Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

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ABSTRACT

Prolonged prednisolone treatment for the initial episode of childhood nephrotic syndrome may reduce relapse rate, but whether this results from the increased duration of treatment or a higher cumulative dose remains unclear. We conducted a randomized, double-blind, placebo-controlled trial in 69 hospitals in The Netherlands. We randomly assigned 150 children (9 months to 17 years) presenting with nephrotic syndrome to either 3 months of prednisolone followed by 3 months of placebo (n=74) or 6 months of prednisolone (n=76), and median follow-up was 47 months. Both groups received equal cumulative doses of prednisolone (approximately 3360 mg/m²). Among the 126 children who started trial medication, relapses occurred in 48 (77%) of 62 patients who received 3 months of prednisolone and 51 (80%) of 64 patients who received 6 months of prednisolone. Frequent relapses, according to international criteria, occurred with similar frequency between groups as well (45% versus 50%). In addition, there were no statistically significant differences between groups with respect to the eventual initiation of prednisolone maintenance and/or other immunosuppressive therapy (50% versus 59%), steroid dependence, or adverse effects. In conclusion, in this trial, extending initial prednisolone treatment from 3 to 6 months without increasing cumulative dose did not benefit clinical outcome in children with nephrotic syndrome. Previous findings indicating that prolonged treatment regimens reduce relapses most likely resulted from increased cumulative dose rather than the treatment duration.


Nephrotic syndrome (NS) is the most common manifestation of glomerular disease in childhood. Despite its relatively low incidence of 1–7 in 100,000 children,1,2 NS poses recurring challenges to many clinicians.

Corticosteroids induce remission of proteinuria in 90%–95% of patients.3–6 Despite this high initial response rate, relapses occur in 60%–90% of the initial responders.5,7 The disease progresses to frequent relapses, often accompanied by steroid dependence, in around 20%–60% of patients. Recurrent or continuous corticosteroid therapy in these patients frequently results in corticosteroid toxicity.1 This finding calls for the improvement of existing treatment regimens, for which no international consensus currently exists.8

The present treatment modalities for initial childhood NS are mostly based on reports by the International Study of Kidney Disease in Children and...
the Arbeitsgemeinschaft für Pädiatrische Nephrologie. Currently used regimens vary in dose and duration (Supplemental Table 1). The regimen prescribed in The Netherlands is made up of 60 mg/m² prednisolone daily for 6 weeks followed by 40 mg/m² prednisolone on alternate days for 6 weeks. The cumulative dose of this regimen is 3360 mg/m².

In 2000, Hodson et al. performed a meta-analysis of corticosteroid therapy in childhood NS to evaluate the potential benefits of different corticosteroid regimens. Based on the analysis of seven clinical trials in patients with an initial episode of NS, it was concluded that the risk of relapse was significantly reduced by prednisolone regimens that were both longer and more intensive. Additional analysis suggested that the benefits were more likely to be related to the increased duration of the treatment than the higher cumulative dose. However, collinearity between treatment duration and dose prevented the work by Hodson et al. from drawing definite conclusions. A subsequent study by Hiraoka et al. comparing 3 months of prednisolone treatment to 6 month of treatment was also inconclusive. In this study, prolonged treatment reduced the relapse rate in children ages under 4 years; however, this intervention also consisted of a higher cumulative dose. The independent effects of treatment duration and cumulative dose, thus, remained undetermined.

Based on these data, we designed a study protocol to explore the independent effect of treatment duration. In the present study, we hypothesized that prolongation of a 3-month initial prednisolone treatment to 6 months using equal cumulative doses would reduce the occurrence of frequently relapsing NS (FRNS) without increasing adverse effects.

RESULTS

From February of 2005 to December of 2009, 212 patients were evaluated for eligibility. Participants and nonparticipants were similar in terms of sex and age at onset (Supplemental Table 2); 150 patients from 69 hospitals (60 general and 9 university hospitals) were randomized to either 3 months prednisolone followed by 3 months placebo or 6 months prednisolone (Figure 1). In both groups, 12 patients could not start trial medication because of either steroid resistance or withdrawn consent. These patients were excluded from the analysis. Median follow-up was 47 months in the 3-month group.
(interquartile range [IQR]=32–60) and 47 months in the 6-month group (IQR=37–60).

Induction therapy and trial medication were administered within a total of 24 weeks in both groups. The prescribed cumulative dose of prednisolone in the 6-month group depended on the number of days to remission, which is shown in Figure 2. Because the median number of days to remission was 10 days in both groups (IQR=8–14 and 7–14 days, respectively), the median prescribed cumulative prednisolone dose was 3360 mg/m² in the 3-month group and 3390 mg/m² in the 6-month group. Baseline characteristics revealed no relevant differences between the two groups (Table 1); 65% of the study population was of Western European descent.

FRNS was scored and analyzed according to strict definitions (strict FRNS) as well as a broader, clinically relevant definition (clinical FRNS) as explained below. The cumulative incidences of FRNS did not reveal a benefit of the 6-month regimen, regardless of the definition used (Table 2). Strict FRNS was found in 28 of 62 children (45%) in the 3-month group and 32 of 64 children (50%) in the 6-month group (log rank test: \( P=0.91 \)) (Figure 3A and Table 3). Three patients in the 3-month group and six patients in the 6-month group did not meet the strict criteria for FRNS, but they were characterized as having clinical FRNS (Supplemental Table 3B). Accordingly, clinical FRNS occurred in 31 of 62 children (50%) in the 3-month group versus 38 of 64 children

![Figure 2](image_url)

**Figure 2.** Treatment regimens were built up of comparable cumulative doses of prednisolone. The dotted line represents the median number of days to remission (10 days in both groups), the gray area represents the IQR. Doses are in mg/m². AD, alternate days; D, daily.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=126)</th>
<th>3 Months Prednisolone (n=62)</th>
<th>6 Months Prednisolone (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>86 (68)</td>
<td>39 (63)</td>
<td>47 (73)</td>
</tr>
<tr>
<td>Age (yr) median (IQR)</td>
<td>4.2 (3.2–6.2)</td>
<td>4.7 (3.2–5.8)</td>
<td>3.8 (3.2–6.4)</td>
</tr>
<tr>
<td>BP* (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, Z-value</td>
<td>1.7±1.3</td>
<td>1.7±1.3</td>
<td>1.6±1.3</td>
</tr>
<tr>
<td>Diastolic, Z-value</td>
<td>1.6±1.1</td>
<td>1.7±1.3</td>
<td>1.6±1.0</td>
</tr>
<tr>
<td>Serum albumin (g/L) median (IQR)</td>
<td>14.0 (10.0–16.2)</td>
<td>14.0 (10.0–17.0)</td>
<td>13.4 (10.0–16.0)</td>
</tr>
<tr>
<td>Microscopic hematuria*, n (%)</td>
<td>40 (33)</td>
<td>19 (32)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Hospital, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>14 (11.1)</td>
<td>5 (8.0)</td>
<td>9 (14.1)</td>
</tr>
<tr>
<td>General</td>
<td>112 (88.9)</td>
<td>57 (92.0)</td>
<td>55 (85.9)</td>
</tr>
<tr>
<td>Descent, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western European</td>
<td>83 (65.9)</td>
<td>46 (74.2)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Non-Western European</td>
<td>16 (12.7)</td>
<td>6 (9.7)</td>
<td>10 (15.6)</td>
</tr>
<tr>
<td>Mixed</td>
<td>13 (10.3)</td>
<td>3 (4.8)</td>
<td>10 (15.6)</td>
</tr>
<tr>
<td>Not reported</td>
<td>14 (11.1)</td>
<td>7 (11.3)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Quarterly distribution of disease onset, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January to March</td>
<td>25 (19.8)</td>
<td>14 (22.6)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>April to June</td>
<td>24 (19.0)</td>
<td>11 (17.7)</td>
<td>13 (20.3)</td>
</tr>
<tr>
<td>July to September</td>
<td>40 (31.7)</td>
<td>19 (30.6)</td>
<td>21 (32.8)</td>
</tr>
<tr>
<td>October to December</td>
<td>37 (29.4)</td>
<td>18 (29.0)</td>
<td>19 (29.7)</td>
</tr>
</tbody>
</table>

*Lowest BP reported in patient’s chart at diagnosis. Z-values are adjusted for sex, age, and height. ^3
bData available for 123 of 126 patients.
Data available for 61 of 62 patients.
Data available for 62 of 64 patients.
Defined as >5 erythrocytes/field; if cell count not available, ≥+ on dipstick analysis.
Data available for 121 of 126 patients.
Data available for 59 of 62 patients.
Data available for 62 of 64 patients.
(59%) in the 6-month group (log rank test: \( P=0.76 \)) (Figure 3B).

The cumulative incidences of first relapses were similar in the two treatment groups. At least one relapse occurred in 48 of 62 children (77%) in the 3-month group and 51 of 64 children (80%) in the 6-month group. Median survival time from randomization to the first relapse was 6 months (95% confidence interval [CI]=4.00–8.00) in the 3-month group and 8 months (95% CI=6.00–10.00) in the 6-month group (log rank test: \( P=0.69 \)) (Figure 3C).

Children allocated to the 6-month group experienced more relapses during follow-up compared with the 3-month group, although differences were not statistically significant. The median total number of relapses during follow-up was 2.5 (IQR=1.0–5.0) in the 3-month group and 4.0 (IQR=1.0–6.0) in the 6-month group (\( P=0.13 \)). The median number of relapses per year of follow-up was 0.6 (IQR=0.2–1.4) and 1.0 (IQR=0.3–1.6), respectively (\( P=0.16 \)). Simultaneous evaluation (performed with Poisson regression) of relapse rates in relation to treatment, sex, age category, and follow-up period (I, II, and III) showed no significant difference between treatments. The adjusted overall relative relapse rate (RRR) for the 3- compared with 6-month group was 0.81 (95% CI=0.60–1.09; \( P=0.16 \)). The RRR was highest in the period between 6 and 12 months after diagnosis (1.5; \( P=0.008 \)). The effect of treatment did not differ between the three follow-up periods (\( P=0.46 \)).

Steroid dependence was noted less often in the 3-month group: 15 of 62 children (24%) versus 24 of 64 children (38%) in the 6-month group (Table 3). The difference did not reach statistical significance (log rank test, \( P=0.10 \)).

Cox regression analysis revealed that boys tended to develop FRNS more often than girls, although differences were not statistically significant. For strict FRNS, the male versus female hazard ratio (HR) was 1.68 (95% CI=0.92–3.01; \( P=0.09 \)); a similar HR was found for clinical FRNS: HR=1.72 (95% CI=0.98–3.03; \( P=0.06 \)) (Table 4). Interaction between sex and treatment group was not significant, indicating that neither boys nor girls benefitted more from one treatment over the other. During follow-up, boys tended to have higher relapse rates than girls (RRR=1.4, \( P=0.05 \)). Sex was not associated with the incidences of a first relapse or steroid dependence (Table 4). Age at onset (<4 or ≥4 years) had no effect on any of the therapeutic outcome events; the same was true for the number of days to remission (Table 4). Hematuria and BP at presentation were not related to development of any of the
therapeutic outcome events (data not shown). Interestingly, five patients achieved remission after more than 4 weeks of daily prednisolone treatment. Of these patients, four patients had only one relapse, and one patient had no relapses at all during follow-up.

Secondary steroid resistance was noted in two patients allocated to the 3-month regimen and one patient allocated to the 6-month regimen.

Adverse effects were mostly transient and similar between the two groups (Table 5). Evaluation of height SD scores showed a significant decrease of growth at 3-months follow-up compared with baseline ($P<0.01$), which was restored within 1 year after the start of initial treatment. Growth did not differ between treatment groups ($P=0.58$) (Supplemental Figure 1). Overall height SD scores at baseline were lower than anticipated ($-0.35\pm0.90$). This observation was irrespective of descent ($P=0.83$).

No effect of treatment was observed in the behavioral visual analog scales at any time. Compared with baseline, children scored significantly higher on eating, overactive behavior, and aggressive behavior at 3-months follow-up (all $P$ value $<0.01$). These scores returned to baseline within 1 year in both groups. Scores for happiness temporarily dropped in the first 6 months, while scores for sleeping remained relatively stable over the whole observation period.

Bone mineral density (BMD) at 6 months was not different from baseline in both groups. Mean change in $Z$-scores of lumbar spine BMD was $0.09$ ($-0.17$ to $0.36$) and $0.33$ ($-0.06$ to $0.71$) in the 3- ($n=17$) and 6-month group ($n=19$), respectively ($P=0.35$). Mean change in Bone Health Index SD scores was $-0.10$ ($-0.35$ to $0.14$) in the 3-month group ($n=33$) and $-0.03$ ($-0.16$ to $0.11$) in the 6-month group ($n=30$; $P=0.56$).

**DISCUSSION**

Our study shows that prolongation of initial prednisolone treatment from 3 to 6 months, while maintaining an equal cumulative dose, does not reduce the risk of frequent relapses in childhood NS. This finding challenges the previous assumption that prolonged treatment duration improves clinical outcome.

The high relapse rate in childhood NS initiated research aimed at improving prednisolone treatment regimens. A Cochrane meta-analysis of seven clinical trials by Hodson _et al._ last updated in 2007 showed that prednisolone regimens with both higher cumulative doses and longer treatment durations (up to 7 months and $5235 \text{ mg/m}^2$) resulted in a reduction of relapses compared with a standard 2-month regimen ($2240 \text{ mg/m}^2$). The works by Hodson _et al._ assumed that longer duration of treatment was of greater importance than increased dose and suggested at least 3 months prednisolone should be given for the first episode of NS. Unfortunately, the existing studies have not led to international

![Figure 3](https://www.jasn.org)
Two matters still deserved attention. First, the independent effects of treatment duration and dose remained unproven. Second, studies comparing 3-month regimens with longer regimens were of limited methodological quality. The present study addresses both issues for the first time.

The main strength of our study is its design. To review our results in the context of other reports, we searched for studies comparing 3- with (approximately) 6-months prednisolone use for the initial episode of NS. Four studies had been reported in the work by Hodson et al.\textsuperscript{7} We found one additional study by Mishra et al.\textsuperscript{13} Characteristics of the five previous studies revealed several limitations (Supplemental Table 4). None of the studies included a placebo or blinding in their design; allocation concealment was inadequate or not reported in three studies.\textsuperscript{12,14,16} In at least one study, patients who did not complete study medication were excluded from the analysis after randomization.\textsuperscript{13} Interestingly, two studies were never fully published. Before our study, the Japanese trial by Hiraoka et al.\textsuperscript{12} was the only published study reporting adequate concealment of allocation. This work found a therapeutic benefit of the 6-month regimen only in a small subgroup of children aged less than 4 years; overall relapse rate and FRNS did not differ significantly between the two groups.\textsuperscript{13} We evaluated the occurrence of FRNS in a meta-analysis, of which the results are shown in Figure 4. Four studies, including our study, reported FRNS. Overall analysis revealed no significant benefit of long versus short regimens; however, significant heterogeneity was present (Figure 4A). Heterogeneity was no longer significant when only fully published studies and our study were included (Figure 4B). Nonetheless, these studies are still quite different from each other with respect to administered dose, design, definitions, and observation time; therefore, overall results of this meta-analysis should be interpreted with caution.

The incidences of both strict and clinical FRNS in our study population were higher than anticipated: 60/126 (48%) and 69/126 (55%), respectively. In previous studies, FRNS was reported in 32%–78% of patients who received 2-month prednisolone treatment (2240 mg/m\textsuperscript{2})\textsuperscript{10,17–21} and 18%–44% of patients who received prednisolone for 3 months (3360 mg/m\textsuperscript{2}).\textsuperscript{10,12,20}

### Table 4. Adjusted multivariate analysis of treatment group, sex, age, and time to remission

<table>
<thead>
<tr>
<th></th>
<th>First Relapse</th>
<th>Strict FRNS</th>
<th>Clinical FRNS</th>
<th>SDNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: 3 versus 6 months</td>
<td>1.11 (0.74–1.64)</td>
<td>1.08 (0.65–1.80)</td>
<td>0.97 (0.60–1.56)</td>
<td>0.62 (0.32–1.18)</td>
</tr>
<tr>
<td>Sex: male versus female</td>
<td>1.19 (0.77–1.84)</td>
<td>1.68 (0.92–3.06)</td>
<td>1.77 (0.98–3.03)</td>
<td>1.96 (0.90–4.28)</td>
</tr>
<tr>
<td>Age: &lt;4 versus ≥4 yr</td>
<td>1.22 (0.82–1.82)</td>
<td>0.97 (0.59–1.62)</td>
<td>0.97 (0.60–1.56)</td>
<td>1.30 (0.69–2.44)</td>
</tr>
<tr>
<td>Time to remission (per day)</td>
<td>1.01 (0.99–1.04)</td>
<td>0.96 (0.92–1.01)</td>
<td>0.98 (0.95–1.02)</td>
<td>0.98 (0.93–1.03)</td>
</tr>
</tbody>
</table>

SDNS, steroid-dependent NS.

### Table 5. Adverse effects

<table>
<thead>
<tr>
<th></th>
<th>3 Months Prednisolone</th>
<th>6 Months Prednisolone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP ≥ P95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>36/61 (59%)</td>
<td>28/62 (45%)</td>
<td>0.15</td>
</tr>
<tr>
<td>At 3 months FU</td>
<td>12/57 (21%)</td>
<td>7/60 (12%)</td>
<td>0.21</td>
</tr>
<tr>
<td>At 6 months FU</td>
<td>8/55 (14%)</td>
<td>10/52 (19%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cushingoid appearance at 6 months FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing (moon face)</td>
<td>14/59 (23.7%)</td>
<td>21/58 (36.2%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Striae</td>
<td>3/58 (5.2%)</td>
<td>4/60 (6.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ophthalmological abnormalities at 6 months FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0/51 (0.0%)</td>
<td>0/45 (0.0%)</td>
<td>—</td>
</tr>
<tr>
<td>Cataract</td>
<td>1/53 (1.9%)\textsuperscript{a}</td>
<td>0/46 (0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Severe infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1/62 (1.6%)</td>
<td>6/64 (9.4%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0/62 (0.0%)</td>
<td>0/64 (0.0%)</td>
<td>—</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0/62 (0.0%)</td>
<td>0/64 (0.0%)</td>
<td>—</td>
</tr>
<tr>
<td>VZV reactivation</td>
<td>2/62 (3.2%)</td>
<td>1/64 (1.6%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>0/62 (0.0%)</td>
<td>2/64 (3.1%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Miscellaneous\textsuperscript{b}</td>
<td>3/62 (4.8%)</td>
<td>1/64 (1.6%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Overall</td>
<td>6/62 (9.7%)</td>
<td>10/64 (15.6%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1/62 (1.6%)</td>
<td>2/64 (3.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0/62 (0.0%)</td>
<td>0/64 (0.0%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are expressed as number of events/number analyzed (percentages). FU, follow-up; VZV, Varicella Zoster virus.

\textsuperscript{a}Mild cataract, which was absent at diagnosis.

\textsuperscript{b}Three-month group: n=1 cellulitis, n=1 muscle abscess, n=1 intracranial abscess. Six-month group: n=1 appendicitis.
This variation may, in part, be explained by regional differences or variations in definitions of FRNS, length of observation, and relapse treatments.

Based on our data, a benefit of the 6-month regimen cannot be excluded if the study had been performed with larger sample sizes. However, the CIs that we found for the difference in FRNS between the two groups exclude a clinically relevant difference in favor of the experimental regimen (Table 2). At 5 years, the difference between the two groups for strict FRNS was 7.30%, with a 95% CI ranging from 210.70% to 25.30%. At best, the experimental 6-month treatment was 10.7 percent points better than the standard 3-month treatment. For clinical FRNS, which in our opinion, represents an even more relevant group for clinicians, this difference was 12.20%, with a 95% CI ranging from 25.70% to 30.10%.

Accordingly, applying the 6-month regimen would gain 5.7 percent points at most. The cumulative incidences of steroid dependence at 5 years further illustrate these statements, because they were 24.90% and 40.10% respectively, corresponding with a between-group difference of 15.20% (95% CI= 22.10% to 32.50%). Based on these results, we are confident that a clinically relevant difference in favor of the 6-month regimen is unlikely.

Previous studies have differed in observing and reporting (frequent) relapses from either the start or end of initial therapy. We chose a transitional type of observation to make a fair comparison but still include early relapses during treatment. We did verify that observing strictly from the end of initial treatment did not lead to differences between the two treatments (data not shown).

Analysis of covariates in our study revealed findings of clinical interest, although not supported by statistical significance. Boys tended to have worse outcomes than girls in terms of frequent relapses and RRR. In the few studies that observed an effect of sex on the clinical course of NS, males were at a disadvantage. It would be interesting to further explore whether boys and girls benefit from different treatment regimens in studies with larger sample sizes. We found no effect of age at onset. The influence of age at onset is still debated, because several studies have reported young age to be associated with FRNS and/or steroid dependence. However, others did not find an effect of age on the clinical course of NS.

Side effects were equally distributed over the two treatment groups. Cushingoid side effects, high BP, and behavioral changes were clearly present but transient in the vast majority of patients. Ophthalmological complications were rare in our study. Cataract and glaucoma have previously most often been reported in Japanese patients; in general, these complications are rare. Our findings indicate that there is no need for standard ophthalmological screening in children with NS at an early stage. The same applies to measurements of BMD, which remained stable over the first 6 months. We found severe infections in a clinically relevant proportion of both treatment groups. This observation is consistent with previous reports and justifies awareness of and early therapeutic intervention in children with NS facing infectious diseases.

Our prospective growth data noticeably illustrated how growth velocity significantly dropped in the first months during highly dosed prednisolone treatment and subsequently returned to its baseline within 1 year. Although this study was not designed to assess a causal relationship, this temporary effect corresponds with previous retrospective studies that describe a dose-dependent effect of corticosteroids on growth in...
children with NS. It is unclear why baseline height SD scores were relatively low in our study population. A similar observation was reported in the work by Schärer et al., whereas others described normal height SD scores at diagnosis of NS.

In countries where a 2-month prednisolone regimen is applied for the first episode of NS, children who do not achieve remission within 4 weeks of daily prednisolone are generally characterized as steroid-resistant. Steroid resistance is associated with increased risk of renal failure and entails more aggressive immunosuppressive therapy. Intriguingly, all five patients in our study who achieved remission after 4–6 weeks of prednisolone treatment subsequently experienced a mild clinical course. As argued in the work by Ehrich et al., this finding suggests that patients who do not respond within 4 weeks of daily prednisolone should be offered at least another 2 weeks of daily prednisolone to prevent late responders from undergoing unnecessary and potentially harmful interventions.

A limitation of our study is the fact that participants were observed and treated at their local hospital. Adverse effects were scored by multiple observers, and ophthalmological and radiologic assessments were not available for all patients. A more centralized approach could have prevented these issues to some extent; however, the setting that we chose made participation feasible throughout the country. We were able to include at least one half of all newly diagnosed patients with NS in The Netherlands. By including patients in a nationwide setting, we believe that we have sufficiently avoided selection bias.

Frequent relapses remain a major challenge in the treatment of childhood NS. In our opinion, FRNS, rather than the occurrence of relapses in general, should be the focus of ongoing research. Broader uniform definitions for FRNS that take into account other clinically relevant aspects besides relapse frequency per se should be considered to facilitate a more evidence-based approach to both treatment and research. A possible effect of higher cumulative prednisolone dose during initial treatment needs additional exploration, because it may explain better outcomes in some of the reported prolonged treatment regimens.

In contrast to what was previously assumed but unproven, the present study shows that extending initial prednisolone treatment from 3 to 6 months, while maintaining an equal cumulative dose, does not improve clinical outcomes in children with NS. We believe that our results offer an important contribution to more evidence-based treatment of this disease.

**CONCISE METHODS**

**Trial Design**

A double-blind, randomized, placebo-controlled, parallel-group trial was carried out in 84 of 87 (97%) general hospitals in The Netherlands along with 1 Belgian and all 8 Dutch university hospitals. The trial was approved by the medical ethics committee of Erasmus University Medical Centre in Rotterdam and registered at The Netherlands Trial Register (www.trialregister.nl; registration number NTR255). Detailed information regarding median inclusion rates per hospital and reasons for not participating can be found in Supplemental Table 5, A and B, respectively.

**Participants**

Children with a first episode of NS ages 9 months to 17 years were assessed for eligibility. NS was defined as >200 mg protein/mmol creatinine in urine and albumin<25 g/L in serum. Renal biopsy was not required to establish the diagnosis, because it is generally not indicated at this stage of childhood NS. Patients with underlying disease, such as Henoch–Schönlein purpura or postinfectious GN, were excluded. Remission was defined as urinary protein excretion<20 mg/L or negative trace on dipstick analysis on 3 consecutive days. Patients who did not achieve remission within 6 weeks of 60 mg/m² daily prednisolone were characterized as steroid-resistant. Relapse was defined as proteinuria≥++ on dipstick analysis or >200 mg protein/ mmol creatinine for 3 consecutive days after previously achieved remission. When milder proteinuria was present, pediatricians were instructed to hold off corticosteroid treatment, particularly when signs of mild infection were present. In these patients, relapse treatment was indicated when spontaneous remission became unlikely: continued proteinuria for more than 10 days, marked edema, or decrease of serum albumin to less than 30 g/L. Relapses were treated with prednisolone (60 mg/m² per day) until remission followed by prednisolone (40 mg/m²) on alternate days for 4 weeks.

For our study, the definition of FRNS was originally restricted to commonly used criteria: (A) Two or more relapses within 6 months after completing initial treatment, or (B) Four relapses within any period of 12 months, including relapses during initial treatment. However, during the blinded data collection phase, it became clear that the use of this definition posed difficulties in some cases. Five patients displayed secondary steroid resistance and/or steroid dependency within 3–6 months after diagnosis. Consequently, they experienced their first relapses before the end of trial therapy; additional treatment measures were taken before these patients could even meet criterion A or B. Four additional patients experienced several relapses within short periods of time but did not fulfill criterion A or B. The high burden of multiple relapses within a relatively short period of time, the prospect of experiencing another relapse in the near future, and several signs of steroid toxicity resulted in a clinical indication for additional measures in these patients. Because we found all of these patients to be clinically relevant, we decided to add a third criterion: (C) FRNS based on a clinical decision that included additional treatment of prednisolone maintenance therapy (>3 months) or other immunosuppressive agents. Detailed information on patients characterized as FRNS based on criterion C can be found in Supplemental Table 3A. We analyzed both modalities of FRNS: strict FRNS (criterion A or B) to facilitate comparison with other studies and clinical FRNS (criterion A, B, or C) to report all clinically relevant outcomes.

Steroid dependence was defined as two or more consecutive relapses either during or within 2 weeks after cessation of prednisolone. All patients were diagnosed and treated according to the study protocol at their local hospital by their own pediatrician. Participants’
descent was obtained from self-reported countries of birth of parents and grandparents.

Procedures
A statistician provided the central trial pharmacy with a computer-generated random number table. Allocation to 3 months of prednisolone plus 3 months of placebo (referred to as the 3-month group) or 6 months of prednisolone was stratified for type of hospital (general or university) and balanced with a ratio of 1:1 in fixed blocks of four patients. The central trial pharmacy fabricated trial medication, controlled allocation concealment, allocated patients, and distributed trial medication after informed consent was obtained. Participants, health care providers, data collectors, and researchers were blinded to group allocation. Trial medication was sent prepackaged to local pharmacies and consisted of identical tasteless capsules containing either prednisolone or placebo. Trial medication was dispensed in five containers, each with a fixed blinded dose and a preset time frame. Although doses of the containers differed between treatment groups, container time frames were exactly the same. Container 1 was used from remission to week 6, 2 was used from weeks 7 to 10, 3 was used from weeks 11 to 12, 4 was used from weeks 13 to 14, and 5 was used from weeks 15 to 24. The first patient was randomized in February of 2005, and the last patient was randomized in December of 2009. Follow-up started at diagnosis and was truncated at either 5 years after diagnosis or July of 2011, at which time the last enrolled patients had a minimum follow-up of 18 months. The randomization code was subsequently broken in September of 2011.

All children diagnosed with NS started induction therapy of 60 mg/m² oral prednisolone one time daily. Participants switched to trial medication only after remission was achieved. If remission was not achieved within 6 weeks of 60 mg/m² daily prednisolone, patients were characterized as steroid-resistant, and trial medication was not started. Both treatment regimens are shown in detail in Figure 2. In both groups, induction therapy and trial medication were administered within a total of 24 weeks. The prescribed cumulative dose of prednisolone in the 3-month group was 3360 mg/m². Depending on the number of days to remission, the prescribed cumulative dose of prednisolone in the 6-month group was 3320–3710 mg/m², corresponding with 99%–110% of the cumulative dose in the 3-month group. Prescribed cumulative doses did not include potential relapse treatments during trial medication, because the occurrence of a relapse and the total dose administered for that particular relapse could not be anticipated. In the event of a relapse occurring during the period of trial medication, relapse treatment temporarily replaced trial medication to maintain a 24-week schedule duration.

Outcomes
The primary outcome event was FRNS. Secondary outcome parameters were cumulative incidences of a first relapse, steroid dependence, number of relapses per patient per year, and adverse effects. Height SD scores, BP, cushingoid appearance (moon face or striae), dyspepsia, thrombosis, severe infections, and behavior were noted at diagnosis and after 3 and 6 months and 1 and 2 years. Height SD scores were calculated with Dutch pediatric reference data.32 High BP was defined as systolic and/or diastolic BP more than or equal to the 95th percentile for sex, age, and height.33 Severe infections were defined as non-self-limiting infections requiring hospital admission. Behavior was scored by parents on visual analog scales for overactive and aggressive behavior, happiness, eating, and sleeping. At diagnosis and after 6 months, participants were screened for cataract and glaucoma by an ophthalmologist; at the same time points, BMD was assessed. Using dual energy x-ray absorptiometry, Z-scores of lumbar spine BMD were calculated according to local reference data. Changes in individual Z-scores over time were calculated from paired measurements. As an additional indicator of BMD, Bone Health Index SD scores from hand x-rays were calculated with BoneXpert.34

Statistical Analyses
Primary outcome events were originally defined as the cumulative incidences of first relapses and FRNS. Subsequently, at the time the study was still blinded, FRNS was chosen as the sole primary outcome, because we considered FRNS to be the most relevant parameter. Incidence of a first relapse became the secondary outcome. For the cumulative incidence of FRNS to decrease by 20% points, 72 patients per treatment arm were sufficient (80% power, $\alpha=0.05$).

A modified intention-to-treat principle was applied in such a way that all patients who started trial medication were included in the analysis. Participants who were subsequently lost to follow-up or in whom trial medication was stopped prematurely were analyzed according to their allocated groups.

Cumulative event rates are expressed as Kaplan–Meier estimates with SEMs. Treatment group, sex, age at onset, and number of days to remission were included as covariates in the Cox regression analysis. Age at onset was stratified as <4 and ≥4 years.23

For comparison of relapses within time intervals between treatments, follow-up was categorized into three periods (period I, 0–6 months; period II, 6–12 months; period III, >12 months after randomization), and within each period, the number of relapses was counted. Poisson regression was used to evaluate relapse rates in relation to treatment, sex, age category, and period. Calculations were done using Generalized Estimation Equations with a log link. Longitudinal data concerning height SD scores and behavior were analyzed with linear mixed models that included treatment, age strata, sex, time, baseline values, and interaction between time and treatment as fixed effects. For the remaining variables, continuous outcome was analyzed with either the t or Mann–Whitney test, and categorical outcome was analyzed with either the Pearson chi-squared or Fisher exact test. P values <0.05 were considered statistically significant. All analyses were performed with SPSS (version 17.0).

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DISCLOSURES
None.

REFERENCES


See related editorial, “Corticosteroid Therapy for Steroid-Sensitive Nephrotic Syndrome in Children: Dose or Duration?,” on pages 7–9.

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