

and membranous nephropathy (Table 527-2). These etiologies have different age distributions (Fig. 527-1). Nephrotic syndrome may also be **secondary** to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 527-1). A number of **hereditary** proteinuria syndromes are caused by mutations in genes that encode critical protein components of the glomerular filtration apparatus (Table 527-3).

PATHOGENESIS

Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and progression of glomerulosclerosis. The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop (see Chapter 508.1). Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters—they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α -actinin 4. Podocyte injury or genetic mutations of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 527-3).

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein “leakiness” across the glomerular capillary wall into the urinary space.

Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

CLINICAL CONSEQUENCES OF NEPHROTIC SYNDROME

Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are 2 opposing theories, the *underfill hypothesis* and the *overfill hypothesis*, that have been proposed as mechanisms causing nephrotic edema.

The *underfill hypothesis* is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis

Chapter 527 Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein:creatinine ratio >2 . The **triad of clinical findings associated with nephrotic syndrome** arising from the large urinary losses of protein are hypoalbuminemia (≤ 2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).

Nephrotic syndrome affects 1–3 per 100,000 children <16 yr of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

ETIOLOGY

Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (Table 527-1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy,

Table 527-1 Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME	SECONDARY CAUSES OF NEPHROTIC SYNDROME
Minimal change disease	Infections
Focal segmental glomerulosclerosis	Endocarditis
Membranous nephropathy	Hepatitis B, C
Glomerulonephritis associated with nephrotic syndrome—membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy	HIV-1
GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME	Infectious mononucleosis
Nephrotic Syndrome (Typical)	Malaria
Finnish-type congenital nephrotic syndrome (absence of nephrin)	Syphilis (congenital and secondary)
Focal segmental glomerulosclerosis (mutations in nephrin, podocin, MYO1E, α-actinin 4, TRPC6)	Toxoplasmosis
Diffuse mesangial sclerosis (mutations in laminin β ₂ chain)	Schistosomiasis
Denys-Drash syndrome (mutations in WT1 transcription factor)	Filariasis
Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation)	Drugs
Mitochondrial disorders	Captopril
Proteinuria With or Without Nephrotic Syndrome	Penicillamine
Nail-patella syndrome (mutation in LMX1B transcription factor)	Gold
Alport syndrome (mutation in collagen biosynthesis genes)	Nonsteroidal antiinflammatory drugs
Multisystem Syndromes With or Without Nephrotic Syndrome	Pamidronate
Galloway-Mowat syndrome	Interferon
Charcot-Marie-Tooth disease	Mercury
Jeune syndrome	Heroin
Cockayne syndrome	Lithium
Laurence-Moon-Biedl-Bardet syndrome	Immunologic or Allergic Disorders
Metabolic Disorders With or Without Nephrotic Syndrome	Vasculitis syndromes
Alagille syndrome	Castleman disease
α ₁ -Antitrypsin deficiency	Kimura disease
Fabry disease	Beesting
Glutaric aciduria	Food allergens
Glycogen storage disease	Serum sickness
Hurler syndrome	Associated With Malignant Disease
Partial lipodystrophy	Lymphoma
Mitochondrial cytopathies	Leukemia
Sickle cell disease	Solid tumors
	Glomerular Hyperfiltration
	Oligomeganepronia
	Morbid obesity
	Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet 362:629–638, 2003.

without the concomitant use of diuretics. Also, reducing the renin-aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The *overfill hypothesis* postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of intravenous albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of

lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. **Spontaneous bacterial peritonitis** presents with fever, abdominal pain, and peritoneal signs. Although *Pneumococcus* is the most frequent cause of peritonitis, Gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic

Table 527-2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
DEMOGRAPHICS					
Age (yr)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex	2:1 male	1.3:1 male	2:1 male	Male-female	Male-female
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10-20%	60-80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10-20 yr	10-20 yr	5-15 yr
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS					
	None except in congenital nephrotic syndrome (see Table 527-3)	Podocin, α -actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS					
	Manifestations of nephrotic syndrome ↑ BUN in 15-30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20-40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels—C1, C4, C3-C9	Normal complement levels—C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY					
	90%	15-20%	Resistant	Not established/resistant	Not established/resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.

↑, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.

Modified from Couser WG: Glomerular disorders. In Wyngaarden JB, Smith LH, Bennett JC, editors: Cecil textbook of medicine, ed 19, Philadelphia, 1992, WB Saunders, p. 560.

factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2-5%) compared to adults, but has the potential for serious consequences.

Bibliography is available at Expert Consult.

527.1 Idiopathic Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is

associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

PATHOLOGY

In minimal change nephrotic syndrome (MCNS) (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

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Table 527-3 Nephrotic Syndrome in Children Caused by Genetic Disorders of the Podocyte				
GENE	NAME	LOCATION	INHERITANCE	RENAL DISEASE
STEROID-RESISTANT NEPHROTIC SYNDROME				
NPHS1	Nephrin	19q13.1	Recessive	Finnish-type congenital nephrotic syndrome
NPHS2	Podocin	1q25	Recessive	FSGS
WT1	Wilms tumor-suppressor gene	11p13	Dominant	Denys-Drash syndrome with diffuse mesangial sclerosis Frasier syndrome with FSGS
LMX1B	LIM-homeodomain protein	9q34	Dominant	Nail-patella syndrome
SMARCAL1	SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1	2q35	Recessive	Schimke immunoosseous dysplasia with FSGS*

*Podocyte expression of SMARCAL1 is presumptive but not yet established. Mutations in another protein, CD2-AP or NEPH1 (a novel protein structurally related to nephrin), cause congenital nephrotic syndrome in mice. A mutational variant in the CD2AP gene has been identified in a few patients with steroid-resistant nephrotic syndrome.

FSGS, focal segmental glomerulosclerosis.

Modified from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet 362:629–638, 2003.

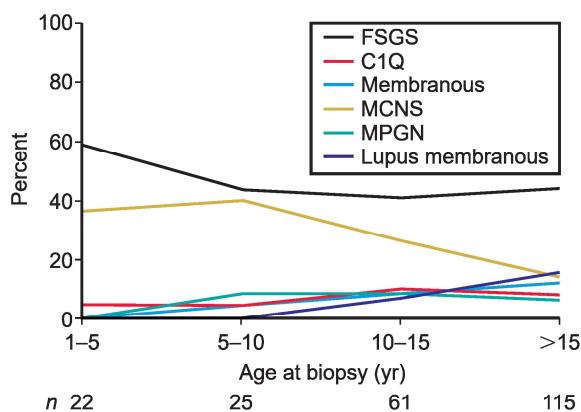


Figure 527-1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; n, number of patients. (From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747–757, 2009.)

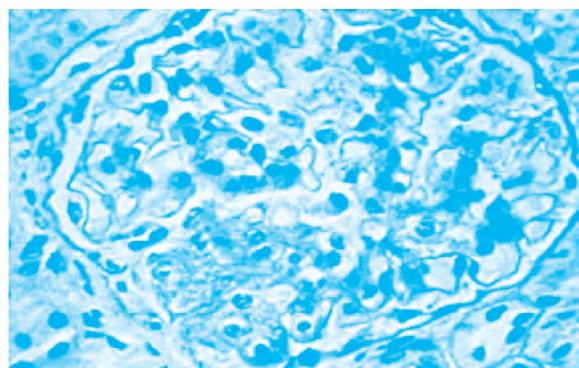


Figure 527-2 Glomerulus from a patient with steroid-resistant nephrotic syndrome showing mesangial hypercellularity and an area of sclerosis in the lower portion ($\times 250$).

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS)**, glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥ 1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 527-2 and see Table 527-2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. Similar lesions may be seen secondary to HIV infection, vesicoureteral reflux, and intravenous use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli, and ultimately leads to end-stage renal disease in most patients.

MINIMAL CHANGE NEPHROTIC SYNDROME

Clinical Manifestations

The idiopathic nephrotic syndrome is more common in boys than in girls (2:1) and most commonly appears between the ages of 2 and 6 yr (see Fig. 527-1). However, it has been reported as early as 6 mo of age and throughout adulthood. MCNS is present in 85–90% of patients <6 yr of age. In contrast, only 20–30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS may be increasing; it may be more common in African-American, Hispanic, and Asian patients.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, bee stings, or poison ivy.

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children <1 yr of age, with a positive

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family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis

Recommendations for the Initial Evaluation of Children with Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome.

The diagnosis of nephrotic syndrome is confirmed by urinalysis with first morning urine protein:creatinine ratio and serum electrolytes, blood urea nitrogen, creatinine, albumin, and cholesterol levels; evaluation to rule out secondary forms of nephrotic syndrome (children ≥ 10 yr): complement C3 level, antinuclear antibody, double-stranded DNA and hepatitis B and C, and HIV in high-risk populations; and kidney biopsy (for children ≥ 12 yr, who are less likely to have MCNS).

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein:creatinine ratio should be >2.0 . The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child's parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out prior to starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative or obtaining an interferon release assay, and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 8 yr of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 yr or >12 yr) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented below are adapted from and based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis.

Treatment of Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of $60 \text{ mg/m}^2/\text{day}$ or 2 mg/kg/day to a maximum of 60 mg daily for 4–6 wk followed by alternate-day prednisone (starting at $40 \text{ mg/m}^2 \text{ qod}$ or 1.5 mg/kg qod) for a period ranging from 8 wk to 5 mo, with tapering of the dose. When planning the duration of steroid therapy, the side effects of prolonged corticosteroid administration must be kept in mind.

Approximately 80–90% of children respond to steroid therapy. **Response** is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy. **Remission** consists of a urine protein:creatinine ratio of <0.2 or $<1+$ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy do so within the first 5 wk of treatment.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be

hospitalized. In addition to sodium restriction ($<1500 \text{ mg}$ daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, **although extreme caution should be exercised**. Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin ($0.5\text{--}1.0 \text{ g albumin/kg}$) as a slow infusion followed by furosemide ($1\text{--}2 \text{ mg/kg/dose IV}$) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when administered as rapid infusions.

Dyslipidemia. Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to $<30\%$ of calories with saturated fat intake $<10\%$ calories. Dietary cholesterol intake should be $<300 \text{ mg/day}$. There are insufficient data to recommend the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections. Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include *Pneumococcus* and Gram-negative bacteria. A 3rd-generation cephalosporin is a common choice of IV antibiotic.

Thromboembolism. Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events appears to be effective—heparin, low-molecular-weight heparin, and warfarin are therapeutic options.

Obesity and Growth. Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome. Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of >2 or $\geq 3+$ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated in a manner similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent based on the number of relapses in a 12 mo period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance. Steroid resistance is defined as the failure to achieve remission after 8 wk of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). Steroid-resistant nephrotic syndrome is

usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Implications of Steroid-Resistant Nephrotic Syndrome.

Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 yr of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with poor patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared to their peers.

Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome.

Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). Cyclophosphamide prolongs the duration of remission and reduces the number of relapses in children with frequently relapsing and steroid-dependent nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8–12 wk. Alternate-day prednisone therapy is often continued during the course of cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm³. The cumulative threshold dose above which oligospermia or azoospermia occurs in boys is >250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with steroid-resistant nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. Mycophenolate can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. Levamisole, an antihelminthic agent with immunomodulating effects that has been shown to reduce the risk of relapse in comparison to prednisone, is not available in the United States. There are also uncontrolled preliminary data regarding prolonged remissions achieved with

rituximab, the chimeric monoclonal antibody against CD20, in children with steroid-dependent and/or steroid-resistant nephrotic syndrome. There are no data from randomized clinical trials directly comparing the various corticosteroid-sparing agents. Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations in Children with Nephrotic Syndrome.

To reduce the risk of serious infections in children with nephrotic syndrome, give full pneumococcal vaccination (with the 13-valent conjugate vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children on immunosuppressive agents varicella-zoster immune globulin if available; immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3–6 wk after vaccination.

Table 527-4 provides monitoring recommendations for children with nephrotic syndrome.

Prognosis

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 mo after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychologic

Table 527-4 Monitoring Recommendations for Children with Nephrotic Syndrome

DISEASE AND TREATMENT	HOME URINE PROTEIN	WEIGHT, GROWTH, BMI	BLOOD PRESSURE	CREATI-NINE	ELECTRO-LYTES	SERUM GLU-COSE	LIPID PROFILE	DRUG LEVELS	LIVER FUNC-TION	URINALYSIS	CPK
DISEASE TYPE											
Mild (steroid responsive)	•	•	•							•	
Moderate (frequent relapsing, steroid dependent)	•	•	•	•			•			•	
Severe (steroid resistant)	•	•	•	•			•			•	
THERAPY											
Corticosteroids		•	•			•		•			
Cyclophosphamide				•			•			•	
Mycophenolate mofetil							•		•		
Calcineurin inhibitors			•	•	•	•	•	•	•		
ACEIs/ARBs			•	•	•		•				
HMG-CoA reductase inhibitors							•	•	•		•

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CBC, complete blood count; CPK, creatine phosphokinase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747–757, 2009.

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effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission.

Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage renal disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30–50% of transplant recipients with FSGS.

Bibliography is available at Expert Consult.

527.2 Secondary Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and Henoch-Schönlein purpura nephritis can all have a nephrotic component (see Tables 527-1 and 527-2). Secondary nephrotic syndrome should be suspected in patients >8 yr and those with hypertension, hematuria, renal dysfunction, extrarenal symptoms (rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probencid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpropamide, phenytoin, trimethadione, paramethadione).

Bibliography is available at Expert Consult.

527.3 Congenital Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the 1st yr of life, when compared to nephrotic syndrome manifesting in childhood. Congenital nephrotic syndrome is defined as nephrotic syndrome manifesting at birth or within the 1st 3 mo of life. Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitis B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 527-3). A number of structural and functional abnormalities of the glomerular

Table 527-5 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year

SECONDARY CAUSES

Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B
HIV
Malaria
Drug reactions
Toxins
Mercury
Systemic lupus erythematosus

Syndromes with associated renal disease

Syndromes with associated renal disease
Nail-patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic-uremic syndrome

PRIMARY CAUSES

Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Saunders, p. 418.

filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried disease-causing mutations in 4 genes (*NPHS1*, *NPHS2*, *WT1*, and *LAMB2*), the first 3 of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by mutations in the *NPHS1* or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic α -fetoprotein levels.

Denys-Drash syndrome is caused by mutations in the *WT1* gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.

Mutations in the *LAMB2* gene, seen in **Pierson syndrome**, lead to abnormalities of β_2 -laminin, a critical component of glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Regardless of the etiology of congenital nephrotic syndrome, diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and increased risk of thrombotic events. Most infants have progressive renal insufficiency.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 527-5). The management of primary congenital nephrotic syndrome includes intensive supportive care with intravenous albumin and diuretics, regular administration of intravenous γ -globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme

inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

Bibliography is available at Expert Consult.

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