Treatment of the Idiopathic Nephrotic Syndrome: Regimens and Outcomes in Children and Adults

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The nephrotic syndrome (NS), consisting of massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia, is a common complication of glomerular disease in children and adults. The authors’ personal experience involves mainly renal diseases of children. Therefore, the present discussion begins with idiopathic pediatric NS, with emphasis on minimal-change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Presenting features, complications, treatment regimens, and outcomes for adults are then compared with those for children.

Etiology

The primary causes of idiopathic NS are not known. There is circumstantial evidence pointing to a role of the immune system in pediatric MCD (1). Several reports have described an association between allergy and MCD in children. Relapses of the syndrome are triggered commonly by minor infections and occasionally by reactions to bee stings or poison ivy. Abnormalities of both humoral and cellular immunity have also been described. Finally, the induction of remissions by corticosteroid, alkylating agent, or cyclosporine therapy provides indirect evidence for an immune etiology. None of these observations, however, provides direct evidence of immunologically mediated pathogenesis.

Pathophysiology

Proteinuria

Children with MCD, although massively proteinuric, do not have a generalized glomerular leak to macromolecules (1). The clearance of neutral macromolecules in MCD is actually less than normal over a range of molecular radii. In contrast, the clearance of anionic macromolecules is significantly increased. This and several other lines of evidence suggest that proteinuria results from a loss of the fixed negative charges of anionic glycosaminoglycans in the glomerular capillary wall (1). The mechanism by which these charges are lost has not been defined. A highly cationic protein in the plasma and urine of children with MCD has been recently described, but the pathogenic significance of this protein has not been determined.

Edema

The traditional view has been that massive albuminuria in NS causes a decrease in intravascular oncotic pressure, which allows extravasation of fluid, resulting in hypovolemia, increased aldosterone and antidiuretic hormone secretion, and renal salt and water retention. Consistent with this mechanism are the observations that, in MCD of childhood, edema seldom occurs when serum albumin levels are above 2.0 g/dL and the elevated hematocrit, prerenal azotemia, and fluid retention during relapse may be improved by intravenous infusions of salt-poor albumin.

Evidence against this model (2) includes the failure of some patients to respond to intravenously administered albumin, the fact that steroid-induced diuresis often occurs before a dramatic rise in serum albumin concentration, and the observation that plasma volumes are normal to increased and plasma renin and aldosterone levels are decreased in many patients with heavy proteinuria and edema. Finally, patients with congenital analbuminemia typically have little or no edema. An alternative explanation for retention of salt and water in NS is a decreased GFR, with a decreased filtration fraction.

Natural History

Before the availability of antibiotics and corticosteroids, 40% of children with NS died of infections (bacterial sepsisemia, peritonitis, cellulitis, etc.), renal failure, or occasionally thromboembolism (3,4). The advent of penicillin and other antimicrobial agents increased the rate of survival from acute infections. However, massive edema, recurrent septic events, and chronic renal failure remained common. If the children survived, sustained spontaneous remissions often occurred only after years of disease activity.

In the early 1950s, oral therapy with adrenal corticosteroids (hereafter designated as steroids) was introduced in the treatment of idiopathic NS, with dramatic benefit (4). Diuresis and disappearance of proteinuria occurred within 4 weeks of daily steroid therapy for the great majority of children. Many who responded, most of whom must have had MCD (5,6), relapsed and responded to retreatment. Alkylating agent therapy with mechlorethamine was successfully tried about the time cortisone was introduced (1) but was quickly abandoned because of its acute toxicity. Better-tolerated oral alkylating agents were introduced later in children with steroid toxicity or resistance (7). Although steroids and alkylating agents are both immuno-
suppressive, the frequency of infectious complications was dramatically reduced because of control of the NS.

The International Study of Kidney Disease in Childhood

In the early 1970s, a series of prospective, multicenter, cooperative studies by the International Study of Kidney Disease in Childhood (ISKDC) established definitions, clinico-pathologic correlations, and recommendations for therapy that became the basis for diagnosis and management of pediatric NS (5,6,8). Idiopathic NS was defined as the combination of proteinuria of ≥40 mg/m²/h and hypoalbuminemia of ≤2.5 g/dL, usually with edema, in a child between 3 months and 16 yr of age without clinical or laboratory evidence of a primary disease known to cause proteinuria (8).

The ISKDC studies identified several groups of lesions in biopsies from children early in the course of idiopathic NS, i.e., MCD, focal glomerulosclerosis, diffuse mesangial proliferation (DMP) characterized by the finding of ≥4 cells/peripheral mesangial area, membranoproliferative glomerulonephritis, and membranous nephropathy (MN) (1,5). Because of the accompanying hypocomplementemia of membranoproliferative glomerulonephritis and the rarity of idiopathic MN in children, these two lesions are now typically excluded from the category of idiopathic pediatric NS.

Focal glomerular or focal global obsolescence, in the absence of segmental sclerosis or significant tubular atrophy and interstitial fibrosis, was recognized as a pattern distinct from and far less ominous than focal segmental hyalinosis (5,9), which is generally identified today as FSGS (10). Mild mesangial hypercellularity (3 cells/peripheral mesangial area), sometimes seen as a focal or diffuse finding in MCD or FSGS, may be predictive of greater difficulty in early management (1) but not necessarily an unfavorable outcome.

Minimal Change Disease

Renal Biopsy

MCD, overwhelmingly the most common of the biopsy patterns in pediatric NS (5,6), is characterized by little or no abnormality on light microscopy; mild or focal mesangial hypercellularity is seen in some cases (“nil-plus” disease). Immunofluorescence is negative or occasionally weakly positive. On electron microscopy, there is epithelial foot process fusion in the absence of immune complexes, other abnormalities of glomerular basement membranes, or proliferation of endothelial or epithelial cells (1).

The proportion of nephrotic children who have MCD varies with the age at the onset of the disease. The great majority of nephrotic children between the ages of 1 and 6 yr have MCD (80 to 95%) (5,6). The frequency of MCD is lower in older children (65%) (6) and still lower in adults (≤20%) (11). Although the great majority of children with MCD respond to 1 to 2 months of oral steroid therapy by entering complete remission, responses to this course of oral steroids alone are less common in children with other biopsy patterns (5,6). Based on the frequency of MCD and extensive clinico-pathologic experience, newly diagnosed, uncomplicated pediatric cases of NS are often treated with oral steroids without a renal biopsy. Patients who respond to this treatment are assumed to have MCD. Renal biopsy is reserved for children who are steroid-resistant or present with features suggestive of lesions other than MCD (Table 1).

Presentation

Children with MCD generally present during early childhood (5,6) but rarely in the neonatal period (12). The usual presenting complaint is facial edema or increased abdominal girth. Periorbital edema is frequently misdiagnosed as being allergic in origin until the urine is examined. Edema is typically of great concern to the parents but can be well tolerated by the children. In extreme cases, massive edema, with ascites and pleural effusions, can produce symptoms of respiratory distress or scrotal or labial pain. Children with NS can present with primary peritonitis, septicemia, or cellulitis (without an apparent entry site). Almost all of these infections are caused by *Streptococcus pneumoniae* or an enteric bacterium.

The majority of children with MCD present with little or no hypertension or hematuria. When present in MCD, these abnormalities typically resolve with a response to steroids (6). The combination of hypertension and hematuria is particularly characteristic of MCD. However, any of the unfavorable features listed in Table 1 can be seen in MCD (except possibly neonatal onset), and their occurrence does not preclude a response to orally administered steroids.

Approach to the New Patient

Children with an initial episode of NS were traditionally hospitalized to rule out complications or other conditions presenting with the syndrome (Table 2), as well as for biopsy or initiation of steroid therapy. However, children with simple idiopathic NS (Table 1) are now hospitalized only if edema is massive or if infection or another life-threatening complication is suspected.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No negative correlates</td>
<td>90 to 95</td>
</tr>
<tr>
<td>Random case</td>
<td>90</td>
</tr>
<tr>
<td>Female</td>
<td>70</td>
</tr>
<tr>
<td>Child ≥6 yr old</td>
<td>65</td>
</tr>
<tr>
<td>Hypertension alone</td>
<td>60</td>
</tr>
<tr>
<td>Hematuria alone</td>
<td>50</td>
</tr>
<tr>
<td>Infant (≥3 months to 1 yr)</td>
<td>20</td>
</tr>
<tr>
<td>Postpubertal</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone resistant*</td>
<td>20</td>
</tr>
<tr>
<td>Hematuria plus hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Infant (&lt;3 months)</td>
<td>0 to 5</td>
</tr>
</tbody>
</table>

*From references 5, 6, 11, and 12.

†Dose of 2 mg/kg or 40 mg/m² daily for 1 month, then 3 of 7 days for 1 month.
is suspected. Otherwise, diagnostic studies, tuberculin skin testing, and steroid therapy are begun in an outpatient setting. Although relapses are common in MCD, home testing for proteinuria allows detection and treatment of most recurrences before gross edema develops. Most parents can be taught to test the urine for protein, initiate steroid therapy in simple relapses, and recognize the features of bacterial infection or other complications. During steroid therapy, nonimmune children exposed to chickenpox require prompt administration of zoster immunoglobulin. With careful coordination between physicians and parents, hospitalization can be avoided in the great majority of cases.

Treatment

Steroids. Steroid-responsiveness of NS was defined by the ISKDC (8) as a total remission (proteinuria of ≤4 mg/m²·h in at least three urine samples obtained within 1 week) within 4 weeks of 60 mg/m² (maximum, 60 mg) of daily prednisone given in divided doses, followed by no more than 4 weeks of 40 mg/m² prednisone administered intermittently (3 consecutive days of 7). Some renal treatment centers use 80 mg as the daily maximum, and most now use alternate-day prednisone as intermittent therapy. Because reliably timed urine specimens are difficult to obtain in children, proteinuria is generally quantified by the ratio of urine protein to urine creatinine (milligram/milligram). Proteinuria is considered to be in the normal range when the urine protein/creatinine ratio is ≤0.2 and nephrotic when the ratio is ≥2 (13). Of the 95% of children with MCD who respond to prednisone, most do so within 2 to 3 weeks of daily therapy.

Until recently, most of the information regarding the optimal duration of steroid therapy in children with MCD was anecdotal. A series of controlled trials comparing three protocols for the administration of oral prednisone has clarified this issue (14). Patients receiving the “short course” received the drug daily until their urine was protein-free for 3 days; they then received alternate-day prednisone until their serum albumin levels became normal (mean, 16 days). “Standard” therapy was 4 weeks of daily prednisone followed by 4 weeks of alternate-day therapy. The “long course” of prednisone involved 6 weeks of daily therapy followed by 6 weeks of alternate-day treatment. When the long course was used to treat the initial episode of NS, patients were more likely to remain in remission. The incidence of relapse after 1 yr was 36% after the long course, 61% after the standard treatment, and 81% with the short course. The improved outcome with the long course of steroids persisted for at least 2 yr. There was no difference in the duration of remissions when the different therapies were compared for treatment of recurrences. Side effects of steroid therapy were comparable in the standard-therapy and long-course groups. As a result of these studies, many centers use the long protocol to treat the initial episode of NS and short courses to treat relapses.

The long-term prognosis for children with steroid-responsive NS is very good. However, relapses may occur for many years, commonly until puberty (15). A small number of children with NS may continue to have recurrences as adults. These relapses are usually not severe and can be treated with short courses of oral prednisone. Even though steroid therapy may be required intermittently throughout childhood, serious sequelae of steroid toxicity are not common.

Alkylating agents. Some steroid-responsive children either relapse frequently or require high daily doses of oral steroids to maintain remission. These frequently relapsing or steroid-dependent children may develop significant steroid side effects, including growth failure, hypertension, posterior sublenticular cataracts, and osteoporotic bone disease. Patients with significant steroid toxicity or acquired resistance to steroids typically respond to oral cyclophosphamide or chlorambucil with a prolonged and sometimes permanent remission of NS (16,17). There is some disagreement regarding the optimal duration of alkylating agent therapy, with suggested ranges being 8 to 12 weeks of 2.0 to 2.5 mg/kg cyclophosphamide (maximum single dose, 100 mg; maximum total cumulative dose, ≤200 mg/kg) or 0.15 to 0.20 mg/kg chlorambucil (maximum single dose, 6 mg; maximum total cumulative dose, ≤12 mg/kg). Second courses of alkylating agents may be used in partially or previously responsive cases. The effectiveness of alkylating agent therapy is enhanced by concomitant administration of alternate-day prednisone.

At these doses, oral alkylating agents are well tolerated. Some children (5 to 10%) develop mild leukopenia. Therefore, white blood cell counts are measured weekly during treatment and the alkylating agent is temporarily withheld or its dosage

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Table 2. Evaluation of child at the onset of the NS

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Condition Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry panel</td>
<td>NS, renal failure</td>
</tr>
<tr>
<td>Antistreptococcal titers</td>
<td>PSAGN (rarely a simple NS)</td>
</tr>
<tr>
<td>Serum complement (C3, C4, and CH-50)</td>
<td>MPGN, SLE, PSAGN</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Hepatitis B-associated nephritis</td>
</tr>
<tr>
<td>Antinuclear or anti-DNA antibodies</td>
<td>SLE (older children with nephritic features)</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>Renal vein thrombosis (infants)</td>
</tr>
<tr>
<td>Tuberculosis skin test</td>
<td>Risk of activation by steroid therapy</td>
</tr>
</tbody>
</table>

*PSAGN, poststreptococcal acute glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus.
reduced in patients with a white blood cell count of $\leq 4000/\text{mm}^3$ or neutrophil count of $\leq 2000/\text{mm}^3$. Some families have noted greater-than-usual amounts of hair on the child’s comb during a course of treatment with cyclophosphamide, but noticeable alopecia is uncommon. The metabolites of cyclophosphamide can cause acute or chronic chemical cystitis, requiring that this medication be given in the morning with a large daily fluid intake to limit concentrations in the urinary bladder. Occasionally, patients receiving chlorambucil may develop seizures, and cyclophosphamide is therefore preferred for children with a history of convulsions.

There is concern regarding the long-term effects of alkylating agents. Sterility has been reported in patients treated as children, particularly with prolonged or repeated courses (1). The incidence of sterility is as high as 15 to 20% in boys and increases with repeated usage. Girls appear to be much less affected. The risk of sterility is dose-dependent and may be less in recent years because the cumulative doses have been limited. Treatment of other conditions with alkylating agents has been associated with an increased incidence of neoplasms. Although there are no data demonstrating that secondary malignancies occur in children who receive the limited alkylating regimens used for NS, the possibility must be discussed with the families and the children (if they are old enough).

**Cyclosporine.** Alkylating agents are not commonly needed in patients with MCD; however, when needed, they are usually effective. Simple cases of MCD that do not respond well to an alkylating agent may respond to cyclosporine ($\leq 200 \text{ mg/m}^2$ or $\leq 5.5 \text{ mg/kg daily}$), but responses are often transient and dependence on cyclosporine is common (18). However, many nephrologists prefer the limited risk of cyclosporine nephrotoxicity in pediatric MCD (19) to the side effects of chronic steroid therapy or the risk of sterility from a second course of an alkylating agent.

**MCD in Adults**

Comparison of the major patterns of idiopathic NS in adults with those in children may be complicated by differences in definitions, criteria for biopsy, and treatment regimens between pediatrics and internal medicine. The prevailing dogma, often supported only by discussions between colleagues, has been that MCD in children is more frequent, more often complicated by massive edema and bacterial infections, more responsive to steroids, and more likely to relapse than that in adults.

In a large series of early biopsies from children with idiopathic NS, White et al. (6) found MCD in 88% of unselected and 64% of referral cases; the difference was probably influenced by the practice of pediatricians not to refer uncomplicated, steroid-responsive NS ("presumed MCD") to renal treatment centers. Because NS in adults is not easily treated (20–24) and because MCD is less frequent as a cause of NS in adults than in children (11,20), early renal biopsy in NS has long been the standard practice in internal medicine. The data regarding the frequency of MCD in nephrotic adults, reported as $\leq 20\%$ and apparently decreasing as FSGS becomes more common (11,20), are therefore probably reliable.

In certain respects, adult MCD is more difficult to treat than its pediatric counterpart. Hypertension and acute renal failure at the onset of the NS occur more commonly than in children, particularly in older adults (20). Although most adults with MCD respond to steroid therapy, the response rate appears to be lower and remissions slower to develop than in children (20,22). Relapses occur, but steroid dependency appears to be less common in adults. Alkylating agents (20,22), and possibly even azathioprine (22), have an additive effect with corticosteroids, producing more prolonged remissions of proteinuria. Cyclosporine ($\leq 5.5 \text{ mg/kg daily}$ for $\geq 12$ months) may also be effective in adult steroid-resistant or steroid-dependent MCD, with limited risk of nephrotoxicity (25). The long-term prognosis in successfully treated adult MCD is generally good, but the mortality rate in older patients with NS exceeds actuarial expectations for age (20).

**Focal Segmental Glomerulosclerosis**

**Renal Biopsy**

A small percentage of children with NS do not enter remission when treated with prednisone. The biopsy in more than half of these children reveals FSGS (5,6). Although uncommon compared with MCD, FSGS is the most frequent progressive glomerular disease in childhood and is second only to congenital anomalies among the causes of pediatric ESRD (26).

The pathologic diagnosis of FSGS is made when any glomeruli have segmental capillary collapse and mesangial sclerosis on light microscopy. Electron microscopy may reveal earlier changes, but these are not specific for FSGS: loss of visceral epithelial cell podocytes, duplication and separation of epithelial cells from the basal lamina of the glomerular basement membrane, and epithelial degeneration or necrosis. Other pathologic features and variants of FSGS, recently reviewed elsewhere (10), are not included in the present discussion.

Rich (3) described a pattern of evolution in a retrospective analysis of autopsy material from 18 children who died with the NS, many before the antibiotic era. In those who had developed fatal acute infections, mostly within 1 yr after diagnosis of the NS, FSGS was absent or was seen only in some juxtamedullary glomeruli. Children who died with hypertension or uremia, generally $>1$ yr after diagnosis, had more widespread and total glomerular obliteration. Although a pattern of evolution of FSGS from MCD was suggested by this study, the postmortem source of the cases precluded firm conclusions.

Churg and White and associates (5,6) reported that children with FSGS in biopsies obtained at the time of diagnosis of NS showed a clinical pattern of initial or rapidly developing resistance to steroid therapy, commonly followed by progression to renal failure. Other investigators (15,27) described a number of cases with evolution to resistant FSGS and ESRD after many years of steroid-responsive NS and/or biopsy-diagnosed MCD. Because FSGS can be missed in a needle biopsy, particularly when juxtamedullary glomeruli are not sampled, it remains uncertain whether these patterns of "early" and "late" FSGS represent separate entities or the extremes of one process. More specific indicators of cause or classification are needed before this question can be resolved.
Treatment

Steroids and alkylating agents. Although the ISKDC found FSGS to be poorly responsive to prednisone, Habib and Gubler (28) reported 20 to 25% steroid-responsiveness in pediatric FSGS. In further studies of the effects of intermittent prednisone plus a cytotoxic agent, compared with prednisone alone, the ISKDC reported no added benefit from azathioprine (60 mg/m²·day for 90 days) (8) or cyclophosphamide (≥2.5 mg/kg body weight daily for 90 days) (29,30) in the treatment of steroid-resistant FSGS. The ISKDC concluded that cyclophosphamide had no role in the treatment of FSGS (29). After the early presentations of this interpretation (29,31), many renal treatment centers abandoned immunosuppressive therapy for children with steroid-resistant FSGS. However, others had already noted a benefit of alkylating agents and continued using them, with some success, in the early and late forms of the disease (28,32-34).

Cyclosporine. Because of its efficacy as an immunosuppressive agent in solid-organ and bone marrow transplantation, cyclosporine has been widely evaluated in a variety of immunologically mediated diseases. In pediatric NS, a consensus has emerged that cyclosporine is more effective in steroid-dependent than steroid-resistant disease, that the efficacy of corticosteroids is a more important determinant of responsiveness to cyclosporine than is the renal biopsy, and that there is a high rate of relapse after discontinuation of cyclosporine (35,36). Moreover, cyclosporine may be more nephrotoxic in steroid-resistant than in steroid-responsive disease (35). Combined use with low-dose or alternate-day steroids increases the effectiveness of cyclosporine in producing sustained reductions of proteinuria in steroid-resistant disease, including FSGS (36), but this effect has not been seen in all studies (37).

The French Society of Pediatric Nephrology (36) treated 20 cases of steroid-resistant FSGS with 6 to 12 months of ≤200 mg/m²·day cyclosporine combined with 30 mg/m²·prednisone daily for 1 month and then every other day. After 3 yr of follow-up, results were as follows: complete or nearly complete remissions (proteinuria of <10 mg/kg·day), 35%; moderate proteinuria, 5%; nephrotic-range proteinuria without ESRD, 30%; ESRD, 30%.

Methylprednisolone/triple-therapy protocol. The highest rates of remission in steroid-resistant FSGS in children have been achieved with a regimen combining a series of methylprednisolone (M-P) pulses with alternate-day prednisone and an alkylating agent (13,38). The M-P pulse/prednisone regimen is detailed in Table 3. An alkylating agent was added in 78% of cases, in which proteinuria had not been fully controlled by M-P plus prednisone, using the following indications: (1) proteinuria not significantly improved by six M-P pulses administered over 2 weeks; (2) a complete or partial response by 2 weeks with a subsequent significant increase of proteinuria at any time during the M-P regimen; and (3) a urine protein/creatinine concentration ratio of ≥2 at week 10 or later. The alkylating agent, chosen at the discretion of the individual nephrologist, was either cyclophosphamide (2.0 to 2.5 mg/kg·day) or chlorambucil (0.18 to 0.22 mg/kg·day) (based on lean nonedematous body weight) for 8 to 12 weeks. The longer courses of treatment were used in patients who responded more slowly. White blood cell counts were measured weekly, and the alkylating agent was temporarily withheld or its dosage reduced in cases of leukopenia.

If the alkylating agent was started at the end of the first 2 weeks of the M-P protocol, pulses were given weekly until the end of the alkylating therapy and then continued as in Table 3. If the alkylating agent was needed later, six pulses were repeated over 2 weeks and then the alkylating agent was given with weekly pulses. When a patient showed a partial or complete response to this M-P/triple-therapy protocol (M-P pulse plus alkylating agent plus alternate-day prednisone) and then either relapsed during the protocol or failed to achieve a urine protein/creatinine ratio of ≤1.0, a second course of alkylating agent was administered. In most cases, the second course produced a more complete and stable response. Late relapses, occurring after completion of the protocol, were treated as if they were new cases of NS, starting with standard daily prednisone therapy and advancing to M-P pulse or triple therapy only as needed.

The numbers of patients without and with abnormal proteinuria and decreased renal function on most recent follow-up examination (38) are shown in Table 4. Two-thirds were in complete remission and receiving no therapy. Four of these patients had relapsed after completing the protocol but re-

Table 3. Intravenous M-P pulse regimen

<table>
<thead>
<tr>
<th>Week</th>
<th>M-Pa</th>
<th>No.</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>30 mg/kg 3 times/wk</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>3 to 10</td>
<td>30 mg/kg every 1 wk</td>
<td>8</td>
<td>2 mg/kg qodb</td>
</tr>
<tr>
<td>11 to 18</td>
<td>30 mg/kg every 2 wk</td>
<td>4</td>
<td>with or without taper</td>
</tr>
<tr>
<td>19 to 50</td>
<td>30 mg/kg every 4 wk</td>
<td>8</td>
<td>slow taper</td>
</tr>
<tr>
<td>51 to 82</td>
<td>30 mg/kg every 8 wk</td>
<td>4</td>
<td>slow taper</td>
</tr>
</tbody>
</table>

a Maximum dose, 1,000 mg.
b Maximum dose, 60 mg: qod, every other day.

Table 4. M-P pulse/triple-therapy protocol: effects on proteinuria and renal function in steroid-resistant pediatric FSGS

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission, normal Cr Cl</td>
<td>21/32</td>
<td>66</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>urine protein/creatinine ratio &gt; 0.2 to 0.5</td>
<td>3/32</td>
<td>9</td>
</tr>
<tr>
<td>urine protein/creatinine ratio &gt; 0.5 to 1.9</td>
<td>2/32</td>
<td>6</td>
</tr>
<tr>
<td>nephrotic protein/creatinine ratio ≥ 2.0</td>
<td>6/32</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal function</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>proteinuria, normal Cr Cl</td>
<td>3/32</td>
<td>9</td>
</tr>
<tr>
<td>decreased Cr Cl</td>
<td>5/32</td>
<td>16</td>
</tr>
<tr>
<td>ESRD</td>
<td>3/32</td>
<td>9</td>
</tr>
</tbody>
</table>

a Cr Cl, creatinine clearance, calculated from serum creatinine (normal, ≥80 mL/min·1.73 m²). Data and methods are from reference 38.
responded to retreatment (three with M-P plus prednisone and one with triple therapy). Although several children required antihypertensive therapy during the protocol, all responders had normal blood pressures, without antihypertensive agents, in follow-up monitoring. Creatinine clearances, estimated from serum creatinine concentrations, were $\geq 80$ mL/min.1.73 m$^2$ in all 21 patients without abnormal proteinuria. In these 21 the most recent urine protein/creatinine ratios averaged 0.06 ± 0.02 (mean ± SE), serum albumin was 4.1 ± 0.2 g/dL, and creatinine clearance was 122 ± 6 mL/min.1.73 m$^2$. Three children with persistent proteinuria also had normal creatinine clearance. All six patients whose protein/creatinine ratios remained $\geq 2.0$ developed chronic renal failure or ESRD, as did one with a urine protein/creatinine ratio of 0.4 (after 12 yr) and one with a ratio of 1.1 (after 5.3 yr).

Complications of the protocol were few and mild, as in a group of children given more aggressive M-P pulse therapy for rheumatologic disease (39). Side effects of the steroids were no greater than those seen with prednisone therapy of relapsing or steroid-dependent MCD, and alkylating agent toxicity was limited to a few cases of mild and transient leukopenia (40). Perhaps steroid toxicity is limited in the M-P protocol because of the avoidance of daily prednisone administration and the long intervals between pulses.

**Other M-P protocols.** Other groups have used modified M-P pulse regimens for steroid-resistant FSGS (13,41,42). Table 5 shows a direct relationship, in four reported series, between the percentage of children given an alkylating agent and the percentage of successful outcomes. The M-P/triple-therapy protocol requires the addition of an alkylating agent in response to persistent or recurrent heavy proteinuria. One child in Birmingham deteriorated rapidly (41) and one in New England (42) died of septicemia, both before treatment could be completed. Except in those two cases, failure to use alkylating agents, which also correlated with less aggressive M-P therapy, represented a deviation from the protocol.

The results of therapy of steroid-resistant nephrotic FSGS with several different regimens in children are compared in Table 6. The majority of children in these studies were white (13). Although FSGS has been reported to be more aggressive and more resistant to therapy among black children than among children of other racial groups (43), this has not been the authors’ experience in the prepubertal children treated with M-P/triple therapy (13).

**FSGS in Adults**

Although a higher frequency of nephrotic-range proteinuria (>50 mg/kg-day) has been reported in children with FSGS (21), the prognosis and response to therapy of FSGS are similar in children and adults. The outcome is poorer for unresponsive nephrotic FSGS than for non-nephrotic or responsive disease in both age groups (21,38,44). Nevertheless, nephrotic FSGS in both adults and children has a newly recognized potential for responding to prolonged or aggressive courses of therapy (38,45).

The recent increase in complete remissions in adults with FSGS treated with oral steroids (to 30 to 60%) appears to correlate with increased duration of treatment, often with 5 to 8 months of daily therapy (45). Among patients who achieved steroid-induced remissions in one study, relapses were less frequent in adults than in children (21). The addition of cyclophosphamide or chlorambucil regimens has not appeared to increase the number of responses (45), but controlled studies have not been done and the steroid regimens in the several studies in this analysis were not standardized. The use of cyclosporine in adults with nephrotic FSGS has proved to be problematic, with a lower likelihood of efficacy and a much higher risk of toxicity than in MCD (25).

The influence of race on the natural history and responsiveness to therapy of FSGS has been studied in greater detail in adults than in children. Black adults with NS are more likely than adults in other racial groups to have FSGS (46). Although black patients with FSGS do not necessarily have a poorer overall prognosis (24), collapsing glomerulopathy, a particularly resistant and progressive variant of FSGS, is much more common among black patients than white patients (47).

In any analysis of response to treatment, comparisons of outcomes in adults with those in children may not be valid. Because the major pediatric studies have been limited to steroid-resistant nephrotic FSGS (by ISKDC criteria), pediatric and adult series may be composed of cases with different treatment histories and different levels of resistance to therapy (30,36,38).

**Diffuse Mesangial Proliferation**

DMP is an uncommon biopsy pattern in pediatric NS (5,6). Pathologically, there is mesangial proliferation in all glomeruli on light microscopy, immunofluorescence is either negative or positive predominantly for IgM, and there are no immune complexes on electron microscopy. Mesangial proliferation, characterized by >3 cell nuclei per mesangial stalk on 1- to 2-μm sections, has been distinguished from focal or diffuse mesangial hypercellularity (3 cells/mesangial area) in biopsies otherwise classified as MCD (1). The latter pattern (nil-plus disease) may be more difficult to control than MCD but often has a favorable response to therapy. As originally described (5,6), DMP was much more resistant to oral steroids than MCD but usually resolved whether treated or not (6). There have been significant variations among studies of pediatric NS in the

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**Table 5. Treatment of steroid-resistant pediatric FSGS with M-P pulses: use of alkylating agent therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>% of Patients</th>
<th>Total Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alkylating Agent Used</td>
<td>(NS, CRF,* ESRD)</td>
</tr>
<tr>
<td>Los Angeles (13)</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>Stanford/UCSD&lt;sup&gt;b&lt;/sup&gt; (38)</td>
<td>78</td>
<td>25</td>
</tr>
<tr>
<td>New England (42)</td>
<td>53</td>
<td>47</td>
</tr>
<tr>
<td>Birmingham (41)</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

* CRF, chronic renal failure.
* UCSD, University of California, San Diego.
Table 6. Treatment of pediatric steroid-resistant FSGS: natural history and the effects of cyclophosphamide, cyclosporine/prednisone, and the M-P/triple-therapy protocola

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Complete</th>
<th>Partial</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard prednisone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Churg et al. (ISKDC) (5)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>White et al. (6)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><strong>Cyclophosphamide (ISKDC) (30)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control: 1 year of prednisoneed</td>
<td>21</td>
<td>28</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>cyclophosphamide + prednisone</td>
<td>32</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td><strong>Cyclosporine/prednisone (36)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>35</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td><strong>M-P/triple therapy (38)e</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>66</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

* Steroid resistance defined as proteinuria persistent after 1 month of daily, followed by 1 month of intermittent (3 of 7 days or alternate-day), oral prednisone or prednisolone, except in the cyclophosphamide study, which used 1 month of daily prednisone followed by iv M-P (3 x 1 g/m² over 1 wk). Follow-up: ISKDC cyclophosphamide study, 3 to 102 months (average, 42 to 45 months); M-P/triple therapy, 9 to 150 months (average, 76 months); cyclosporine, 28 to 58 months (average, 38 months).

b Complete response proteinuria: ISKDC and White et al., <4 mg/m²; M-P/triple therapy, urinary protein/creatinine ratio ≤ 0.2; cyclosporine, <10 mg/kg/day. Partial response: ISKDC, abnormal but a decrease of at least one of four categories of proteinuria (<4 to 40, 41 to 100, and >100 mg/m²); M-P/triple therapy, urinary protein/creatinine ratio > 0.2 to 0.5; cyclosporine, proteinuria of 10 to 50 mg/kg/day. Failure: persistent NS or ESRD.

c One year of alternate-day prednisone (40 mg/m²).

d One year of alternate-day prednisone (40 mg/m²) plus 90 days of cyclophosphamide (2.5 mg/kg-day).

e Complete plus partial responses (75%) with M-P/triple therapy are comparable to complete responses (35%) with cyclosporine.

reported frequency and resistance to therapy of DMP (6,48), possibly because of the criteria used to establish the diagnosis. The authors have not seen many cases of true DMP but have not been impressed that it is a spontaneously resolving form of pediatric NS. The few cases that have been treated suggest that M-P/triple therapy is effective in the treatment of NS resulting from DMP.

Other Therapies

The angiotensin-converting enzyme inhibitors (ACEI) are effective antihypertensive agents for patients with NS who develop blood pressure elevation either from their primary renal disease or from steroid therapy. Moreover, patients with FSGS that is incompletely responsive to immunosuppressive therapy may have decreased proteinuria and benefit from slower deterioration of renal function when treated with an ACEI (49). Caution must be used when administration of one of these antihypertensive agents is begun, to avoid hemodynamic compromise of renal function by vigorous ACEI or combined ACEI/diuretic therapy.

Thromboembolic disease is a relatively uncommon, but very dangerous, complication of the NS. Preventive strategies have not been systematically studied, but the authors use the following precautions: (1) avoidance of aggressive diuretic therapy, particularly when an immunosuppressive regimen may soon produce remission of the NS; (2) the concomitant use of intravenous albumin to prevent or correct hypovolemia and hemoconcentration when aggressive diuresis is necessary; and (3) the use of small doses of aspirin for patients with NS complicated by hemoconcentration and/or thrombocytosis.

The chronic hypertriglyceridemia and hypercholesterolemia of treatment-resistant NS may contribute to later atherosclerotic disease and deterioration of renal function. A preliminary report of lowering of plasma lipids by a hydroxymethylglutaryl-coenzyme A reductase inhibitor in steroid-resistant NS suggests a potentially valuable approach to this long-term complication (50).

Summary

This review compares the biopsy patterns, complications, responses to therapy, and long-term outcomes of idiopathic NS in children and adults. On first examination, distinctions between the pediatric and adult diseases seem more quantitative than absolute. However, underlying determinants of outcome, including immunocompetence, growth, maturity, and senescence, can present very different challenges for pediatricians and internists.

The major biopsy patterns in pediatric NS include MCD, FSGS, and DMP. MCD is overwhelmingly the most frequent and most steroid-responsive of the three but commonly presents problems of massive edema, serious bacterial infections, and multiple relapses. Because of the prompt response of pediatric MCD to corticosteroids, steroid resistance in children has generally been defined as persistence of proteinuria after 1 month of daily followed by 1 month of intermittent prednisone administration. By this criterion, nephrotic FSGS is usually steroid-resistant and, if not controlled by more aggressive therapy, typically progresses to ESRD. DMP is commonly steroid-resistant but may slowly resolve. It is not clear to what extent remissions of DMP represent a delayed response to steroids or would have occurred without treatment. Biopsies showing a few globally obsolescent glomeruli or mild mesan-
glial hypercellularity may be associated with greater difficulty in management but have been included in the broad category of MCD. Moreover, evolution of patterns in serial biopsies, variable steroid-responsiveness of FSGS and DMP, and progression of some cases of MCD to ESRD suggest common features in the three major categories.

Among adults with idiopathic NS, FSGS is the most frequent biopsy pattern, followed by MN (which is rare in children) and then by MCD. In contrast to its pediatric counterpart, MCD in adults is less regularly and more slowly responsive to corticosteroids and in the elderly is more commonly associated with hypertension and renal failure. MCD in adults is less likely to relapse once remission is achieved. Adults with FSGS present less commonly with severe edema than do children with this lesion. Although children and adults with FSGS present similar challenges of resistance to therapy and loss of renal function, the more aggressive oral steroid regimens used by internists preclude strict comparisons between pediatric and adult series. There is insufficient information to support a systematic analysis of DMP in adults.

Cytotoxic agents and cyclosporine have been used with varying success in children and adults with difficult cases of NS. In MCD, an alkylating agent can increase the likelihood and duration of remission. Cyclosporine can also improve control in MCD, but continued treatment is often needed to maintain remission. Significant control of steroid-resistant FSGS has not been achieved with limited courses of an alkylating agent or cyclosporine. Longer courses of either of these immunosuppressants, especially when combined with intermittent steroid administration, can produce more complete and/or more sustained remissions. However, cyclosporine nephrotoxicity is more severe in FSGS than in MCD and in steroid-resistant than in steroid-dependent NS, regardless of biopsy pattern. A protocol combining iv M-P pulses, alternate-day prednisone, and an alkylating agent in steroid-resistant pediatric FSGS has produced the highest percentage of sustained remissions with normal renal function, of all reported regimens. Controlled trials of this and other combined-drug protocols are needed in children and adults.

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