSGS. Adjuvants to initial therapy in the otherwise stable outpatient population may include the use of diuretics (ie, furosemide) to help with management of edema, especially if edema is severe enough to impair ambulation. Patients with ongoing proteinuria should undergo serial monitoring of dyslipidemia, and statin drugs might be considered in children who are frequent relapsers or are resistant to corticosteroids. However, these medications are generally not needed in most patients with MCNS.

The fact that most children with nephrotic syndrome are receiving corticosteroids for at least 3 to 5 months necessitates the discussion of prolonged corticosteroid use in this population. The adverse effects of prednisone are well known and include (but are not limited to) growth impairment, weight gain with increased body mass index and obesity, glucose intolerance, decreased bone mineralization, cataracts, disturbances in behavior and/or mood, and hypertension. Prednisone is an immunosuppressant and as such will cause increased susceptibility to infections. The pediatrician should monitor for infections while the patient is undergoing therapy and have a lower threshold

TABLE 4. **Alternative Therapies for Nephrotic Syndrome**

DRUG	CLASSIFICATION	MECHANISM OF ACTION	ADVERSE EFFECTS	NEED TO KNOW FACTS
Cyclophosphamide	Alkylating agent	Depletes immune competent cells by adding an alkyl group to DNA	Alopecia, bone marrow suppression, gonadal toxicity with risk of infertility, hemorrhagic cystitis, secondary malignant tumor	Shown to decrease risk of relapse at 6–12 months. Observational studies have found variation in reported remission rates <sup>16</sup>
Chlorambucil	Alkylating agent	Same as cyclophosphamide	Bone marrow suppression, seizures	One head-to-head trial found effect to be similar in relapse risk when compared with cyclophosphamide. <sup>16</sup>
Levamisole	Antihelminthic and immunomodulator	Exact mechanism not well understood	Leukopenia, agranulocytosis, hepatotoxicity, vasculitis, and encephalopathy	Withdrawn from the US market in 2000. Decrease in relapse rate when compared with placebo or prednisone but relapses would recur shortly after discontinuation. <sup>16</sup>
Cyclosporine	Calcineurin inhibitor	Lowers the activity of T cells and stabilizes the podocyte actin cytoskeleton	Nephrotoxicity, hirsutism, diabetes, hypertension, hyperkalemia, dyslipidemia, gingival hyperplasia	Effective in inducing and maintaining remission in patients. Patients often relapse after discontinuation. Found to be similar to cyclophosphamide in maintaining remission at 12 months in a meta-analysis. <sup>16–18</sup>
Tacrolimus	Calcineurin inhibitor	Same as cyclosporine	Nephrotoxicity, diabetes, hypertension, hyperkalemia	No advantage when compared in small head-to-head trials with cyclosporine. <sup>16,19</sup>
Mycophenolate mofetil	T- and B-cell proliferation inhibitor	Inhibits a vital enzyme (IMP dehydrogenase) for T and B cells	Abdominal pain, diarrhea, leukopenia	Limited data when compared with cyclosporine and tacrolimus. Larger controlled trials needed. Small trials or studies found some effect on patients with CDNS. <sup>16,20</sup>
Rituximab	Monoclonal antibody	Antibody specific to CD20 found on B cells	Pulmonary toxicity, bone marrow suppression	Case series and trials have found use in conjunction with other medications in CDNS allowed for discontinuation of $\geq 1$ immunosuppressant medications. Patient relapses often correlate with recovery of B-cell counts. <sup>5,16,21–22</sup>

*Continued*

TABLE 4. (Continued)

DRUG	CLASSIFICATION	MECHANISM OF ACTION	ADVERSE EFFECTS	NEED TO KNOW FACTS
ACTH	Hormone	Contains peptides related to melanocortin, which binds to melanocortin receptors expressed in podocytes	Hypertension, fluid retention, glucose intolerance	Pilot study used in membranous nephropathy found decrease in proteinuria. Small studies found potential in inducing remission in FSGS. <sup>23,24</sup>

ACTH=adrenocorticotrophic hormone; CDNS=corticosteroid-dependent nephrotic syndrome; FSGS=focal segmental glomerular sclerosis; IMP=inosine-5'-monophosphate dehydrogenase.

for workup of the febrile child receiving prednisone or any immunosuppressive treatment. In addition, there is likely to be some suppression of the hypothalamic-pituitary-adrenal axis because patients with nephrotic syndrome are receiving daily supraphysiologic doses of corticosteroids for at least 4 weeks and those who are deemed frequent relapsers may be receiving high-dose prednisone for longer periods. Although there has not been extensive research on adrenal suppression with the recommended dosing regimen of prednisone, there is potential for this to occur, and pediatricians should be aware of this risk.

Patients who relapse are treated with another course of prednisone with the goal of decreasing the chance of corticosteroid toxicity by weaning soon after the patient is in remission. The therapy includes 60 mg/m<sup>2</sup> per day of corticosteroids as with initial presentation with weaning to alternate-day therapy (40 mg/m<sup>2</sup> per dose) after a urine dipstick test result is negative or trace for protein for 3 consecutive days. Infrequent relapsers differ from frequent relapsers in recommendations concerning length of treatment once the patient is receiving alternate-day therapy (4 weeks vs at least 3 months in frequent relapsers). Alternative therapy under the guidance of a pediatric nephrologist is recommended for children who are either frequent relapsers or steroid dependent. These alternative therapies, largely immunosuppressive agents, have their own adverse effects and toxicity and have varying success rates (Table 4).

Children who do not respond to the initial course of prednisone are defined as corticosteroid resistant, which occurs in a small percentage of the children who present with nephrotic syndrome (approximately 10%).<sup>(15)</sup> Most of these children are likely to have a diagnosis other than MCNS. As such, referral to a pediatric nephrologist is recommended for further management, which would include renal biopsy to aid in diagnosis. Prognosis for these children is poor

because they tend to have higher rates of progression to end-stage renal disease (estimated glomerular filtration rate of <15 mL/min or dialysis dependency) and will continue to require dialysis or renal transplantation for management. Although transplant is curative in some forms of nephrotic syndrome (CNF, for example), certain forms of nephrotic syndrome have increased likelihood of recurrence; for example, FSGS has at least a 15% chance of recurrence in the transplanted kidney,<sup>(25)</sup> and other studies report rates of recurrence greater than 30%. Therapies for these children often mirror those of the alternative therapies used for frequent relapsers who are dependent on corticosteroids (Table 4). No one drug is superior to others, and there is ongoing research to determine disease mechanisms to better tailor therapy. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can also be used as a supplemental therapy to help decrease persistent proteinuria in corticosteroid-resistant nephrotic syndrome. These classes of drugs both reduce proteinuria and slow the progression of chronic kidney disease through the blockade of the renin-angiotensin system.

Children who do not respond to treatment or who are frequent relapsers may encounter substantial strain on their daily lives and are at risk for long-term sequelae of chronic illness. Outside the medication effects outlined in Table 4, patients and families have to deal with the psychosocial stressors and their effect on quality of life. Beside difficulties coping with long-term medication administration, multiple office visits and hospitalizations inevitably lead to missed work and schooling. In addition, one should be cognizant of the cosmetic adverse effects of many of the medications used to treat nephrotic syndrome. Prednisone-induced obesity, striae, acne, cushingoid facies, or cyclosporine-induced hirsutism may have significant social implications for children and adolescents and may affect medication adherence.



## CONCLUSION

Nephrotic syndrome encompasses a variety of disease processes with heavy proteinuria and hypoalbuminemia at its core. Despite ongoing research efforts in the mechanism of disease, first-line therapy has remained relatively unchanged for decades, and corticosteroids remain the mainstay of treatment. Guidelines published by the American Academy of Pediatrics and the KDIGO can guide the pediatrician in the treatment of MCNS. Most children have MCNS, which portends a good prognosis; renal failure is uncommon in patients with MCNS. The course of patients with nephrotic syndrome is variable, but most patients will have periods of relapse and remission. There are alternatives to corticosteroid therapy that have had success in induction and/or maintenance of remission, although findings are inconsistent, necessitating further multicenter trials to compare these medications head to head. Genetic testing has increasingly become a valuable tool in the identification of genetic variations associated with nephrotic syndrome and may obviate the need for a significant number of biopsies in the future. Pediatricians must be aware of the complications secondary to nephrotic syndrome and its therapies, with the primary goal of minimizing these issues in their patients to allow for improved growth, development, and quality of life.

## Summary

- On the basis of observational studies, the most common cause of nephrotic syndrome in school-aged children is minimal change disease. (8)
- On the basis of research evidence and consensus, corticosteroids are considered first-line therapy for treatment of nephrotic syndrome. (11)(12)
- On the basis of consensus, prednisone therapy should be initiated at doses of 60 mg/m<sup>2</sup> per day (2 mg/kg per day) administered for 4 to 6 weeks, followed by 40 mg/m<sup>2</sup> per dose (1.5 mg/kg) every other day for at least 6 to 8 weeks. (12)(13)
- On the basis of consensus and expert opinion, it is important to recognize and manage the complications that can arise in patients with nephrotic syndrome, such as dyslipidemia, infection, and thrombosis. (9)(11)(12)
- On the basis of research evidence, consensus, and expert opinion, several alternative therapies have been observed to have variable efficacy in children with both corticosteroid-dependent and corticosteroid-resistant nephrotic syndrome, although caution must be exercised in the administration of these corticosteroid-sparing medications secondary to toxic adverse effects.
- On the basis of observational studies, the course of nephrotic syndrome in most patients is that of relapse and remission. (15)

*References for this article are at <http://pedsinreview.aappublications.org/content/36/3/117.full>.*

## PIR Quiz

1. Which of the following is the most common cause of nephrotic syndrome in school-aged children:
  - A. Finnish type.
  - B. Focal segmental glomerulosclerosis.
  - C. IgA nephropathy.
  - D. Membranous nephropathy.
  - E. Minimal change disease.
2. Children with nephrotic syndrome are at particular risk for:
  - A. Appendicitis.
  - B. Gastritis.
  - C. Hepatitis.
  - D. Myositis.
  - E. Peritonitis.
3. Children with recurrent nephrotic syndrome and ongoing disease are at risk for infection with encapsulated organisms. For this reason, it is important that they receive the 23-valent pneumococcal polysaccharide vaccine at the time of diagnosis and:
  - A. Annually.
  - B. Every other year.
  - C. In 5 years.
  - D. In 6 months
  - E. In 10 years.
4. A 7-year-old boy presents to your office with a recent history of periorbital and pedal edema. He has been well except for a recent upper respiratory tract infection, which has resolved. You suspect nephrotic syndrome. Your initial workup should include all of the following except:
  - A. Albumin.
  - B. Cholesterol and lipid panel.
  - C. Serum electrolytes.
  - D. Urine culture.
  - E. Urinalysis.
5. You have recently diagnosed a 3-year-old child as having nephrotic syndrome. The first-line treatment for this patient is:
  - A. Angiotensin-converting enzyme inhibitor.
  - B. Angiotensin II receptor blocker.
  - C. Antibiotic.
  - D. Renal dialysis.
  - E. Corticosteroids.

**REQUIREMENTS:** Learners can take *Pediatrics in Review* quizzes and claim credit online only at: <http://pedsinreview.org>.

To successfully complete 2015 *Pediatrics in Review* articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2017, however, credit will be recorded in the year in which the learner completes the quiz.