CHAPTER

12 Nephrotic Syndrome

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Nephrotic syndrome is a common type of kidney disease seen in children. Historically, Roelans is credited with the first clinical description of nephrotic syndrome in the late fifteenth century, whereas Zuinger later provided a detailed description of the clinical course of the disease and its importance as a cause of chronic renal failure in the presteroid era.[1] Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia, and edema, although additional clinical features such as hyperlipidemia are also usually present. In the first few years of life, children with this condition often show periorbital swelling with or without generalized edema. The disease is due to development of structural and functional defects in the glomerular filtration barrier, resulting in its inability to restrict urinary loss of protein. Physiologically, the liver tries to compensate for the excessive loss with increased protein and lipoprotein synthesis. Nephrotic syndrome develops when the loss of protein in urine exceeds the rate of albumin synthesis in the liver, resulting in hypoalbuminemia and edema. Nephrotic syndrome may be caused by a variety of glomerular and systemic diseases, but by far the most common type in childhood is idiopathic nephrotic syndrome. Before the introduction of antibiotics, corticosteroids, and other immunosuppressive therapies, nephrotic syndrome was associated with mortality as high as 67%, usually following infections. The first significant improvement in mortality was seen in 1939 after the introduction of sulfonamides and then penicillin. The introduction of adrenocorticotropic hormone and cortisone in the 1950s contributed to an even greater decrease in mortality (to 9%), which was noted to occur in association with dramatic resolution of proteinuria.[2]

DEFINITIONS

The observations that nephrotic syndrome was responsive to corticosteroids and that its clinical course could be characterized by remission and relapse led to several further observations that remain highly relevant to both the treatment and prognosis of nephrotic syndrome today. It is estimated that about 80% of children with idiopathic nephrotic syndrome will respond to corticosteroid treatment with complete resolution of proteinuria and edema. Among this steroid-responsive group, the clinical course is variable, with up to 60% having frequent relapses or becoming dependent on steroid therapy to maintain them in remission. Based on these findings, it became important to establish some clinically relevant definitions for the diagnosis of nephrotic syndrome and to clarify various patient responses to treatment.

Nephrotic Syndrome: Diagnosis of nephrotic syndrome requires the presence of edema, massive proteinuria (>40 mg/m^2/hr or a urine protein/creatinine ratio >2.0 mg/mg), and hypoalbuminemia (<2.5 g/dl).[3,4]

Remission: Remission is characterized by a marked reduction in proteinuria (to <4 mg/m^2/hr or urine albumin dipstick of 0 to trace for 3 consecutive days) in association with resolution of edema and normalization of serum albumin to at least 3.5 g/dl.[3,4]

Relapse: Relapse is defined as recurrence of massive proteinuria (>40 mg/m^2/hr, urine protein/creatinine ratio >2.0 mg/mg, or urine albumin dipstick ≥2+ on 3 consecutive days), most often in association with recurrence of edema.[3,4]

Steroid-Sensitive Nephrotic Syndrome: Patients who enter remission in response to corticosteroid treatment alone are referred to as having steroid-sensitive nephrotic syndrome (SSNS).

Steroid-Resistant Nephrotic Syndrome: Patients who fail to enter remission after 8 weeks of corticosteroid treatment are referred to as having steroid-resistant nephrotic syndrome or (SRNS).[3,4] It should be noted, however, that significant discrepancies exist in the literature about the definition of SRNS. Whereas some authors define this state as a failure to enter remission after 4 weeks of treatment with prednisone at a dosage of 60 mg/m^2/day, others define it as failure to enter remission after 4 weeks of prednisone at a dosage of 60 mg/m^2/d followed by 4 weeks of prednisone taken on alternate days at a dosage of 40 mg/m^2/dose, or as 4 weeks of prednisone at a dosage of 60 mg/m^2/d followed by three intravenous pulses of methylprednisolone at a dosage of 1000 mg/1.73 m^2/dose.[5,6] Although these discrepancies make direct comparison of reports of the efficacy of newer treatments for nephrotic syndrome more difficult, the most important implication for patients who have been given the label SRNS is that they are at significantly higher risk for development of complications of the disease (discussed later in this chapter), as well as progression of the disease to chronic kidney disease (CKD) or end stage renal disease (ESRD).

Steroid-Dependent Nephrotic Syndrome: Some patients respond to initial corticosteroid treatment by entering complete remission but develop a relapse either while still receiving steroids or within 2 weeks of discontinuation of treatment

following a steroid taper. Such patients typically require continued low-dose treatment with steroids to prevent development of relapse, and are therefore referred to as having steroid-dependent nephrotic syndrome (SDNS).[7]

Frequent Relapsing Nephrotic Syndrome: Patients in this group enter complete remission in response to steroids. They remain in remission for several weeks following discontinuation of treatment but develop frequent relapses. If relapses occur 4 or more times in any 12-month period, these patients are referred to as having frequent relapsing nephrotic syndrome (FRNS)[7]

Both SDNS and FRNS patients are at increased risk of developing complications of nephrotic syndrome and complications from frequent use of steroids and other immunosuppressive agents. Although it is not well documented, children with FRNS and SDNS can also develop CKD or ESRD. The likelihood of these risks is generally considered to fall between those for SSNS patients and the significantly increased risks for SRNS patients.

EPIDEMIOLOGY

The annual incidence of nephrotic syndrome in most countries in the Western Hemisphere is estimated to range from 2 to 7 new cases per 100,000 children,[4,8-11] and the prevalence is about 16 cases per 100,000 children.[4] There is a male preponderance among young children, at a ratio of 2:1 to females, although this gender disparity disappears by adolescence, making the incidence in adolescents and adults equal among males and females.[9,12-15]

The incidence of nephrotic syndrome has been fairly stable over the last 30 years, but there are suggestions that the histopathologic patterns may be changing. For example, reports from different parts of the world indicate an increasing occurrence of focal segmental glomerulosclerosis (FSGS) not only after adjusting for variations in renal biopsy practices but also based on the generous assumption that all patients who did not have a renal biopsy had minimal change nephrotic syndrome (MCNS).[9,12-15]

The incidence and the histologic pattern of nephrotic syndrome are also affected by geographic location and ethnic origin. In a report from the United Kingdom, idiopathic nephrotic syndrome was found to be 6 times more common in children of Asian descent living in the United Kingdom than among their European counterparts.[16] In contrast, hospital-based data from Sub-Saharan Africa suggest that idiopathic nephrotic syndrome is relatively less common among African children, where the disease is more often due to glomerular lesions induced by infectious agents.[17-19] In the United States, nephrotic syndrome appears to occur relatively proportionately among children of various ethnic backgrounds. A recent review of children diagnosed with nephrotic syndrome in Houston, Texas, revealed that the distribution of patients closely resembled the ethnic composition of the surrounding community.[12] These data in conjunction with data from African countries seem to suggest that the interaction of genetic and environmental factors is important in the pathogenesis of nephrotic syndrome. However, race appears to have an important impact on the histologic lesion associated with nephrotic syndrome. In this same study the authors found that although only 11% of Hispanic and 18% of Caucasian patients with nephrotic syndrome had FSGS, 47% of African American children had this less favorable diagnosis.[12]

Age also correlates with both the frequency of presentation and the biopsy findings associated with nephrotic syndrome. The most common age for presentation is 2 years, and 70% to 80% of cases occur in children younger than 6.[4,8] To some extent age also predicts the histologic lesion associated with nephrotic syndrome. Children diagnosed before age 6 represented 79.6% of those with MCNS compared with 50% of those with FSGS and only 2.6% of those with membranoproliferative glomerulonephritis (MPGN).[20] When these data were analyzed on the basis of renal histology, the median ages at presentation were found to be 3 years for MCNS, 6 years for FSGS, and 10 years for MPGN.[20] Thus excluding the first year of life, these data combined suggest that the likelihood of having MCNS decreases with increasing age, whereas the likelihood of having the less favorable diagnosis of FSGS or MPGN increases.[20,21]

The histologic lesion associated with nephrotic syndrome has important ramifications for the likelihood of response to steroid treatment. Although almost 80% of children diagnosed with nephrotic syndrome in a multicenter International Study of Kidney Diseases in Children (ISKDC) study entered remission following an initial 8-week course using prednisone, when these children were analyzed based on histology, steroid responsiveness was found in 93% of those with MCNS compared with only 30% of those with FSGS and 7% of those with MPGN.[5,20] In addition to histology, response to steroids also varies with geographic location and ethnicity. Whereas 80% of children in western countries will be steroid responsive, studies from South Africa, Nigeria, and more recently Ghana show that only 9% to 50% of children with nephrotic syndrome are steroid responsive.[19,22,23]

Failure to respond to steroid treatment has important ramifications for the risk of developing progressive renal failure later in life. In a multicenter evaluation of 75 children with FSGS, it was found that within 5 years after diagnosis, 21% had developed ESRD, 23% had developed CKD, and 37% had developed persistent proteinuria, whereas only 11% remained in remission.[24] Thus once a child is given the diagnosis of FSGS, the risk for development of CKD or ESRD within 5 years is almost 50%.

ETIOLOGY

Nephrotic syndrome in childhood is largely primary or idiopathic, although a small proportion of cases are secondary to infectious agents and other glomerular and systemic diseases. The etiology of nephrotic syndrome is also age dependent. Most cases appearing in the first 3 months of life are referred to as congenital nephrotic syndrome (CNS) and are due to genetic diseases. Although there has been no systematic study of the etiology of nephrotic syndrome presenting in the rest of the first year of life (3 to 12 months), there are data suggesting that up to 40% of cases during this time may also be due to genetic causes.[25] Beyond the first year of life and in the first decade, most cases are due to primary or idiopathic nephrotic syndrome, whereas the proportion of secondary nephrotic syndrome cases increases beyond the first 10 years of life.

Congenital Nephrotic Syndrome

Nephrotic syndrome appearing in the first 3 months of life is referred to as congenital nephrotic syndrome (CNS). Most cases in this age group are due to genetic causes (see Chapter 13), the majority being mutations in the gene encoding nephrin, a podocyte slit diaphragm protein. These mutations were first described in the Finnish, hence the name congenital nephrotic syndrome of the Finnish type (CNF).[26] The incidence of CNF is highest in Finland but occurs in other populations as well. Congenital nephrotic syndrome is not synonymous with CNF, because mutations in other genes encoding podocyte slit diaphragm proteins, such as podocin, can also cause early-onset nephrotic syndrome. In one series mutations in the podocin gene *(NPHS2)* were shown to be responsible for up to 40% of all cases of nephrotic syndrome occurring in the first 3 months of life.[25] Nephrotic syndrome in the first 3 months of life may also be part of multisystemic syndromes such as Pierson syndrome, nail-patella syndrome, Denys-Drash syndrome, and others (see Chapter 13), or a result of congenital infections such as syphilis and cytomegalovirus (Table 12-1).

Nephrotic Syndrome Beyond Infancy

Beyond the first year of life, most cases of nephrotic syndrome are idiopathic. The most common histologic variant is MCNS, which is responsible for more than 80% of all cases.[14] Other, less common histopathologic types in this age group include FSGS, MPGN, and mesangial proliferative glomerulonephritis (Table 12-2). Genetic disease is also responsible for some cases in this age group. In one series it was shown that mutations in *NPHS2*, inherited in an autosomal recessive manner, were responsible for 10% to 25% of all cases of familial and sporadic SRNS.[27,28] The phenotype typically associated with *NPHS2* mutations includes onset of nephrotic syndrome in early childhood, resistance to steroid treatment, predominant FSGS histopathologic findings on renal biopsy, progression to ESRD within 5 years of diagnosis, and significantly reduced risk of disease recurrence following renal transplantation.[27,28] Other genetic factors include autosomal dominant transmitted causes such as mutations in the Wilms' tumor suppressor gene *(WT1)*, *α-actinin 4*, *CD2AP*, and *TRPC6*.[29-33] Apart from those in *WT1*, most of these mutations tend to result in adult-onset disease.

Nephrotic syndrome may also be secondary to a number of systemic diseases in children. Pediatric illnesses such as systemic lupus erythematosus, especially membranous (WHO Class V) SLE; Henoch-Schönlein purpura; diabetes mellitus; and sarcoidosis may all present with nephrotic syndrome.

Infectious agents may also cause nephrotic syndrome and can be viral, bacterial, or parasitic. Although it is not yet fully understood how these agents cause nephrotic syndrome, in most cases it is probably due to an aberrant immune response to them, resulting in the formation and deposition of immune complexes in the glomerulus. The importance of these agents as a cause of nephrotic syndrome tends to parallel their prevalence in particular regions of the world. For example, hepatitis B and C are important causes of nephrotic syndrome in Hong Kong and countries in Africa.[34,35] Malaria, especially quartan malaria, is also an important cause in areas where malaria is endemic.[18] Human immunodeficiency virus (HIV), too, can cause nephrotic syndrome in both adults and children. Although the renal lesion associated with HIV can be variable, the most common histologic finding associated with HIV is FSGS, especially the collapsing variant. Although the effect of treatment of the underlying infection on the nephropathy is not well documented, but there are reports that hepatitis B–associated nephrotic syndrome may be amenable to treatment of the hepatitis.[22] A list of infectious agents associated with nephrotic syndrome is shown in Table 12-2. Other, less common causes of nephrotic syndrome include drugs such as gold, penicillamine, angiotensin converting enzyme inhibitors (ACEIs), nonsteroidal antiinflammatory drugs (NSAIDs), sickle cell disease, lymphoma, leukemia, bee stings, and various types of food allergies. In addition, nephrotic syndrome is being seen more often in children with obesity. The histologic lesion most commonly found in this setting is FSGS.

TABLE 12-1 **Etiologies of Congenital Nephrotic Syndrome (0-3 Months of Age)**

Genetic	Congenital nephrotic syndrome of the Finnish type (CNF) due to mutation in nephrin *(NPHS1)* gene Autosomal recessive FSGS due to mutation in podocin *(NPHS2)* gene Autosomal dominant diffuse mesangial Sclerosis (DMS) due to mutation in *WT1* gene Congenital nephrotic syndrome due to mutation in laminin β_2 gene
Syndromes	Denys-Drash syndrome due to *WT1* mutation with DMS Pierson syndrome Galloway Mowat syndrome Nail-patella syndrome due to mutation in LIM-homeodomain protein *(LMX1B)* Schimke immunoosseous dysplasia with FSGS due to mutation in *SMARCAL1* Cockayne syndrome Jeune's syndrome
Idiopathic	Minimal change nephrotic syndrome FSGS Nonsyndromic DMS
Infections	Congenital syphilis Congenital cytomegalovirus (CMV) infection Congenital toxoplasmosis

PATHOGENESIS

The central abnormality in all cases of nephrotic syndrome is the development of massive proteinuria. Although the molecular basis for this is still speculative, there is evidence in the literature that nephrotic syndrome may be a consequence of a primary glomerular defect, circulating factors, or an immunological abnormality.

Primary Glomerular Defect

One of the most important functions of the kidney is the filtration of blood by glomeruli, which allows excretion of fluid and waste products while retaining the majority of blood

TABLE 12-2 **Etiologies of Nephrotic Syndrome (Beyond 3 Months of Age)**

Idiopathic	Minimal change nephrotic syndrome (MCNS) Focal segmental glomerulosclerosis (FSGS) Mesangial proliferative glomerulonephritis Membranoproliferative glomerulonephritis (MPGN) Membranous nephropathy (MN) IgM nephropathy C1q nephropathy
Genetic	Autosomal recessive FSGS due to mutation in gene encoding podocin *(NPHS2)* Autosomal dominant diffuse mesangial sclerosis (DMS) due to mutation in gene encoding *WT1* Autosomal dominant FSGS due to mutation in gene encoding *α-actinin 4* Autosomal dominant FSGS due to mutation in gene encoding CD2-associated protein *(CD2AP)* Autosomal dominant FSGS due to mutation in gene encoding transient receptor potential cation channel 6 *(TRPC6)*
Infections	Hepatitis B and C HIV Malaria Schistosomiasis Filariasis
Systemic diseases	Henoch-Schönlein purpura Systemic lupus erythematosus Diabetes mellitus Sarcoidosis
Metabolic diseases	Fabry's disease Glutaric acidemia Glycogen storage disease Mitochondrial cytopathies
Hematologic and oncologic diseases	Leukemia Lymphoma (Hodgkin's most likely can lead to minimal change) Sickle cell disease
Drugs	Nonsteroidal antiinflammatory drugs (NSAIDs) Gold Penicillamine Angiotensin converting enzyme inhibitors (ACEIs) Pamidronate Interferon Mercury Heroin Lithium
Others	Bee stings (MCNS) Food allergies Obesity (usually with FSGS) Oligomeganephronia Pregnancy

proteins and all blood cells within the vasculature. This process of filtration is made possible by the glomerular filtration barrier, which is made up of specialized fenestrated endothelial cells, the glomerular basement membrane (GBM), and glomerular epithelial cells (podocytes) whose distal foot processes are attached to the GBM (Figure 12-1).[36] Neighboring podocyte foot processes are connected to each other by networks of specialized cell-cell junctions known as slit diaphragms. In addition, the GBM has an abundant supply of negatively charged heparin sulfate proteoglycan, resulting in negatively charged molecules being relatively more restricted from passage than positively charged molecules of the same size.[37] In health, molecules greater than 42 Å in diameter, or more than 200 kDa, are unable to cross the filtration barrier.[38] This restriction depends largely on the structural integrity of the podocyte foot processes and slit diaphragms, as well as the GBM charge. In nephrotic syndrome there is loss of negative charge of the GBM.[39-41] Other morphologic changes in podocytes that occur during development of nephrotic syndrome include swelling, retraction, and effacement (spreading) of the podocyte distal foot processes, vacuole formation, occurrence of occluding junctions, displacement of slit diaphragms, and detachment of podocytes from the GBM.[8-10,20]

The importance of podocyte and slit diaphragm structure to the pathogenesis of nephrotic syndrome is further reinforced by recent observations in humans and experimental animals that mutations in genes encoding some of the slit diaphragm proteins or their transcription factors can cause SRNS and/or FSGS.[26,29-33,42] These findings have been the subject of many recent reviews in the literature.[43-45] Mutations in the gene encoding the slit diaphragm protein nephrin

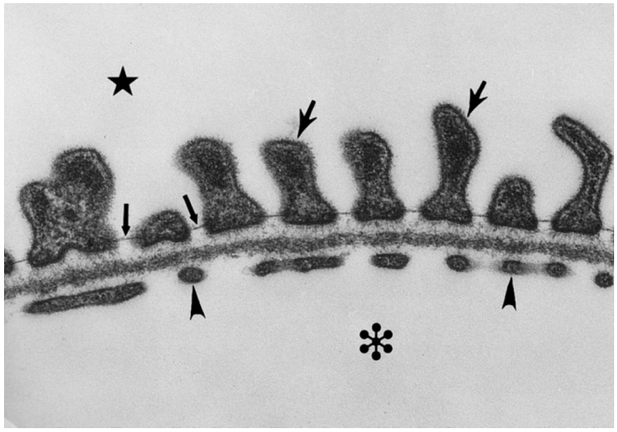

Figure 12-1 Electron micrograph of the components of the glomerular filtration barrier. During normal glomerular filtration, plasma water is filtered from the glomerular capillary lumen *(asterisk)* through the fenestrated endothelial cell layer *(arrowheads)*, then across the glomerular basement membrane (GBM) and through the slit diaphragms *(small arrows)* that bridge the filtration slits between adjacent podocyte foot processes *(large arrows)*, and finally into the urinary space *(star)* where it enters the lumen of the proximal tubule. These podocyte foot processes are normally tall and evenly spaced along the GBM, but during nephrotic syndrome they become spread out along the GBM, with apical displacement of the slit diaphragms. The layer of negatively charged glycocalyx can be seen in this image as a blurry coating on the apical surfaces of the podocyte foot processes. (Adapted with permission from Smoyer WE, Mundel P: Regulation of podocyte structure during the development of nephrotic syndrome, *J Mol Med* 76 (3-4):172-83, 1998.)

(NPHS1) causes CNF in infants.[26] In addition, mutations in *NPHS2* are estimated to be responsible for up to 25% of cases of familial and sporadic SRNS in children.[27,28] Mutations in the transcription factor suppressor gene *WT1* result in Denys-Drash syndrome and Frasier syndrome in children, although they may also cause isolated FSGS and diffuse mesangial sclerosis (DMS).[33,46,47] Mutations in other genes encoding podocyte and GBM proteins include (1) the actin-bundling protein α-actinin 4, which causes adult-onset FSGS; (2) laminin β_2, which results in Pierson syndrome; (3) CD2-associated protein (CD2AP), which results in adult-onset FSGS; (4) the LIM-homeodomain protein (encoded by *LMX1B*), which results in nail-patella syndrome; and (5) the chromatin regulator encoded by *SMARCAL1*, which results in FSGS associated with Schimke immunoosseous dysplasia.[29,48-50] This subject is discussed in greater detail in Chapter 13.

Circulating Factors

There are experimental data to support the existence of soluble mediators that may alter capillary wall permeability in nephrotic syndrome.[40,51-53] Evidence for this includes (1) development of nephrotic syndrome in newborn babies born to mothers with nephrotic syndrome who apparently transferred a soluble factor to their fetuses in utero,[52] (2) marked reduction of proteinuria following treatment with protein A immunoadsorption in various types of primary nephrotic syndromes,[54] (3) recurrence of FSGS in transplanted kidneys in patients with primary FSGS, with remission of recurrent disease induced by treatment with protein A immunoadsorption due to presumed removal of circulating factors,[55] and (4) induction of enhanced glomerular permeability in experimental animals injected with serum from patients with FSGS recurrence in transplanted kidneys.[56] Furthermore, inhibitors of glomerular permeability have also been isolated from the serum of children with FSGS and identified as components of apolipoproteins, suggesting that an imbalance between serum permeability factors and permeability inhibitors may have a pathogenic role in FSGS.[57]

Immunological Abnormality

The theory that nephrotic syndrome may be due to dysregulation of the immune system has existed for more than 30 years. There are numerous reports of abnormalities of both the humoral and cellular immune responses during relapse of nephrotic syndrome. However, the idea that nephrotic syndrome may be due to dysregualtion of T lymphocyte function was first proposed by Shalhoub and his colleagues.[51] Evidence for this includes (1) responsiveness of most forms of primary nephrotic syndrome to corticosteroids, alkylating agents, calcineurin inhibitors, and mycophenolate mofetil, all of which are known inhibitors of T lymphocyte function, (2) induction of remission of nephrotic syndrome following infections with measles and malaria, diseases known to depress cell-mediated immunity, and (3) identification of MCNS as a paraneoplastic manifestation of Hodgkin's disease and other lymphoreticular malignancies. Other reports have also suggested an important role of the cell-mediated immune system in nephrotic syndrome, including depressed cell-mediated immunity during relapses of MCNS alterations in T cell subsets during relapses,[58,59] and increased cell surface expression of IL-2 receptors on T cells, reflective of T cell activation.[59] In addition, numerous cytokines, released in part by T lymphocytes, have been reported to be variably altered during nephrotic syndrome.[60,61] It should be noted, however, that despite numerous reports, none of these cytokines has proven to be both present in the majority of cases of MCNS and able to induce significant proteinuria in experimental animals.

PATHOPHYSIOLOGY

Accumulation of fluid in the interstitial compartment, which typically manifests as facial or generalized edema, is the cardinal symptom in children with nephrotic syndrome. By definition, edematous nephrotic patients always have a total body excess of both sodium and water. The edema in nephrotic syndrome is generally presumed to result from massive proteinuria, which leads to hypoalbuminemia and retention of sodium and water to compensate for intravascular volume depletion.

The pathogenesis of edema in nephrotic syndrome can be most easily understood by analysis of the classic Starling equation, which explains the regulation of fluid movement across capillary walls[62]:

$$\text{Net filtration} = \text{LpS}\ (\Delta \text{ hydraulic pressure} - \Delta \text{ oncotic pressure})$$
$$= \text{LpS}\ [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})]$$

where:
Lp = the capillary permeability
S = the surface area of the capillary wall

P_{cap} = the capillary hydrostatic pressure
P_{if} = the interstitial fluid hydrostatic fluid pressure
s = the reflection coefficient for proteins (0 = complete permeability and 1 = complete impermeability)
π_{cap} = the capillary oncotic pressure
π_{if} = the interstitial fluid oncotic pressure

In healthy patients, edema formation is prevented by a balance between forces favoring edema (capillary hydrostatic pressure [P_{cap}]) and those opposing it (capillary oncotic pressure [π_{cap}]). In the normal state, the slight tendency toward fluid accumulation in the interstitial space is counterbalanced by the lymphatics, which return this fluid to the circulation. Hypoalbuminemia develops in nephrotic patients when the rate of urinary loss of albumin exceeds the ability of the liver to synthesize it. The resultant hypoalbuminemia leads to low capillary oncotic pressure (π_{cap}), which leads to relatively unopposed capillary hydrostatic pressure (P_{cap}) and subsequent edema formation. The edema formation then results in relative intravascular volume depletion, which triggers neurohumoral compensatory mechanisms to try to replete the intravascular volume. The key mediators of these mechanisms include the sympathetic nervous system (SNS), the renin angiotensin aldosterone system (RAAS), and arginine vasopressin (AVP), with the net result being sodium and water retention by the kidney. In the setting of nephrotic syndrome, mechanoreceptors in the carotid sinus, aortic arch, left ventricle, and afferent arterioles in the glomeruli detect decreased pressure distension. This produces (1) increased SNS outflow from the central nervous system, (2) activation of the RAAS, and (3) nonosmotic release of AVP from the hypothalamus. These three changes result in peripheral vasoconstriction (increased SNS and angiotensin II), sodium retention (increased SNS, angiotensin II, and aldosterone), and water retention.

Although it is widely accepted that patients with nephrotic syndrome have an excess of total body sodium and water as a result of these compensatory mechanisms, the status of their intravascular volume is somewhat controversial. There are two hypotheses that explain the intravascular state in nephrotics: the so-called underfill hypothesis and overfill hypothesis. The underfill hypothesis (Figure 12-2) proposes the existence of a reduced effective circulating blood volume in nephrotic syndrome. It is supported by findings of low urine sodium in the setting of edema, most likely due to activation of the RAAS with resultant elevation of aldosterone levels and reduction in urinary sodium excretion. Furthermore, suppression of atrial natriuretic peptide (ANP) also contributes to low urinary sodium.[63] Additional evidence for the underfill hypothesis includes improvement in sodium excretion with albumin infusion or head-out water immersion, and decreased cardiac output and increased vascular

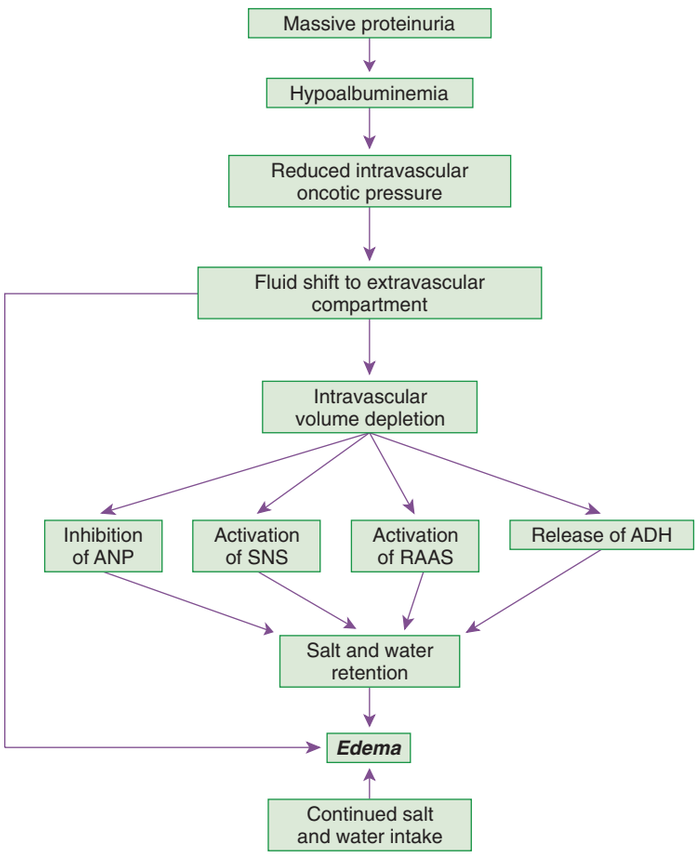

Figure 12-2 Underfill hypothesis of edema formation in nephrotic syndrome. Proposed sequence of pathophysiologic events leading to the formation of edema in nephrotic syndrome according to the underfill hypothesis. Some authors have suggested that the underfill hypothesis is seen more in human clinical disease, whereas the overfill hypothesis is seen more in animal models of nephrosis. *ADH*, Antidiuretic hormone; *ANP*, atrial natriuretic peptide; *RAAS*, renin angiotensin aldosterone system; *SNS*, sympathetic nervous system. (From Schrier RW, Fassett RG: A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome, *Kidney Int* 53 (5):1111-17, 1998.)

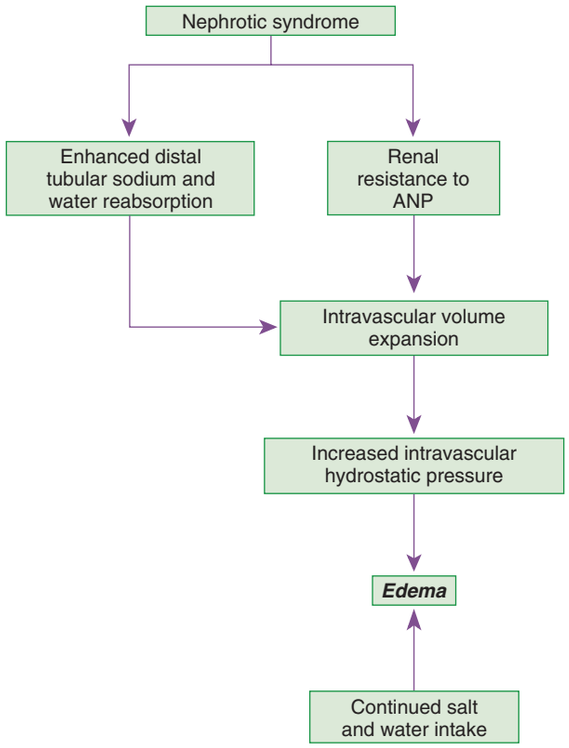

Figure 12-3 Overfill hypothesis of edema formation in nephrotic syndrome. Shown is the proposed sequence of pathophysiologic events leading to the formation of edema in nephrotic syndrome according to the overfill hypothesis. Some authors have suggested that the overfill hypothesis is seen more in animal models of nephrosis than in the human clinical setting. ANP, Atrial natriuretic peptide. (From Schrier RW, Fassett RG: A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome, *Kidney Int* 53 (5):1111-17, 1998.)

resistance in animal models of nephrotic syndrome.[64] Findings that do not support the underfill hypothesis as the sole explanation for edema formation in nephrotic syndrome include reports of normal or increased intravascular volume in some patients and variable plasma renin levels in others.[65,66]

In contrast, the overfill hypothesis (Figure 12-3) proposes the existence of an expanded intravascular volume in nephrotic syndrome. Proponents of this hypothesis postulate that nephrotic patients have a primary defect in sodium excretion from the distal convoluted tubules, resulting in an expanded circulatory volume that then leads to suppression of the RAAS. This distal tubular sodium reabsorption has been suggested as secondary to resistance to the effects of ANP.[67] Evidence includes a finding of increased sodium reabsorption from proteinuric kidneys in a rat unilateral proteinuria kidney model,[68] as well as the finding that urinary sodium excretion is not affected by albumin infusion or head-out water immersion in some nephrotic patients.[69] Some authors have argued that the overfill hypothesis is seen more in animal models of nephrosis than in humans in the clinical setting.[70] It should be noted, however, that overfilled and underfilled states are not mutually exclusive, and that the volume status may depend on the stage of disease when a child is being evaluated. It is possible that the underfilled state may be predominant in the acute setting in which massive proteinuria causes rapid development of hypoalbuminemia and an abrupt drop in plasma oncotic pressure, whereas the overfilled state may be predominant in the chronic phase during which patients may have continuing sodium retention due to persistent low-grade hypoalbuminemia.

Because management of edema in children with nephrotic syndrome may be different for those believed to be intravascularly volume-expanded as opposed to volume-contracted, establishing whether a child is overfilled versus underfilled can be clinically important. One group has advocated measuring the fractional excretion of sodium (FE_{Na}) and the relative urinary potassium excretion $[U_K/(U_K + U_{Na})]$ to clarify the distinction.[69] Nephrotic patients with a low FE_{Na} (<1%) and high urinary potassium excretion (>60%) would be expected to have a low intravascular volume. In addition, these urinary findings have been shown to correlate with elevated plasma renin, aldosterone, norepinephrine, and vasopressin levels.[69]

CLINICAL FEATURES AND DIAGNOSIS

History and Physical Examination

The clinical diagnosis of idiopathic nephrotic syndrome is often very simple. In a child with periorbital or generalized edema, the primary care physician can quickly make this diagnosis by documenting significant proteinuria with more than 2+ albumin on urine dipstick or a spot urine protein/creatinine ratio greater than 2 mg/mg and serum albumin of less than 2.5 g/dl. In addition, a careful history should exclude possible complications and identify children with atypical presentations that might reflect other serious systemic illnesses. It should include an evaluation of any abdominal distension, which is usually due to ascites and sometimes edema of the anterior abdominal wall. Although severe distension may be accompanied by abdominal discomfort, persistent abdominal pain may be due to primary bacterial peritonitis (a potentially life-threatening complication), gut edema, or relative gut ischemia due to hypoperfusion secondary to intravascular volume depletion. Other causes of an acute abdomen should also be considered. A history of coughing or breathing difficulties or both may indicate pleural effusion. Pulmonary edema, though rarely found in idiopathic nephrotic children, should lead to consideration of secondary causes of nephrotic syndrome that might cause significant intravascular fluid retention. Although a history of gross hematuria is unusual in nephrotic syndrome, microscopic hematuria may be seen in up to 23% of patients with MCNS and in a higher percentage of patients with other histologic variants.[20] Severe intravascular volume depletion may cause acute renal failure, and some children may present with oliguria or anuria. In such cases prompt intravascular volume repletion is important to correct prerenal acute renal failure and to prevent development of acute tubular necrosis. A history of possible systemic symptoms including fevers, weight loss, night sweats, polyuria, polydipsia, hair loss, oral ulcers, rashes, abdominal pain, and joint pain or swelling should also be elicited, because they may be manifestations of systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, or diabetes mellitus, which can

all cause nephrotic syndrome. A medication history should also be taken in that medications such as NSAIDs, gold, and penicillamine can also cause nephrotic syndrome. The history should exclude other causes of generalized edema, such as chronic liver failure, heart failure, and malnutrition in areas of the world where clinical malnutrition is prevalent.

Regarding physical examination, blood pressure should be carefully determined in nephrotic children; it can be either low (due to intravascular volume depletion) or elevated (due to neurohumoral responses to hypovolemia, intrinsic renal causes, or occasionally renal vein thrombosis). Hypertension has been reported in up to 21% of children 6 years and under with biopsy-confirmed MCNS, and may be present in up to 50% of children with other histologic types.[20] A careful examination of the abdomen should also be performed to exclude abdominal tenderness or guarding that may be signs of bacterial peritonitis. In addition, extremities should be examined to exclude warmth, tenderness, or pain that may suggest venous thrombosis. Finally, obtaining a detailed family history is also important, because some causes of nephrotic syndrome are familial, as previously discussed.

Laboratory Evaluation

Diagnosis of nephrotic syndrome is confirmed by the triad of generalized edema, proteinuria, albuminuria (>2+ on dipstick or urine protein/creatinine ratio >2 mg/mg), and hypoalbuminemia (serum albumin <2.5 g/dl), although hypercholesterolemia is also commonly present. In addition to documenting proteinuria, urinalysis with microscopy should be carried out to look for hematuria and possible red blood cell casts. In patients with a typical presentation, serum studies should include an evaluation of complete blood count, electrolytes, blood urea nitrogen (BUN), creatinine, and albumin levels. For patients at an older age at presentation or with atypical presentation, additional serum studies to exclude secondary causes of nephrotic syndrome should include C3 and C4 complement levels; antinuclear antibody (ANA) and possibly anti-double-stranded DNA; HIV antibody; hepatitis A, B, and C serologies; and consideration of other viral serologies such as HIV antibodies.

Because immunosuppressive therapy is the mainstay of treatment for most cases of childhood nephrotic syndrome, many pediatric nephrologists recommend placing a PPD (purified protein derivative) test to screen for occult tuberculosis before instituting immunosuppression. This is particularly important in areas of the world where tuberculosis is endemic and for recent immigrants from such regions. In addition, many nephrologists obtain a varicella IgG titer before treatment to classify patients as varicella-naive or varicella-immune, which can be of great aid when suspecting or confirming varicella exposure in children who are immunocompromised during treatment. A varicella-naive patient receiving immunosuppressive treatment for nephrotic syndrome who is exposed to varicella should be treated with varicella zoster immunoglobulin (VZIG) within 96 hours of exposure if possible.[71] This passive immunization can sometimes be lifesaving due to the potential severity of a primary varicella infection in an immunocompromised host.

Renal ultrasound does not usually have a role in the evaluation of childhood nephrotic syndrome. However, in the setting of a nephrotic child who develops gross hematuria, thrombocytopenia, or unexplained persistent hypertension, a renal ultrasound should be considered to exclude possible development of renal vein thrombosis.

Renal Biopsy

More than 80% of children with idiopathic nephrotic syndrome will respond to steroid therapy by entering complete remission. Based on this statistic, an initial trial of 4 to 8 weeks of high-dose daily steroid therapy is usually prescribed in children under 10 before considering renal biopsy. In general, renal biopsy is indicated only in the setting of atypical features such as (1) age at onset (less than 1 year or more than 10), (2) SDNS or SRNS, (3) gross or persistent microscopic hematuria or presence of red cell casts, (4) abnormal serologies, or (5) significant persistent renal failure. Due to the known nephrotoxicity (interstitial fibrosis) of calcineurin inhibitors such as cyclosporine and tacrolimus, renal biopsy is also indicated before initiation of these second-line or third-line immunosuppressive agents, as well as approximately every 2 years as long as use of these medications continues.

TREATMENT OF NEPHROTIC SYNDROME

Specific Therapy

The initial treatment for new-onset nephrotic syndrome generally includes 60 mg/m^2/day (maximum 80 mg/d) of prednisone for 4 to 8 weeks, followed by 40 mg/m^2 every other day for 4 to 8 weeks, and then a gradual taper until it is discontinued.[4,14] In a recent Cochrane review, a direct correlation was reported between longer duration of steroid therapy and longer duration of remission, and an indirect correlation with frequency of relapses.[72] In patients with FRNS and SDNS, alternative agents with potential steroid-sparing effects are often used, including cyclophosphamide, levamisole, cyclosporine, tacrolimus, and mycophenolate mofetil. In patients with SRNS, however, the most commonly used agents include cyclosporine, tacrolimus, high-dose intravenous methylprednisolone, and mycophenolate mofetil (MMF), although the efficacy of almost all these agents is lower in these patients compared with FRNS or SDNS patients. A more detailed discussion of the variety of specific therapies for nephrotic syndrome in children is presented in Chapters 15 and 16.

General Management

Edema

Patients with nephrotic syndrome have increased total body fluid and sodium during active disease. General measures to control edema include salt restriction, moderate fluid restriction, and judicious use of diuretics. Dietary recommendations include maintenance of protein intake at approximately 130% to 140% of the RDA for age, as well as avoidance of saturated fats that can worsen hyperlipidemia.

Because the intravascular volume status in children with nephrotic syndrome is typically low, diuretics should generally be used only when significant intravascular depletion has been either excluded or corrected. Typically correction of intravascular depletion can be achieved by initiating

intravenous 25% albumin at 1-2 g/kg/d either as a continuous infusion or divided q 6-8 hours. Albumin treatment should continue for 4 to 6 hours before initial administration of diuretics to minimize the risk of worsening any intravascular volume depletion that may be present. In general, slowly increasing the serum albumin level to approximately 2.8 g/dl adequately restores the intravascular oncotic pressure and volume, but there appears to be little additional clinical benefit to increasing the albumin level to normal values.

The most commonly used diuretic in this setting is the loop diuretic furosemide. It acts by inhibiting the sodium-potassium-2 chloride transporter in the thick ascending limb of the loop of Henle. During nephrotic syndrome, however, several factors may impair its efficacy. Because furosemide is highly protein bound, hypoalbuminemia may result in reduced delivery of albumin-bound furosemide to the proximal tubular cells for secretion into the tubular lumen. Hypoalbuminemia also causes an increased volume of distribution of furosemide due to diffusion of the free drug into the expanded interstitial compartment.[73] Another potential cause for the tubular resistance to furosemide seen during nephrotic syndrome results from massive proteinuria, leading to binding of urinary albumin to furosemide in the tubular lumen and a reduction of free drug available to act in the thick ascending limb of the loop of Henle.[73]

Measures to overcome resistance to furosemide include increased doses, coadministration with albumin, and coadministration with distal tubular diuretics. Doses ranging from 200% to 300% of normal can often achieve the desired clinical effects, although high doses in the presence of significant renal impairment may increase the risk for ototoxicity, which has been shown to be related to the peak levels.[74] Clinically effective dosing strategies for intravenous furosemide in nephrotic children with normal renal function typically range from 0.5-1 mg/kg q 6-12 hours, although reports in children with cardiac disease have shown that continuous infusion of furosemide results in a more efficient diuresis compared with intermittent administration.[75,76] Alternatively, coadministration of furosemide with albumin, which has been reported to improve furosemide efficacy by expanding the intravascular volume, resulting in improved renal perfusion and drug delivery to the kidney, is also widely used.[76,77] Another approach to improve the clinical efficacy of furosemide is coadministration with thiazides or the thiazide-type diuretic metolazone, which acts primarily in the distal tubule but has some effects on the proximal tubule.[78] When diuretics are used, physicians should watch closely for common and serious side effects of 3 agents, which include increased risk of thrombosis, electrolyte disturbances such as hypokalemia and metabolic alkalosis, hypercalciuria and nephrocalcinosis, and ototoxicity.[76]

Nonpharmacologic management of edema has also proven to be useful. Elevation of the extremities, or scrotum in cases of severe scrotal edema, to the level of the heart or higher increases the tissue hydrostatic pressure and helps redistribute edema fluid back into the intravascular space. Another safe and effective treatment, although not widely used, is head-out water immersion.[79] This treatment has been reported to have a potent diuretic and natriuretic effect, resulting in significant increases in central blood volume and urine output and reductions in plasma arginine vasopressin, renin, aldosterone, and norepinephrine levels.[79]

Hyperlipidemia

Hyperlipidemia is commonly found in children with nephrotic syndrome. The characteristic lipid profile includes elevations in total plasma cholesterol, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol, triglyceride, and lipoprotein A, as well as variable alterations (more typically decreased) in high-density lipoprotein (HDL) cholesterol.[80,81] Although hyperlipidemia in children with SSNS is often transient and usually returns to normal after remission, children with SRNS refractory to therapy often have sustained hyperlipidemia. Such chronic hyperlipidemia has been associated with increased risk for cardiovascular complications and progressive glomerular damage in adults.[82-86] Thus pharmacologic treatment of hyperlipidemia in children with refractory nephrotic syndrome may reduce both the risk for cardiovascular complications later in life and the risk of disease progression.

The potential usefulness of hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors (statins) in children with SRNS has been reported in a few uncontrolled trials. One study reported a 41% reduction in cholesterol and a 44% reduction in triglyceride levels within 6 months of treatment.[87] A second study found a significant reduction within 2 to 4 months in total cholesterol (40%), LDL cholesterol (44%), and triglyceride (33%) levels, but no significant changes in HDL cholesterol levels.[88] Treatment was found to be safe, with no associated adverse clinical or laboratory events. Although the long-term safety of statins in children has not yet been established, they appear to be generally well tolerated in adults with nephrotic syndrome, with only minor side effects such as asymptomatic increases in liver enzymes, creatine kinase, and rarely diarrhea.[89]

Antiproteinuric Agents

Angiotensin converting enzyme inhibitors (ACEIs) are increasingly being used in the management of persistent proteinuria and control of hypertension in children with SRNS or SDNS. The antiproteinuric effects of ACEIs are due to their ability to reduce glomerular capillary plasma flow rate, decrease transcapillary hydraulic pressure, and alter the permselectivity of the glomerular filtration barrier.[90-92] Numerous uncontrolled studies in adult and pediatric patients with SRNS have reported significant reductions in proteinuria in response to ACEI treatment.[90-94] In addition, a recent randomized crossover trial revealed that, compared with pretreatment values, low-dose enalapril reduced the median urine albumin/creatinine ratio by 33%, whereas high-dose enalapril reduced the ratio by 52%, confirming a dose-related reduction in proteinuria in response to enalapril.[95] In some studies angiotensin receptor blockers (ARBs) have been shown to have the same effect.[96,97] Additionally, a recent metaanalysis in adults with both diabetic and nondiabetic proteinuric renal disease reported the combination of ACEIs and ARBs to be associated with a significant decrease in proteinuria without clinically meaningful changes in serum potassium or GFR.[97]

COMPLICATIONS

Infection

Intercurrent infections represent one of the most serious complications of nephrotic syndrome. Risk factors for infection include low serum IgG levels due to urinary loss of IgG, abnormal T lymphocyte function, and decreased levels of factors B (C3 proactivator) and D, each a component of the alternative complement pathway, which result in a decreased ability to opsonize encapsulated bacteria such as *Streptococcus pneumoniae*.[98,99] In addition, use of steroids and other immunosuppressive medications during relapses further increases the risk of infection.

The most common and serious type of infection is primary bacterial peritonitis, which is estimated to have an incidence of 5% in children with nephrotic syndrome.[100] Other types of infections include cellulitis, sepsis, meningitis, and pneumonia. Most infections are due to *S. pneumoniae* (peritonitis) or *Staphylococcus* (cellulitis), although infections due to gram-negative organisms such as *Escherichia coli* and *Haemophilus influenzae* may also occur.

Children with nephrotic syndrome and peritonitis typically present with fever, abdominal tenderness, and leukocytosis in the setting of overt edema and ascites. Diagnosis of peritonitis may be difficult, because some of the systemic symptoms and signs of infection can be masked by concurrent use of corticosteroids. If the diagnosis is suspected, an abdominal paracentesis is recommended and fluid should be sent for both microscopy and culture. The diagnosis can be confirmed based on the clinical features of peritonitis and a peritoneal fluid WBC count of more than 250/mm^3.[101,102] *S. pneumoniae* and *E. coli* are the most common pathogens in peritonitis, but others have been reported. Broad spectrum antibiotics should be used initially, with coverage narrowed based on culture results.

Strategies for preventing peritonitis include immunization against potential pathogens along with prophylactic antibiotics. Immunization against *Pneumococcus* is recommended, and has been shown to be more effective in children with SSNS than in those with SRNS, and in those not receiving steroids than in those receiving steroids at the time of immunization.[103] Vaccination against *Pneumococcus* has also been shown to be efficacious even in nephrotic children receiving steroids.[104] Despite this, one recent study reported after a 36-month follow-up that patients with SSNS immunized with a polyvalent pneumoccoccal vaccine had a reduction in antipneumoccoccal antibodies.[105] The 2000 American Academy of Pediatrics statement on the use of heptavalent conjugated pneumococcal vaccine recommends universal vaccination of all children up to 23 months old, with children, including those with nephrotic syndrome, ages 24 to 59 months to receive the vaccine only if they are believed to be at moderate or high risk.[106,107]

Viral infections, especially varicella, may also be life threatening in children with nephrotic syndrome. Verification of immunity to varicella, or immunization once patients are on alternate-day steroids, should be performed. If a nonimmune immunosuppressed child is exposed to varicella, passive immunization with VZIG should be performed within 96 hours of exposure to minimize the risk of serious systemic Varicella infection.

The use of prophylactic antibiotics to prevent infections in children with nephrotic syndrome is controversial. They have been recommended in a recent review, particularly for high-risk patients such as those under 2 years, those with SRNS and FRNS, and those with a previous pneumococcal infection.[108] However, some authors have questioned the potential development of resistant organisms with this approach.[109]

Thromboembolism

The risk of thromboembolic phenomenon in children with nephrotic syndrome is estimated at 1.8% to 5%,[110] with higher risk reported in children with SRNS than in those with SSNS.[111] Factors contributing to an increased risk of thrombosis during nephrotic syndrome include abnormalities of the coagulation cascade, such as increased clotting factor synthesis in the liver (factors I, II, V, VII, VIII, X, and XIII), and loss of coagulation inhibitors such as antithrombin III in the urine. Other prothrombotic risks in these children include increased platelet aggregability (and sometimes thrombocytosis), hyperviscosity resulting from increased fibrinogen levels, hyperlipidemia, prolonged immobilization, and use of diuretics. In one series, diuretics were found to be the major iatrogenic risk factor for thrombosis.[111]

The majority of episodes of thrombosis are venous in origin. The most common sites for thrombosis are the deep leg veins, ileofemoral veins, and the inferior vena cava. In addition, use of central venous catheters can further increase the risk of thrombosis. Renal vein thrombosis (RVT) can also occur and may manifest as gross hematuria with or without acute renal failure. Development of these features should prompt either renal Doppler ultrasonography or magnetic resonance angiography to rule out RVT. Pulmonary embolism is another important complication that may be fatal if not recognized early. Although rare, cerebral venous thrombosis, most commonly in the sagittal sinus, has also been reported.[112] In addition to prompting imaging studies, development of thrombosis should prompt an evaluation for possible inherited hypercoagulable states. Typical acute management of thrombosis in nephrotic children includes initial heparin infusion or low molecular weight heparin, followed by transition to warfarin for 6 months. These children should also receive prophylactic anticoagulation therapy during future relapses.[113]

Cardiovascular Disease

Development of cardiovascular disease is increasingly recognized as an important complication of nephrotic syndrome in patients with prolonged clinical courses. Risk factors include the presence of hypertension, hyperlipidemia, long-term treatment with steroids and other immunosuppressive drugs (such as cyclosporine) that can alter serum lipid levels, oxidant stress, and hypercoagulability.[14] Based on these findings, aggressive treatment of chronic hyperlipidemia and hypertension in children with SRNS or prolonged clinical courses is recommended.

Respiratory Distress

Respiratory distress may occur as a complication of nephrotic syndrome or its treatment. In the presence of severe hypo-

albuminemia, pleural effusions may develop and can become clinically significant. In addition, aggressive infusion of albumin with inadequate use of diuretics may induce acute pulmonary edema due to the rapid shift of fluid from the interstitium to the intravascular compartment. Possible development of a pulmonary embolism should also be considered in any nephrotic child who develops acute tachypnea or hypoxia.

Bone Disease

Corticosteroid therapy can cause decreased bone formation and increased bone resorption, placing children with nephrotic syndrome at increased risk for developing reduced bone mineral density. Surprisingly, data to support this theoretical risk are controversial. In a recent study of nephrotic children on long-term, high-dose steroids that used dual-energy x-ray absorptiometry to assess total body and spine mineral content, Leonard et al. found no difference in whole body mineral content between patients and controls, although the bone mineral content of the spine was significantly lower in patients than in controls.[114] Another study reported that 22% of nephrotic children had reduced bone mass, although it did not take into consideration the children's height z scores and the children were not compared with normal controls.[115] A further risk factor for reduced bone mineral density is loss of vitamin D binding protein (a carrier protein for 25-hydroxyl cholecalciferol) in the urine.[116] In addition, Weng et al. reported low plasma 25-hydroxyl cholecalciferol levels in a group of children with FRNS who were in remission at the time of the study.[117] Based on these studies, the role of vitamin D supplementation in SSNS children remains somewhat unclear; however, supplementation may be beneficial for SRNS children at high risk for CKD.

Acute Renal Failure

Acute renal failure (ARF) is a relatively uncommon complication of nephrotic syndrome in children. Potential causes include (1) reduced renal perfusion, (2) acute tubular necrosis, (3) renal vein thrombosis, (4) renal interstitial edema, and (5) altered glomerular permeability. In a report of oliguric ARF that developed among children with MCNS on renal biopsy, altered glomerular permeability was found to have played a greater role than did reduced renal perfusion as a cause for ARF.[118]

Other Complications

Other complications reported in children with nephrotic syndrome include anemia, subclinical hypothyroidism, intussusception, and treatment-related side effects such as growth failure, hypertension, cataracts, and hyperlipidemia (Table 12-3).

PROGNOSIS

The single most important prognostic factor for maintenance of long-term normal renal function in nephrotic syndrome is the patient's initial response to corticosteroids. Although children who enter complete remission during an 8-week initial course of oral corticosteroids have an excellent prognosis, the prognosis for those who fail to enter remission is more guarded. Overall, close to 80% of newly diagnosed children treated with corticosteroids will achieve complete remission.[5]

TABLE 12-3 **Complications of Nephrotic Syndrome**

Infectious	Peritonitis Cellulitis Disseminated Varicella infection
Cardiovascular	Hypertension Hyperlipidemia Coronary artery disease
Respiratory	Pleural effusion Pulmonary embolism
Hematologic	Venous (more common) or arterial (less common) thrombosis Anemia
Gastrointestinal	Intussusception
Renal	Acute renal failure Renal vein thrombosis
Endocrinologic	Reduced bone mineral density Hypothyroidism, clinical and subclinical (more common in CNS)
Neurologic	Cerebral venous thrombosis
Treatment-related	
General	Infection, hypertension
Steroids	Growth impairment, reduced bone density, posterior capsular cataracts, avascular necrosis of femoral head
Alkylating agents	Hemorrhagic cystitis, dose-related oligospermia and premature ovarian failure, increased risk of malignancy
Calcineurin inhibitors	Gingival hyperplasia, hirsutism, hyperkalemia, encephalopathy
Mycophenolate mofetil (MMF)	Nausea, vomiting, diarrhea, constipation, dose-related leukopenia, headache

Steroid responsiveness varies by renal histologic type, with 93% of children with MCNS being steroid responsive compared with 56% with mesangial proliferative glomerulonephritis (IgM nephropathy in some centers), 30% with FSGS, 7% with MPGN, and 0% with membra-nous nephropathy.[5] In addition, the frequency of steroid responsiveness generally decreases with increasing age at presentation.

Among children with SSNS, relapse is common. It is estimated that 70% of children with nephrotic syndrome will experience one or more relapses. However, the frequency of relapses decreases over time. A large study of children with MCNS reported a gradual increase in the number of nonrelapsing patients over time, such that 8 years after disease onset 80% of children were relapse-free.[119] In addition, 75% of those children with no relapses in the first 6 months after treatment either had rare relapses or continued in remission for their entire clinical course. Risk factors for frequent relapses or a steroid-dependent course have not been carefully studied, but the literature suggests that an age of less than 5 years at onset and a prolonged time to initial remission are possible risk factors.[120,121] More recently Tsai et al. reported a higher incidence of the DD (homozygous deletion) genotype for the angiotensin converting enzyme (ACE) gene in SDNS and SRNS children compared with SSNS children, suggesting a potential role for ACE in regulating clinical response to steroids.[122]

Initial steroid resistance clearly identifies a subset of patients at high risk for progressive kidney disease. It is estimated that 40% to 50% of children with SRNS will progress to CKD or ESRD within 5 years of diagnosis, despite aggressive immunosuppression. Among children with nephrotic syndrome due to FSGS who progress to ESRD, renal transplantation can also pose serious challenges. Nephrotic syndrome recurs in the allograft in up to 30% of children with FSGS and leads to graft loss in about 50% of such patients.[123] Among children with FSGS due to *NPHS2* mutations, the risk for recurrence has been controversial.[27,28,124]

The introduction of antibiotics and steroids in treating nephrotic syndrome has led to a significant reduction in mortality, from 60% to 70% to less than 5%. In an ISKDC series of 521 children with nephrotic syndrome, 10 deaths were reported, resulting in a mortality rate of 1.9%.[125] Of note, 9 of these 10 children had either early relapses or SRNS and 6 (60%) died from infections, confirming infection as an important cause of mortality in nephrotic syndrome.

Nephrotic syndrome is one of the most common forms of renal disease seen in children. Although the introduction of antibiotics and refinement of immunosuppressive medications have greatly decreased mortality and improved the quality of life for children with this disease, neither the mechanism(s) of action nor the target cell for these therapies is known. In spite of this, the prognosis for long-term maintenance of normal renal function is excellent unless complete remission cannot be achieved. Hopefully our growing understanding of the pathobiology of nephrotic syndrome will lead to development of more effective therapies in the future.

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