

**DEFINITION**

Among pediatric nephrologists there are two definitions of steroid-resistant nephrotic syndrome (SRNS). The definition introduced by the International Study of Kidney Disease in Children (ISKDC) and used by the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) is widely accepted as follows<sup>1</sup>: *No urinary remission within 4 weeks of prednisone therapy 60 mg/m<sup>2</sup>/day*. The other definition, employed by the Society of French Speaking Pediatric Nephrologists,<sup>2</sup> states: *No urinary remission following 4 weeks of prednisone 60 mg/m<sup>2</sup>/day followed by three intravenous pulses of methylpredisolone*. The rationale for both definitions is the experience that almost all patients with minimal change who respond will do so within 4 weeks (Figure 16-1) and only a small percentage will respond later (often called *late responders*). It is of great importance for interpretation of clinical data and studies to know the patient's age and the definition used.

**INTRODUCTION**

Treatment of SRNS remains a difficult challenge in pediatric nephrology. Because of poor prognosis in the past, the majority of children have received intensive treatment regimens and many of them have been overtreated. At the moment there is no diagnostic marker for children displaying with nephrotic syndrome that can be used as a predictor of steroid responsiveness or resistance. The most important prognostic marker for children with nephrotic syndrome is their response to steroid treatment. Initial steroid treatment can be avoided only in patients with a family history of SRNS or in those who have a known gene mutation. There is an urgent need to distinguish as soon as possible those patients who may benefit from prolonged immunosuppressive treatment from those who will not benefit from such treatment and who will just suffer from its major side effects. There is emerging evidence that the majority of genetic forms of SRNS should receive symptomatic treatment only.

**INCIDENCE**

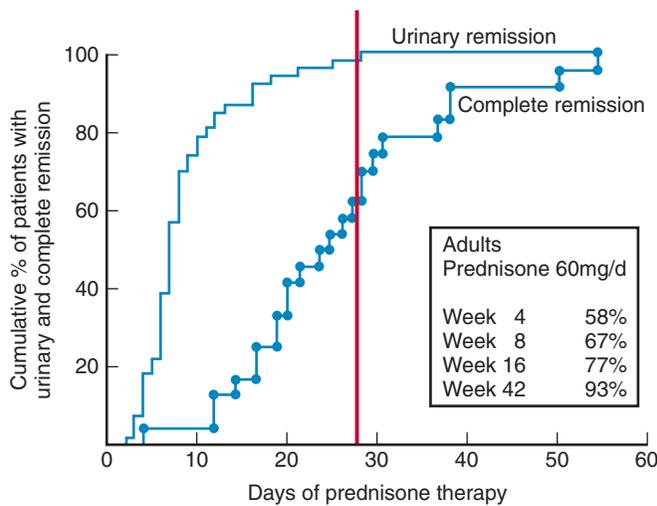
The incidence of SRNs varies throughout the world. As shown in Table 16-1, the incidence of minimal change versus other histologies in patients biopsied because of nephrotic syndrome varies among children and adults and among

children from the Northern Hemisphere and those from Africa. There are also different patterns in South America and Asia. It should be kept in mind that these comparisons are relative, because the initial therapy with steroids cannot be compared between children and adults. Furthermore there are no data about how different pharmacogenetic backgrounds and therapeutic doses of prednisone with different pharmacokinetic and pharmacodynamic profiles influence response to treatment. In addition, race appears to have an important impact on the histology associated with nephrotic syndrome. Although the incidence of nephrotic syndrome has remained stable over the last 30 years, evidence from the literature suggests that the total number of patients with focal segmental glomerulosclerosis (FSGS) is increasing, especially in South Africa and India.<sup>3-5</sup> A weak predictor for the probability of FSGS as opposed to minimal change nephrotic syndrome (MCNS) is age. In children with MCNS, about 80% are diagnosed before the age of 6 compared with 50% of those with FSGS lesions in histology.

**HISTOLOGY**

Because nephrotic syndrome is just a clinical description, the incidence of the different histomorphologic entities (Figures 16-2 and 16-3) behind the SRNS is expected to vary according to patients' age and regional and race factors. The most dominant lesion is FSGS, although a minority of steroid-resistant patients have MCNS. There has long been a debate that MCNS may transition to FSGS in selected cases, but this hypothesis has never been proven. A major reason for misdiagnosing FSGS as MCNS is due to the sampling error in renal biopsies. Kidneys with FSGS show preferentially early involvement of only a few glomeruli in the juxamedullary area, which can easily be missed on biopsies. The risk of misdiagnosing FSGS is estimated at 35% if only 10 glomeruli are harvested, and falls to about 12% if 20 glomeruli can be examined.

FSGS is defined as loss of glomerular capillary lumina due to an increase in mesangial matrix. An important feature in FSGS is diffuse effacement of podocyte foot processes, which is subtle in primary FSGS. Secondary forms of FSGS usually show effacement of about 50% or less of foot processes. For the disease to qualify as primary FSGS, other causes for podocyte damage with segmental glomerular scarring, such as immune complex glomerulonephritis, have to be excluded by immunohistology and electron microscopy.



**Figure 16-1** Steroid response with prednisone treatment: cumulative percentage of patients with urinary remission and serum remission. Curves demonstrate that about 50% of patients will respond within 7 to 10 days, more than 90 within 3 weeks, and almost all patients within 4 weeks. Complete remission will be achieved 2 to 3 weeks after urinary remission. In the box is percentage of adult patients in remission receiving a total dose of 60 mg/day. (From Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft für Pädiatrische Nephrologie, *Lancet* I(8582):380-83, 1998.)

**TABLE 16-1 Underlying Histologies Studied in Patients with Nephrotic Syndrome in Children and Adults from Europe, the United States, and Africa**

Histology	Children*	Adults*	Zimbabwe†	Durban‡
MCNS	76	20	9.2	14
FSGS	8	15	15.1	28
MemGN	7	40	15.1	41 (35 hepatitis B)
MPGN	4	7	33.6	9
Miscellaneous	5	18	17.0	5

Note: There is evidence that FSGS is more common in African children than in children from the Northern Hemisphere.

\* Lewis MA, Baildom EM, Davies N, Houston IB, Postlethwaite RJ: Steroid-sensitive minimal change nephrotic syndrome. Long-term follow-up, *Contrib Nephrol* 67:226-28, 1988.

† Combined study of children and adults.<sup>51</sup>

‡ Study with pediatric patients.<sup>5</sup>

A nomenclature for idiopathic FSGS has been proposed by a group of nephrologists.<sup>6</sup> It lists five precisely defined FSGS variants: collapsing, cellular, tip, perihilar, and FSGS not otherwise specified (NOS). This classification was derived from patients over 21 years of age. The glomerular disease collaborative network found FSGS not otherwise specified in 42% of the population, the perihilar variant in 26%, the tip lesion in 17%, the collapsing lesion in 11%, and the cellular variant in 3% of patients. The collapsing form was seen in over 90% of African Americans, whereas the tip lesion

was most common in Caucasian patients. The degree of proteinuria was highest in the collapsing variant followed by patients with a tip lesion, and was less in patients with perihilar FSGS and those with FSGS NOS. The usefulness of such a classification is controversial, because some of the patients with tip lesions show progression to other forms. Nonetheless, use of this classification is encouraged and may help segregate specific entities from the “big basket” of FSGS.

There are no similar studies in pediatric patients. Although renal pathologists usually try to classify pediatric patients according to the aforementioned classification, its impact has not been evaluated. One recent study looked for clinical and histologic markers predicting outcome.<sup>7</sup> Sixty-six patients, 38 male and 28 female, were followed for at least 10 years. Multivariate analysis identified the presence of mesangial expansion ( $p = 0.011$ ) and tip lesions ( $p = 0.005$ ) as the independent predictors of favorable response to cytotoxic therapy, whereas the presence of renal impairment ( $p = 0.008$ ) and extensive focal segmental sclerosis ( $p = 0.025$ ) were independent predictors of unfavorable response.

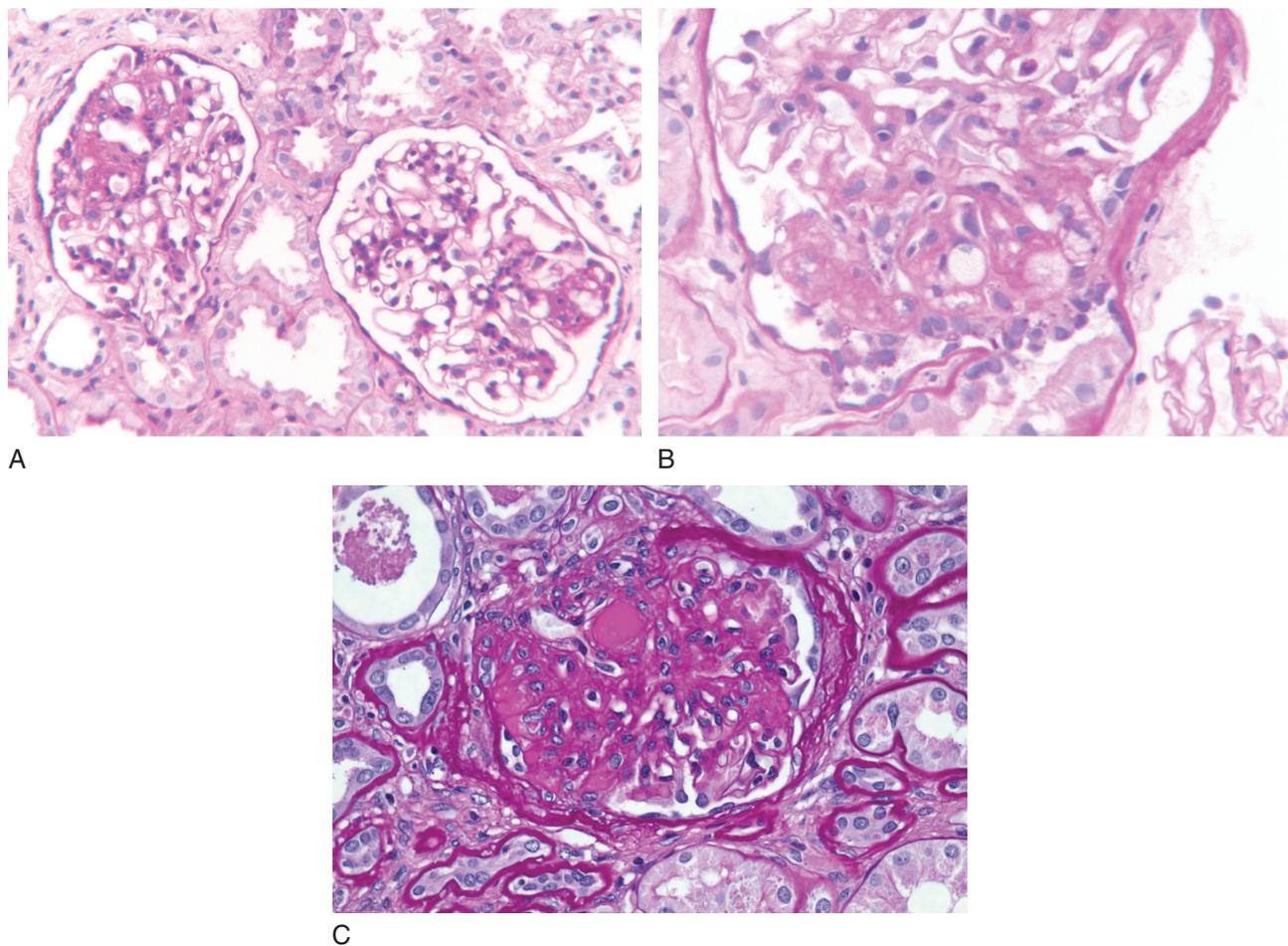
Membranous glomerulonephritis (MGN) (Figure 16-4) is another important histomorphologic entity in patients with SRNS. In children it is much less common than FSGS compared with the adult population, in which this diagnosis is much more frequent. The list of etiologies leading to membranous nephropathy in adults is quite long, whereas in the pediatric population it is mainly secondary to hepatitis B or is idiopathic.

## PATHOGENESIS

As described in earlier chapters, the key element in the pathogenesis of proteinuria in nephrotic syndrome is the podocyte. Since the discovery of a mutation in the nephrin gene in patients with congenital nephrotic syndrome of the Finnish type, the biology of the podocyte has become a center of interest. With the description of new gene mutations and altered gene products responsible for the structure function and signaling of podocytes, understanding of diseases with proteinuria has increased; however, with more knowledge, the number of questions has also increased. In general, one can distinguish two mechanisms leading to proteinuria: congenital and acquired.

During embryonic development, the outer part of the GBM is made by podocytes. Major podocytes need a full complement of proteins for building up complex structures as well as for signaling (Figure 16-5). A major function of podocytes is to perform as a buttress against the pressure of the glomerular capillaries. Any stress and functional impairment, as well as podocyte loss, may compromise the filtration barrier and lead to proteinuria.

It is logical that congenital defects may be somewhat resistant to any kind of pharmacologic treatment. In acquired diseases the major goal should be eliminating the cause of podocyte injury, as well as allowing the podocytes to recover and restoring their function after injury. Since podocytes have not been shown to replicate, any loss must be compensated by those remaining. Continuing podocyte loss may be critical below a certain threshold, which is estimated as a loss of



**Figure 16-2** Histologies of renal biopsies of patients with steroid-resistant nephrotic syndrome. **A**, Histomorphology of FSGS NOS in a 9-year-old patient. Two glomeruli with segmental sclerosis. The right glomerulus with a recently sclerosed segment with foamy matrix at 3 o'clock, and the left glomerulus with a more mature, dense segmental sclerosis at 9 o'clock to 1 o'clock. PAS, original magnification  $\times 200$ . **B**, Histomorphology of tip-lesion variant FSGS in a 19-year-old patient. The sclerosed glomerular segment at the 6 o'clock position is situated directly at the glomerulotubular junction. PAS, original magnification  $\times 400$ . **C**, Histomorphology of diffuse mesangial sclerosis in Denys-Drash syndrome in a 12-year-old male patient. Mesangial proliferation with a slightly nodular appearance. PAS, original magnification  $\times 400$ .

more than 20%<sup>8,9</sup> (Figure 16-6). As shown by Kriz<sup>10,11</sup> and others, a decreasing podocyte number leads to denuded GBM areas that will come into contact with the parietal epithelial cells lining Bowman's capsule by force of the intracapillary pressure. Once sclerotic lesions are established, a point of no return for these lesions is reached. Misdirected filtration (Figure 16-7) via the glomerular basement areas attached to Bowman's capsule and into the periglomerular and peritubular interstitium leads to inflammation and scarring of the renal cortex. Therefore any treatment should try to regenerate podocyte function before sclerotic lesions appear. It is amazing that the classical hypothesis of the immortal podocyte has never been questioned. The fact that a cell with such a highly developed structure should live for almost 70 years is doubtful. If there is podocyte turnover, it might be so low that it has escaped the attention of investigators. To what extent stem cells might contribute to podocyte turnover has to be studied. However, such a possibility may be attractive for future therapeutic approaches.

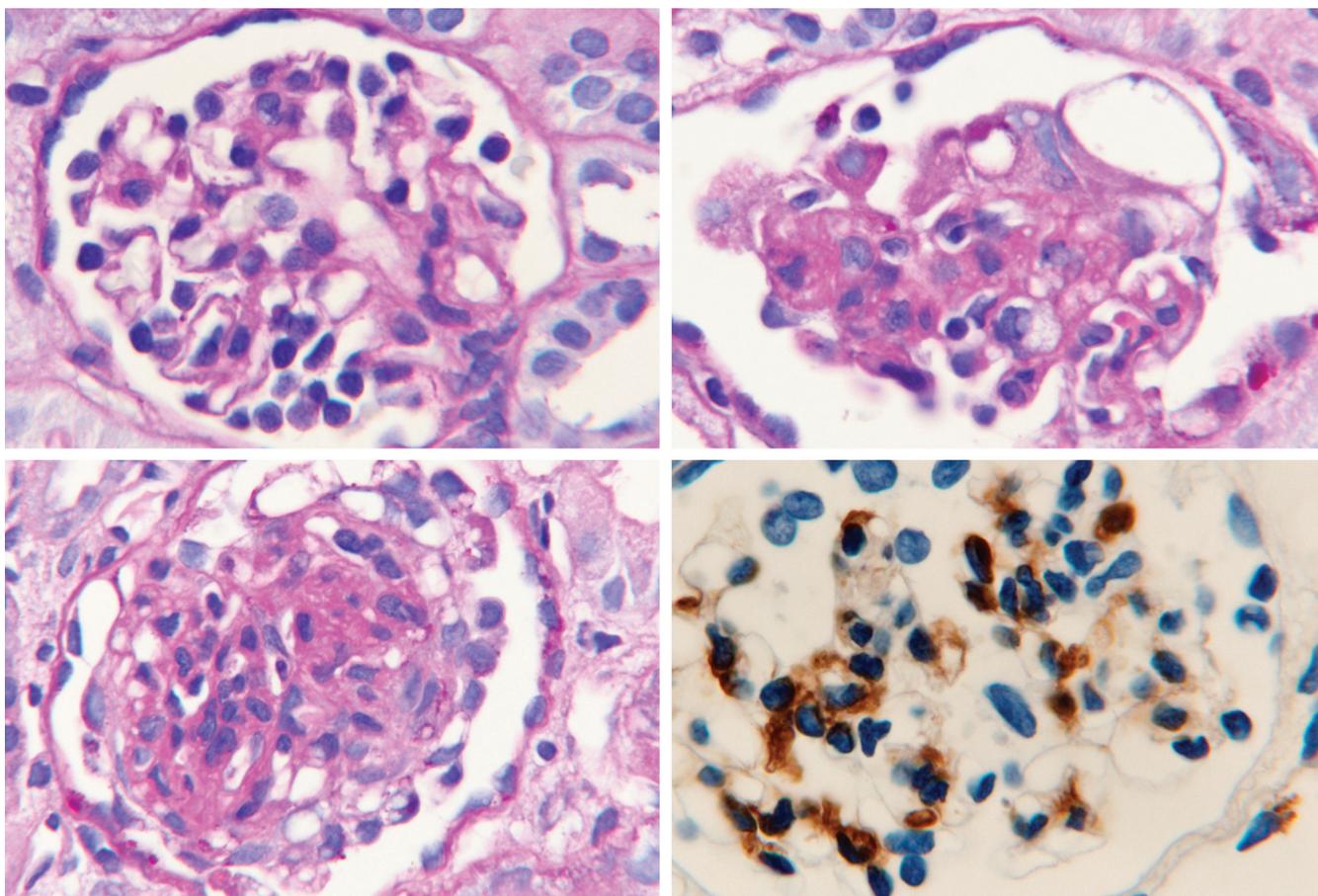
The inflammatory changes leading to tubulointerstitial scarring should be regarded as an important part of this

disease leading to end-stage renal failure. The understanding of such processes, especially the epithelial mesenchymal transition (EMT), is of great interest. A detailed understanding may provide a rationale for specific interventions in the future. Until then, nonspecific immunosuppressive effects that dampen this process are used.

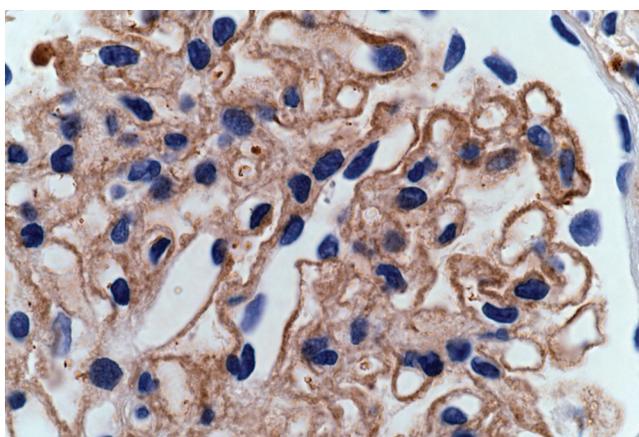
## GENETICS

An overview of the variety of conditions associated with FSGS is given in Table 16-2, and recent advances in genetics and mutations associated with SRNS are covered in Chapter 13.

Recently Hinkes<sup>12</sup> described a new mutation leading to SRNS, called *NPHS3*. The gene product is phospholipase C epsilon (PLCE1). This mutation causes early-onset nephrotic syndrome leading to end-stage kidney disease in young children. Kidney histology of affected individuals show diffuse mesangiosclerosis (DMS). The gene product is expressed in the developing kidney in mature glomerular podocytes, which has been shown to lead to an arrest of normal glomerular



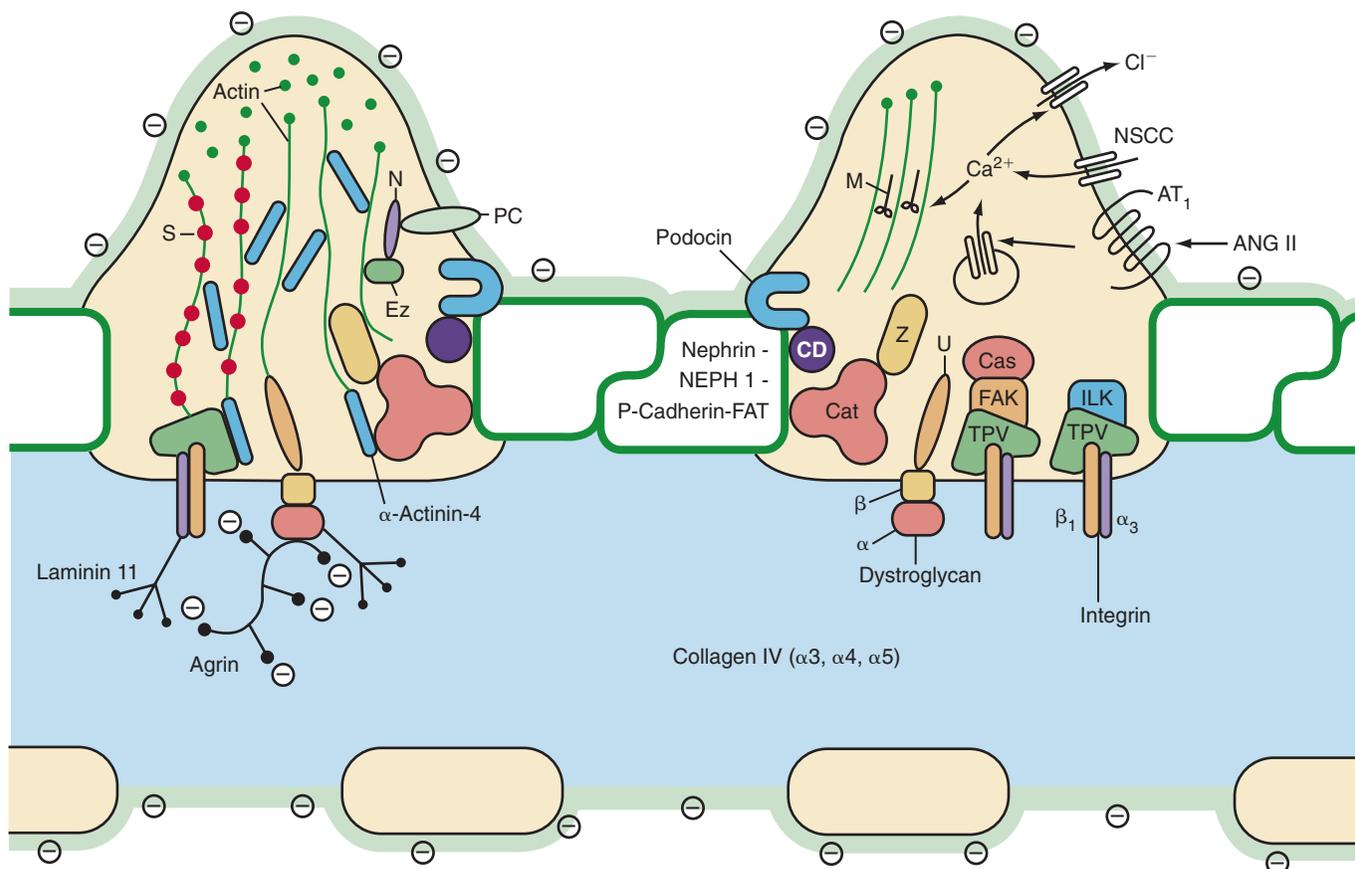
**Figure 16-3** Histomorphology of mesangioproliferative IgA glomerulonephritis. This 2-year-old boy showed steroid-resistant nephrotic syndrome. Slight mesangial expansion with open capillary loops (top left) and mesangial proliferation with sclerosis in a focal and segmental fashion (bottom left and top right) are morphologically similar to primary FSGS. However, IgA-dominant mesangial immune deposits (brown, bottom right) are diagnostic of IgA glomerulonephritis. PAS and immunoperoxidase, original magnification  $\times 600$ .



**Figure 16-4** Histomorphology of membranous glomerulonephritis in a 16-year-old patient. Massive granular deposits of IgG (brown) along the glomerular basement membrane. Immunoperoxidase, original magnification  $\times 600$ .

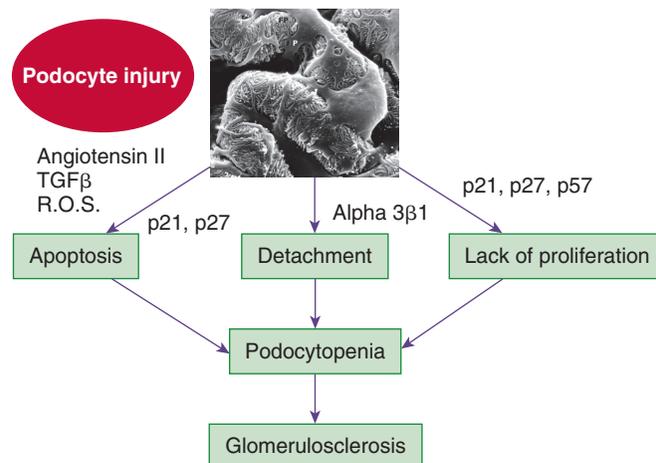
development. Interestingly, a few patients with this mutation might respond to immunosuppressive therapy.

SRNS may be part of syndromic diseases as listed in Table 16-2 (see examples, Figures 16-8 and 16-9). Careful clinical examination is essential to rule out minor abnormalities suggestive of syndromic forms of nephrotic syndrome to avoid unnecessary steroid treatment. In many cases, however, steroid therapy will start first and genetic investigations will be initiated only if steroid resistance has been confirmed by the classical definition. In the clinical day-to-day practice there is sometimes a tremendous delay between the request for genetic testing and when the result will be available. Because there are no markers predicting a gene defect, many patients may undergo further immunosuppressive therapy until a clear diagnosis is established. During this time, any therapy with irreversible or severe side effects should be avoided. Up to now it has been shown that immunosuppressive therapy is of no value in patients with *NPHS1*, *NPHS2*, *WT1*, and *TRPC6* mutations. Ruf et al.<sup>13</sup> have reported that out of 165 families with SRNS, 43 (26%) showed homozygote or compound heterozygote mutations in the *NPHS2* gene (podocin). In contrast, no mutations were found in 120 families with steroid-sensitive



**Figure 16-5** Schematic drawing of the molecular equipment of the podocyte foot processes. Cas, p130Cas; Cat, catenins; CD, CD2-associated protein, Ez, ezrin; FAK, focal adhesion kinase; ILK, integrin-linked kinase; M, myosin; N, NHERF2; NSCC, nonselective cation channel; PC, podocalyxin; S, synaptopodin; TPV, talin, paxillin, vinculin; U, utrophin; Z, ZO-1. (Redrawn from Pavenstadt<sup>48</sup>; [Pavenstadt modified from Endlich<sup>49</sup>].)

**Figure 16-6** Podocyte injury and podocytopenia (modified from Mundel<sup>9</sup>). After injury, podocytes can undergo apoptosis or detachment or fail to proliferate. These events lead to a decrease in podocyte number (podocytopenia), which contributes to the development of progressive glomerulosclerosis. The mechanisms underlying podocytopenia are being elucidated. Apoptosis results from increased transforming growth factor- $\beta$  (TGF- $\beta$ ), angiotensin II, reactive oxygen species (ROS), and a decrease in the cyclin-dependent kinase (CDK) inhibitors p21 and p27. The  $\alpha$ 3 $\beta$ 1 integrin is most likely to be critical in podocyte detachment from the underlying glomerular basement membrane (GBM). In contrast to other glomerular cells, podocytes do not typically proliferate in response to injury and cannot replace those lost by apoptosis and detachment. The inability to proliferate is secondary to increased levels of the CDK-inhibitors p21, p27, and/or p57. (Micrograph from Pavenstadt H, Kriz W, Kretzler M: Cell biology of the glomerular podocyte, *Physiol Rev* 83:253-307, 2003.)



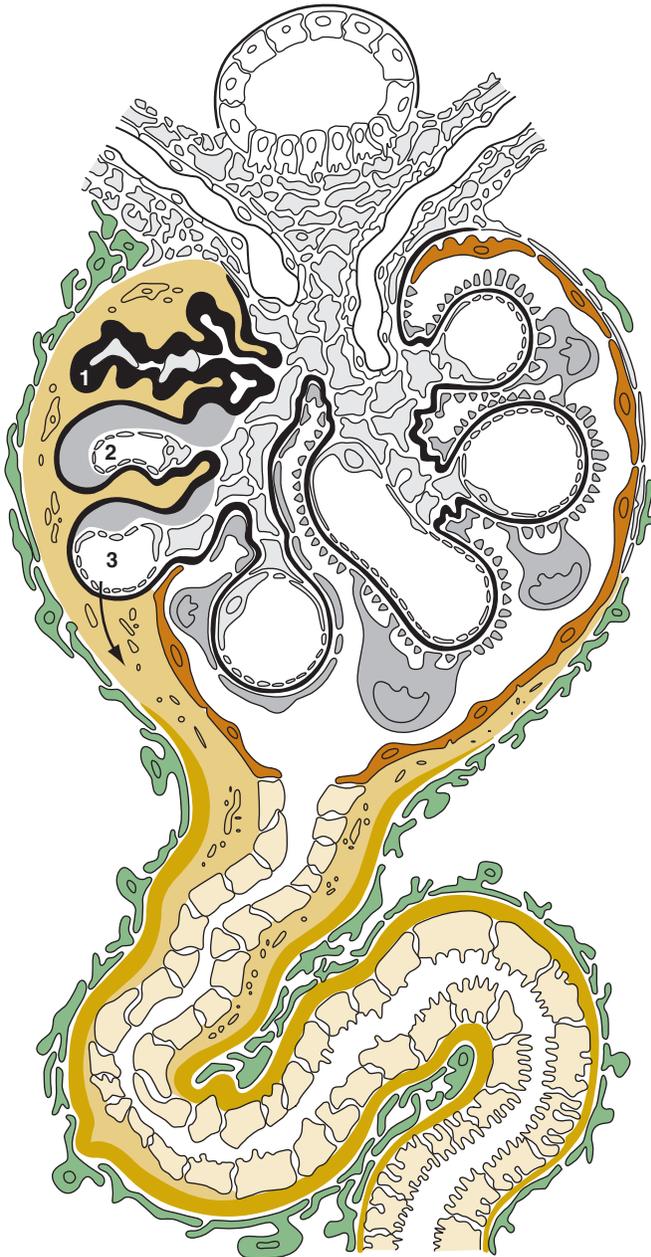
nephrotic syndrome. None of the patients with homozygous or compound heterozygous mutations in the *NPHS2* gene who were treated with cyclosporine or cyclophosphamide demonstrated complete remission of the nephrotic syndrome.

The geographic variation of *NPHS2* mutations is of importance. Maruyama et al.<sup>14</sup> reported that mutations in the

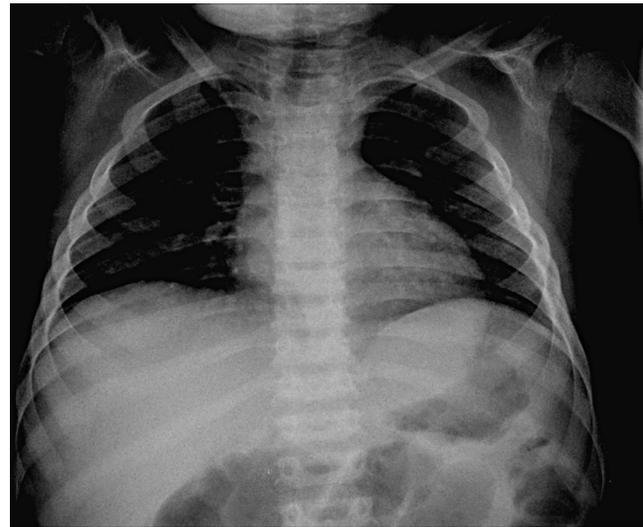
*NPHS2* gene are uncommon in Japanese pediatric patients with SRNS.

### Nongenetic FSGS

There is evidence from many clinical observations that a circulating factor targets the kidney, leading to proteinuria and glomerular sclerotic lesions. Most striking are



**Figure 16-7** The Kriz hypothesis of misdirected filtration.<sup>10</sup> Schematic showing the essential feature of misdirected filtration and filtrate spreading at an intermediate stage of nephron degeneration. The GBM is shown in black; podocytes are densely stippled; parietal epithelial cells are less densely stippled; and interstitial endothelial cells are loosely stippled; and mesangial cells are hatched. The tuft adhesion contains several collapsed capillary loops. It also contains a perfused loop, which is partially hyalinized. The filtrate of this loop is delivered into a paraglomerular space that is separated from the interstitium by a layer of fibroblasts. This newly created space extends onto the outer aspect of the tubule by expanding and/or separating the tubular basement membrane from its epithelium.



**Figure 16-8** Schimke syndrome. Chest x-ray demonstrating spondyloepiphyseal dysplasia of the vertebral bodies.



**Figure 16-9** X-ray of the left hand showing enchondromatosis in a child with SRNS.

TABLE 16-2 Focal Segmental Glomerulosclerosis as Listed in OMIN PubMed

1: #603278 FOCAL SEGMENTAL GLOMERULOSCLEROSIS 1; FSGS1 Gene map locus 19q13	13: #232220 GLYCOGEN STORAGE DISEASE 1b Gene map locus 11q23
2: #603965 FOCAL SEGMENTAL GLOMERULOSCLEROSIS 2; FSGS2 Gene map locus 11q21-q22	14: *608414 PHOSPHOLIPASE C, EPSILON-1; PLCE1 Gene map locus 10q23
3: #607832 FOCAL SEGMENTAL GLOMERULOSCLEROSIS 3; FSGS3 Gene map locus Chr.6	15: #600995 NEPHROTIC SYNDROME, STEROID-RESISTANT, AUTOSOMAL RECESSIVE; SRN1 Gene map locus 1q25-q31
4: %609469 NEPHROPATHY, PROGRESSIVE, WITH DEAFNESS Gene map locus 11q24	16: *590100 TRANSFER RNA, MITOCHONDRIAL, TYROSINE; MTTY
5: *603652 TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY C, MEMBER 6; TRPC6 Gene map locus 11q21-q22	17: #607426 COENZYME Q10 DEFICIENCY Gene map locus 9p13.3, 6q21, 4q21-q22
6: *604638 ACTININ, ALPHA-4; ACTN4 Gene map locus 19q13	18: *167409 PAIRED BOX GENE 2; PAX2 Gene map locus 10q24.3-q25.1
7: +232200 GLYCOGEN STORAGE DISEASE I GLUCOSE-6-PHOSPHATASE, CATALYTIC, INCLUDED; G6PC, INCLUDED Gene map locus 17q21	19: *602716 NEPHRIN; NPHS1 Gene map locus 19q13.1
8: #242900 IMMUNOOSSEOUS DYSPLASIA, SCHIMKE TYPE Gene map locus 2q34-q36	20: %191830 UROGENITAL ADYSPLASIA, HEREDITARY
9: *604241 CD2-ASSOCIATED PROTEIN; CD2AP Gene map locus Chr.6	21: #173900 POLYCYSTIC KIDNEYS POLYCYSTIC KIDNEY DISEASE, ADULT, INCLUDED; APKD, INCLUDED Gene map locus 16p13.3-p13.12
10: *607102 WILMS TUMOR 1 GENE; WT1 Gene map locus 11p13	22: *604766 PODOCIN; NPHS2 Gene map locus 1q25-q31
11: #610725 NEPHROTIC SYNDROME, TYPE 3; NPHS3 Gene map locus 10q23	23: #609049 PIERSON SYNDROME NEPHROTIC SYNDROME, CONGENITAL, WITH OR WITHOUT OCULAR ABNORMALITIES, INCLUDED Gene map locus 3p21
12: #232240 GLYCOGEN STORAGE DISEASE 1c GLYCOGEN STORAGE DISEASE 1d, INCLUDED; GSD1D, INCLUDED Gene map locus 11q23	24: %104200 ALPORT SYNDROME, AUTOSOMAL DOMINANT

observations about the recurrence of proteinuria within hours after renal transplantation in some patients who had end-stage renal failure with FSGS.

The nature of the factor has yet to be defined. Some call it the Savin factor, because major work has been carried out by Virginia Savin<sup>15</sup> and her group to isolate it.<sup>16</sup> This factor is believed to be removable by plasma separation, and anecdotal data on successful treatment after recurrence of FSGS posttransplant support this possibility. Some clinical observations point toward suppressive effects with the use of immunosuppressive drugs, especially calcineurin inhibitors. Such concepts are attractive treatment strategies; however, no reliable tests for identifying such a factor have been elaborated.

## THErapy

A review of the current literature about treatment of children with SRNS reveals that many children with familial or syndromic FSGS or with the known mutations still receive too much immunosuppressive therapy either initially or after an escalation with current available immunosuppressive drugs.

A metaanalysis of randomized controlled prospective trials in SRNS with FSGS without genetic testing demonstrates that cyclosporin may lead to a complete remission in almost one third of children. In contrast, neither oral nor intravenous cyclophosphamide demonstrates any effect on remission.

A major problem in reviewing the literature was that most studies were nonrandomized and retrospective, with low

numbers of patients. In approximately two thirds of the studies, the number of patients was less than 10. Other studies have included both children and adults with MCNS and mesangial proliferation. The fact that different age groups may have different underlying diseases has been ignored. A further problem is that the steroid therapy used, as well as the definitions, did not meet the international accepted standards. Most studies focused on short-term effects, and long-term studies are lacking. In children, attention should be focused on side effects of therapy and comorbidity, such as impaired growth and body configuration.

### Specific Agents Glucocorticosteroids

In the early 1990s, Mendoza et al.<sup>17-19</sup> treated patients with SRNS due to FSGS with a protocol involving infusions of high doses of methylprednisolone, often in combination with oral alkylating agents. Twenty-three children have been treated in this manner, with a follow-up of 46 +/- 5 months. Twelve of them went into complete remission, six had minimal to moderate proteinuria, and four remained nephrotic. Each had a normal glomerular filtration rate. One child developed chronic renal failure and subsequently died while on dialysis. These results appear significantly better than in previous series of children with FSGS. More cases have been added to this first series, and the so-called Mendoza protocol has been used in many centers. However, a prospective randomized controlled trial has never been published. Concerns about methylprednisolone side effects left many clinicians reluctant to employ this protocol but stimulated a search for new drugs allowing steroid sparing.

The mode of action of corticosteroids was speculative and unclear until recently. Experimental data from Fujii et al.<sup>20</sup> may offer new insights into possible mechanisms for efficacy. Fujii demonstrated defective nephrin transport following endoplasmic reticulum-stress; that is, endoplasmic reticulum stress in podocytes may cause alteration of nephrin N-glycosylation, which may be an underlying factor in the pathogenesis of the proteinuria in nephrotic syndrome. Dexamethasone may restore this imbalance by stimulating expression of mitochondrial genes, resulting in production of ATP, which is an essential factor for proper folding machinery aided by the ER chaperones. It is unclear if there will be a place for dexamethasone in future therapeutic proposals.

### Calcineurin Inhibitors

Calcineurin inhibitors have been used more in an empirical manner than on the basis of clear rationale. Cyclosporin is a calcineurin inhibitor that suppresses immune response by downregulating the transcription of various cytokine genes. The most significant of these cytokines is interleukin-2, which serves as the major activation factor for T cells in numerous immunologic processes. Cyclosporin inhibits cytokine production from T helper cells (Th1 and Th2) and also has an inhibitory effect on antigen-presenting cells (Langerhans and dendritic cells), which are the main agents of T-cell stimulation. A further effect of interleukin-2 inhibition is a reduction in B-cell activation and subsequent antibody production. Interleukin-2 levels are known to become elevated during proteinuria and to normalize during remission in adults with

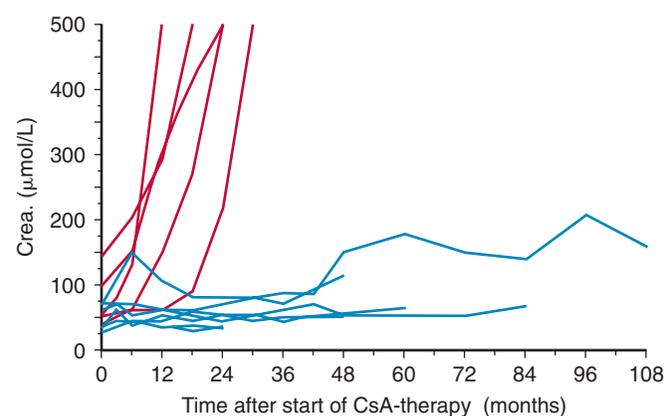
idiopathic nephrotic syndrome and in children with MCNS or FSGS.<sup>21</sup> However, this pattern of interleukin-2 activity is felt to be part of a more widespread disorder of cellular immunity that results in nephrotic syndrome rather than being causal of proteinuria.

It has been reported that cyclosporin has some antiproteinuric action on glomerular perm-selectivity to proteins that is unrelated to its immunosuppressive properties. Among these are an influence on perm-selectivity and charge selectivity, and impairment of glomerular filtration rate. These data come from various human studies<sup>22-25</sup> and animal models<sup>26-28</sup> with no immunologically mediated disease. Some studies revealed that lesions from the primary glomerular disease had either not regressed or had continued to progress.<sup>23,24,29</sup>

An uncontrolled trial in the early 1990s showed that about half of the patients had a stable course during cyclosporin treatment, whereas the others were resistant to the treatment (Figure 16-10). Knowledge of the various genetic and nongenetic causes of SRNS might easily explain this difference in response.

The first controlled data about efficacy of cyclosporin in SRNS came from Lieberman and Tejani<sup>30</sup>; they performed a randomized double-blind placebo-controlled trial of cyclosporin in 25 children with steroid-resistant idiopathic FSGS. Cyclosporin significantly reduced proteinuria and increased serum albumin levels. Interestingly, hypercholesterolemia seemed to antagonize the effect of cyclosporin, leading to the proposal to increase the dose according to cholesterol levels. This has been cited in the literature quite often, but apparently has not been translated into clinical use as discerned from review of the literature. Major concerns were the nephrotoxic side effects of cyclosporin, as well as a fear that progression of the disease might be indistinguishable from toxicity.

The French Society of Pediatric Nephrology published its experience with 65 children with steroid-resistant idiopathic nephrosis.<sup>2</sup> Patients were treated with cyclosporin at 150 to 200 mg/m<sup>2</sup> in combination with prednisone at 30 mg/m<sup>2</sup> daily for 1 month and on alternate days for 5 months. Renal biopsy



**Figure 16-10** Clinical course under CsA in an unselected group of children with SRNS with FSGS lesion (our own observations before the genetic diagnoses became available). Interestingly, half of the patients improve under CsA therapy, whereas the others remain therapy resistant. This is clearly evidence for the variety of underlying diseases and an argument against uniform treatment based only on the definition "steroid resistance."

showed minimal change disease in 45 children and FSGS in 20. Twenty-seven patients achieved complete remission.

A study in adult patients<sup>31</sup> provided Level I evidence for efficacy of cyclosporin. In this study a 26-week regimen of cyclosporin therapy was compared with placebo in 49 patients with steroid-resistant FSGS; both groups also received low-dose prednisone. Further evidence was provided by Ponticelli et al.<sup>32</sup> Cyclosporin was compared to symptomatic treatment in 44 patients (adults and children) with SRNS. Eight (57%) cyclosporin-treated patients attained remission (complete or partial). Three (16%) control patients had partial remissions, but details regarding their diagnoses were incomplete. The majority of remitters had relapsed by the end of month 12 when cyclosporin was stopped.

The Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) conducted a prospective randomized trial that included children with SRNS at initial manifestation. Six months of treatment with cyclosporin (trough level 80 to 120 ng/L) versus 6 months of treatment with cyclophosphamide ( $6 \times 500 \text{ mg/m}^2$ ) were compared. Although the goal was to involve 60 patients, the study was stopped after the inclusion of 32. A complete remission was achieved in 2 out of 15 receiving cyclosporin and in 2 out of 17 receiving cyclophosphamide; a partial remission was obtained in 7 out of 15 versus 2 out of 17. It was concluded that initial response with cyclosporin was better than with cyclophosphamide pulses (60% vs. 17%). Complete remission after week 24 was similar in both groups. In those who did not respond to cyclophosphamide, a successful remission was achieved in 45% with cyclosporin. Safety in both arms was comparable.

Recently Franz and colleagues<sup>33</sup> presented data that cyclosporin protects podocyte stress fibers through stabilization of synaptopodin protein expression. If this is supported by future experimental data, a nonimmunologic approach for the treatment might be envisaged.

A pilot trial of tacrolimus in the management of SRNS was published by McCauley et al. in 1993.<sup>34</sup> All patients except one experienced at least a 50% reduction in protein excretion at some time during tacrolimus therapy. No con-

trolled study has been carried out, and only uncontrolled experiences have been published. Loeffler<sup>35</sup> reported a series of 16 patients resistant to other immunosuppressive drugs. In this mixed group he concluded that tacrolimus is an effective, well-tolerated medication for treatment-resistant forms of nephrotic syndrome in children, resulting in a complete remission rate of 81% and a partial remission rate of 13%. More data and a prospective trial are needed to confirm these promising results and to demonstrate the safety of this approach.

As of now, of the newer immunosuppressive agents only cyclosporin has been approved for use in nephrotic syndrome by licensing authorities in some countries.

An algorithm for the use of cyclosporin in SRNS (Figure 16-11) has been proposed.<sup>35a</sup> (Result of an expert meeting, London, 2005.)

### Antiproliferative Agents

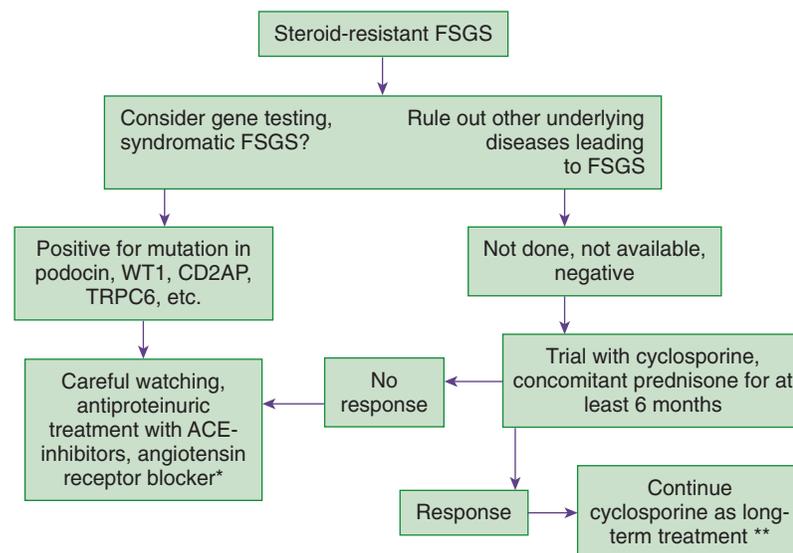
Azathioprine and vincristine have been used by some individuals but have not been widely recommended because of the lack of positive results. Cyclophosphamide has failed to prove any benefit, although many investigators have included this drug in their armamentarium. In most of the reports, drug combinations were employed that did not allow separation of single drug effects. The prospective trial of the APN mentioned earlier was stopped because of the inferiority of cyclophosphamide to cyclosporin.

Mycophenolate mofetil (MMF) has attracted investigators' interest because of its nonnephrotoxic profile. Some uncontrolled trials point toward possible benefits, but (a) the lack of control data, (b) the anecdotal character, (c) the possible selection bias in reporting, and (d) the fact that this drug has been in routine use for more than 10 years in the transplant setting but no robust data are available demonstrating any effect for prevention of posttransplant recurrence of original disease all argue against premature recommendations. One should await the results of the trial being undertaken in the United States under the auspices of the National Institutes of Health, wherein treatment with cyclosporin over 26

**Figure 16-11** Proposed algorithm for treatment based on current knowledge (according to recommendations for the use of cyclosporin in patients with nephrotic syndrome developed by an expert meeting in London, 2005).

\* The recommendation of ACE inhibitors and AT1 receptor blockers is based mainly on evidence from adult patients. Pediatric data are uncontrolled observations and the use has not been approved by licensing authorities.

\*\* Treatment should be continued for years, but it remains unclear for exactly how long.



weeks will be compared with MMF/pulse steroids and continued for 52 weeks if response of proteinuria occurs. Both treatment arms include low-dose prednisone and ACE inhibitor therapy. Patients will be recruited at more than 130 sites in North America.

### Antiproteinuric Treatment

There is strong evidence from studies in adult patients that ACE inhibitors effectively lower proteinuria in various diseases involving proteinuria.<sup>36-41</sup> These results have been accepted by many pediatric nephrologists as a robust argument for introducing ACE inhibitors for their patients with proteinuria. The dilemma is that in pediatric patients this has led to off-label use without proper phase II and III trials.

A large series of pediatric patients have been treated with ramipril in the Escape Trial<sup>42</sup>—a prospective assessment of the renoprotective efficacy of ACE inhibition and intensified blood pressure control. In this assessment, 397 children (ages 3 to 18 years) with chronic renal failure (GFR 11 to 80 ml/min/1.73 m<sup>2</sup>) and elevated or high-normal BP received ramipril (6 mg/m<sup>2</sup>) following a 6-month run-in period, including a 2-month washout of any previous ACE inhibitors.

Blood pressure was reduced with equal efficacy daytime and nighttime. Urinary protein excretion was reduced by 50% on average, with similar relative efficacy in patients with hypo/dysplastic nephropathies and glomerulopathies. The magnitude of proteinuria reduction depended on baseline proteinuria ( $r = 0.32$ ,  $p < 0.0001$ ), and was correlated with the antihypertensive efficacy of the drug ( $r = 0.22$ ,  $p < 0.001$ ). Small, uncontrolled trials in pediatric patients with persistent nephritic syndrome also found some reduction of proteinuria.<sup>43-47</sup>

The positive interpretation of a renoprotective effect of ACE inhibitors with and without AT1 receptor antagonist has made it unlikely that children are left without such treatment.

### CONCLUSION

Steroid-resistant nephrotic syndrome is not a single entity. The most dominant lesion is focal segmental glomerulosclerosis (FSGS). Better understanding of the underlying diseases and mechanisms will guide future treatment. Early genetic diagnosis might help to avoid ineffective but harmful immunosuppressive therapy.

### REFERENCES

1. Brodehl J, Krohn HP, Ehrich JH: The treatment of minimal change nephrotic syndrome (lipoid nephrosis): Cooperative studies of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN), *Klin Padiatr* 194:162-65, 1982.
2. Niaudet P: Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French society of pediatric nephrology, *J Pediatr* 125:981-86, 1994.
3. Srivastava T, Simon SD, Alon US: High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood, *Pediatr Nephrol* 13:13-18, 1999.
4. Coovadia HM, Adhikari M, Morel-Maroger L: Clinico-pathological features of the nephrotic syndrome in South African children, *Q J Med* 48:77-91, 1979.
5. Bhimma R, Coovadia HM, Adhikari M: Nephrotic syndrome in South African children: Changing perspectives over 20 years, *Pediatr Nephrol* 11:429-34, 1997.
6. D'Agati V: Pathologic classification of focal segmental glomerulosclerosis, *Semin Nephrol* 23:117-34, 2003.
7. Abeyagunawardena AS, Sebire NJ, Risdon RA, Dillon MJ, Rees L et al: Predictors of long-term outcome of children with idiopathic focal segmental glomerulosclerosis, *Pediatr Nephrol* 22(2):215-21, 2006.
8. Wharram BL, Goyal M, Wiggins JE, Sanden SK, Hussain S et al: Podocyte depletion causes glomerulosclerosis: Diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene, *J Am Soc Nephrol* 16:2941-52, 2005.
9. Mundel P, Shankland SJ: Podocyte biology and response to injury, *J Am Soc Nephrol* 13:3005-15, 2002.
10. Kriz W: The pathogenesis of 'classic' focal segmental glomerulosclerosis—lessons from rat models, *Nephrol Dial Transplant* 18 Suppl 6:vi39-44, 2003.
11. Kriz W, Hartmann I, Hossler H, Hahnel B, Kranzlin B et al: Tracer studies in the rat demonstrate misdirected filtration and peritubular filtrate spreading in nephrons with segmental glomerulosclerosis, *J Am Soc Nephrol* 12:496-506, 2001.
12. Hinkes B, Wiggins RC, Gbadegesin R, Vlangos CN, Seelow D et al: Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible, *Nat Genet* 38:1397-1405, 2006.
13. Ruf RG, Lichtenberger A, Karle SM, Haas JP, Anacleto FE et al: Patients with mutations in *NPHS2* (podocin) do not respond to standard steroid treatment of nephrotic syndrome, *J Am Soc Nephrol* 15:722-732, 2004.
14. Maruyama K, Iijima K, Ikeda M, Kitamura A, Tsukaguchi H et al: *NPHS2* mutations in sporadic steroid-resistant nephrotic syndrome in Japanese children, *Pediatr Nephrol* 18:412-16, 2003.
15. Savin VJ, Sharma R, Sharma M, McCarthy ET, Swan SK et al: Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis, *N Engl J Med* 334:878-83, 1996.
16. Sharma M, Sharma R, McCarthy ET, Savin VJ: The focal segmental glomerulosclerosis permeability factor: Biochemical characteristics and biological effects, *Exp Biol Med (Maywood)* 229:85-98, 2004.
17. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM: Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents, *Pediatr Nephrol* 4:303-07, 1990.
18. Mendoza SA, Tune BM: Treatment of childhood nephrotic syndrome, *J Am Soc Nephrol* 3:889-94, 1992.
19. Mendoza SA, Tune BM: Management of the difficult nephrotic patient, *Pediatr Clin North Am* 42:1459-68, 1995.
20. Fujii Y, Khoshnoodi J, Takenaka H, Hosoyamada M, Nakajo A et al: The effect of dexamethasone on defective nephrin transport caused by ER stress: A potential mechanism for the therapeutic action of glucocorticoids in the acquired glomerular diseases, *Kidney Int* 69:1350-59, 2006.
21. Tejani A, Ingulli E: Current concepts of pathogenesis of nephrotic syndrome, *Contrib Nephrol* 114:1-5, 1995.
22. Zietse R, Wenting GJ, Kramer P, Schalekamp MA, Weimar W: Effects of cyclosporin a on glomerular barrier function in the nephrotic syndrome, *Clin Sci (Lond)* 82:641-50, 1992.
23. Meyrier A, Noel LH, Auriche P, Callard P: Long-term renal tolerance of cyclosporin a treatment in adult idiopathic nephrotic syndrome. Collaborative group of the society de nephrology, *Kidney Int* 45:1446-56, 1994.
24. Ambalavanan S, Fauvel JP, Sibley RK, Myers BD: Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy, *J Am Soc Nephrol* 7:290-98, 1996.
25. Heering P, Schneider A, Grabensee B, Plum J: [Effect of cyclosporin a on renal function in patients with glomerulonephritis], *Dtsch Med Wochenschr* 126:1093-98, 2001.

26. Kokui K, Yoshikawa N, Nakamura H, Itoh H: Cyclosporin reduces proteinuria in rats with aminonucleoside nephrosis, *J Pathol* 166:297-301, 1992.
27. Schrijver G, Assmann KJ, Wetzels JF, Berden JH: Cyclosporin a reduces albuminuria in experimental anti-gbm nephritis independently from changes in GFR, *Nephrol Dial Transplant* 10:1149-54, 1995.
28. Desassis JF, Raats CJ, Bakker MA, van den Born J, Berden JH: Antiproteinuric effect of ciclosporin a in adriamycin nephropathy in rats, *Nephron* 75:336-41, 1997.
29. Chen H, Tang Z, Zeng C, Hu W, Wang Q et al: Pathological demography of native patients in a nephrology center in China, *Chin Med J (Engl)* 116:1377-81, 2003.
30. Lieberman KV, Tejani A: A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children, *J Am Soc Nephrol* 7:56-63, 1996.
31. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA et al: A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America nephrotic syndrome study group, *Kidney Int* 56:2220-26, 1999.
32. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E et al: A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome, *Kidney Int* 43:1377-84, 1993.
33. Franz S, Faul C, Mundel P: Cyclosporin protects stress fibers through stabilization of synaptodin protein expression, *JASN* 16:109A, 2005.
34. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE: Pilot trial of fk 506 in the management of steroid-resistant nephrotic syndrome, *Nephrol Dial Transplant* 8:1286-90, 1993.
35. Loeffler K, Gowrishankar M, Yiu V: Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome, *Pediatr Nephrol* 19:281-87, 2004.
- 35a. Cattran DC, Alexopoulos E, Heering P, Hoyer PF, Johnston A, et al: Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations, *Kidney Int* 2007 (epub ahead of print Sep. 27).
36. MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD: Combination therapy with an angiotensin receptor blocker and an ace inhibitor in proteinuric renal disease: A systematic review of the efficacy and safety data, *Am J Kidney Dis* 48:8-20, 2006.
37. Remuzzi G, Macia M, Ruggenenti P: Prevention and treatment of diabetic renal disease in type 2 diabetes: The BENEDICT study, *J Am Soc Nephrol* 17:S90-97, 2006.
38. Kelly DJ, Zhang Y, Cox AJ, Gilbert RE: Combination therapy with tranilast and angiotensin-converting enzyme inhibition provides additional renoprotection in the remnant kidney model, *Kidney Int* 69:1954-60, 2006.
39. Remuzzi A, Gagliardini E, Sangalli F, Bonomelli M, Piccinelli M et al: Ace inhibition reduces glomerulosclerosis and regenerates glomerular tissue in a model of progressive renal disease, *Kidney Int* 69:1124-30, 2006.
40. Song JH, Cha SH, Lee HJ, Lee SW, Park GH, Kim MJ: Effect of low-dose dual blockade of renin-angiotensin system on urinary TGF-beta in type 2 diabetic patients with advanced kidney disease, *Nephrol Dial Transplant* 21:683-89, 2006.
41. Pozzi C, Del Vecchio L, Casartelli D, Pozzoni P, Andrulli S et al: Ace inhibitors and angiotensin II receptor blockers in iga nephropathy with mild proteinuria: The ACEARB study, *J Nephrol* 19:508-14, 2006.
42. Wuhl E, Mehls O, Schaefer F: Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure, *Kidney Int* 66:768-76, 2004.
43. Chiarelli F, Casani A, Verrotti A, Morgese G, Pinelli L: Diabetic nephropathy in children and adolescents: A critical review with particular reference to angiotensin-converting enzyme inhibitors, *Acta Paediatr Suppl* 425:42-45, 1998.
44. Camacho Diaz JA, Gimenez Lloret A, Garcia Garcia L, Jimenez Gonzalez R: [long-term effect of angiotensin-converting inhibitors in children with proteinuria], *An Esp Pediatr* 55:219-24, 2001.
45. Srivastava RN: Isolated asymptomatic proteinuria, *Indian J Pediatr* 69:1055-58, 2002.
46. Peco-Antic A, Virijevec V, Paripovic D, Babic D: [Renoprotective effect of ramipril in children with chronic renal failure—the experience of one centre], *Srp Arh Celok Lek* 132 Suppl 1:34-38, 2004.
47. Artero M, Biava C, Amend W, Tomlanovich S, Vincenti F: Recurrent focal glomerulosclerosis: Natural history and response to therapy, *Am J Med* 92:375-83, 1992.
48. Pavenstadt H, Kriz W, Kretzler M: Cell biology of the glomerular podocyte, *Physiol Rev* 83:253-307, 2003.
49. Endlich K, Kriz W, Witzgall R: Update in podocyte biology, *Curr Opin Nephrol Hypertens* 10:331-40, 2001.

