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Evaluation of Hypothalamic-Pituitary-Adrenal Axis Suppression following Cutaneous Use of Topical Corticosteroids in Children: A Meta-Analysis

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Hypothalamic-pituitary-adrenal axis suppression · Cutaneous treatment of atopic dermatitis · Topical corticosteroids

Abstract
Background/Aims: A meta-analysis was performed to determine the likelihood of hypothalamic-pituitary-adrenal (HPA) axis suppression following short-term cutaneous treatment of atopic dermatitis with topical corticosteroids (TCS) in pediatric patients. ***Methods:*** All published pediatric clinical trials evaluating TCS use with pre- and post-treatment HPA axis assessment by cosyntropin stimulation testing were included. ***Results:*** Of 128 eligible trials, 12 were selected for meta-analysis with a total of 522 participants. There were 20 observed cases of HPA axis suppression (3.8%, 95% CI 2.4–5.8). The percentage of HPA axis suppression with low- (classes 6–7), medium- (classes 3–5) and high-potency (classes 1–2) TCS use was 2% (3 of 148 patients, 95% CI 0.7–5.8), 3.1% (7 of 223 patients, 95% CI 1.5–6.3), and 6.6% (10 of 151 patients, 95% CI 3.6–11.8), respectively. ***Conclusion:*** There is a low rate of reversible HPA axis suppression with the use of mid- to low-potency TCS compared to more potent formulations. In pediatric clinical practice, the limited use of mid- to low-potency TCS is rarely associated with clinically significant adrenal insufficiency or adrenal crisis. In the absence of signs and symptoms of adrenal insufficiency, there is little need to test the HPA axis of these patients.

Introduction

Topical corticosteroids (TCS) are widely prescribed to treat children and adolescents with atopic dermatitis (AD), an inflammatory skin disorder characterized by erythema and often intensely pruritic, eczematous lesions. AD affects as many as 20% of children, approximately 90% with onset before age 5 years [1–3]. Although it commonly arises at a young age, AD may persist well into the 2nd decade of life [4] and up to 2–3% of adults have lifelong disease [4, 5].

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Table 1. Classes of topical corticosteroids

Potency	Class	Topical corticosteroid	Formulation
Ultra high	1	Clobetasol propionate	Cream, 0.05%
High	2	Betamethasone dipropionate	Ointment, 0.05%
		Fluocinonide	Cream, ointment or gel, 0.05%
	3	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	4	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	5	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	6	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	7	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Derived from [53].

Most children have mild-to-moderate AD. For this group, lower-potency TCS (classes 6–7) are generally applied once or twice daily or medium-potency TCS (classes 3–5) once or twice weekly as maintenance therapy [6]. Higher-potency TCS are reserved for the treatment of acute disease flares with pediatric guidelines limiting the use from several days to a few weeks [6, 7]. However, repeated or prolonged use of high-potency TCS is often warranted for those with severe skin disease. Following the prolonged use of lotions, creams or ointments containing corticosteroids (CS) to inflamed skin, percutaneous absorption of these agents can suppress the hypothalamic-pituitary-adrenal axis (HPA axis) [7–9]. Although biochemical HPA axis suppression may be observed on dynamic testing, very few children develop symptomatic adrenal insufficiency (AI). That is seemingly true whether under clinical study or with routine pediatric use of TCS [10].

The available TCS are divided into 7 classes based on potency. Class determination was originally based on the skin vasoconstriction assay, which measures skin blanching on topical application [11, 12]. Class 1 TCS (e.g., clobetasol) are the most potent and class 7 TCS (e.g., hydrocortisone) are the least potent. The potencies of the TCS commonly used in pediatrics and featured in this meta-analysis are illustrated in Table 1. The amount of percutaneous absorption may be altered by the skin thickness, permeability, and degree of inflammation. Infants and young children have an increased risk of systemic effects due to the ratio of high body surface area (BSA) of TCS application relative to their smaller body size. In addition, application to delicate or denuded areas of skin as in the diaper area, typically under occlusion, further enhances percutaneous absorption [13].

Systemic effects of CS are the most common cause of secondary AI, leading to decreased pituitary production of adrenocorticotropin (ACTH) [14]. The severest of these systemic effects include symptomatic AI, Cushing syndrome, and adrenal crisis, which are reported in young children following prolonged or inappropriate cutaneous application of very-high-potency TCS [15–22]. By contrast, there has been little evidence for *clinically meaningful* HPA axis suppression following routine use of the lower-potency or even the highest-potency TCS, when used as approved [10].

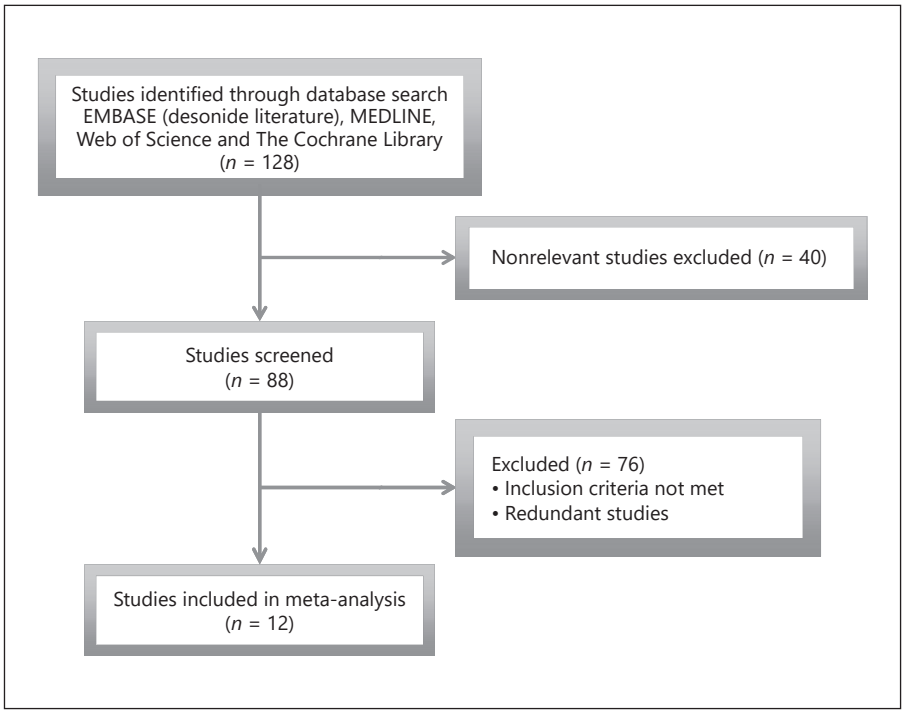

Fig. 1. CONSORT flow diagram of search results.

The goal of this meta-analysis is to address the prevalence of biochemical HPA axis suppression as assessed by a standardized cosyntropin stimulation cortisol secretion test following limited, routine use of TCS in children aged 18 years and younger with AD.

Methods

Reviewers conducted a systematic review and meta-analysis of the published English-language literature to determine the risk of AI in children and adolescents (age <18 years) using cutaneous application of CS.

Clinical studies were derived from three electronic databases (MEDLINE, Web of Science, and The Cochrane Library) through March 2017. EMBASE was used selectively and articles meeting search criteria were obtained from a desonide-specific search initiated by the Degge Group Ltd. (used with permission from Earl Goehring to A.D.R.). We used the following keywords in our search: pituitary-adrenal axis AND glucocorticoids AND topical administration OR skin OR topical OR cutaneous administration with filters: humans, English, Child: birth-18 years. Initial search yielded 128 results, and 12 met the inclusion criteria as shown in Figure 1. Studies were included if they met the following inclusion criteria: (1) English language, (2) patients aged 18 years and younger, (3) randomized controlled trials or prospective cohort studies, (4) sample size of at least 10 subjects, (5) TCS use was restricted to the transdermal route, excluding intra-lesional, intranasal and inhaled CS, (6) duration of CS use of at least 2 weeks, (7) no CS use (by any route) for at least 2 weeks prior to trial, and (8) assessed HPA axis using ACTH stimulation testing, measuring serum cortisol levels at baseline and following at least 2 weeks of TCS application.

The definition of HPA axis suppression was a post-stimulated cortisol level less than or equal to 18 μg/dL (equivalent to 497 nmol/L). TCS were ranked from class 7 low potency to class 1 ultra-high potency using the World Health Organization classification of CS (Table 1). Duration and location of use with treated BSA were included in the analysis, if described in the selected studies.

Three reviewers (L.K.W.H., L.D.G., and A.D.R.) independently and in duplicate screened all titles, abstracts, and full texts for potential eligibility. Abstracts were reviewed, followed by full-text articles. References from the retrieved articles were reviewed for further relevant studies. Disagreements were resolved by arbitration. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was employed during the conduct of these quantitative meta-analyses [23].

Estimates of the proportion of patients with AI along with 95% confidence intervals were computed using the method of Agresti and Coull [24]. These estimates and confidence intervals were computed separately for each study, or pooling studies using drugs of the same potency class. Meta-regression methods based on logistic regression were used to assess the effect of study characteristics, such as average age or drug potency class, on the risk of AI [25]. Analyses were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and GAUSS 17.0 (Aptech Systems, Chandler, AZ, USA).

Table 2. Characteristics of trials included in the analysis

Study	Potency class	Total duration	Corticosteroid name	*n* with AI	Total *n*	Mean or median age, years	Infant, %	Female, %	Average TBSA, %
Kimball et al. [36]	1	2 weeks	Clobetasol propionate emulsion foam 0.05%	7	30	12	0	58	N/A
Schlessinger et al. [35]	1	2 weeks	0.1% fluocinonide cream	3	121	7.2	25	47	38
Moshang [32]	5	3 weeks	Prednicarbate, emollient cream 0.1%	0	55	5.1	17	63	47
Friedlander et al. [28]	5	3–4 weeks	fluticasone propionate, cream 0.05%	2	43	2.7	63	47	64
Eichenfield et al. [33]	5	4 weeks	hydrocortisone butyrate 0.1%	0	20	9	0	50	50
Hebert et al. [34]	5	3–4 weeks	fluticasone propionate 0.05% lotion	0	42	2.6	59	50	65
Abramovits and Oquendo [29]	5	29 days	hydrocortisone butyrate 0.1% cream	5	63	6.3	35	45	41
Dohil et al. [30]	6	4 weeks	Fluocinolone acetonide 0.01%	0	24	1.1	100	50	48
Eichenfield et al. [31]	6	4 weeks	desonide hydrogel 0.05%	0	34	3.3	44	59	51
Hebert [27]	6	4 weeks	Desonide 0.05% foam	3	75	6.7	27	63	39
Lucky et al. [26]	6 and 7	4 weeks	desonide 0.05% ointment, hydrocortisone 2.5% ointment	0	15	4.7	N/A	35	38
Total				20	522				

AI, adrenal insufficiency; N/A, data not available.

Results

In Table 2, we show characteristics of the 12 included studies. Study duration ranged from 2 to 4 weeks. Participants were aged between 3 months and 18 years. All studies were prospective, open-label cohort studies with the exception of the study by Lucky [26], which was a randomized open-label study. All studies included patients with AD. The average affected percent BSA of the primary disease is shown in Table 2.

Overall, there were 20 observed children with evidence of biochemically defined AI from the 522 participants included in 12 studies (3.8%, 95% CI 2.4–5.8), as shown in the forest plot in Figure 2a. The higher proportion of AI can be attributed to higher-potency CS use, although there is heterogeneity in the studies and overlap between TCS potencies and risk of AI. None of those with low-potency TCS (classes 6–7) had children with evidence of AI except for that of Hebert [27], in which 3 out of 75 subjects showed minimal biochemical adrenal suppression. These 3 subjects had post-cosyntropin stimulation cortisol levels of 18.0 (497 nmol/L), 17.5 (483 nmol/L), and 16.1 μg/dL (444 nmol/L); and all reverted to normal on follow-up testing performed 1–10 weeks following treatment discontinuation. There were 2 children with AI on post-treatment testing who were lost to follow-up and thus unable to undergo retesting [28, 29].

The proportion of children with biochemical AI by CS drug class is shown in Figure 2b. As TCS potency increased, the percentage of children with AI increased; however, this relationship was not statistically significant ($p = 0.109$). There was a significant difference in the percentage of AI seen between the high-potency (classes 1–2) and combined medium- and low-potency TCS (classes 5–7) ($p = 0.04$), but not between medium- and low-potency TCS ($p = 0.52$) or between high- and low-potency TCS ($p = 0.066$). Figure 2c displays the subgroup analysis for children aged 3 years or younger, of whom 1.3% had AI after treatment with TCS (95% CI 0.4–4.6). With every increase in age by 1 year, the odds of AI increased by 48% (OR 1.48, 95% CI 1.19–1.83, $p \leq 0.001$); this effect is shown in Figure 2d.

Discussion

This meta-analysis aimed to estimate the rate of biochemical AI following the limited use of TCS in children. The results show that 2% of children demonstrated HPA axis suppression after daily use of low-potency TCS (classes 6–7) for up to 4 weeks. As expected, we identified an increasing proportion of children with biochemical AI following the use of moderate- (classes 3–5), high- and very-high-potency (classes 1–2) TCS at 3.1 and 6.6%, respectively; however, this difference was not statistically

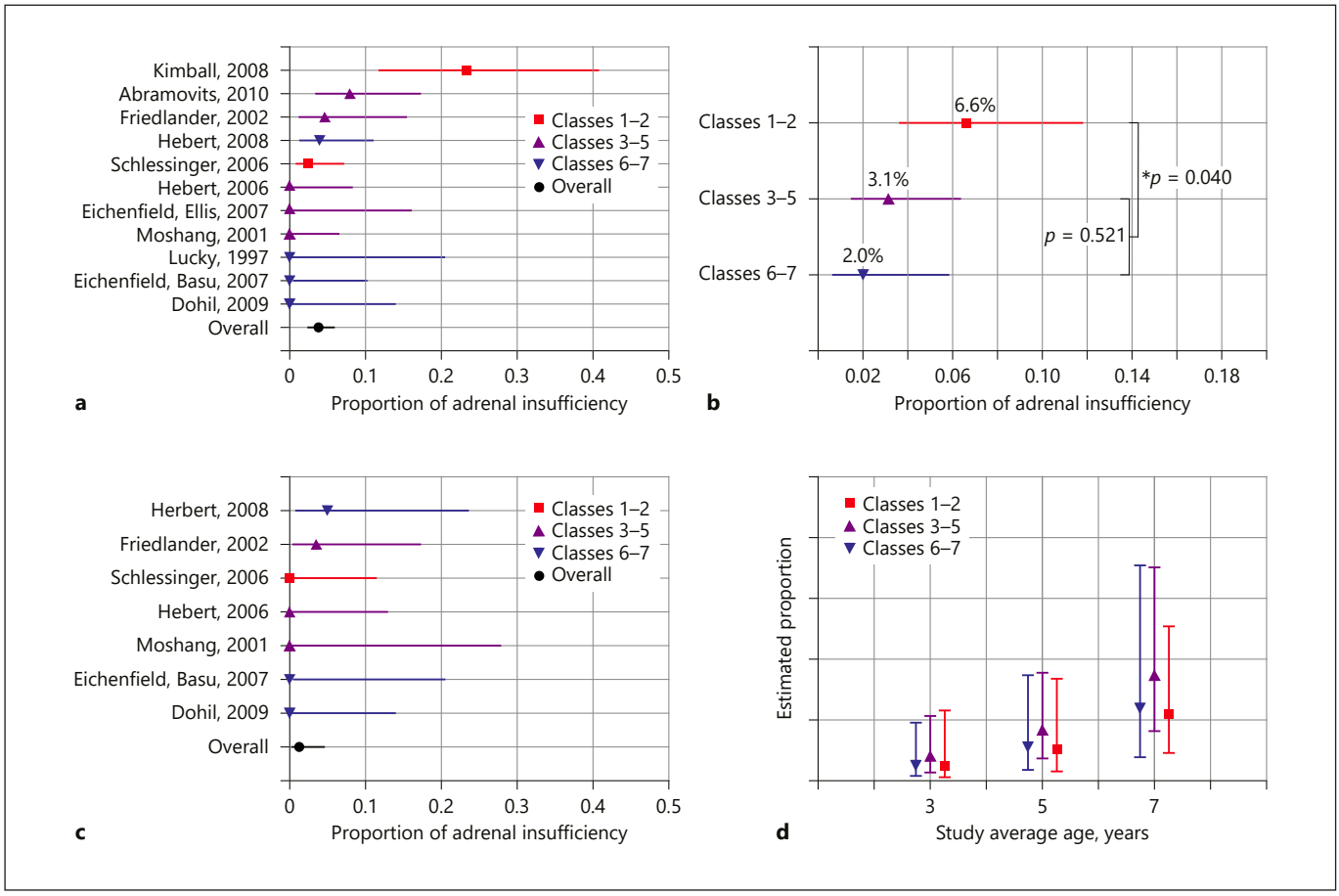

Fig. 2. a Proportion of subjects with adrenal insufficiency by study and drug class. The overall rate is 3.8% with a 95% CI of 2.4–5.8. **b** Proportion of adrenal insufficiency by drug class. **c** Proportion of adrenal insufficiency in the 7 studies that included children aged 3 years or younger: the overall rate in children aged 3 years or younger is 1.3% (2 of 154 patients) with a 95% CI of 0.4–4.6. **d** Estimated proportion of adrenal insufficiency as a function of study average age and drug class.

significant ($p = 0.109$). Children using the highest-potency TCS, classes 1–2, showed significantly more biochemical AI than the pooled groups of classes 5–7, indicating a dose-related effect on HPA axis suppression ($p = 0.04$). No clinical symptoms of AI were noted among subjects reported during these studies [26–37]. Upon retesting, children with biochemical AI had complete resolution after discontinuation of TCS therapy [27–29, 35–37].

The overall percentage of HPA axis suppression in children and adolescents receiving any potency TCS was 3.8% (95% CI 2.4–5.8). This is similar to a meta-analysis of data in adults that showed 4.7% of patients had AI following cutaneous TCS use (95% CI 1.1–18.5) [38]. To the best of our knowledge, no previous meta-analysis has been performed on AI from TCS use in pediatrics, although other forms of systemically absorbed CS have been studied. Children with asthma, another atopic condition commonly treated with CS, show a higher percentage of HPA axis suppression following the use of inhaled CS at rates of 7.7–42% depending on the potency and duration of use [39–43]. These findings prompted new Pediatric Endocrine Society guidelines recommending dynamic HPA axis testing for children with asthma treated with chronic high-dose inhaled CS or those with specific clinical features suggestive of AI [44, 45]. Unlike inhaled CS, there are currently no specific monitoring guidelines for AI in children following topical CS use, but formal testing is recommended if clinical signs of AI are noted [46].

Young children are thought to be particularly vulnerable to the systemic effects of TCS due to their large BSA relative to the body mass as well as risk of enhanced per-

cutaneous absorption. Seven studies in the meta-analysis included data for children less than 3 years of age ($n = 154$, 29.5% of the 522 children), with the results of each study stratified by TCS potency in Figure 2c. Interestingly, our results suggest a trend towards greater odds of AI with *increasing* age shown in Figure 2d ($p \leq 0.001$). This trend is thought to be due to selection bias leading to the exclusion of younger children from studies with high-potency TCS. In fact, 80% of the 154 children younger than age 3 were treated with low- to medium-potency (classes 5–7) TCS [35]. Based on these factors, our results may not reflect the true incidence of AI following high-potency TCS use in young children.

One of the strengths of this meta-analysis is that all 12 studies used pre- and post-treatment ACTH stimulation testing to measure HPA axis suppression. With regard to ACTH stimulation testing, there was some variability amongst the cosyntropin dose (low or high) used in the studies, but within the studies testing methods were consistent. This test (either iteration) has been criticized for yielding significant false-positive results [47–49]. Therefore, our estimates of HPA axis suppression are likely conservative *overestimates* of the actual proportion of *clinically significant* AI. The gold standard for evaluation of HPA axis suppression in children includes insulin-induced hypoglycemia or overnight metyrapone stimulation. Both tests are costly, time-consuming and carry significantly more risks to the child than the ACTH stimulation test, which is more commonly used in practice [50, 51]. During the analysis, we also identified several subjects from a single study who had biochemical HPA suppression following the use of class 6, low-potency TCS (desonide foam 0.05%) [27]. The degree of adrenal suppression found in this study was minimal with post-ACTH peak cortisol levels of 18, 17.5, and 16.1 μg/dL (equivalent to 497, 483, and 444 nmol/L, respectively). Despite being labeled as "secondary AI," many pediatric endocrinologists would not consider this test result abnormal as there are many vagaries of the test, not the least of which is the method of cortisol determination. Most guidelines suggesting normal post-stimulated serum cortisol thresholds range from greater than 16 μg/dL (441 nmol/L) to greater than 18 μg/dL (497 nmol/L). Kazlauskaite and Maghnie [48] showed that cortisol values less than 16 μg/dL (441 nmol/L) best predicted central AI on the low-dose ACTH stimulation test confirmed by reference testing. Given the lack of consensus, our cutoff of 18 μg/dl (497 nmol/L) is a conservative estimate of biochemical HPA axis suppression.

Another strength of the current meta-analysis was that most studies included specified exclusion of all other CS use for at least 2 weeks prior to the study (or at least 1 week prior in Hebert [27]), minimizing confounding HPA axis effects of other forms of CS. In studies that did not mention exclusion of prior TCS use [26, 29, 32, 35, 36], the exclusion of children with abnormal baseline HPA axis testing prevented significant confounding from previous CS use. There are groups who report potential baseline abnormalities on ACTH stimulation testing in children with asthma. Priftis et al. [52] found that approximately 10% of children aged 2–6 years with allergic asthma show an abnormal cortisol response to stress even though the basal salivary cortisol level is similar to that in controls. While baseline HPA axis abnormalities in pediatric AD patients have not been studied as extensively as in asthmatic children, the potential for abnormal baseline HPA axis function was considered outside the scope of the current study and children were excluded if their pre-treatment ACTH stimulation testing was abnormal.

A limitation of this meta-analysis is the pooling of data from heterogeneous studies. This should also be taken into account when evaluating the generalizability of this study. We attempted to control for confounding variables by accounting for duration of TCS use (in weeks), percentage of infants in the study, and the average total BSA (expressed in %) to which the TCS was applied, when included in the original studies (Table 2). There was no significant effect of these variables on the proportion of children with AI after logistic regression analysis. Since individual risk variables (total BSA %, disease severity) were not available for every child in the studies, we were not able to further characterize the few children who experienced HPA axis suppression. Despite this limitation, our data accurately reflect the difficulty in quantifying actual use of TCS once prescribed, which most providers experience in their regular practice.

Another potential limitation of our analysis is the inclusion of very few studies with medium- and high-potency TCS use in children. On search of available literature, we found no prospective trials including class 3 or 4 TCS (including triamcinolone acetonide) in children who met inclusion criteria. Regardless of these limited data on class 3–4 TCS, conservative recommendations based on class 1–2 TCS may be extrapolated to the medium-potency TCS.

We conclude from this meta-analysis that low-potency TCS administered at the recommended dosages and duration do not cause clinically significant suppression of

the HPA axis. Even children younger than age 3 likely do not require dynamic HPA axis testing following limited daily use of low- or mid-potency TCS. This conclusion is based on the low overall percentage of children with reversible HPA axis suppression in this age group at 1.3% (95% CI 0.4–4.6). We did identify a dose-related effect of TCS potency on the percentage of AI in children, but the overall incidence with limited use is very low at 6.6% even amongst the highest-potency TCS. Based on these findings, we do not recommend routine testing of the HPA axis following up to 4 weeks of use of any TCS, even the highest potencies, unless there are symptoms of AI. Future studies should evaluate AI incidence after TCS use of longer duration and identify which children are at the highest risk of systemic absorption of TCS.

Disclosure Statement

A.D.R. was a consultant with Perrigo, Inc. with regard to topical corticosteroid treatment. No grants, honoraria or royalties were received supporting the writing of the paper. All authors have no financial or other potential conflicts of interest to report.

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