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# Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children

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**Abstract.** Two regimens of steroid treatment for the initial attack of idiopathic nephrotic syndrome (NS) in children were compared in a controlled prospective multicentre study. Long prednisone therapy consisted of 60 mg/m$^2$ per 24 h for 6 weeks, followed by alternate day 40 mg/m$^2$ per 48 h for 6 weeks. The standard prednisone therapy was 60 mg/m$^2$ per 24 h for 4 weeks, followed by 40 mg/m$^2$ per 48 h for 4 weeks. A total of 71 children with an initial attack of idiopathic NS were allocated at random to the two groups. The cumulative rate of patients with sustained remissions after 2 years was significantly higher after the long course than after the standard treatment (49% vs 19%, $P = 0.0079$). The mean relapse rate per patient at intervals of 3, 6 and 12 months was lower in the long-course prednisone group than in the standard prednisone group, and the proportion of children with frequent relapses during any subsequent 6 months period was lower in the long-course group than in the standard group (29% vs 57%, $P = 0.03$). Mild side-effects of corticosteroid therapy were observed more frequently after long-course prednisone treatment. It is concluded that long-course prednisone therapy of the initial attack of steroid responsive NS is preferable to the standard regimen because it reduces the rate of subsequent relapses without increasing the risk for severe steroidal side-effects.

**Key words:** Steroid sensitive nephrotic syndrome – Prednisone

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*Abbreviations:* NS = nephrotic syndrome; ISKDC = International Study of Kidney Disease in Children; APN = Arbeitsgemeinschaft für Pädiatrische Nephrologie

## Introduction

The minimal change nephrotic syndrome (NS) usually responds to corticosteroids and proteinuria disappears in 90% of all steroid responsive cases within 21 days [1, 3, 5, 9]. A standard regimen for the initial attack is now used almost world-wide, consisting of 4 weeks continuous prednisone (60 mg/m$^2$ per day) and 4 weeks of intermittent prednisone (40 mg/m$^2$ on 3 out of 7 days) [1] or alternate day prednisone (40 mg/m$^2$ per 48 h) [2, 6]. The International Study of Kidney Disease in Children (ISKDC) showed that 55% of children relapsed after the initial prednisone regimen within 6 months and that 34% of patients had two or more relapses during the first 6 months [10]. The controlled multicentre study of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) revealed that a shorter regimen – giving only half the cumulative prednisone dosage for the initial attack – resulted in a higher rate of relapsers and a shorter duration of remission when compared with the standard prednisone therapy [3]. This study suggested that the initial immunosuppressive attack determines the length of benefit from corticosteroid treatment in steroid responsive NS and that an attempt to increase the initial steroid treatment might be justified. A multicentre controlled study on the initial prednisone treatment of children with idiopathic NS was therefore conducted to compare the standard initial prednisone regimen with a long initial prednisone regimen.

## Methods

A total of 71 children, aged 2–16 years, with an initial attack of an idiopathic NS were entered into the study with informed consent

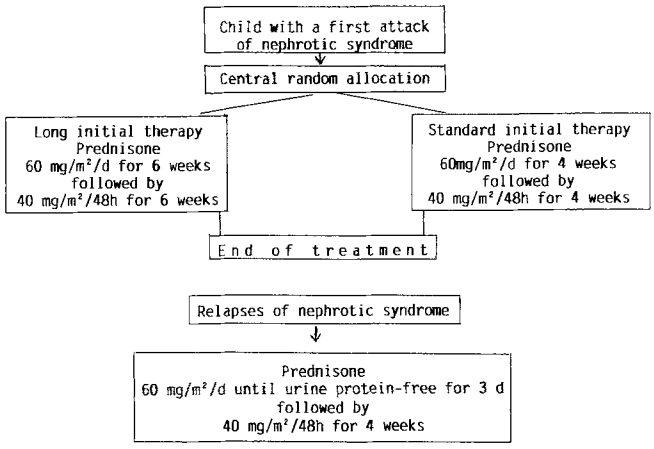


**Fig. 1.** Protocol of study

of their parents. All patients had NS (gross oedema, proteinuria $> 40\,mg/m^2$ per h and a serum albumin concentration $< 25\,g/l$) and a preserved glomerular filtration rate (creatinine clearance $> 68$ ml/min per $1.73\,m^2$). The children had had no previous treatment with corticosteroids or immunosuppressive agents and none had any contraindications to corticosteroid therapy. Renal biopsy was not requested for admission to the study. All patients with a low C3 complement, postinfectious glomerulonephritis, systemic diseases such as lupus erythematosus, diabetes mellitus or amyloidosis, vasculitis, or Henoch-Schoenlein nephritis, metabolic or toxic nephritis, and hereditary glomerular disease were excluded. Definitions and criteria for NS, remission and relapses were the same as those used by the ISKDC [1] and our own group [2].

Patients were randomised into groups receiving long prednisone treatment or the standard prednisone dose (Fig. 1). If a patient did not reach a remission within 4 weeks of continuous treatment, he was removed from the study and treated individually. Patients who relapsed during or after the initial therapy were treated as shown in Fig. 1. In both groups, diuretic or antihypertensive drugs were given as required. Proteinuria was assessed daily using reagent test strips. The study aimed to follow each patient for 2 years at intervals of 6 months to assess the occurrence of remission and relapse, cumulative doses of prednisone, and side-effects of steroid treatment. If the full 2-year follow up was not possible, the patient's data were used up to the data of withdrawal. In case of a therapeutic fault or an observation period $< 6$ months, the patient's data were withdrawn from the final evaluation. Statistical analysis was performed with the Mann-Whitney test, the paired and unpaired $t$-test, and the rank-test for life table analysis.

## Results

Out of 86 patients reported to the co-ordinating office, 15 had to be removed at an early stage due to steroid resistance ($n = 8$) or early deviation from the protocol ($n = 6$). One child died from thrombo-embolism before reaching remission during the initial treatment and showed focal and segmental glomerulosclerosis on histology. Of the remaining 71 children, 34 were randomly assigned to long-course prednisone therapy, and 37 to the standard regimen. There were no statistically significant differences between the two groups with respect to age, sex, blood pressure, serum albumin, serum cholesterol, IgG, IgM or IgA (Table 1).

A total of 53 patiens completed the study for the full 2 years. Before the end of 2 years, 13 patients (5 with long prednisone therapy and 8 with standard prednisone therapy) required cytotoxic drug therapy due to frequent relapses and steroid toxicity. Five patients (3 with long therapy and 2 with standard therapy) were lost to follow up or refused further co-operation before ending the full study period. The mean duration of follow up was 20 months in the long group and 22 months in the standard group.

Median total prednisone dose in the initial long course was $3360\,mg/m^2$ body surface (range = 3220–4060) and thus significantly higher ($P = 0.001$) than in the initial standard group ($2240\,mg/m^2$, range = 2080–2560). All patients went into remission. Serum analysis after completion of the initial prednisone therapy revealed no significant differences in concentrations of albumin, cholesterol, IgG, IgM and IgA between the two groups.

The cumulative rate of patients with sustained remission 2 years after the initial attack was significantly higher in the long-course group than in the standard group (49%

**Table 1.** Age, blood pressure and serum parameters of children with a first attack of idiopathic NS

| | Long prednisone group | Standard prednisone group | Significance |
|---|---|---|---|
| Age (years) | 3.9 (1.5–8) | 4.4 (1.5–14) | NS |
| *Blood pressure* | | | |
| Syst. (mmHg) | 108 ± 10 | 110 ± 11 | NS |
| Diast. (mmHg) | 72 ± 9 | 72 ± 11 | NS |
| *Serum* | | | |
| Total protein (g/l) | 40 ± 5 | 41 ± 5 | NS |
| Albumin (g/l) | 14 ± 3 | 16 ± 4 | NS |
| Cholesterol (mmol/l) | 12.3 ± 4.4 | 11.9 ± 3.6 | NS |
| IgA (g/l) | 1.0 ± 1 | 1.3 ± 1 | NS |
| IgG (g/l) | 2.8 ± 2 | 2.0 ± 2 | NS |
| IgM (g/l) | 2.0 ± 1 | 2.0 ± 1 | NS |

Data on age show median values and ranges; all other data give mean values ± SD; NS, not significant

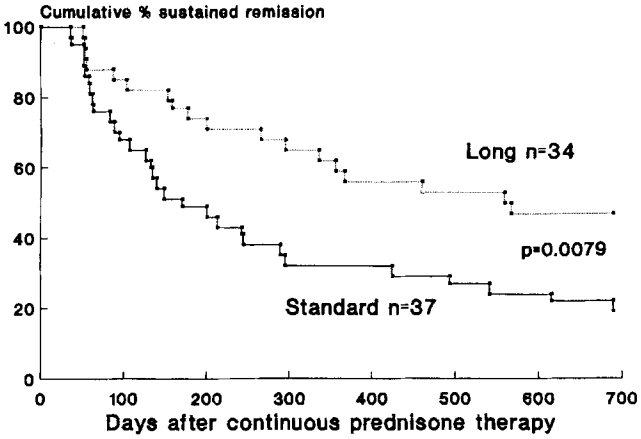


**Fig. 2.** Cumulative percentage of sustained remissions in children with nephrotic syndrome after long and standard prednisone treatment

**Table 2.** Patients with or without relapse in the two study groups 3, 6, and 12 months after the end of continuous steroid therapy for initial attack

| | Long prednisone therapy | | Standard prednisone therapy | | Significance |
|---|---|---|---|---|---|
| | With relapse | Without relapse | With relapse | Without relapse | |
| After 3 months | 5 | 29 | 11 | 26 | NS |
| After 6 months | 8 | 26 | 18 | 19 | $P = 0.047$ |
| After 12 months | 13 | 21 | 24 | 13 | $P = 0.033$ |

* Chi-square test

**Table 3.** Mean relapse rate per patient at intervals of 3, 6, and 12 months after the end of continuous steroid therapy for initial attack

| Time interval | Long prednisone therapy | Standard prednisone therapy | $P$* |
|---|---|---|---|
| 0–3 months | 0.18 | 0.43 | NS |
| 0–6 months | 0.58 | 1.03 | 0.048 |
| 0–12 months | 1.35 | 1.77 | NS |

* Mann-Whitney test, NS, not significant

**Table 4.** Median duration of remission in relapsers

| | Long prednisone therapy | Standard prednisone therapy | $P$* |
|---|---|---|---|
| Days after initial attack | 158 | 132 | NS |
| First relapse | 71 | 66 | NS |
| Second relapse | 78 | 70 | NS |

* Mann-Whitney test, NS, not significant

vs 19%, $P = 0.0079$) (Fig. 2). In both groups the majority of patients relapsed during the first 6 months after cessation of prednisone therapy, however, this proportion was 23% in the long group and 49% in the standard group ($P = 0.047$) (Table 2). The difference was obvious irrespective of whether the end of daily prednisone or alternate day prednisone was used as starting point of observation. The mean relapse rate of all patients at intervals of 3, 6 and 12 months after initial treatment was lower in the long prednisone group than in the standard prednisone group (Table 3). The proportion of patients with frequent relapses (two or more relapses) during the first 6 months after cessation of daily prednisone therapy was lower in the long-course group than in the standard group (18% vs 33%). The percentage of children who had two or more relapses in any subsequent 6-month period was 29% in the long group and 57% in the standard group ($P = 0.03$). The median duration of remission after completion of initial prednisone therapy, in patients who had a relapse, was not significantly longer after the long-course than after standard treatment (Table 4). In relapsing patients of both groups, remission lasted longer

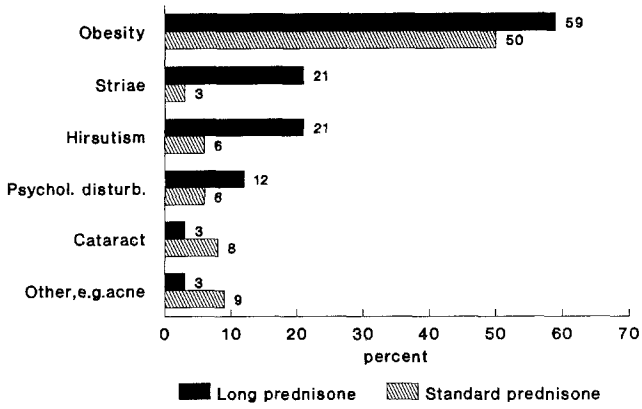


**Fig. 3.** Side-effects of initial prednisone treatment in the two groups

after the initial treatment than after treatment of the first or second relapse ($P = 0.02$) (Table 4).

During the initial attack, sequelae of steroid therapy such as striae and hypertrichosis were detected more frequently after long therapy (Fig. 3). However, no patient developed severe side-effects such as convulsions, pseudotumour cerebri, arterial hypertension, growth failure (growth velocity < 5th percentile), thrombo-emoblism, pancreatitis, osteochondritis or life-threatening infections. Radiologically proven osteoporosis was found in one child in each treatment group. Patients in the long-course group had a higher initial cumulative prednisone dosage but a lower mean cumulative dosage for the treatment of relapses than patients with standard prednisone therapy. Thus the mean cumulative prednisone dosage during the first 12 months after start of initial steroid therapy was not significantly different in the two treatment groups (long = 4590 mg/m$^2$ body surface, standard = 4308 mg/m$^2$ body surface). During the 2-year follow up, steroid toxicity requesting cytotoxic drug therapy for a further relapse was recorded in 13 patients (5 out of 34 in the long-course group and 8 out of 37 in the standard group). This steroid toxicity was attributed to frequent relapses which were treated with standard relapse prednisone therapy and not to initial prednisone therapy.

## Discussion

When the ISKDC started its multicentre study in 1967 [1] it decided rather arbitrarily on a standard regimen for the treatment of the initial attack of minimal change NS in children which consisted of an 8-week course of prednisone (4 weeks continuous and 4 weeks intermittent therapy). Later on it was claimed that the degree of the adrenal suppression by steroid therapy was positively correlated with the rate of relapses [13]. Therefore the APN conducted a previous study [3] in which a short prednisone course of 4 weeks (2 weeks continuous and 2 weeks alternate day therapy) for the initial attack was compared with a standard regimen. Surprisingly, the short regimen led to a shorter duration of remissions and to a higher rate of relapses than the standard prednisone regimen [3]. Consequently, the APN conducted this study

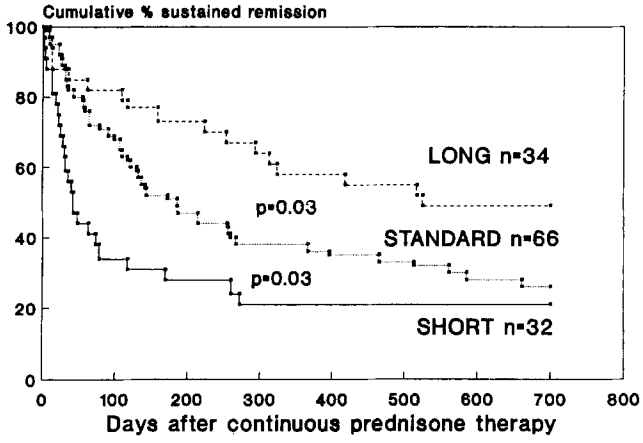


**Fig. 4.** Cumulative percentage of sustained remissions in children with nephrotic syndrome after long, standard and short prednisone treatment. All patients of the APN initial steroid studies [3, and present study] are involved

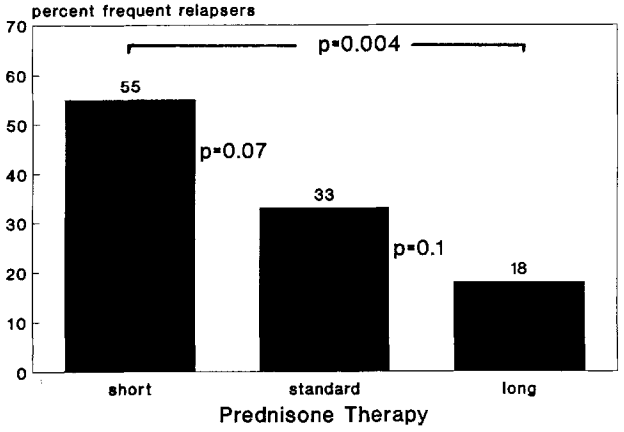


**Fig. 5.** Proportion of patients of APN steroid studies [3, and present study] with frequent relapses (two or more) during the first 6 months after cessation of initial prednisone therapy

in which the same standard prednisone regimen was used as in the previous one but a long-course group was included giving prednisone for a total of 12 weeks (6 weeks continuous and 6 weeks alternate day). The results demonstrate that indeed the longer initial prednisone treatment was followed by fewer relapsers and relapses. Both APN studies [3, present study] on prednisone therapy of the initial attack of idiopathic NS followed the same protocol concerning critera, follow up controls and standard prednisone treatment. It seems therefore justified to compare the results and combine the data of the standard treatment groups. The analysis of the cumulative percentage of sustained remission in the three groups of children with steroid responsive NS after short, standard and long prednisone treatment clearly show that the number of relapsers was highest in the short course group, intermediate in the standard group, and lowest after the long regimen (Fig. 4). Furthermore, the percentage of patients with frequent relapses during the first 6 months after cessation of initial prednisone therapy was also higher after the short regimen and the standard regimen that after the long treatment (Fig. 5).

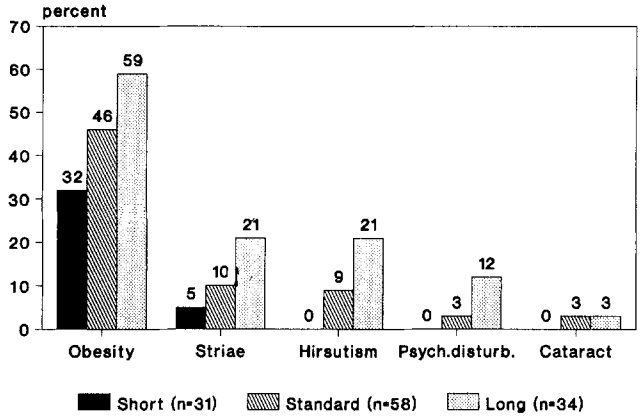


**Fig. 6.** Side-effects of three different prednisone regimens for the treatment of the initial attack of idiopathic NS (data derived from present and previous APN study [3]

Although the number of patients in these two studies was small, their combined data clearly show that the initial immunosuppressive attack determines the length of benefit from corticosteroid treatment in steroid responsive NS. The results confirm the earlier reports on relapse rates following a prolonged initial steroid treatment [4, 12] as well as a recent report [16] in which it was shown that a long-term tapering regimen with a 4 weeks continuous prednisone therapy followed by a 6 month alternate day treatment was more effective than a standard therapy of the initial attack. It remains however unclear whether the benefitial effect of a longer prednisone regimen in these studies was due to the increased cumulative steroid dosage or to the longer duration of immunosuppression during the extended prednisone therapy.

In our study, a renal biopsy was not mandatory which is usual in such patients [5]. The responsiveness to prednisone makes it likely that probably almost all of the patients in these studies belonged to the minimal change category. Therefore the results are not likely to be significantly biased by a heterogenicity of patients. The percentage of patients following exactly the treatment protocol was 90%. Only 10% of patients deviated mildly from the protocol by taking prednisone for a shorter (range = 1–4 days) or a longer period (range = 1–10 days). It can therefore be ruled out that the results were biased significantly by a heterogenicity of therapeutic intervention.

The results on the occurrence of steroidal side-effects show an increase of striae and hypertrichosis in patients after the long initial treatment (Fig. 6). Cushingoid obesity, with "buffalo hump" and "moon face", was seen frequently after both standard and long treatment and disappeared in those patients who received no further treatment course. The increased rate of serious and even fatal side-effects of corticosteroid therapy of steroid responsive NS after long or repeated courses was shown by others [7, 8, 11, 14, 15]. In the majority of our patients of both groups, side-effects of corticosteroids were reversible or mild if further treatment courses were not at all or rarely required. Thus, the long-term outcome concerning steroidal side-effects was similar in the two treat-

ment groups; cytotoxic drug therapy for frequently relapsing patients with side-effects of steroids was requested in 22% of patients with standard prednisone therapy and 15% of patients with long prednisone treatment. This study therefore suggests that a prolongation of the initial standard steroid treatment is justified and that a course of 6 weeks continuous prednisone plus 6 weeks alternate day prednisone therapy is keeping the rate of relapses low, and is thus decreasing the risk of repeated relapses and persistent and life-threatening steroidal side-effects which may occur during treatment of frequent relapses.

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