Short Course of Daily Prednisolone During Upper Respiratory Tract Infection for Children With Relapsing Steroid Sensitive Nephrotic Syndrome

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SUMMARY

PREDNOS 2 was a double blind placebo controlled trial done to investigate the use of daily low-dose prednisolone for the treatment of upper respiratory tract infection –related relapses. It evaluated 365 children with relapsing steroid-sensitive nephrotic syndrome with and without background immunosuppressive treatment at 122 pediatric departments in the UK from February 1, 2013, to January 31, 2020. At the beginning of an upper respiratory tract infection, children received 6 days of prednisolone, 15 mg/m^2 daily, or matching placebo preparation. Those already taking alternate-day prednisolone rounded their daily dose using trial medication to the equivalent of 15 mg/m^2 daily or their alternate-day dose, whichever was greater. The primary outcome was the incidence of first upper respi-ratory tract infection-related relapse. The modified intention-to-treat analysis population comprised 271 children (mean (SD) age, 7.6 (3.5) years; 64.2% male), with 134 in the prednisolone arm and 137 in the placebo arm. The number of patients experiencing an upper respiratory tract infection-related relapse was 56 (42.7%) in the predniso-lone arm and 58 (44.3%) in the placebo arm (adjusted risk difference, 0.02; 95% CI, 0.14 to 0.10; *P* =0.70). No evidence was found that the treatment effect differed according to background immuno-suppressive treatment. A post hoc subgroup analysis assessing the primary outcome in 54 children of South Asian ethnicity (risk ratio, 0.66; 95% CI, 0.40-1.10) vs 208 children of other ethnicity (risk ratio, 1.11; 95% CI, 0.81-1.54) found no difference in efficacy of intervention in those of South Asian ethnicity (test for interaction *P*=0.09). The authors concluded that, results of PREDNOS 2 suggest that administering 6 days of daily low-dose prednisolone at the time of an upper respiratory tract infection does not reduce the risk of relapse of nephrotic syndrome in children in the UK and further work is needed to study the inter-ethnic differences in the study response.

COMMENTARIES

Evidence-Based Medicine Viewpoint

A group of researchers in the United Kingdom conducted a randomized controlled trial (RCT) to evaluate whether a short course of daily prednisolone administered to children with steroid sensitive relapsing nephrotic syndrome, at the onset of upper respiratory infection (URI) episodes, would reduce the occurrence of URI associated relapses [1]. Although, they did not specify a clinical question in the PICOT format, it can be deduced from the information provided, as follows. Population (P): Children (1-18y old) with relapsing nephrotic syndrome (irrespective of current treatment); Intervention (I): Oral prednisolone (dose at least 15 mg/m^2) for six days, started at the onset of a URI episode; Comparison (C): Placebo taken at the onset of a URI episode; Outcomes (O): URI-associated relapse, other relapses, cumulative dose of steroid, adverse events, behavior and quality of life indices; Timeframe of outcome measurement (T): 12 months from enrolment. The RCT is summarized in **Table I**.

Critical Appraisal

Overall, the trial was well designed and meticulously conducted. The investigators chose an appropriate study design, used a placebo for comparison of the trial intervention, and minimized common sources of bias. There were several refinements in the RCT, notably the use of strict definitions for frequently used concepts such as relapse, URI episode, and adherence. This diminishes subjective variations and fosters confidence. The investigators paid particular attention to the ethnic background of the RCT participants, given that all the previous four trials were conducted in Asian countries. A detailed critical appraisal of the trial methodology using the currently applicable Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2) [3], is summarized in

Table I Summary of the Trial

Study setting	A total of 122 Pediatrics departments across the United Kingdom were involved, 13 of which offered specialist Pediatric Nephrology services.
Study duration	February 2013 to January 2020. Follow-up was conducted for 12 months after enrolment.
Inclusion criteria	Age 1-18y, with steroid sensitive nephrotic syndrome (not defined further), with >2 relapses during the preceding year.
Exclusion criteria	Steroid resistant nephrotic syndrome (no definition specified), cyclophosphamide or rituximab therapy (current or within the previous 3 months), daily steroid therapy, or alternate day steroid therapy if the dose exceeded 15 mg/m^2.
Recruitment procedure	A Participant Information Sheet (PIS) was posted to families of potentially eligible children, approximately 1-2 weeks before scheduled clinic visits. Eligibility criteria were assessed (although it is not mentioned when and where), and participants were recruited when they visited the clinic.
Execution of the Intervention (and Comparison)	Participants were provided trial medication (as 5mg prednisolone or placebo tablets) by post. They were instructed to start treatment as per the number of tablets prescribed, for a total of 6 days. The dosage was calculated as follows. Those not already taking prednisolone received 15 mg/m^2 (upper limit 40 mg) per day; those already taking prednisolone received their alternate day dosage, or 15 mg/m^2 (upper limit 40 mg) per day, whichever was greater. Those in the Comparison group received placebo tablets in an identical fashion. Participants were instructed to identify an upper respiratory infection on the basis of presence for >24 hours of >2 among: sore throat, ear ache, ear discharge, runny nose, cough, hoarseness, or fever (tympanic temperature >37 deg C). Those with URI were instructed to start the trial medication.Participants were taught to identify a relapse defined as >3+ proteinuria on dipstick on 3 consecutive mornings, or the combination of generalized edema with proteinuria >3+ on dipstick. The relapse was deemed to be caused by the URI, if it occurred within 14 days of the URI episode. Relapses were treated with the usual (standard-of-care) treatment for relapses, with cessation of the trial medication if required. Current therapy was escalated in those who experienced >2 relapses within 6 months, or unacceptable side effects of steroids; these participants received a new immune-modulator agent. Therapy was reduced by omitting any ongoing immune-modulator medication in those who experienced remission for 6 months, or unacceptable adverse effects of current therapy.
Outcomes	The primary outcome was the proportion of participants with a URI-related relapse. Other outcomes were the overall rate of relapses, need for escalation of current therapy, reduction in current therapy, cumulative prednisolone dosage during 12 months, serious adverse events, adverse events, adherence to trial medication, behaviour and quality of life indices, and cost.
Follow-up protocol	Participants made 3-montly clinic visits. At each visit, they underwent clinical examination, and outcomes were recorded.
Sample size	The researchers assumed that URI was associated with a 50% relapse rate in children with relapsing steroid sensitive nephrotic syndrome. In order to detect a 35% relative reduction to 32.5%, 250 participants were required allowing for 80% power, and 5% Type I error. They planned to enroll at least 300 participants, making allowance for 15% drop-out. The sample size had to be increased to 360 during the trial because several enrolled participants did not qualify to receive the intervention (or placebo) throughout their participation in the trial.
Data analysis	Intention-to-treat analysis was planned, however rather than including all those who were randomized, data were analysed only in those who qualified to receive the trial medication. Thus, children who did not experience a URI episode during the 12 months following enrolment (hence were ineligible to receive trial medication) were excluded. Appropriate statistical methods were used to analyze the data.
Comparison of groups at baseline	Mean age, gender distribution, multiple anthropometric parameters, age at diagnosis, and duration from previous relapses to randomization, and mean dose of current prednisolone therapy, were comparable between the groups. The groups also had similar proportions of children taking no treatment, long-term prednisolone, combination of prednisolone with immune-modulator, and only immunomodulator. Ethnic background of participants was also comparable.
Summary of results	Intervention vs Comparison *Primary outcome*: • Proportion with URI related relapse: 56/134 vs 58/137

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Secondary outcomes:

- Number of single, double, triple and quadruple 'URI related relapses': 36 vs 41, 15 vs 10, 4 vs 7, and 1 vs 0, respectively.
- Proportion with any relapse: 91/134 vs 98/137
- Number of 1, 2, 3, 4, 5 and ≥6 relapses: 28 vs 39, 24 vs 24, 2 vs 11, 11 vs 14, 6 vs 5, and 0 vs 5, respectively.
- Proportion with escalation of current immunomodulator therapy: 72/130 vs 71/128
- Proportion with reduction in current immunomodulator therapy: 55/128 vs 62/129
- Median (IQR) cumulative prednisolone dosage in mg: 2060 (1128, 3355) vs 1880 (1115, 3295)
- Serious adverse events: No difference reported (data in a Supplementary file)
- Adverse events: No difference reported (data in a Supplementary file)
- Adherence to trial medication:
  - Timely initiation of trial medication during URI episodes: 328/384 vs 363/407
  - Median (IQR) time to starting trial medication: 0 (0,1) vs 0 (0,1)
  - Rate of adherence (at 3 monthly intervals): Reported as similar, but data not shown.
- Behavior score: No difference reported (data in a Supplementary file)
- Quality of life score: No difference reported (data in a Supplementary file)
- Cost: GBP 252 vs GBP 254 (reported in another publication) [2]

None of the differences was statistically significant.

Table II. Other than lack of clarity about blinding of outcome assessors, there were no other major concerns.

Although, there are no major lacunae in the RCT, some aspects merit consideration. The investigators chose trial medication dosages based on body surface area, but did not report the surface area of the participants at baseline or at any of the follow-up visits. The basis for choosing a prednisolone dose of 15 mg/m^2 for six days, was not explained.

It is unclear why the investigators defined a 'URI related relapse' as occurring within 14 days of a URI episode. On the one hand, this wide interval is beneficial, as it would presumably not miss any URI-related relapse. On the other hand, most URI episodes resolve within the first week of onset, suggesting that some of the relapses counted as URI-related relapses, may not have been so. It can also be argued that the duration of trial therapy i.e., six days may have been chosen to coincide with the usual upper limit of a URI episode. Therefore, it may be worth re-examining the data to check whether there was any difference in the proportion of children experiencing relapse within the first week of a URI episode.

In this RCT, 30% of participants in the intervention group, and 25% in the comparison group, were receiving long-term maintenance prednisolone at the time of enrolment. Considering the anthropometric parameters reported, this would translate to fairly robust dose of steroids. Since the maintenance doses were not ceased during the trial, it is somewhat surprising that the cumulative median dosage of prednisolone over the entire 12-month trial period was just around 2g in both the groups. In fact, a table in the publication reported that the mean pre-trial prednisolone dose was only 0.3 mg/kg on alternate days, which was lower than in other trials. One wonders if this could be a reason that 55% children in either group in this trial required escalation of therapy.

The investigators reported that the trial concluded on 31 January, 2020. Presumably, this means that the last follow-up visit of all children was concluded before that date. If yes, then there would be no COVID-19 related URI in the study population. However, if recruitment ended in January, 2020 with a further 12-month follow-up, then COVID-associated URI could be a cause for some relapses, in which case the short course of low dose prednisolone may make no difference.

The investigators' assumption that 50% URI episodes lead to relapses did not hold, as only about 20% of these episodes led to relapse in the non-intervention arm. Some experts may contend that a much larger sample size would be required to detect clinically meaningful differences with this relatively infrequent background event rate.

In the study population, more than 50% participants were overweight or obese. The situation may be quite different in other population settings, which should be kept

Table II Critical Appraisal of the Study

Criteria	*Response*	*Comments*
Domain 1: Risk of bias arising from the randomization process		
Was the allocation sequence random?	Yes	An internet-based randomization program was used to generate the allocation sequence, although no details were specified. Randomization was stratified on the basis of current treatment.
Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	The allocation sequence was not available to investigators enrolling trial participants. At the time of enrolment, allocation was done wither using the internet program, or by a phone call to the coordinating centre.
Did baseline differences between intervention groups suggest a problem with the randomization process?	No	As shown in Table 1, the groups were comparable. However, body surface area of participants was not reported.
Domain 2: Risk of bias due to deviations from the intended interventions.		
Were participants aware of their assigned intervention during the trial?	Unclear	It was reported that families of participating children, as well as the investigators were blinded to the allocation. However, it is unclear whether they were (or remained) blinded to the intervention after allocation.
Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Unclear	This was not reported in the trial.
Were there deviations from the intended intervention that arose because of the trial context?	No	
Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	The investigators used a modified intention to treat analysis (as described in Table 1).
Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were rendomized.	No	There were no protocol deviations reported i.e., participants received the medications as per the allocation sequence.
Domain 3: Risk of bias due to missing outcome data		
Were data for the outcomes available for all, or nearly all, participants randomized?	Yes	All randomized participants who qualified to receive the trial intervention (or comparison) were included in the analysis (of all outcomes), whereas those who remained in the trial without receiving the intervention (or comparison) were not included in the analysis. There was a very low drop-out rate.
Is there evidence that the result was not biased by missing outcome data?	No	Although there was low attrition, no additional analyses were performed to ensure that the overall result was not biased by missing data.
Could missingness in the outcome depend on its true value?	No	The attrition rate appears to be too low to influence the overall result.
Is it likely that missingness in the outcome depended on its true value?	No	
Domain 4: Risk of bias in measurement of the outcome		
Was the method of measuring the outcome inappropriate?	No	However, all the outcomes were patient/family reported outcomes. Although the determination of these outcomes is not complex, a moderate level of education/ empowerment may be necessary for reliable ascertainment and reporting.
Could measurement or ascertainment of the outcome have differed between intervention groups?	Unclear	The baseline literacy level of parents/children was not described.
Were outcome assessors aware of the intervention received by study participants?	Unclear	This was not specifically reported.
Could assessment of the outcome have been influenced by	Yes	Although fairly objective criteria were used to define

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knowledge of intervention received?		concepts like URI, relapse, and URI related relapse, these could have been influenced by knowledge of the allocation.
Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Unclear	No data were provided to interpret whether participants could guess their allocation.
Domain 5: Risk of bias in selection of the reported result		
Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	There were no apparent deviations in the analysis plan from that reported in the Trial registration.
Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements	No	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No	

in mind, if trial results are extrapolated to other settings.

Conclusion: This well-designed RCT did not demonstrate any benefit of administering a short course of prednisolone (6 days at 15 mg/m^2) at the onset of URI episodes, in children with frequently relapsing steroid sensitive nephrotic syndrome.

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Contemporary Researcher's Viewpoint

Idiopathic nephrotic syndrome, characterized by heavy proteinuria, hypoalbuminemia and edema, is the most common chronic kidney disease of childhood [1]. Steroid sensitive nephrotic syndrome, constituting the majority of cases, is a self-limiting disease with favorable long-term outcomes. However, the occurrence of frequent relapses is associated with significant morbidities due to the illness and the toxicity of medications. Even short-term use of high dose corticosteroids has significant implications: every 1 mg/kg increment in dose increases the risk of adverse events 2.5-fold, comprising of 1.4- to 3.6-fold risk of hypertension, obesity, diabetes and fractures [2]. Therefore, preventing frequent relapses is a major goal when managing nephrotic syndrome [1]. Therapy with prednisolone in low doses on alternate days (AD) is usually the first strategy; however, breakthrough relapses are common, and corticosteroid adverse effects may necessitate use of steroid-sparing agents [3].

Almost one-half of disease relapses are precipitated by minor infections, usually of the upper respiratory tract (URTI). Encouraging findings from a prospective study [1] were confirmed by two randomized controlled trials (RCTs) from South Asia that found that giving the AD dose of prednisolone daily for 5-7 days, beginning with the onset of infection, reduces the risk of relapses in patients with frequently relapsing nephrotic syndrome managed on AD prednisolone. The placebo-controlled cross-over trial from Sri Lanka on 48 patients [4], and the open-label RCT from India on 100 patients [5], formed the basis for the Kidney Disease Improving Global Outcomes (KDIGO) 2012 [6] and Indian Society of Pediatric Nephrology 2021 [1] recommendations that, in patients receiving long term alternate-day prednisolone, the same dose should be administered daily for 5-7 days during fever or respiratory tract infections. Based on additional evidence from another placebo-controlled cross-over RCT from Sri Lanka on 48 patients not on corticosteroids at the time of a similar intervention [7], the KDIGO 2021 extended the recommendation to use prednisone at 0.5 mg/kg daily for 5-7 days during episodes of URTI and other infections to reduce the risk of relapse in all patients, whether on or off corticosteroids [8].

Results from the recent PREDNOS 2 have cast doubt over the utility of this strategy in preventing infection-associated relapses of nephrotic syndrome. This multi-

center, prospective, double-blind, placebo-controlled RCT randomized 365 patients with relapsing nephrotic syndrome (≥2 relapses/year) during 2013-2020 at 122 centers across the United Kingdom to receive either prednisolone or matching placebo at 15 mg/m^2 daily for 6 days, beginning at the start of an URTI. Baseline characteristics and outcomes are presented only for the 271 patients who reported experiencing an URTI during the 1-yr follow-up. Almost half of these patients were on non-steroidal immunosuppression, and 23% were off immuno-suppressive medications; one-fifth of patients reported South Asian ancestry. Similar proportions of patients in the prednisolone and placebo groups experienced an infection-associated relapse (42.7% vs 44.3%) or any relapse (68.9% vs 74.2%). Post hoc analysis ruled out any influence of ethnicity or concomitant immunosuppression on the direction and size of intergroup differences. Strengths of the PREDNOS 2 include its large size, placebo-controlled design, inclusion of diverse ethnic groups, and generalizability to all patients with steroid-sensitive nephrotic syndrome.

The reasons for differences in results between this and the prior RCTs are unclear, and may reflect variations in patient characteristics and study methodologies. The prior RCTs have been criticized for being single-center small studies that were at high risk of bias due to either cross-over or open-label design. The inclusion of participants on levamisole in the Indian study might have introduced heterogeneity and/or attenuated efficacy estimates [5]. However, relapse is an objective outcome that is unlikely to be influenced by biased assessment, and the finding of statistically significant differences despite the small study sizes, supports the use of the intervention. PREDNOS 2 included patients with infrequent relapses as well as patients with frequent relapses managed on other immunosuppressive agents [9]. While this strategy improved its generalizability, it may have attenuated the impact of the intervention since both category of patients may be inherently less prone to develop relapses following infections. Other concerns, stemming from pragmatic choices made when planning study methods, include a high (34.7%) proportion of post-randomization exclusions, and dependence on patient reporting for both the intervention and assessment of outcome.

Infection-associated relapses are as relevant in developed as developing countries, as was illustrated by the reduced incidence of relapses during lockdowns imposed during the SARS-CoV-2 pandemic [10]. Differences in climate, hygiene and ethnicity are unlikely to influence corticosteroid efficacy in suppressing relapses following infections. While awaiting consensus, it appears prudent to continue to recommend the use of daily prednisolone during episodes of URTI in patients with frequently relapsing or steroid-dependent nephrotic syndrome who are using altenate day prednisolone as maintenance therapy. Prednisolone use should not be advocated during infections in patients not on mainte-nance therapy with altenate day prednisolone, nor in those receiving other immuno-suppressive agents. Future trials should either focus on, or examine in adequately-sized subgroups, participants with frequent or infrequent relapses, and those receiving altenate day prednisolone, other agents and no therapy.

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Pediatric Nephrologist's Viewpoint

Globally nephrotic syndrome remains the most common glomerular disease encountered by pediatricians with higher incidence reported among South Asians [1]. Corticosteroids remain the first line therapy but although over 80% are

steroid sensitive (SSNS), 50% -70% of SSNS may evolve into frequent relapsers (FRNS) or steroid dependent (SDNS) requiring multiple courses of steroids and predisposing them to short- and long-term complications of steroid therapy [2]. Trial of long-term alternate day steroid (LTAD) at low dose has been advocated to avoid steroid toxicity while keeping these children in remission. If this strategy fails then the child is usually tried on various steroids sparing agent which includes levamisole, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors and rituximab [3, 4]. Despite use of these strategies, breakthrough relapses are common and studies have shown that nearly 50% of relapses are triggered by viral upper respiratory infections (URTI) and vis-à-vis over half of URTI may precipitate a relapse [4-8]. Although the mechanism by which infections result in relapses is not clear, it is postulated that viral URTI results in T lymphocyte up-regulation which results in cytokine release which plays a key role in inducing relapse [9, 10]. Few studies have also shown that LTAD steroid increases the risk of adreno-cortical suppression and children with suppressed adreno-cortical axis are at increased risk for relapse [11]. Hence increasing the dose of steroid at onset of viral URTI seems rational as this may attenuate the up regulation of T cells and prevent infection associated relapses [12]. Previous studies [13-16] primarily from Asian continent have consistently supported this hypothesis (**Web Table I**) and this strategy has also been endorsed by recent guideline updates [3,4]. Kidney Disease Improving Global Outcome (KDIGO) glomerular disease guideline 2021 recommends single dose daily glucocorticoids at 0.5 mg/kg/day for episodes of upper respiratory tract and other infections for 5-7 days [4] whereas Indian Society of Pediatric Nephrology (ISPN) guideline recommends switch to daily steroid for a similar duration if on alternate day steroid regime at onset of infection [3]. Despite this, one needs to remember that most of the previous studies on which these endorsements are based had various methodological flaws including lack of blinding, small sample size, post-randomization exclusions and crossover design as highlighted by the Cochrane report [17]. Additionally, these studies did not explore the usefulness of increasing steroid dose for URTI among those on other steroid sparing agents' particularly potent agents such as mycophenolate mofetil or calcineurin inhibitors. Lastly, these studies were done among Asians, making their extrapolation to multi-ethnic populations tricky. With this perspective, the pediatric nephrology community was eagerly awaiting the outcome of the PREDNOS 2 trial wherein they re-examined whether increasing steroids during viral URTI decreases relapse rates in a multi-ethnic population [18].

PREDNOS 2 had multiple strengths. It was a well conducted study with robust trial design and their cohort strength far exceeded the combined number of children recruited in the four previous studies (**Web Table I**). This large cohort size is likely to have significant influence in any future meta-analysis. Additionally, unlike previous studies, the cohort was multi-ethnic, included children on all type of background treatment and systematically recorded corticosteroid adverse events including effects on behavior. Evidence based medicine has always been a rapidly changing paradigm and newer evidence through well conducted studies with robust methodology negating previously accepted notions is not uncommon. A recent example in pediatric nephrology being the various RCTs over the last decade questioning the utility of prolonged tapering of steroids after first episode nephrotic syndrome in reducing subsequent relapse rates [19].

Keeping these in perspective, should we in India change our practice of switching to daily steroid at onset of viral URTI among FRNS/SDNS which has been advocated even in the recent ISPN guideline [3]. While acknowledging the robust clinical design of PREDNOS 2 and its large cohort size, it might be still too hasty for us to change our Indian guidelines. Even in PREDNOS 2, lower rate of URR was noted among South Asian population; and although this was not statistically significant, South Asians only comprised a fifth of the total cohort and the trial was not powered enough to show significant difference among various ethnic sub groups. Moreover, the PREDNOS 2 trial was done in UK, which has a temperate climate which is quite different to the mostly tropical climate of Indian subcontinent and might explain their significantly lower URTI episodes than those reported from the Indian sub-continent. Etiology of the underlying viral URTI was also not explored and one can argue this to be a confounding factor as the etiologies might differ between Asia and UK. Lastly, although URR are common, some children do relapse without any evidence of URTIs [5,7]. PREDNOS 2 did not attempt to differentiate between these two groups at onset and it may be argued that steroids might be more useful among those children who have frequent URR than those who usually relapse without any URTIs. Hence, a repeat of PREDNOS 2 among a South Asian population with a high incidence of URTI and URR in a tropical country might give different results. We always have a tendency to generalize our findings but unfortunately one size fits all formula hardly works in medical science and personalized medicine is increasingly been recognized as the optimum goal [20].

In conclusion, a pragmatic approach might be to identify the sub group of children who have high URR and implement the strategy of increasing steroids during URTI attacks among them. As the PREDNOS 2 trial did not show any difference in side effects between the steroid and the placebo group, it might be justified to continue the current

recommendation of increasing steroid during URTI in our sub-continent till availability of robust trials focusing on the sub population likely to show more benefit from such strategy.

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Pediatrician's Perspective

The PREDNOS 2 study is a double-blind placebo control study to evaluate the usefulness of short course of steroids during upper respiratory infections to prevent relapse in children with SSNS. The study concluded that there was no difference in the relapse rates in both groups.

In my opinion, giving intermittent short course of steroids during episodes of upper respiratory infections will lead to overuse of steroids as these infections are common and are bound to occur frequently in children attending daycare and schools. There should also be clear criteria to define upper respiratory infection as allergic rhinitis can be confused as upper respiratory infection and will again lead to overuse of steroids.

Relapses during upper respiratory infections does not usually occur and aiming at reducing the risk of relapse by giving short course of steroids for 5-6 days is not really necessary nor is it helpful. When we weigh the risk vs benefits, the risks of overuse of steroids and the danger of self-medication by parents are more than the benefits.

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Web Table I Summary of the Studies

Study, year, sample size[a]	*Type of study*	*Study population*	*Intervention arm*	*Control arm*	*Outcome*
Pre PREDNOS 2					
Mattoo et al., 2000, *n*=36 (not reported)	Single center study with a follow up of 2 years wherein study population was divided in two arms alternately	Those on low dose (0.5 mg/kg) a/d maintenance prednisolone. 14 had received cyclophosphamide. Included cohorts were not on any other immunosuppressant.	Group 1: At onset of viral URTI a/d prednisolone dose was switched to daily dose for 5 d.	Group2: Advised to continue on a/d steroid as before despite viral URTI	Total number of relapses over the 2-year period in group 1 was 40 with a mean of 2.2 (0.87) per patient, and in group 2 it was 99 with mean of 5.5 (1.33) per patient (*P*=0.04)
Abeyagunawardena, et al., 2008, *n*=48 (40)	Single center randomized double-blind placebo controlled cross over trial. At onset of URTI patientwas randomly allocated to either place-bo arm or pred arm for the first viral URTI and the other arm for the second viral URTI.	Those on low dose (0.1-0.6mg/kg) a/d maintenance pred. Included cohorts were not on any other immunosuppressant.	The first viral infection was treated with placebo in 22 children and with pred in 18, and a relapse of NS was seen in 10 and four children, respectively. As this was a crossover trial, the second viral infection was treated with placebo in 18 children and with prednisolone in 22. A relapse was noted in nine and three children respectively.		48% relapses were noted when URTI was treated with placebo and 18% relapses were noted when episodes treated with extra dose of steroid (*P*=0.014).
Gulati, et al., 2011, *n*=100 (89)	Single center open label parallel group randomized control trial.	Those on low dose (0.5 to 0.75 mg/kg) a/d maintenance prednisolone with vermisole (*n*=32) or without levamisole (*n*=68). Those with steroid threshold >1mg/kg were excluded. Included cohorts were not on any other immunosuppressant.	At onset of viral URTI a/d pred dose was switched to daily for 7 d.	Advised to continue on a/d steroid as before despite viral URTI	Lower IAR in the intervention arm (rate difference, 0.7 episodes / patient per year; 95% CI 0.3, 1.1). 59% reduction in frequency of relapses seen in intervention arm (rate ratio, 0.41; 95% CI 0.3, 0.6). Reduction in IAR was not significant among those on levamisole along with low dose a/d steroid.
Abeyagunawardena, et al., 2017, *n*=48 (33)	Single center randomized double blind placebo controlled cross over trial. If the criteria for viral URTI were met, the patient was randomly allocated to either placebo arm or pred arm for the first year. The allocation was switched for the next year.	Previous SDNS but currently off any immunosuppressant for ≥3 mo.	In group 1, the 19 patients who completed the study received pred for the first year of observation and placebo for the secondyear. In group 2, the 14 patients who completed the study received placebo for the first year and pred for the second year. The study was completed in 2 years.		Within the intervention group, 65.6% did not relapse in contrast, to 40.6% in the control group (*P*=0.014).

[a]*Final number assessed given in parentheses.*