Daily Corticosteroids Reduce Infection-associated Relapses in Frequently Relapsing Nephrotic Syndrome: A Randomized Controlled Trial

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Summary

Background and objectives Relapses of nephrotic syndrome often follow minor infections, commonly of the upper respiratory tract. Daily administration of maintenance prednisolone during intercurrent infections was examined to determine whether the treatment reduces relapse rates in children with frequently relapsing nephrotic syndrome.

Design, setting, participants, & measurements In a randomized controlled trial (nonblind, parallel group, tertiary-care hospital), 100 patients with idiopathic, frequently relapsing nephrotic syndrome eligible for therapy with prolonged low-dose, alternate-day prednisolone with or without levamisole were randomized to either receive their usual dose of alternate-day prednisolone daily for 7 days during intercurrent infections (intervention group) or continue alternate-day prednisolone (controls). Primary outcome was assessed by comparing the rates of infection-associated relapses at 12-month follow-up. Secondary outcomes were the frequency of infections and the cumulative amount of prednisolone received in both groups.

Results Patients in the intervention group showed significantly lower infection-associated (rate difference, 0.7 episodes/patient per year; 95% confidence intervals [CI] 0.3, 1.1) and lower total relapse rates (0.9 episodes/patient per year, 95% CI 0.4, 1.4) without increase in steroid toxicity. Poisson regression, adjusted for occurrence of infections, showed that daily administration of prednisolone during infections independently resulted in 59% reduction in frequency of relapses (rate ratio, 0.41; 95% CI 0.3, 0.6). For every six patients receiving this intervention, one showed a reduction of relapse frequency to less than three per year.

Conclusions Daily administration of maintenance doses of prednisolone, during intercurrent infections, significantly reduces relapse rates and the proportion of children with frequently relapsing nephrotic syndrome.

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Introduction

Although most children with idiopathic nephrotic syndrome respond to treatment with corticosteroids, 40 to 50% show frequent relapses and a prolonged course of the illness with risks of life threatening infections, thromboembolic complications, and side effects of therapy (1,2). Whereas the availability of novel medications has resulted in improved management of patients with relapsing nephrotic syndrome, there are concerns about the adverse effects of these therapies (3–5). There is therefore a need to examine safe and effective treatment regimens for patients with frequently relapsing nephrotic syndrome.

Relapses of nephrotic syndrome often follow minor infections of the upper respiratory or gastrointestinal tracts (6,7). It is estimated that 50 to 70% of relapses of nephrotic syndrome among children in developing countries follow infections chiefly of the upper respiratory tract (7). Although the mechanism by which infections result in relapses is not clear, therapy with immunosuppressive agents is believed to attenuate the upregulation of T cells (8–10) and reduce the risk of infection-associated relapses.

On the basis of this assumption, two recent studies have examined the role of short-term daily administration of corticosteroids in reducing infection-associated relapses in patients with frequently relapsing nephrotic syndrome (11,12). Although both studies found an effect of this intervention on relapse rates, the first was conducted on a small number of patients (11), and the second did not examine its long-term benefit (12). We therefore proposed to examine, in a prospective, adequately powered, randomized controlled trial, whether the strategy of short-term administration of small daily doses of prednisolone during infectious illnesses was effective in reducing annual relapse rates in patients with frequently relapsing nephrotic syndrome.

Subjects and Methods

This randomized controlled trial was conducted from September 2006 to October 2009 (enrollment, 18 months) on patients aged 1 to 16 years with recently diagnosed frequently relapsing nephrotic syndrome (at least two relapses in 6 months or more than three relapses in 12 months) eligible for therapy with long-term, alternate-day prednisolone with or without levamisole. Patients with any of the following were excluded: (*1*) impaired renal function (serum creatinine >1.2 mg/dl confirmed once over a period of 2 weeks), (*2*) intake of immunosuppressive medications other than oral prednisolone in the preceding 6 months, or (*3*) steroid threshold exceeding 1 mg/kg on alternate days for maintaining remission and one or more features of steroid toxicity (body mass index, >95th percentile for age [13], cataract, or stage 2 hypertension [14]). The study was approved by the Institutional Ethics Board, and an informed written consent was taken from a parent before inclusion.

Standard Treatment and Randomization

Patients recently diagnosed to have frequently relapsing nephrotic syndrome were included during steroid-induced remission. They received alternate-day prednisolone, at a dose of 1.5 mg/kg for 4 weeks, followed by tapering by 0.25 mg/kg every 2 weeks until a dose of 0.5 to 0.75 mg/kg on alternate days was reached. Patients requiring prednisolone at a dose of >1 mg/kg on alternate days to maintain remission but without the above features of steroid toxicity were treated with the combination of levamisole (2 mg/kg on alternate days) and alternate-day prednisolone as above. Dosing was on the basis of the most recent clinical weight. Treatment with long-term, alternate-day prednisolone with or without levamisole was given for 1 year.

Eligible patients were randomized by stratified randomization on the basis of therapy with or without levamisole into intervention and control groups. Allocation was concealed in opaque sealed envelopes that were opened at inclusion.

Intervention and Follow-up

The presence of an infection was defined by any one of the following: (*1*) fever (>38°C on two measurements of axillary temperature at least 1 hour apart), (*2*) rhinorrhea or cough for more than 1 day, and (*3*) diarrhea (three or more semiformed stools/d for >2 days). During episodes of infection, patients in the intervention group were instructed to increase the frequency of prednisolone administration from alternate-day to daily treatment for 7 days, without changing the dose of prednisolone. Patients in the control group continued treatment with alternate-day prednisolone. The frequency of administration of prednisolone was not increased during allergies, insect bites, injuries, immunization, and any presumed noninfectious illness.

All patients received supplements of calcium carbonate (250 mg/d for patients <6 years old; 500 mg/d for patients >6 years old). Parents in both groups were instructed to daily examine the first morning urine specimen by dipstick and maintain a written record. Details of infections and treatment taken were also recorded. Written instructions on therapy were given, including telephonic advice followed by a hospital visit within 1 week. The site of infection was defined by clinical criteria and laboratory studies, if necessary.

Patients showing proteinuria during infections were managed by supportive therapy. Relapse was defined as the presence of 3 to 4+ proteinuria for 3 consecutive days after 7 days of the onset of an infectious illness. These were treated with prednisolone, at a dose of 2 mg/kg per d until remission (trace/negative protein for 3 consecutive days), followed by 1.5 mg/kg on alternate days for 4 weeks, and then tapered.

Follow-up visits were scheduled every 2 months for 1 year; at each visit the records maintained by the parents were reviewed, and advice was given. Blood levels of creatinine, albumin, and cholesterol were measured at enrollment, 6 months, and 12 months.

Management of Serious Infections

Patients with serious infections (lower respiratory tract infection, peritonitis, and cellulitis) were hospitalized. Patients in both groups received prednisolone (0.5 mg/kg per d orally) or an equivalent dose of IV hydrocortisone during therapy of these infections.

Study Outcomes

The primary outcome was assessed by comparing the rates of infection-associated relapses (relapses occurring in the week after the 7-day intervention period) and expressed as episodes/patient per yr. Secondary outcomes included the frequency and type of infections and the cumulative amount of prednisolone received in both groups. The occurrence of two or more relapses in any 6-month period was considered treatment failure. These patients exited the study and were treated using alternative medications.

Sample Size and Statistical Analyses

On the basis of the relapse rate of 4.6 ± 1.4 relapses/yr in patients with frequent relapses (*7*), 70% of which are presumed to follow infections, 50 patients were required in each group to show 50% reduction in frequency of infection-associated relapses at a power of 80%, alpha error of 5%, and dropout rate of 10%. The data were analyzed using Stata, version 9.1. Continuous data were expressed as the means ± SD and by the difference in means with 95% confidence intervals (CI); $P < 0.05$ was considered significant. The analysis was on the basis of intention to treat. Incidence (relapse) density rates and rate differences were calculated. Poisson regression was used to compare relapse rates in the groups after adjusting for the number of infections. One-way ANOVA was used to assess the association between the number of relapses and infections. On the basis of the rate ratio, we calcu-

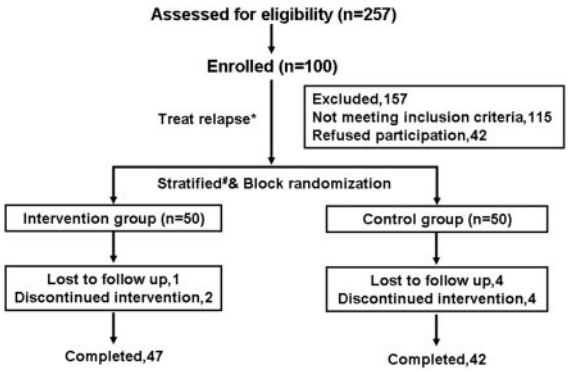

Figure 1. | Trial flow; five patients were lost to follow up (intervention group, one; control group, four) after the first visit. *Relapses were treated with prednisolone 2 mg/kg daily until remission, followed by 1.5 mg/kg on alternate days for four weeks. The dose was then reduced by 0.25 mg/kg every two weeks until 0.5 to 0.75 mg/kg on alternate days for 10 months. #Strata 1 (n = 68): long-term alternate day steroids; strata 2 (n = 32): long-term alternate day steroids with levamisole.

lated the number needed to be treated to reduce the frequency of relapses to less than three per year (15).

Results

Of 142 eligible patients, 42 refused consent. Of those included, 68 patients were treated with alternate-day prednisolone alone (strata 1), and 32 received alternate-day prednisolone and levamisole (strata 2) (Figure 1). Baseline characteristics were similar in patients allocated to intervention and control groups (Table 1). Outcomes were assessed in 95 patients, because 5 patients did not return after the first visit.

Relapse Rates

At the 12-month follow-up, there were 44 relapses (31 infection-associated) in the intervention group as compared with 76 (56 infection-associated) in the controls. Patients in the intervention group showed significantly lower infection-associated relapse rates with a rate difference of 0.7 episodes/patient per yr (95% CI 0.3, 1.1). The total number of relapses was also significantly lower in the former, with a rate difference of 0.9 episodes/patient per yr (95% CI 0.4, 1.4) (Table 2). Nineteen (38.7%) patients in the intervention group remained relapse-free during the 12-month follow-up as compared with 15.2% in the control group (Table 3; P = 0.03).

Infection Relapse Correlation

There were 226 and 161 episodes of infections in the intervention and control groups, respectively (P = 0.04). Most (92%) infections involved the upper respiratory tract, and the remaining were gastroenteritis (6%) and fever without any localizing signs (2%). Table 4 shows the association between the number of relapses and infections in the intervention and control groups. One-way ANOVA showed an increase in relapses with the number of infections in the study population, although this trend was more apparent in controls as compared with the intervention group, with significance reached when the number of infections exceeded four (P = 0.03).

Adjusted Analysis and Number Needed to Treat

The mean numbers of relapses per infection in the intervention and control groups were 0.13 ± 0.1 and 0.35 ± 0.2, respectively; the mean difference was 0.22 (95% CI 0.16, 0.28) (P = 0.04). Poisson regression, adjusted for occurrence of infections, showed that daily administration of prednisolone during infections independently resulted in a 59% reduction in the rate of relapses (rate ratio, 0.41; 95% CI 0.3, 0.6). This intervention was likely to reduce the frequency of relapses to less than three per year, for every one out of six patients with frequent relapses.

Prednisolone Dosage, Side Effects, and Treatment Failures

The mean prednisolone dosages in patients during remission were 0.6 ± 0.1 and 0.7 ± 0.2 mg/kg on alternate days in the intervention and control groups,

Table 1. Patient characteristics at enrollment

Patient Characteristics	Intervention Group (n = 50)	Control Group (n = 50)
Age (months)	78.5 ± 35.6	81.7 ± 38.7
Age at onset of nephrotic syndrome (months)	68.7 ± 21.2	71.2 ± 30.7
Boys (n)	35	32
Weight (kg)	21.5 ± 9.8	22.6 ± 9.6
Height (cm)	113.5 ± 34.2	113.8 ± 38.6
Serum albumin (g/dl)	3.3 ± 1.2	3.1 ± 1.4
Serum cholesterol (mg/dl)	209.0 ± 98.2	262.0 ± 96.2
Serum creatinine (mg/dl)	0.5 ± 0.2	0.6 ± 0.3
Relapses/patient per yr	4.1 ± 0.2	4.2 ± 0.4

The values are given as the means ± SD. Note: conversion factors for serum albumin in g/dl to g/l, × 10; serum cholesterol in mg/dl to mmol/l, × 0.02586; and serum creatinine in mg/dl to μmol/l, × 88.4

Table 2. Relapse rates and cumulative prednisolone dosage at 12-month follow-up

	Intervention Group (n = 49)	Control Group (n = 46)	Rate Difference	P
Infection associated relapses-(episodes/patient per yr)[a]	0.7 ± 0.3 (0.6, 1.1)	1.4 ± 0.5 (1.2, 1.9)	0.7 (0.3, 1.1)	<0.01
Total relapses (episodes/patient per yr)[a]	0.9 ± 0.4 (0.7, 1.2)	1.8 ± 0.5 (1.4, 2.2)	0.9 (0.4, 1.4)	<0.0001
			Mean Difference	
Cumulative prednisolone (mg/kg per yr)[b]	120 ± 32 (105, 131)	138 ± 22 (112, 144)	16 (−26, 38)	0.3

[a]Relapse rates are the mean incidence density rates ± SD (95% confidence interval).
[b]The data are expressed as the means ± SD (95% confidence interval).

Table 3. Relapse frequency in patients in the intervention and control groups

Number of Relapses	Intervention Group (n = 49)	Control Group (n = 46)	P
No relapses	19 (38.7%)	7 (15.2%)	0.03
One or two relapses	23 (46.9%)	24 (52.2%)	0.7
Three relapses	7 (14.3%)	15 (32.6%)	0.03

Table 4. Association between number of relapses and infections in the intervention and control groups

Number of Infections	Relapse Rates (Episodes/Patient/Yr)[a]		Rate Ratio (95% CI)	P
	Intervention Group (n = 49)	Control Group (n = 46)		
No infections	0.3	0.7	0.4 (0.1, 3.6)	0.7
One or two infections	1.5	1.2	1.3 (0.5, 3.0)	0.7
Three or four infections	1.2	1.6	0.7 (0.3, 1.5)	0.6
More than four infections	0.8	3.3	0.2 (0.1, 0.4)	0.03

[a]The relapse rates are the mean incidence density rates.

respectively. The cumulative doses of prednisolone were 120 ± 32 mg/kg per yr (3.3 ± 0.4 g/m^2) in the intervention and 138 ± 22 mg/kg per yr (3.7 ± 0.3 g/m^2) in the control groups (Table 2). The height SDS for patients in the intervention and control groups at enrollment was −1.6 (95% CI −2.2, −1.2) and −1.5 (−2.1, −1.3), and that at the 1-year follow-up was −1.5 (−2.1, −1.2) and −1.4 (−2.2, −1.1) respectively (P = 0.7). Cushingoid features were seen in four and five patients in the intervention and control groups, respectively; two patients had cataract. Four patients in the intervention group (three with peritonitis and one with cellulitis) and three in the control group (all with peritonitis) required admission for their management. Two patients in the intervention group (at 6- and 10-month follow-ups) and four in the control group (one at 6-month follow-up and three at 9-month follow-up) were considered treatment failures and were treated with cyclophosphamide (n = 2) or calcineurin inhibitors (n = 4). Enalapril was used, at a dose of 0.2 mg/kg per d, in one patient in the intervention group and two in the control group for stage 1 hypertension.

Subgroup Analysis

Relapse rates in patients in the two strata are shown in Table 5. Among patients receiving long-term, alternate-day prednisolone alone, the infection-associated and total relapses were significantly lower in the intervention group. Although there was a similar trend in patients receiving treatment with alternate-day prednisolone and levamisole, the difference in relapse rates in the intervention and control groups was NS.

Table 5. Relapse rates in patients receiving alternate day prednisolone alone (strata 1) and alternate day prednisolone with levamisole (strata 2)

	Alternate Day Prednisolone ($n = 68$)			
	Intervention ($n = 35$)	Controls ($n = 33$)	Rate Difference	P
Infection-associated relapses (episodes/patient per yr)[a]	0.6 ± 0.2	1.5 ± 0.4	0.9 (0.3, 1.4)	<0.001
Total relapses (episodes/patient per yr)[a]	0.9 ± 0.3	1.9 ± 0.5	1.1 (0.4, 1.7)	<0.001
	Alternate Day Prednisolone and Levamisole ($n = 32$)			
	Intervention ($n = 15$)	Controls ($n = 17$)	Rate Difference	P
Infection-associated relapses (episodes/patient per yr)[a]	0.7 ± 0.2	1.1 ± 0.4	0.4 (−0.3, 1.1)	0.2
Total relapses (episodes/patient per yr)[a]	1.0 ± 0.3	1.6 ± 0.4	0.6 (−0.3, 1.3)	0.2

[a]The relapse rates are the mean incidence density rates ± SD (95% confidence interval).

Discussion

This study included newly diagnosed patients with frequently relapsing nephrotic syndrome, eligible for therapy with alternate day corticosteroids with or without levamisole. During infectious illnesses, they were randomized to either receive prednisolone every day for 7 days (intervention group) or continue with alternate day therapy (controls). The study was powered to show a 50% reduction in infection-associated relapses in the former. With follow-up over 1 year, we showed that daily administration of maintenance doses of prednisolone during intercurrent infections reduced the rates of relapses by almost one-half, resulting in a higher proportion of patients with sustained remission. Furthermore, one of every six patients receiving this intervention showed infrequent relapses, thereby changing the course of nephrotic syndrome.

The reduction in relapse rates in this study was chiefly due to a reduced number of infection-associated relapses. Seventy percent of relapses in the intervention group and 74% in the controls were preceded by infections, chiefly of the upper respiratory tract. The mechanism by which infections induce relapses of nephrotic syndrome is unclear but might be related to the upregulation of T cells and cytokine-mediated increase in proteinuria (16,17). Although not proven, we speculate that daily therapy with corticosteroids might abrogate this upregulation, thereby reducing the risk of relapses.

Two previous studies have reported beneficial results of a similar strategy (11,12). From Saudi Arabia, Mattoo *et al.* (11) reported their experience with 36 patients with steroid-dependent nephrotic syndrome receiving prednisone at a maintenance dose of 0.5 mg/kg on alternate days. Alternate patients were allocated to either receive daily prednisone for 5 days during episodes of upper respiratory infections or continue on alternate-day prednisone. The results, at a 2-year follow-up, showed a significant reduction in relapse rates in the former. However, the study was conducted on a small number of patients, was not randomized, and did not provide estimates of infections and prednisone dosage in the two groups.

A randomized, placebo-controlled trial from Sri Lanka enrolled 48 patients with steroid-dependent nephrotic syndrome receiving long-term treatment with low-dose (<0.6 mg/kg), alternate-day prednisolone (12). The patients were allocated to receive prednisolone or placebo daily, in the same dose as that prescribed on alternate days during remission, for 7 days at the first sign of an upper respiratory tract infection. Therapy with medication or placebo was switched during the second infectious illness. Forty (83.3%) patients completed the study and showed significantly lower relapse rates when receiving daily prednisolone compared with the placebo. Because the patients were only observed for two consecutive infections, the effect of the intervention on the long-term course of nephrotic syndrome was unclear.

Whereas the previous studies enrolled patients who were in stable remission and managed on low-dose alternate-day prednisolone (11,12), we included freshly diagnosed patients with frequent relapses who were considered eligible for treatment with long-term, alternate-day prednisolone, with or without levamisole. Because these therapies form the initial standard of care for patients with frequent relapses, we assumed that a beneficial effect of this intervention should improve their care. The results from this study confirm our hypothesis that short-term administration of daily doses of prednisolone during infections significantly reduces the risk of relapses in frequently relapsing nephrotic syndrome. Although not powered for subgroup analysis, the benefits of this intervention were unequivocally present in the 68 patients receiving therapy with long-term, alternate-day prednisolone (Table 5). Although not statistically

significant, a similar trend was also found in the 32 subjects receiving the combination of alternate-day prednisolone and levamisole.

Patients in the intervention group had a significantly higher number of infections, most involving the upper respiratory tract. Although the precise reason for this observation is unclear, this group included four patients, each with 12 to 14 episodes of upper respiratory tract infections. Most infections were mild and self-limiting and did not require antibiotic therapy. The increase in infections did not appear to be related to corticosteroid administration, because despite the higher frequency of infections there was a trend toward lower cumulative steroid dose in the intervention group. The risk of serious infections that required hospitalization and corticosteroid side effects was similar in the two groups.

Although there was an increase in relapses with the number of infections, this trend was more apparent in the control group. After adjustment for the occurrence of infections, daily administration of prednisolone during these episodes independently resulted in 59% reduction in the rate of relapses. Our results also suggest that the benefit of the intervention is more apparent in children with a higher number of infections (Table 4).

This study has some limitations, the chief being the lack of a placebo arm. Although there was adequate allocation concealment before randomization, the physicians were subsequently aware of the allocation and therefore the potential for bias. Also, the diagnosis of infection was clinical, no efforts were made for virological or bacteriological confirmation, and the judgment of excluding allergies was on the basis of clinical presentation, past patient history, and family history. Although the usual number of infectious episodes in this study was three to four per patient/yr, the possibility of overdiagnosis of such episodes cannot be excluded. Epidemiologic studies show that school children in India have five to seven episodes of febrile illnesses annually (18), similar to that observed in the study presented here.

Finally, patients with frequent relapses who were selected had relatively mild courses of nephrotic syndrome. Subjects with difficult nephrotic syndrome with a prolonged duration of disease or high steroid threshold or those showing steroid toxicity were excluded. Because the steroid threshold in this study was 0.5 to 0.75 mg/kg every other day, it is unclear whether this intervention shall be useful in patients with a lower steroid threshold. It is also uncertain whether similar benefits shall be seen in patients with frequently relapsing nephrotic syndrome cotreated with other immunosuppressive agents, *e.g.,* mycophenolate mofetil or calcineurin inhibitors. The effect of the intervention in patients from developed countries and in populations where infections do not constitute a major cause for relapses of nephrotic syndrome also needs to be evaluated.

The occurrence of frequent relapses is associated with multiple complications and morbidity, including side effects of immunosuppressive medications. This study confirms that patients receiving long-term, alternate-day prednisolone with or without levamisole show reduced relapses if given a small daily dose of prednisolone during infectious illnesses. The concept of daily administration of the same dose of the corticosteroid during minor infections was convenient and understood by the parents. In view of the findings from this and previously published studies, we recommend that this intervention be considered for reducing infection-associated relapses in selected patients with frequently relapsing nephrotic syndrome.

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Disclosures

None.

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