Characteristics Associated with Variation in Corticosteroid Exposure in Children with Steroid-Sensitive Nephrotic Syndrome: Results from a Canadian Longitudinal Study

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Key Points
- Variability exists in regards to corticosteroid prescriptions for children with steroid-sensitive nephrotic syndrome across Canadian sites.
- Children’s age and ethnicity are associated with average corticosteroid dose and duration of therapy.
- Variation observed in corticosteroid prescriptions could be attributed to unmeasured differences between patients.

Abstract
Background Variation in dose and duration of corticosteroids for childhood-onset steroid-sensitive nephrotic syndrome occurs worldwide, likely reflecting the evolving evidence on optimal dosing and variable severity of the disease observed between patients. We conducted a study to determine the associations between site, physician, and patient factors, and average daily corticosteroid dose and duration of therapy.

Methods Data were derived from the Canadian Childhood Nephrotic Syndrome (CHILDNEPH) Project, an observational longitudinal study from 2013 to 2019 of children with nephrotic syndrome involving pediatric nephrologists in 11 sites across Canada. The primary outcome was average daily corticosteroid dose prescribed per episode of proteinuria, reported as mg/m² prednisone equivalents. Secondary outcome was duration of treatment for each episode of proteinuria in days. Exposure variables were categorized into site-, physician-, and patient-level variables.

Results In total, 328 children, median age at enrollment of 4.3 years old (interquartile range [IQR], 3.6), participated and were followed for a median time of 2.62 years (IQR, 2.6). The observed variability in average daily corticosteroid dose and in duration of therapy was mostly attributed to the site where the patient was treated. Accounting for between patient, physician, and site differences, average daily corticosteroid dose decreased with increasing age (beta coefficient, −0.07; 95% confidence interval [95% CI], −0.09 to −0.05, P<0.001). African and Indigenous ethnicity was associated with longer treatment duration compared with White patients (beta coefficient: African, 42.29, 95% CI, 7.85 to 76.73, P=0.02; Indigenous, 29.65, 95% CI, 2.79 to 56.52, P=0.03).

Conclusions We found practice variation with respect to corticosteroid prescriptions across 11 Canadian sites, and that variation is mostly explained at the site level. Age and ethnicity are important factors to be considered, because they are significantly associated with the average corticosteroid dose and duration of therapy.

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Introduction
Childhood nephrotic syndrome is considered a rare condition due to its relatively low incidence worldwide (1). However, it is the most common glomerular disease in children. Management of nephrotic syndrome is challenging for patients, families, and
health care providers due to a frequently relapsing course in >50% of children (2). Corticosteroids are universally accepted as the main therapy for the initial episode and for successive relapses of the disease. Although corticosteroids are effective in inducing remission of proteinuria in the majority of patients (approximately 90%) (3), they have well known and potentially serious adverse effects, raising the need for finding the optimal dose to achieve and maintain remission with the least toxicity. Several studies have, therefore, investigated different durations and therapy doses, leading to an international consensus that supports a broad range of recommendations for therapy (4). Variation in care in regards to the dose and duration of treatment with corticosteroids of children with steroid-sensitive nephrotic syndrome occurs worldwide, likely reflecting the evolving evidence on what is considered optimal dosing and variable severity of the disease observed between patients. Similar to others (5,6), we published a survey in 2013 (7) reporting on significant practice variation among Canadian pediatric nephrologists in various aspects of the management of nephrotic syndrome, including corticosteroid dosing regimens, duration, and taper. Then, to evaluate factors associated with dosing and variation in treatment, we conducted a Canada-wide longitudinal study from 2013 until 2019. Our objectives were to determine the associations between site (existence of a standardized protocol), physician (demographics, training), and patient factors (demographics), and average daily corticosteroid dose prescribed per episode of treatment for proteinuria and duration of therapy. We hypothesized that patient-, physician-, and site-related characteristics would be associated with both the dose and the duration of the corticosteroids prescribed for the treatment of nephrotic syndrome.

Materials and Methods
This study was approved by University of Calgary Conjoint Health Research Ethics Board (REB 13-0059) and institutional ethics boards in all other sites. Ethics approval numbers from other sites are listed in the Supplemental Material.

Data
Data were derived from the Canadian Childhood Nephrotic Syndrome (CHILDNEPH) Project, an observational longitudinal study of children with incident and prevalent nephrotic syndrome and of pediatric nephrologists providing care in 11 sites across Canada. A detailed description of the study design and inclusion/exclusion criteria of the CHILDNEPH study has been reported previously (8). In brief, children 1–18 years of age were included if they met clinical criteria for nephrotic syndrome (edema, proteinuria ≥3+ on dipstick or ≥3 g/L on urinalysis, or urine protein-creatinine ratio ≥200 mg/mmol for 3 consecutive days) were recorded with start dates, marked by the date of start of full dose prednisone (60 mg/m² or 2 mg/kg, as per dosing regimen indicated in each prescription). For the purpose of the study, we defined an episode of treatment as the period between the date of start of full-dose prednisone (for a relapse of proteinuria) to the date of discontinuation of corticosteroid after taper, or date of restart of full-dose corticosteroid (as in a patient with a relapse while tapering prednisone).

Outcome and Exposures
The primary outcome was defined as the average daily corticosteroid dose per episode, calculated by dividing the total dose (in mg of prednisone equivalents) prescribed during an episode divided by the duration (in days) of the episode, for each episode, for each patient. The average daily corticosteroid dose is reported as mg/m² prednisone equivalents. This outcome definition is consistent with measures of corticosteroid exposure used in prior nephrotic syndrome corticosteroid-dosing studies (9,10). All episodes observed were included in the analysis, and they were categorized as either first presentation or relapse. The secondary outcome was duration of treatment of each episode in days.

Exposure variables of interest were categorized into site-, physician-, and patient-level variables, which were collected a priori in the study. The only site-level variable used was the existence of a standardized protocol within the site for treating first presentation and relapses (information was obtained from the site investigator as existence of site-based protocols [yes/no] at the beginning of the study, and did not change during the study). Standardized protocols refer to protocols that the site has established for treatment, which are shared among physician groups. Physician-level variables included self-reported sex, year of graduation from nephrology fellowship, and location of nephrology training (Canada versus outside Canada). These site- and physician-level variables were selected because they were observed to affect variability in practice patterns according to our published survey (7). Patient-level variables included age, sex, ethnicity (White, South Asian, African, Indigenous, East Asian, other), status at entry into study (first presentation, first or second relapse), follow-up time, parent education (below or above post-secondary education), and family income. These variables are further described in Table 1.

Statistical Analyses
Medians, interquartile range (IQR) or mean±SD, and percentages were used to summarize site-, physician-, and patient-level variables (Table 1). To determine the associations between site-, physician-, and patient-level characteristics and average daily corticosteroid prescribed for first presentation and subsequent relapses of nephrotic syndrome, we used mixed-effects models with fixed effects for site (standardized protocols yes/no), physician (sex, years
in practice, location of training), and patient (age, sex, ethnicity, status at entry into study) characteristics, and random effects to account for physicians clustering within site, and episodes clustering within physicians (Figure 1). The variation in average daily corticosteroid dose was measured by the SD of the random effects of the three levels (site, physician, patient). Linear mixed models were used to examine primary and secondary outcomes. The unit of analysis was the episode. Linear mixed-model regression estimates and 95% confidence intervals (95% CI) were reported. Statistical analyses were conducted using a significance alpha level of 0.05. All analyses were conducted using STATA 14.2 (11). Linear mixed models were repeated for the cohort of patients who entered the study at first presentation only, and results are provided in Supplemental Tables 1 and 2. All model assumptions were checked and dealt with appropriately.

## Results

### Characteristics of the Cohort

After informed consent, data from a total of 328 children (129 females and 199 males) with a median age at enrollment of 4.3 (IQR, 3.6) were collected; 58 pediatric nephrologists across the 11 sites participated between 2013 and 2019. Of all the patients, 164 (50%) were White and 113 (34%) had families with a household income >C$99,000 during the follow-up period. The majority of the participants’ parents had post-secondary and higher education, 232 (71%) for their mother and 195 (59%) for their father. A majority of physicians (n=35, 60%) were males and around half of them completed their training in Canada (n=164, 50%), Table 1. The physician cohort had a median clinical experience of 15 (IQR, 11) years. Among the 11 participating sites, six (55%) reported using common treatment protocols within their site.

The total number of episodes observed was 1251 (270 were first presentations and 981 were relapses) over a median follow-up of 2.62 (IQR, 2.6) years. Overall, 69% of the participants had 1–4 relapses and 4% experienced ≥10 episodes during the follow-up. The median (IQR) number of relapses was three (3).

### Outcome and Exposures

Figure 2 shows the average daily corticosteroid dose (in 10 mg/m² per day increments) per episode (either during first presentation or relapses) varied by site when patients within a site were grouped.

The median (IQR) of the daily corticosteroid dose (in 10 mg/m² per day increments) per episode for first presentation and relapses were 3.2 (1.2) and 2.5 (1.5), respectively. Similarly, we observed variation in duration of treatment between patients, by site (Figure 3), for first presentation and relapse therapy. The median (IQR) duration of treatment per episode (in days) for first presentation and relapses were 86 (30) and 50 (34), respectively.

Table 2 presents a summary of the results from the linear mixed-model analysis of average daily corticosteroid dose. Accounting for between-patients, between-physician, and between-site difference, we observed significant differences in average daily corticosteroid dose depending on the age of the patient. The average daily corticosteroid dose significantly decreased with increasing age (beta coefficient, \(-0.07, 95\%\, CI, -0.09\, to\, -0.05, P<0.001\)). The other covariates were not significant. There was higher variability in average daily corticosteroid dose observed between sites (SD, 0.48), followed by patients (SD, 0.36), and lastly physician (SD, 0.09), Table 2.

When duration of treatment with corticosteroids per episode was examined with respect to site-, physician-, and patient-level characteristics using a linear mixed model, we found that being African or Indigenous in

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### Table 1. Characteristics of the cohort, by patient, site, and physician levels

| Characteristics                  | Median (Interquartile Range) or n (%) | Missing, n (%) |
|----------------------------------|---------------------------------------|----------------|
| Patients (n=328)                 |                                       |                |
| Age at enrollment, yr            | 4.3 (3.6)                             | 4 (1.2)        |
| **Female**                       |                                       |                |
| Status at enrollment             |                                       |                |
| First presentation               | 273 (83.2)                            |                |
| First relapse                    | 38 (11.6)                             |                |
| Second relapse                   | 17 (5.2)                              |                |
| Ethnicity                        |                                       |                |
| White                            | 164 (50)                              | 5 (1.5)        |
| South Asian                      | 36 (11)                               |                |
| African                          | 9 (2.7)                               |                |
| Indigenous                       | 11 (3.3)                              |                |
| East Asian                       | 38 (11.6)                             |                |
| Other                            | 65 (19.8)                             |                |
| Parent education                 |                                       |                |
| **Mother**                       |                                       |                |
| Postsecondary and above          | 232 (70.7)                            |                |
| Below postsecondary              | 65 (19.8)                             |                |
| Did not answer                   | 31 (9.5)                              |                |
| **Father**                       |                                       |                |
| Postsecondary and above          | 195 (59.4)                            |                |
| Below postsecondary              | 70 (21.3)                             |                |
| Did not answer                   | 63 (19.2)                             |                |
| Family income, US$               |                                       |                |
| <20K                             | 22 (6.7)                              | 12 (3.7)       |
| 20K–49K                          | 51 (15.5)                             |                |
| 50K–99K                          | 81 (24.7)                             |                |
| >99K                             | 113 (34.4)                            |                |
| Do not know                      | 49 (14.9)                             |                |
| Follow-up, yr                    | 2.6 (2.6)                             |                |
| **Physician (n=58)**             |                                       |                |
| Female                           | 23 (39.7)                             | 16 (27.6)      |
| Training location                |                                       |                |
| Canada                           | 32 (55.2)                             | 16 (27.6)      |
| Foreign                          | 9 (15.5)                              |                |
| Both                             | 1 (1.7)                               |                |
| Experience, yr                   | 15 (11)                               | 17 (29.3)      |
| **Sites (n=11)**                 |                                       |                |
| Protocol                         | 6 (54.5)                              |                |
| Standardized                     | 5 (45.5)                              |                |

IQR, interquartile range.
descent was associated with increased duration of treatment with corticosteroids for each episode compared with being White (African beta coefficient, 42.29, 95% CI, 7.85 to 6.73, \( P < 0.02 \), and Indigenous beta coefficient, 29.65, 95% CI, 7.29 to 56.52, \( P < 0.03 \)) respectively (Table 3). Higher variability in duration of treatment was observed between sites (SD, 18.49), followed by physicians (SD, 14.91), and lastly patients (SD, 12.71), Table 3.

Discussion

In this pan-Canadian longitudinal study on childhood-onset steroid-sensitive nephrotic syndrome, we observed variability in both the average corticosteroid daily dose and the duration of therapy across pediatric nephrology sites within Canada.

The observed variability in average daily corticosteroid dose in the linear mixed model was mostly due to the site where the patient was treated, followed by patient characteristics, then physician characteristics. Similar practice patterns among physicians belonging to the same site and different between sites may explain why we observed that “site” was contributing to the most variation observed in the average daily corticosteroid dose. However, having a standardized protocol at a site was not associated with differences in average daily corticosteroid dose. Other unmeasured variables may be contributing to the variability observed, such as low-dose corticosteroid therapy used in some sites for children with steroid-dependent nephrotic syndrome. The only significant fixed-effect variable was patient age. None of the fixed effects at the physician level were significant in the linear mixed models. Likewise, the variability in duration of therapy with corticosteroids in the linear mixed model was mostly driven by the site where the patient was treated, followed by physician, and patient characteristics. We also found a high residual in the random effects parameters suggesting the existence of genetic and environmental factors that we were not able to account for and contribute to the variability in duration of treatment. For example, information regarding time to remission was not consistently collected and patients who took longer to achieve remission may have been prescribed longer courses of corticosteroids. In this model, the only significant fixed-effect variable was patient ethnicity.

We found that patient’s age was significantly associated with differences in average daily corticosteroid dose, after accounting for between-patient, between-physician, and between-site differences. Average daily corticosteroid dose

![Figure 1. A hierarchical dataset: Site, physician, and patient characteristics. IP, initial presentation.](image1)

![Figure 2. Average daily corticosteroid dose per episode of proteinuria by site (in 10 mg/m² per day increments). S, standard protocol; NS, nonstandard protocol.](image2)
per episode (in mg/m² prednisone equivalents) was significantly lower with increasing age. A possible explanation is the fact that most physicians prescribe 60 mg of prednisone as a maximum dose, regardless of age, weight, or body surface area, and thus older children (with body surface area >1 mg/m²) will receive less prednisone for body size compared with younger children (12). Average daily dose was calculated using total mg prescribed during an episode divided by total days on treatment, then we calculated what the dose would have been in mg/m² for

![Table 2](attachment:image.png)

95% CI, 95% confidence interval; ref, reference.  
*P value is <0.05, the result is statistically significant.
the patient’s height and weight recorded at the start of the episode. Therefore, it is clear from the data that older children indeed receive less corticosteroids per mg/m², as expected. Further, this observed result may also indicate that older patients (adolescents) are prescribed lower doses of corticosteroids to limit side effects, which are particularly harmful during that period of life (sometimes causing growth retardation, cosmetic side effects, mood, and behavioral problems). Our study did not explore this potential reason.

Ethnicity was associated with variation in duration of treatment. African and Indigenous children received longer corticosteroid therapies compared with White children. This finding may indicate alignment in prescribing practices in response to prior publications reporting differing response to immunosuppressants and disease course by ethnicity (13). Different pharmacokinetics of corticosteroids in these patients may also play a role (14). However, this observation will require formal testing as the African and Indigenous sample size (n=9, 3%, and n=11, 3%, respectively) was too small to draw a conclusion. Our cohort was limited to steroid-sensitive nephrotic syndrome and patients did not need to undergo a biopsy to enter the study as biopsies are not routinely conducted in clinical care for patients with steroid-sensitive nephrotic syndrome. Therefore, we cannot examine further whether treatment duration in African or Indigenous patients was due to focal segmental glomerulosclerosis or another pathology, which is more difficult to treat with corticosteroids (15).

Although we did not evaluate outcomes on the basis of corticosteroid dosing in this study, our findings reiterate that the optimal corticosteroid dose and duration of therapy to improve clinical outcomes remain unclear. Various treatment protocols have been published, including the international Kidney Disease Improving Global Outcomes Guidelines in 2012 (4), but in Canada and many other countries no consensus exists on the most appropriate corticosteroid regimen to achieve and maintain remission with the least adverse effects. Evidence synthesized in a 2007 Cochrane review (16) initially suggested that 6 versus 3 months, and higher cumulative corticosteroid doses for the first presentation of nephrotic syndrome was associated with fewer relapses without any increase in the number of adverse events. It was unclear whether the increase in benefit was related to increased duration or increased dose, although indirect analyses suggested that duration was more important. The 2015 update of that review (17) added three well-designed trials (18–20), which led to the change in conclusions of the review and likely to the modification of prescriptions in many centers worldwide. In the study Teeninga et al., children received the same total dose of prednisone administered over 3 or 6 months; however, children in the other two studies received a higher total dose of prednisone in the 6-month treatment group compared with the shorter treatment group. There was no significant difference in the risk for a frequently relapsing course between the shorter treatment group. There was no significant difference in the risk for a frequently relapsing course between the shorter treatment group. There was no significant difference in the risk for a frequently relapsing course between the shorter treatment group. There was no significant difference in the risk for a frequently relapsing course between the shorter treatment group.

In regards to the treatment of relapsing nephrotic syndrome with corticosteroids, data are even more scarce. Optimal duration of taper schedules is unknown and studies addressing the use of long-term alternate-day corticosteroid therapy to maintain remission are lacking (21). Kainth

Table 3. Linear mixed model analysis of duration of corticosteroid treatment (in days) with fixed effects at three levels (site, physician, and patient), n=328

| Variable (Fixed-Effects Parameters) | Coefficient | P Value | 95% Confidence Interval |
|-------------------------------------|-------------|---------|------------------------|
| Age at enrollment, yr               | 0.42        | 0.55    | -0.96 to 1.81          |
| Sex (ref: Male)                     | 6.71        | 0.19    | -3.36 to 16.78         |
| Status at entry (ref: first presentation) |            |         |                        |
| First relapse                       | 3.35        | 0.67    | -11.91 to 18.62        |
| Second relapse                      | -2.80       | 0.77    | -21.27 to 15.67        |
| Ethnicity (ref: Caucasian)          |             |         |                        |
| South Asian                         | -0.77       | 0.92    | -16.59 to 15.05        |
| African                             | 42.29       | 0.02    | 7.85 to 76.73          |
| Indigenous                          | 29.65       | 0.03    | 2.79 to 56.52          |
| East Asian                          | 2.80        | 0.74    | -13.76 to 19.37        |
| Others                              | 2.34        | 0.72    | -10.21 to 14.90        |
| Physician sex (ref: Male)           | 15.7        | 0.06    | -0.41 to 31.84         |
| Physician practice years            | -0.69       | 0.13    | -1.60 to 0.21          |
| Physician university (ref: Canadian) |           |         |                        |
| Non-Canadian                        | 8.84        | 0.40    | -11.69 to 29.36        |
| Both                                | 4.38        | 0.89    | -35.93 to 64.68        |
| Site protocol (ref: no standard protocol) |        |         |                        |
| First presentation                  | -0.47       | 0.98    | -30.07 to 29.13        |

| Variable (Random-effects parameters) | Estimate (SD) | SEM | Value 95% Confidence Interval |
|-------------------------------------|---------------|-----|------------------------------|
| Site                                | 18.49         | 6.49 | 9.30 to 36.77               |
| Physician                           | 14.91         | 4.55 | 8.19 to 27.12               |
| Patient                             | 12.71         | 6.55 | 4.63 to 34.90               |
| Residual                            | 70.47         | 1.84 | 66.95 to 74.18              |

95% CI, 95% confidence interval; ref, reference.

*P value is <0.05, the result is statistically significant.
et al. recently published a randomized clinical trial reporting on the efficacy of prednisolone as a “short regimen” (40 mg/m² on alternate days for 2 weeks) compared with “standard regimen” (40 mg/m² on alternate days for 4 weeks) for children with infrequent relapses of nephrotic syndrome. They observed that a similar proportion of patients developed a frequently relapsing or steroid-dependent course, suggesting no benefit from using longer courses. Another clinical trial is underway in the Netherlands (22), investigating a reduced corticosteroid schedule for the treatment of relapsing nephrotic syndrome. To summarize the protocol in brief, after achieving remission for 3 days with standard therapy, children will be randomized to receive either 2 weeks of alternate-day prednisolone, or their “standard” predni- sone dose for 6 weeks. We will await the results on effectiveness of therapy on the frequency of relapses.

The practice variation with respect to corticosteroid prescription in our study deserves further analysis. Because nephrotic syndrome is a relapsing condition in most patients, physicians aim not only to induce remission, but also to modify the course of the disease by prescribing different corticosteroid schedules. However, evidence we can achieve that goal with corticosteroids has not been yet demonstrated in this condition. The longitudinal nature of our data and its clustering effects suggest a real-life tendency of prescriptions habits to become similar across groups of physicians in Canada. This ongoing variability in treatment, despite increasing evidence, suggests the importance of unmeasured differences between patients that require more personalized treatment approaches. A more reflective approach on the basis of patient characteristics, clinical response, and less protocol-driven prescription would potentially reduce the exposure to corticosteroids in patients who respond faster or have a milder form of the disease, and promote earlier initiation of alternative treatments for patients with a more complicated course or with corticosteroid toxicity. Future studies on optimal corticosteroid dosing in childhood-onset steroid-sensitive nephrotic syndrome should target efforts to investigate if more personalized treatment approaches are possible and beneficial to the patients.

Our study has the limitations of inferences made from an observational study, and there may be residual confounding due to unmeasured variables. We were not able to measure adherence of patients to prescribed therapy, and this may be one of the unmeasured confounders. Nevertheless, this study has significant strengths. It is one of the largest, prospective, multicenter, and multiethnic cohort studies with patients with incident childhood-onset steroid-sensitive nephrotic syndrome. Although the variability in care will require further study, we have started to unravel the reasons for this variability, aiming to improve the management of these patients.

In conclusion, longitudinal observational study of patients with steroid-sensitive nephrotic syndrome showed there is significant practice variation with respect to corticosteroid prescriptions across 11 Canadian sites, and the variation is mostly explained at the site level. Age and ethnicity are important factors to be considered, because they are significantly associated with average corticosteroid dose and duration of therapy. Future studies on optimal corticosteroid dosing in childhood-onset steroid-sensitive nephrotic syndrome should target their efforts to investigate if more personalized treatment approaches are possible and beneficial to the patients.

Disclosures
A-L. Lapeyraque reports advisory board attendances for Alexion Inc. All remaining authors have nothing to disclose. The fund- ing agencies had no role in the design of study, collection, analysis, or interpretation of data.

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Author Contributions
A. Nettel-Aguirre and S. Samuel conceptualized the study; R. Chanchlani, A. Dart, A.-L. Lapeyraque, C. Morgan, M. Perina- nayagam, S. Rodriguez-Lopez, S. Samuel, and J. Tee were responsible for the data curation; A. Brobbey, A. Nettel-Aguirre, S. Samuel, and S. Rodriguez-Lopez were responsible for the formal analysis; S. Samuel, A. Dart, C. Morgan, and A. Nettel-Aguirre were responsible for the funding acquisition; S. Samuel was responsible for the investigation; A. Nettel-Aguirre and S. Samuel were responsible for the methodology; S. Samuel and M. Perinpanayagam were responsible for the project administration; M. Perinpanayagam and A. Nettel-Aguirre were responsible for the resources; S. Samuel, M. Perinpanayagam, and A. Nettel-Aguirre provided supervision; A. Nettel-Aguirre and S. Samuel were responsible for the validation and visualization; A. Brobbey, A. Nettel-Aguirre, S. Rodriguez- Lopez, and S. Samuel, wrote the original draft; and R. Chanchlani, A. Dart, A.-L. Lapeyraque, C. Morgan, M. Perinpanayagam, and J. Tee reviewed and edited the manuscript.

Supplemental Material
This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl doi:10.34067/KID.0002692021/-/DCSupplemental.

Supplemental Table 1. Linear mixed-model analysis of average daily corticosteroid dose (in 10 mg/m²) with fixed effects at three-levels, for first presentation patients.

Supplemental Table 2. Linear mixed-model analysis of duration of corticosteroid treatment (in days) with fixed effects at three-levels, for first presentation patients.

Ethics Approval (Identification) Numbers from CHILDEPH sites.
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