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Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease

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Abstract. If not aggressively treated, oral steroid-resistant (SRst) nephrotic focal segmental glomerulosclerosis (FSGS) is likely to progress to end-stage renal failure. Three observations challenge the conclusion of the International Study of Kidney Diseases in Children (ISKDC) that SRst FSGS is unresponsive to further immunosuppression: (1) The ISKDC definitions of response and relapse, which fit the patterns in minimal change disease, precluded appropriate recognition of partial or gradual responses. (2) In two ISKDC studies, a small number of children with FSGS in one case, and the use of a year of alternate-day prednisone as a control in the other, may have obscured the effects of cyclophosphamide. (3) Recent studies of more aggressive therapies have provided strong evidence of benefit. High-dose methylprednisolone infusion therapy, with alternate-day prednisone alone or with alternate-day prednisone plus an alkylating agent (the M-P/triple therapy protocol) has achieved sustained, complete remissions with stable renal function in 66% of children with SRst FSGS, and near-complete resolution of proteinuria in another 9%. Cyclosporine (CsA) plus alternate-day prednisone has produced complete or near-complete remissions in 35% of similar cases. Whether or not controlled studies will confirm the apparently greater efficacy of the M-P/triple therapy protocol, the favorable outcomes with both the M-P and the CsA regimens support the conclusion that a conservative approach to SRst FSGS is no longer appropriate.

Key words: Steroid-resistant glomerulosclerosis – Aggressive treatment

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Introduction

The nephrotic syndrome (NS), typically presenting with edema, heavy proteinuria, and hypoalbuminemia, is the most common manifestation of glomerular disease in children. Minimal change disease (MCD) is diagnosed in 85%–90% of biopsies from random new cases of pediatric NS [1, 2]. Although focal segmental glomerulosclerosis (FSGS) is found in only 5% of random cases of recent-onset NS [1, 2], and possibly in a similar number of later biopsies [3–7], it is the most common glomerulopathy causing end-stage renal disease (ESRD) in children [8], and the most common cause of serious recurrent disease after renal transplantation (46%) in children in the United States [8, 9].

The development of a focal sclerosing glomerulopathy in pediatric lipoid nephrosis was recognized by Fahr in 1925 [10]. A pattern of evolution was later described by Rich [11] in a retrospective analysis of autopsy material from 18 children who died with the NS, many in the pre-antibiotic era. In those who had developed fatal acute infections, mostly within a year after diagnosis of the NS, FSGS was absent or was seen only in some juxtamedullary glomeruli. Children who died with hypertension or uremia, generally more than a year after diagnosis, had more widespread and total glomerular obliteration. Although a pattern of evolution of FSGS was suggested by this study, the post-mortem source of the cases precluded any firm conclusion.

Churg et al. [1] and White et al. [2] 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. McGovern [12], Hayslett et al. [4], and Siegel et al. [3, 5] described a number of cases with evolution to resistant FSGS and ESRD after many years of steroid-responsive (SRsp) NS and/or biopsy-diagnosed MCD. 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 will be needed before this question can be resolved.

Table 1. Intravenous methylprednisolone (M-P pulse) regimen

Week	M-P[a]	*n*	Prednisone
1– 2	30 mg/kg thrice weekly	6	None
3–10	30 mg/kg per week	8	2 mg/kg every other day[b]
11–18	30 mg/kg per 2 weeks	4	± Taper
19–50	30 mg/kg per 4 weeks	8	Slow taper
51–82	30 mg/kg per 8 weeks	4	Slow taper

[a] Maximum dose 1,000 mg
[b] Maximum dose 60 mg

The International Study of Kidney Diseases in Children Reports

A series of prospective, multicenter cooperative studies by the International Study of Kidney Diseases in Children (ISKDC) in the 1970s established definitions, clinicopathological correlations, and recommendations for therapy that provided a basis for diagnosis and management of pediatric NS [1, 2, 13]. The study criteria permitted systematic analysis of data from different centers on the treatment of pediatric MCD, but left uncertainties regarding the overall "natural history" and treatment of pediatric FSGS.

Idiopathic pediatric NS was defined as the combination of heavy proteinuria ($\geq$ 40 mg/m^2 per hour), hypoalbuminemia ($\leq$ 2.5 g/dl), and usually edema, in a child between 3 months and 16 years of age without clinical or laboratory evidence of a primary disease known to cause proteinuria [13]. The three major biopsy categories of idiopathic NS were MCD, FSGS, and DMP (diffuse mesangial proliferation, characterized by the finding of $\geq$ 4 cells per peripheral mesangial area) [1, 14]. Focal glomerular or focal global obsolescence, in the absence of segmental sclerosis or significant tubular atrophy and interstitial fibrosis, was recognized as a distinct and far less-ominous pattern than focal segmental hyalinosis [1, 15], which is generally identified today as FSGS [16]. Mild mesangial hypercellularity (3 cells per peripheral mesangial area), sometimes seen as a focal or diffuse finding in glomeruli with MCD or FSGS, may be predictive of a more guarded prognosis [14, 17]. Several other pathological features and/or variants of FSGS, recently reviewed elsewhere [16, 18], will not be included in the present discussion.

In the ISKDC therapeutic trials [13], nephrotic-range and normal levels of proteinuria were defined as $\geq$ 40 and $\leq$ 4 mg/m^2 per hour, respectively. A response to therapy was defined as the elimination, or more accurately the reduction to normal, of proteinuria in all of at least three urine samples obtained within a week. Non-response or resistance to therapy was the persistence, and relapse the return, of proteinuria ($>$4 mg/m^2 per hour) in three or more samples within a week. Children were identified as resistant to oral corticosteroid therapy (SRst) if they had abnormal proteinuria after 4 weeks of 60 mg/m^2 per day of prednisone in divided doses, followed by at least 40 mg/m^2 intermittently (3 consecutive days out of 7) for another 4 weeks.

By these criteria, MCD was characterized as almost always SRsp but commonly relapsing, FSGS as infrequently SRsp and commonly progressing to total steroid resistance and renal failure within several years, and DMP as usually SRst but capable of recovering completely [1, 2]. In further studies of the effects of prednisone (intermittent or alternate-day) plus a cytotoxic agent, compared with prednisone alone, the ISKDC reported no added benefit from azathioprine (60 mg/m^2 per day for 90 days) [13] or cyclophosphamide ($\geq$ 2.5 mg/kg body weight daily for 90 days) [19, 20] in the treatment of FSGS.

The ISKDC concluded that cyclophosphamide had no role in the treatment of FSGS [20]. Following the early presentations of this interpretation [19], many renal centers abandoned further immunosuppressive therapy in children with SRst 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 [5, 15, 21–24].

High-dose methylprednisolone infusion therapy

Based on their partial success with combined alkylating agent/alternate-day prednisone therapy of SRst FSGS, the Pediatric Renal Services of Stanford University and the University of California at San Diego (SU/UCSD) began a study of a modification of the methylprednisolone (M-P) "pulse" regimen of Cole et al. [25] in the treatment of this disease [26]. Because several FSGS patients responded initially with only partial reductions of proteinuria (average 60%, range complete remission to a 30% increase), the regimen of six pulses over 2 weeks was extended by the addition of a series of intravenous pulses at increasing intervals (Table 1).

An alkylating agent was added in children not fully controlled with that combination, 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; (3) a urine protein/creatinine concentration ratio (Pr_u/Cr_u) $\geq$ 2 at week 10 or later. The alkylating agent, chosen at the discretion of the individual nephrologist, was either cyclophosphamide (2.0–2.5 mg/kg per day) or chlorambucil (0.18–0.22 mg/kg per day), based on lean, non-edematous body weight, for 8–10 weeks. The longer courses of treatment were used in patients who responded more slowly. White blood cell (WBC) counts were measured weekly, and the alkylating agent temporarily withheld or its dosage reduced for a WBC count $\leq$ 4,000/mm^3 or neutrophil count $\leq$ 2,000/mm^3.

If the cyclophosphamide or chlorambucil was started at the end of the first 2 weeks of the protocol, weekly M-P pulses were given until the end of the alkylating therapy, then continued as in Table 1. 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 re-

Table 2. M-P pulse/triple therapy protocol. Effects on proteinuria in steroid-resistant pediatric FSGS[a]

	Pr_u/Cr_u	*n*	%
Remission, off therapy	≤0.2	21/32	66%
Mild proteinuria	>0.2–0.5	3/32	9%
Moderate proteinuria	>0.5–1.9	2/32	6%
Nephrotic proteinuria	≥2.0	6/32	19%

FSGS, Focal segmental glomerulosclerosis; Pr_u/Cr_u, urine protein/creatinine ratio

[a] Data from reference [29]

lapsed during the protocol or failed to achieve a Pr_u/Cr_u ratio ≤ 1.0, a second course of alkylating agent was given. 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 the M-P pulse or triple therapy only as needed. In all cases, alternate-day prednisone was used during M-P pulse therapy, as described in Table 1.

As in a group of children with serious rheumatological diseases treated with more prolonged and aggressive M-P pulse therapy [27], complications of this regimen were limited in frequency (delayed growth in 17%, hypertension in 17%, cataracts in 22%) and severity [28], presumably because of the avoidance of daily prednisone once the M-P regimen was begun.

Outcome: the M-P/triple therapy protocol

Thirty-two patients (3 black, 5 Hispanic, 21 white, 2 Pacific Islander, 1 Asian) treated with this regimen were evaluated after 0.75–12.5 (average 6.33) years [29]. Twenty-five children (78%) received an alkylating agent: one course in 14 cases, two in 8 cases, three in 1 case; and four in 2 cases. Those receiving three or four courses had been given an alkylating agent, usually in inadequate dosage, before M-P/triple therapy and received only one or two courses under the protocol. Except for the most recent case, who was followed for 9 months, all patients were followed for at least 2 years.

The numbers of patients without and with abnormal proteinuria on most recent follow-up are shown in Table 2. Two-thirds were in complete remission and receiving no therapy. Four of these had relapsed after completing the protocol but responded to retreatment: three with M-P plus prednisone, and one with triple therapy. Although several children had required antihypertensive therapy during the protocol, all responders had normal blood pressures without antihypertensives on follow-up. Creatinine clearances (C_{Cr}), estimated from serum creatinine concentrations using the Schwartz formula [30, 31], were ≥ 80 ml/min per 1.73 m² in all 21 patients without proteinuria. In these 21 the most recent Pr_u/Cr_u averaged 0.06 ± 0.02 (SEM), serum albumin was 4.1 ± 0.2 g/dl, and C_{Cr} was 122 ± 6 ml/min per 1.73 m². Three children with persistent proteinuria also had normal C_{Cr} (11.5, 6, and 2.3 years after the start of therapy). All 6 patients with Pr_u/Cr_u remaining ≥ 2.0 developed chronic renal failure or ESRD, as did 1 with a Pr_u/Cr_u of 0.4, after 12 years, and 1 with a Pr_u/Cr_u of 1.1, after 5.3 years.

The magnitude of proteinuria, severity of hypoalbuminemia, and C_{Cr} at the start of therapy were not reliable predictors of outcome [29]. The response to the initial six M-P pulses was typically greater in patients who later achieved partial or complete remissions, and persistent moderate or heavy proteinuria 12–18 months after entry into the protocol carried an almost certain prognosis of progression to renal failure.

Escape from control during or after the weekly M-P treatments was not predictive of unresponsiveness to the addition of an alkylating agent. Moreover, some disappointing initial responses were followed by excellent outcomes. One child, whose proteinuria increased by 30% during the initial six M-P infusions, soon entered a nearly complete, sustained remission. Another, who had diuresed on prednisone but whose proteinuria decreased by only 7% in the first 2 weeks of M-P, gradually responded during an extended regimen of 3 months of cyclophosphamide (154 mg/kg total dose) with weekly M-P infusions, 2 more months of weekly and 12 months of biweekly M-P infusions, with slow tapering of alternate-day prednisone. Six years following completion of this course of therapy he remains in complete remission, normotensive, with a normal glomerular filtration rate (GFR), and without sequelae of his disease or its treatment. His height remained between the 50th and 75th percentiles for age throughout and subsequent to therapy.

Efficacy of other M-P regimens

Three other studies using M-P infusions in patients with SRst FSGS, which produced varying results, require careful analysis. Ten children (7 black, 3 white) were treated at the University of Alabama at Birmingham and followed for 3–64 (mean 48) months [32]. After withdrawal of oral steroid therapy for 1 month, the patients received infusions of 20 mg/kg of M-P at the intervals shown in Table 1 up to 18 weeks, and then monthly. Alternate-day prednisone (40 mg/m²) was given between the eight weekly M-P treatments only. Two children entered complete remission (proteinuria ≤ 0.2 g/m² per day) and then relapsed; they were retreated once with M-P plus added chlorambucil (0.2 mg/kg per day for 8 weeks). Two children whose proteinuria decreased to <1.0 g/m² per day, and two who had 43% and 77% reductions of proteinuria (but with levels >1.0 g/m² per day), received 3–4 months in total of M-P therapy without an alkylating agent. All six relapsed or remained nephrotic, and four developed ESRD. The remaining four children did not respond to 1–3 months of M-P infusions and did not receive an alkylating agent; all four remained proteinuric and two developed ESRD.

Fifteen children (1 black, 1 Hispanic, 13 white) treated in seven New England centers were retrospectively analyzed 0–36 months after they received 3–30 (mean 15) infusions of 20–33 (mean 28) mg/kg of M-P [33]. Treatment was terminated early in 4 cases: 2 because of sepsis (1 fatal) and 2 by patient choice. Eight patients were given an

Table 3. Treatment of steroid-resistant pediatric FSGS. Use of alkylating agent therapy with M-P pulses

	Alkylating agent used	Total failures (NS, CRF, ESRD)
CHLA[a]	100%	18%
Stanford/UCSD [29]	78%	25%
New England [33]	53%	47%
Birmingham [32]	20%	100%

NS, Nephrotic syndrome; CRF, chronic renal failure; ESRD, end-stage renal disease; CHLA, Children's Hospital of Los Angeles; UCSD, University of California at San Diego

[a] Data in the present report, from CHLA, provided by E. L.

alkylating agent. Patient status at follow-up was: 4 complete remissions, 4 partial remissions, 2 nephrotic, 1 chronic renal failure, 3 in ESRD, and 1 dead.

Eleven children (1 black, 6 Hispanic, 4 white) were treated at the Children's Hospital of Los Angeles (CHLA). All received M-P, alternate-day prednisone, and chlorambucil (0.2 mg/kg per day for 8 weeks). Initially, 7 entered complete remission, 2 achieved partial remission, and 2 were unresponsive. Their status at follow-up, 12–79 (mean 40) months after treatment, was: 5 in sustained remission; 3 responded and relapsed, then responded to cyclosporine (2 cases) or prednisone (1 case); 1 mildly proteinuric; 1 nephrotic with chronic renal insufficiency; and 1 in ESRD.

A pattern can be seen in comparing these three M-P regimens with one another and with the M-P/triple therapy protocol. Two characteristics distinguished the Birmingham series from the other three. First, 70% were black, a feature that has been associated with an unfavorable outcome in SRst FSGS [34]. Second, the regimen used in this series was very conservative, with less aggressive use of oral and intravenous steroids than in the M-P/triple therapy protocol, no retreatment after partial initial responses followed by increases of proteinuria, and the use of an alkylating agent in only two of ten cases – and for only one course in those two [29, 32].

The New England series was published only in abstract form, and detailed comparison with the other studies is not possible. It is not clear whether the overall outcome would have been better if the 3 patients withdrawn from therapy had completed treatment. However, the 15 M-P infusions given was less than half the number in the M-P/triple therapy protocol (Table 1), and an alkylating agent was used in a smaller percentage of patients. Although less favorable than in the SU/UCSD and CHLA series, the overall outcomes were comparable to those achieved with cyclosporine (CsA) plus prednisone [7, 33]. The CHLA series, which followed the M-P/triple therapy protocol most closely, had a comparably high proportion of successful outcomes and low frequency of persistent NS or renal failure.

Table 3 shows a direct relationship in the four M-P therapy series between the percentage of children receiving an alkylating agent and the percentage of successful outcomes. Only 2 cases in these series represented failures of therapy before an alkylating agent could have been used: (1) a child in Birmingham who deteriorated rapidly [32] and (2) a child in New England who died of septicemia [33]. Because the M-P/triple therapy protocol requires the addition of an alkylating agent in response to persistent or recurrent heavy proteinuria, the frequency of alkylating agent use in the four series appears to represent a measure of close adherence to the protocol.

CsA regimens

Because of its efficacy as an immunosuppressive agent in solid organ and bone marrow transplantation, CsA has been widely evaluated in a variety of immunologically mediated diseases. The effects of CsA on SRsp or SRst NS have been a major focus of study. The efficacy and toxicity of CsA in treating pediatric NS have been discussed in detail elsewhere [35, 36], and will therefore be reviewed only briefly here.

Different studies of CsA in pediatric NS have shown conflicting results, but a consensus has emerged that it is more effective in SRsp/dependent than in SRst disease, that the efficacy of corticosteroids is a more important determinant of responsiveness to CsA than the renal biopsy, and that there is a high rate of relapse after discontinuation of CsA [18, 35, 36]. Combined use with low-dose or alternate-day steroids increased the effectiveness of CsA in producing sustained reductions of proteinuria in SRst disease, including FSGS [7], but not in all studies [37].

The French Society of Pediatric Nephrology [7] treated 20 cases of SRst FSGS with 6–12 months of $\leq$ 200 mg/m^2 per day of CsA plus prednisone, 30 mg/m^2 daily for 1 month then every other day. After 3 years of follow-up results were: complete or nearly complete remissions (proteinuria $<$10 mg/kg per day) 35%, moderate proteinuria 5%, nephrotic-range proteinuria without ESRD 30%, and ESRD 30% (Table 4).

Comparative studies are needed

There are few controlled studies of the treatment of SRst FSGS. Results in the ISKDC study of azathioprine were disappointing [13]. Although the ISKDC concluded from two studies that cyclophosphamide was also ineffective against SRst FSGS, a salutary effect of the alkylating agent may have been obscured in one case by a small sample size and in the other case by the use of an extended course of prednisone as the control treatment. In the first study three of seven cyclophosphamide-treated and none of three control children with "focal lesions" cleared their proteinuria [19]. In the second study complete remissions were seen in 27% of children in both prednisone (1 year) and cyclophosphamide/prednisone (90 day) treatment groups [20], while the outcome in earlier trials had been uniformly poor in FSGS resistant to 2 months of the steroid (Table 4) [1, 2]. The partial efficacy of a longer course of prednisone is supported by recent studies in adults with SRst FSGS [38].

Lieberman and Tejani [39] showed a significant reduction of proteinuria by CsA by the end of a 6-month controlled study of pediatric SRst FSGS. There was no sys-

Table 4. Treatment of pediatric steroid-resistant FSGS[a]: natural history and the effects of cyclophosphamide, cyclosporine/prednisone, and the M-P/triple therapy protocol[b]

	No. of patients	Responses[c] Complete	Partial	Failure
Standard prednisone				
Churg et al. (ISKDC) [1]	10	0%		100%
White et al. [2]	10	0%		100%
Cyclophosphamide (ISKDC) [20]				
Control: prednisone (1 year)[d]	26	27%	8%	65%
Cyclophosphamide/prednisone[e]	37	27%	5%	68%
Cyclosporine/prednisone [7]	20	35%	5%	60%
M-P/triple therapy protocol [29][f]	32	66%	9%	25%

ISKDC, International Study of Kidney Diseases in Children

[a] Steroid resistance: urine protein persistent after 1 month of daily, followed by 1 month of intermittent (3/7 days or alternate-day) oral prednisone or prednisolone, except in cyclosporine study, which used 1 month of daily prednisone followed by intravenous M-P, 3×1 g/m^2 over 1 week

[b] Follow-up: 1–7 years in ISKDC cyclophosphamide study, 28–58 (average 38) months in cyclosporine study, 9–150 (average 76) months in M-P/triple therapy study

[c] Complete response proteinuria: ISKDC and White et al. ≤4 mg/m^2 per day; cyclosporine study <10 mg/kg per day; M-P study Pr_u/Cr_u ratio ≤0.2. Partial response: defined as "improved" by ISKDC; proteinuria 10–50 mg/kg per day in cyclosporine study; Pr_u/Cr_u >0.2–0.5 in M-P study. Failure: persistent nephrotic syndrome or ESRD

[d] 1 year of prednisone, 40 mg/m^2 on alternate days

[e] 90 days of cyclophosphamide, 2.5 mg/kg per day, plus prednisone, 40 mg/m^2 (alternate-day)

[f] "Complete" response (35%) in cyclosporine study comparable to "complete + partial" responses (75%) in M-P/triple therapy study

tematic follow-up of this effect. There are no controlled studies of the effects of the M-P/triple therapy protocol in pediatric SRst FSGS. Comparison of outcomes with the Protocol [29] and CsA/prednisone [7] shows higher rates of complete remission and normal renal function and lower rates of nephrotic-range proteinuria and renal failure ($P < 0.001$ by chi-squared test) with the Protocol (Table 4). Considering the poor prognosis of SRst FSGS without therapy, and the cost and complexity of controlled multicenter trials, it is tempting to rely on the apparent superiority of the Protocol shown in the available uncontrolled studies. However, there are several potential risk factors for progression in FSGS, and there is not enough uniformity of detail to allow reliable comparisons between the different reports.

One major determinant is race [16, 34], with black and Hispanic children reported to have poorer outcomes than white children (78% vs. 33% ESRD after 8.8 ± SD 4.8 years). Using their own historical controls in black and Hispanic children with SRst FSGS [34], Ingulli and Tejani [40] reported a partial reduction of proteinuria and a decreased frequency of ESRD (24%) after 8.4 years of aggressive CsA therapy. The French Pediatric Nephrology Society study of CsA plus prednisone [7], discussed above and shown in Table 4, included no black or Hispanic children (Patrick Niaudet, personal communication).

The SU/UCSD and CHLA studies, which used essentially the same M-P/triple therapy protocol, found the following outcomes in different ethnic groups: (1) persistent proteinuria with decreased GFR, black 2 of 4 (50%); Hispanic 1 of 10 (10%); white/other 7 of 29 (24%) and (2) ESRD, black 0 of 4 (0%); Hispanic 0 of 10 (0%); white/other 4 of 29 (14%). The number of black children is too small for meaningful interpretation. It remains to be determined whether the largely Mexican ethnicity of Hispanics in California accounts for their favorable outcomes compared with the Hispanic children in New York [34, 40].

While there is disagreement over other factors predictive of poor outcomes in FSGS [16, 41–43], some appear likely to be important. Older or post-pubertal age in black patients [16] and younger age in European populations [44] may identify patients at increased risk. Familial FSGS may have a poor prognosis [45], as illustrated by the two familial cases from different kindreds in the 43 children treated with M-P/triple therapy at SU, UCSD, and CHLA, who accounted for 2 of 10 of the treatment failures.

Early biopsy findings suggesting a poor prognosis include mesangial hypercellularity or proliferation [17] and glomerular collapse [46]; extensive glomerular obliteration and interstitial fibrosis are signs of advanced disease [41, 47]. Diagnosis on early biopsy is an unfavorable correlate of progression in the first years after onset of the NS [1, 2]; a severe NS, especially with extreme hypercholesterolemia, can be another unfavorable early finding [47].

FSGS has a unique characteristic that could influence apparent prognosis or responsiveness to therapy in different centers or at different times. The adequacy of size and processing of biopsy specimens, which was rarely documented in past clinical reports, can affect the likelihood of early recognition of FSGS. Examination of greater numbers of glomeruli [48] or a series of evenly spaced sections [49, 50] can increase the probability of diagnosing FSGS by a factor of more than 2–4. Churg et al. [1] suggested that some children with very mild FSGS might have been classified as MCD in the ISKDC clinicopathological study of recent-onset NS, and that these were the children classified as having MCD who later developed steroid resistance and ESRD. Under these circumstances, the use of more optimal procurement and processing of biopsies in one center could shift its spectrum of FSGS to include initially more responsive or more slowly progressive disease.

The question: how to treat, not whether to treat

The achievement of both complete remissions and prolonged renal survival after complete or partial remissions provides a basis for recognizing that SRst FSGS can be controlled by immunosuppression (Table 4). High-dose M-P infusion therapy, with alternate-day prednisone alone or with alternate-day prednisone plus cyclophosphamide or chlorambucil (the M-P/triple therapy protocol), has achieved sustained, complete remissions with stable renal function in 66% of children with SRst FSGS, and near-complete resolution of proteinuria in another 9%. Toxic side effects have been infrequent and mild. CsA plus alternate-day prednisone has produced complete or near-complete remissions in 35% of similar cases. Both CsA and M-P/triple therapy regimens have been successfully applied in several centers.

The following elements of the M-P/triple therapy protocol deserve emphasis: (1) It is a graded regimen, used only in SRst cases and using an alkylating agent only for specific indications. (2) The M-P pulses often produce earlier partial or complete control of edema than is achieved by conventional oral steroid plus alkylating agent therapy in SRst NS, generally reducing the risk of complications while awaiting resolution of proteinuria. (3) Alkylating agents, the most successful class of medications in producing prolonged or sustained remissions in difficult cases of MCD [19, 51–53], have an additive effect with M-P plus prednisone in many resistant cases of FSGS. (4) Where the protocol has been correctly applied, it has been more effective than the CsA regimens.

Whether or not future studies confirm the apparently greater efficacy of the M-P/triple therapy protocol, the favorable outcomes with both the M-P and the CsA regimens support the conclusion that a conservative approach to SRst FSGS is no longer appropriate.

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Literature abstract

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Congenital nephrotic syndrome

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Congenital nephrotic syndrome (CNS) can be caused by neonatal infections, renal diseases which exceptionally occur in early infancy and syndromes with a renal histology of DMS. The most common CNS is the Finnish-type (CNF), an autosomal recessively inherited disease characterized by intrauterine onset of massive proteinuria. The CNF gene has been localized to the long arm of chromosome 19, but the pathogenesis remains unclear. Forty-six CNF patients have been treated at our institution. The diagnosis was based on family history, severe proteinuria of intrauterine onset (serum albumin <10 g/liter at presentation and urinary protein >20 g/liter when serum albumin was corrected to >15 g/liter), a large placenta ($>25\%$ of birth wt), exclusion of other CNS-types and normal glomerular filtration rate during the first six months. Treatment included i.v. albumin substitution, optimal nutrition, thyroxine and anticoagulation. Forty-one patients had been nephrectomized bilaterally at a mean age of 1.2 years, and after 3 to 25 months on peritoneal dialysis renal transplantation (Tx) had been performed on 34 who were a mean age of 2.2 years. Growth and development has been normal. Patient survival after Tx was 97%, graft survival 94%, 81% and 81% one, three and five years after Tx (50% cadaver grafts). Mean GFR was 75 ml/min/1.73 m^2 after three years, mean height SDS –1.42, and the nine oldest patients attend school in a normal class.