Adrenal Insufficiency in Pediatric Eosinophilic Esophagitis Patients Treated with Swallowed Topical Steroids

Stephanie Hsu, MD, PhD,¹ Colleen Wood, MD,¹ Zhaoxing Pan, PhD,^{2,3} Haseeb Rahat, BS,¹
Philip Zeitler, MD, PhD,¹ David Fleischer, MD,^{3,4} Calies Menard-Katcher, MD,^{3,5}
Glenn T. Furuta, MD,^{3,5} and Dan Atkins, MD^{3,4}

Swallowed topical steroids (STS) are the only effective pharmacological therapy for eosinophilic esophagitis (EoE). Thus far, studies of small populations of EoE patients have reported conflicting results in relation to adrenal insufficiency (AI). We sought to measure AI in a clinical setting in children taking STS for EoE. We performed a quality improvement study of pediatric EoE patients seen in a multidisciplinary clinic, who were treated with STS for at least 3 months. Two hundred twenty-five patients completed questionnaires to assess for signs of AI. All patients were requested to have fasting morning cortisol levels completed and if abnormal ($<5 \mu\text{g/dL}$ or 139 nmol/L) twice, endocrinology consultation, and low-dose adrenocorticotrophic hormone stimulation test were performed. A peak stimulated cortisol level of $<18 \mu\text{g/dL}$ or 500 nmol/L was diagnostic of AI. Five of 106 STS-treated EoE patients who had morning cortisol levels drawn had AI. All 5 of these patients had asthma and were on additional topical steroid treatments. The number of steroid modalities and dose of steroid were not significant risk factors. Despite this low percentage, the life-threatening potential of AI warrants patient screening, as patients with iatrogenic AI are typically asymptomatic until an emergency triggers adrenal crisis. Further multicenter studies are needed to better define the risk attributable to STS alone, particularly in patients receiving combined steroid modalities.

Keywords: asthma, safety, esophagitis, eosinophilic esophagitis, cortisol

Introduction

EOSINOPHILIC ESOPHAGITIS (EoE) is a chronic, immune- or antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation. EoE affects 1–4 per 10,000 people worldwide^{1,2} and is increasing in prevalence.^{3,4}

Swallowed topical steroids (STS) are the only known effective pharmacological treatment for EoE.⁵ In contrast to inhalation of topical steroids for asthma, STS for EoE are sprayed from a multidose inhaler into the back of the throat or mixed with a suspension vehicle and swallowed. Local effects and systemic absorption of topical inhaled steroids raise concerns for steroid complications such as adrenal insufficiency (AI), local infections, altered bone metabolism, and slowed linear growth.^{6,7} Whether the use of STS leads to biologically relevant circulating steroid levels in EoE patients is unknown, but is predictably less likely to do so than inhaled steroids as the esophagus is less vascularized

than the lung and STS likely undergo first-pass metabolism by the liver.^{8–10}

Studies addressing risks of steroid complications related to STS in patients with EoE are conflicting. With respect to short-term exposures of 8–12 weeks, retrospective and prospective EoE STS trials identified AI in 0%–43% of patients.^{11–15} Studies examining longer STS exposures ranging from 12 weeks to 4 years yielded variable results, likely reflecting differences in AI testing methods, the number of patients studied, and exposures to concomitant steroids for other reasons.^{16–18} Since EoE is a chronic disease and STS may positively impact the course of EoE, knowledge of potential side effects is critical to patient care.

Both fasting morning cortisol levels and adrenocorticotrophic hormone (ACTH) stimulation tests are routinely used to evaluate children for AI. Morning cortisol levels measure the physiologic release of cortisol and typically are highest upon awakening. Morning cortisol levels can fluctuate based on assay differences, individual circadian rhythm differences,

¹Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, Colorado.

²Biostatistics Core of the Children's Hospital Colorado Research Institute, Aurora, Colorado.

³Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Aurora, Colorado.

⁴Pediatric Allergy and Immunology, University of Colorado School of Medicine, Aurora, Colorado.

⁵Digestive Health Institute, Children's Hospital Colorado, Aurora, Colorado.

and whether the patient was fasting when it was drawn. ACTH stimulation tests assess the ability of the adrenal gland to release cortisol in response to the natural pituitary stimulating hormone.

In a patient who has been receiving chronic supraphysiologic doses of glucocorticoids, the endogenous morning cortisol release is blunted as well as the response to ACTH stimulation since the lack of endogenous trophic hormone stimulation over time is believed to cause atrophy of the adrenal gland. Typically, a stimulated cortisol of $>18 \mu\text{g/dL}$ is considered adequate, although this was established using adult data and has not been well studied in children. When clinical signs and symptoms of AI correspond with low cortisol levels, the diagnosis of AI is clear. Stimulation testing is often used to differentiate ambiguous basal cortisol levels or in situations where a fasting morning cortisol is impractical or inaccurate due to the clinical context.

We hypothesized that children with EoE would have a low incidence of AI (due to first-pass metabolism and lack of reports of clinical AI). We tested this hypothesis using a 3-tiered testing method to screen children attending a pediatric EoE program.

Methods

From October 2013–June 2015, universal screening for AI began as a quality improvement initiative for EoE patients treated with STS for at least 3 months. Consecutive patients diagnosed with EoE, based on published Consensus Recommendations and cared for in the Gastrointestinal Eosinophilic Diseases Program at the Children's Hospital Colorado, were provided questionnaires to assess for signs of AI and complications of glucocorticoid therapy at their routine clinic visit. The number, dose, and duration of steroid modalities (STS, inhaled, nasal, and dermatologic) were recorded. Patients treated with oral systemic steroids for any indication were not tested for AI for at least 3 months after this exposure. Patients were requested to fast for at least 8 h before blood samples were obtained between 7 and 9 am. Patients received reminder calls and follow-up letters to encourage completion of blood samples that were not provided at the time of a clinic visit. No other exclusion criteria were used.

Based on prior evidence that $5 \mu\text{g/dL}$ is the bottom 10% of morning cortisol levels in normal children, we considered fasting morning cortisol levels of $<5 \mu\text{g/dL}$ (139 nmol/L) as low to allow for a more generous capture of potentially affected children, $>10 \mu\text{g/dL}$ (278 nmol/L) were considered normal, and levels of $5\text{--}10 \mu\text{g/dL}$ ($139\text{--}278 \text{ nmol/L}$) were indeterminate.¹⁹ If a morning level was abnormal, and the patient did not have any symptoms/signs of AI, the test was repeated and if again abnormal, endocrinology consultation (C.W., S.H.) was performed to assess for all underlying causes of AI. No patients were found to have an additional cause for AI other than topical steroid exposure. As a part of the consultation, a fasting low-dose ACTH stimulation test was completed²⁰ by collecting cortisol levels at baseline and 30 and 60 min post $1 \mu\text{g}$ Cosyntropin administered intravenously. A peak cortisol level $<18 \mu\text{g/dL}$ (500 nmol/L) on the ACTH stimulation test was considered diagnostic for AI.

Heights and weights were measured at clinic visits using a wall-mounted Harpenden Stadiometer and digital scale; retrospective growth data and verification of positive responses to the questionnaire were accessed in the electronic

medical record after completion of the quality improvement project as part of an IRB-approved protocol (COMIRB 08-2108) for which all patients had provided prior written consent. Age-based percentiles were calculated using Center for Disease Control (CDC) growth charts published in 2000. Cortisol assays performed at the Children's Hospital Colorado laboratory were completed using a chemiluminescent immunoassay on the Vitros 5600. Because of travel distance to our institution and the necessity of the morning blood draw, some patients had cortisol levels drawn at laboratories closer to home.

Statistical analyses

Data analyses for this article were generated using SAS[®] software, Version 9.4 of the SAS System for Windows 7. Copyright © 2014 SAS Institute, Inc. For continuous variables, mean and 95% confidence intervals (CIs) were reported. Analysis of variance and its nonparametric counterpart, as appropriate, were used to make between-group comparisons. Continuous variables were analyzed with the Wilcoxon rank-sum test, whereas categorical variables were analyzed using Fisher's exact test for a two-tailed probability. For categorical variables, percentage distribution was reported and chi-square test was used to make between-group comparisons. Given that all analyses were exploratory, $P < 0.05$ was deemed to be statistically significant.

Results

Of the 225 STS-treated EoE patients provided questionnaires, 106 completed fasting morning cortisol measurements. Baseline characteristics of the patients assessed are shown in Table 1. Of the remaining group, who was screened with questionnaires, but did not complete the fasting morning cortisol testing, no significant difference was found in any baseline characteristic, except for fewer reported fractures compared with those who had cortisol testing completed.

Subsequent analyses focus on the 106 patients who had cortisol levels measured. Steroid exposures of the 106 patients revealed that 38 took only STS, 40 received 2 modalities, 21 received 3 modalities, and 7 received 4 modalities of steroids for other allergic conditions. With respect to STS, the mean doses used were fluticasone ($508 \mu\text{g/m}^2/\text{day}$, 95% CI 429–587, range 88–880 $\mu\text{g/day}$), budesonide ($1148 \mu\text{g/m}^2/\text{day}$, 95% CI 989–1307, range 0.25–2 mg/day), ciclesonide ($465 \mu\text{g/m}^2/\text{day}$, 95% CI 382–548, range 320–960 $\mu\text{g/day}$), and beclomethasone ($186 \mu\text{g/m}^2/\text{day}$, 95% CI 132–240, range 160–320 $\mu\text{g/day}$).

Thirty percent (32/106) of patients with STS-treated EoE had a fasting morning cortisol value of $<5 \mu\text{g/dL}$ (139 nmol/L). See Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/pep) for a summary of all cortisol data. Of these 32 patients, 26 completed a repeat fasting morning testing and 7 had a second abnormal cortisol (7% of the total number screened). Six patients with initial low cortisol levels (4 of whom had laboratories drawn after 9 am) did not complete a second cortisol level despite repeated contacts by phone and mail. The 7 patients with 2 low fasting cortisol levels and 2 additional patients [1 patient with an initial cortisol of $0.5 \mu\text{g/dL}$ (13.9 nmol/L) and another patient with fluctuating cortisol levels] were evaluated by our

TABLE 1. CHARACTERISTICS OF PATIENT POPULATION SEEN

	<i>No cortisol result received (n=119)</i>	<i>Cortisol obtained (n=106)</i>	<i>P</i>
Age in years	9.3 (8.3–10.2)	8.4 (7.5–9.3)	0.18
Males	79% (71–86)	75% (65–83)	0.43
Race	6% Black/African American 10% Other 2% Unknown 82% White	1% Black/African Americans 7% Other 5% Unknown 87% Caucasian	0.13
Height <10% for age	21% (14–30)	20% (13–30)	1.0
BMI in kg/m ²	17 (17–18)	17 (16–18)	0.40
BMI percentile for age	43 (36–49)	42 (36–48)	0.87
Time from diagnosis of EoE to data collection in months	26 (22–30)	26 (22–30)	0.95
STS duration in months	20 (16–24)	18 (15–22)	0.51
STS type	13% Ciclesonide 34% Budesonide 53% Fluticasone	18% Ciclesonide 30% Budesonide 47% Fluticasone 5% Beclomethasone	0.06
Number of steroid modalities	2 (2–2)	2 (2–2)	0.64
Asthma	42% (33–51)	50% (40–60)	0.28
Atopic dermatitis	42% (33–51)	44% (35–54)	0.79
Allergic rhinitis	51% (42–61)	41% (31–51)	0.14
Vitamin D <30 ng/mL	14% (9–22)	11% (5–18)	0.42
Fracture	4% (1–10)	13% (7–21)	0.02

Mean or % (95% confidence intervals) is reported for continuous variables.

BMI, body mass index; EoE, eosinophilic esophagitis; STS, swallowed topical steroids.

endocrinologists and completed a low-dose ACTH stimulation test. None was found to have another cause for AI. Of this group, 4 patients had an abnormal ACTH test and were diagnosed with AI. Three of the 4 patients with abnormal ACTH stimulation tests had 2 low cortisols (1 of these had fluctuating cortisols) and 1 had a very low morning cortisol (0.5 µg/dL) and was from out of town and therefore had an expedited stimulation test. In addition, another patient was diagnosed with AI due to ACTH stimulation testing done independently as part of an endocrine evaluation for short stature, which was performed just before his first cortisol screening for EoE was scheduled.

All 5 patients diagnosed with AI had a diagnosis of asthma that was treated with inhaled topical steroids. Initial analysis did not show any differences between patients with EoE and asthma (48 patients) and those with EoE, asthma, and AI (5 patients). Since some of the patients with a diagnosis of asthma did not report use of an inhaled steroid and all of the patients with AI used inhaled steroids, we then restricted the analysis to those patients on topical steroids for both asthma and EoE without AI (27 patients) to those diagnosed with AI (5 patients). As noted in Table 2, no significant differences were observed in patients with EoE and asthma who had AI compared with those without AI in

TABLE 2. COMPARISON OF PATIENTS WITH EOSINOPHILIC ESOPHAGITIS TAKING SWALLOWED TOPICAL STEROIDS AND THOSE WITH ASTHMA WHO WERE TAKING INHALED STEROIDS WITH AND WITHOUT ADRENAL INSUFFICIENCY

	<i>Patients with asthma and EoE on STS and inhaled steroids</i>		<i>P</i>
	<i>No AI (n=27)</i>	<i>With AI (n=5)</i>	
Age in years	9.4 (7.4–11.3)	11.0 (10.1–11.9)	0.11
BMI in kg/m ²	18 (16–20)	18 (15–21)	0.98
BMI percentile for age	52 (38–66)	41 (1–80)	0.48
Number of steroid modalities	3 (2–3)	3 (2–3)	0.56
STS duration in months	20 (14–26)	24 (–5 to 53)	0.61
STS type, % of patients	41% Fluticasone 41% Budesonide 18% Ciclesonide	60% Fluticasone 20% Ciclesonide 20% Beclomethasone	0.07
Dose of STS in µg/m ²	692 (514–870)	523 (292–754)	0.42
Inhaled steroid type, % of patients	81% Fluticasone 4% Budesonide 11% Ciclesonide 4% Beclomethasone	60% Fluticasone 20% Budesonide 20% Beclomethasone	0.16
Mean dose of inhaled steroid in µg/m ²	256 (195–316)	341 (6–676)	0.32
Patients with a fracture	15% (4 patients)	20.0% (1 patient)	1.00
Patients with height <10% for age	15% (4 patients)	40% (2 patients)	0.23

Mean (95% confidence interval) reported for continuous variables.

AI, adrenal insufficiency.

TABLE 3. CHARACTERISTICS OF ADRENAL INSUFFICIENCY PATIENTS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age in years	10	11	12	12	11
Sex	Male	Male	Female	Male	Male
BMI percentile for age in months	47.1	6.1	54.4	12.3	84.0
Type of STS	Fluticasone	Beclomethasone	Fluticasone	Fluticasone	Ciclesonide
Dose of STS mcg/day	440	320	880	880	960
Dose of STS/m ² /day	379	278	698	672	589
Number of steroid modalities	3	2	3	3	2
Length of STS treatment in months	3	6	60	26	29
Height percentile for age	49.3	1.2	1.5	61.0	78.0
History of fractures	No	No	No	No	Yes
Peak cortisol from ACTH stimulation test (μg/dL)	3.2	15.3	15.1	11.7	13.8

ACTH, adrenocorticotrophic hormone.

terms of age, body mass index (BMI), number of steroid modalities, type of STS, dose of STS, or duration of STS. The dose of inhaled steroid was not significantly different between those with AI and those without AI (341 μg/m² versus 256 μg/m² respectively, $P=0.3$). Specific forms and doses are noted in Table 3.

Detailed descriptions of the 5 patients with AI are presented in Table 3. AI was not associated with overt symptoms of steroid excess such as cushingoid appearance, hyperphagia, or excessive weight gain. One patient had a history of a fracture. Hypotension during endoscopy was seen in Patient 5 and this self-resolved without any intervention during the procedure, which suggests that it was not likely due to AI. Of the 2 AI patients with short stature, 1 had long-standing short stature present before the start of steroids and 1 was adopted and no parental heights were available. Due to the small number of patients with AI, we were unable to identify any association between AI and age, BMI, type of STS, length of STS treatment, or growth.

Patient 2 showed recovery of his adrenal axis (with an increase in peak cortisol from 15.3 to 17.5 μg/dL on ACTH stimulation testing) after stopping only his inhaled steroids and continuing STS. Patient 3 had a normal fasting morning cortisol of 11.7 μg/dL after stopping all meds (against advice of providers) for 8 months. The other 3 patients continue to show adrenal suppression or are awaiting retesting.

Discussion

With the increasing incidence of EoE in children, the successful impact of STS treatment on clinicopathological features of EoE, and increasing concern about systemic side effects of chronic STS use, we utilized a practical method to screen and assess children for AI. Using 2 metrics, a screening morning cortisol and a low-dose ACTH stimulation test, we found that 5 of 106 patients (4.7%, 95% CI 1.5%–10.7%) had AI. All 5 patients with AI had comorbid allergic diseases that were treated with additional topical steroids, but none experienced symptoms related to AI. Our findings suggest that STS does not lead to clinically significant AI in patients with EoE and that biochemical AI is associated with concomitant use of other topical steroids. Our findings are based on a clinical screening test that was ordered for all, but adhered to by less than 50% of our total EoE patients who were taking STS during the time period of

the study. Thus, there is a possibility that another portion of patients could have had biochemical AI that was missed. Multicenter studies using a standardized screening protocol will be needed to confirm this with larger patient numbers and more detailed assessments.

Our conclusion that STS are relatively safe is based on several findings. First, no patient exhibited symptoms related to AI. One patient experienced transient hypotension during an endoscopy that did not require treatment. Second, patients who were treated with STS alone were not found to have AI. This finding would fit with the concept of first-pass metabolism of STS and minimization of systemic exposure. In addition, it is consistent with past work documenting the potential systemic impact of inhaled topical steroids used for asthma where there may be more systemic exposure than encountered with STS. Third, we examined the impact of prolonged use of STS ranging from 3 to 53 months, a time frame that provides a long period for potential systemic exposure. We appreciate that not all STS-treated EoE patients were fully evaluated as a part of this study, but consistent with the published literature in randomized controlled studies, our results suggest that AI is an uncommon finding.^{11,21}

Our findings may not provide absolute confidence that patients treated with STS will not develop AI. Despite repeated efforts to obtain follow-up studies, over half of patients did not complete the requested cortisol testing. However, we speculate that if the nonadherent group were included, the prevalence of AI would be similar since the clinical characteristics provided in Table 1 are the same. Nonetheless, this may not be the case and is deserving of more study. We acknowledge that the lack of complete evaluation of all patients limits conclusions as it could contribute to bias.

We did not address adherence to medications as a part of this study in a rigorous fashion. Perhaps a portion of the patients did not have AI because they were not taking their medications. Our study was performed in a pediatric EoE subspecialty program, where parents and patients are highly motivated and specialty nurses are able to provide education (instructional videos—http://youtu.be/L_186ze9I-4, <http://youtu.be/XkP2JDmp-zA>) and follow-up; these 2 factors help to maximize the likelihood of medication adherence. Finally, since we have few patients with AI, we appreciate that this could limit the ability to make comparisons between the AI and no AI cohorts. While intriguing, further

analyses of AI related to treatment duration, type of corticosteroids used, and other factors could not be performed due to the number of patients studied. Future multicenter studies with high patient retention and assessments of adherence are clearly needed.

We performed a study that was consistent with our clinical practice in the evaluation of suspected AI. Much variability exists with respect to this assessment as it relates to instructions for measuring cortisol levels as well as timing, dosing, and repeated sampling related to ACTH stimulation tests. To determine a clinically meaningful outcome, achieve patient and family satisfaction, and perform an economically feasible, real life assessment of AI, we performed 2 screening morning cortisol levels followed by a low-dose ACTH stimulation test to assess for AI. This approach was feasible within the context of an outpatient setting and well tolerated by patients and families.

We chose to use this stepwise diagnostic approach for several reasons. Screening fasting morning cortisol level is reproducible with a similar sensitivity and specificity as the ACTH stimulation test depending on which threshold is used to determine AI.¹⁹ In addition, it is practical since patients can have it completed at the laboratory instead of needing to make a separate clinic appointment for an ACTH stimulation test with intravenous catheter placement. Early morning cortisol levels (drawn between 8 and 9 am) of $<3 \mu\text{g/dL}$ (87 nmol/L) are diagnostic of AI and $>19 \mu\text{g/dL}$ (525 nmol/L) effectively rule out AI,²² although in pediatric practice, morning cortisol levels $>10\text{--}12 \mu\text{g/dL}$ are considered effective to rule out AI.¹⁹ We used a more conservative threshold of $<5 \mu\text{g/dL}$ to capture a greater number of at-risk individuals. Patients with indeterminate morning cortisols continue to be followed clinically and we have a low threshold for performing the ACTH stimulation test if there are any suggestions of AI. We have not yet had any patient present with overt clinical AI (clear growth suppression, adrenal crisis) since starting this study in 2013.

Our findings are consistent with some but not all previous studies. For instance, most prospective short-term studies of 8–12 weeks that measured morning cortisol levels determined that most patients who used swallowed fluticasone or budesonide did not experience low cortisol levels and did not report AI-associated symptoms. In 1 prospective study, using a fluticasone dose of $1,760 \mu\text{g/day}$ in patients between 3 and 30 years of age, 14% were found to have AI with 5 of the 7 patients identified by abnormal salivary cortisol levels and 2 patients with random serum cortisol levels less than the reference range.¹¹ Two recent retrospective studies and 1 prospective study measured AI in pediatric STS-treated EoE patients. Philla et al., measured fasting serum cortisol levels in 14 children between the ages of 2 and 17 years, before and after fluticasone (79%) or budesonide (21%) treatment ranging from 8 to 43 weeks.¹⁶ No significant differences were identified between pre- and post-treatment cortisol measurements. In contrast, Harel et al., assessed all children treated with oral viscous budesonide for >3 months using a $1 \mu\text{g}$ ACTH stimulation test. Of 14 children tested, 6 (43%) had an abnormal test without identifiable association, including treatment duration, dose, or use of other topical steroids.¹⁷ Golekoh et al., performed a prospective study that recruited 58 EoE patients between 2 and 20 years of age who were treated with fluticasone or budesonide for a minimum of 6 months and who did not use other forms of

steroids.¹⁸ Using a low-dose ACTH stimulation test, they determined that 10% had AI [based on peak cortisol $<18 \mu\text{g/dL}$ (500 nmol/L)], and other than a lower BMI, characteristics differentiating AI from non-AI patients, including age or treatment duration, were not found. All 5 AI patients from that study were on fluticasone $880 \mu\text{g/day}$ or greater and none developed adrenal crisis. Most recently, in a prospective study, Ahmet et al. found that 2/3 of 29 children developed AI as assessed by low-dose ACTH stimulation test performed after they stopped treatment for 2 weeks.²³ This high prevalence of AI is greater than what has been reported in previous studies, perhaps related to small sample size or site-specific differences in population, doses or methods.

Of note, several studies relied on the low-dose ACTH stimulation test as the only indicator of AI. The true stimulated cortisol level for clinically significant AI in children has not been well established and remains controversial. In the interest of preventing adrenal crisis, a conservative approach, with regard to the threshold for initiating stress dose steroid precautions, is typically used. However, this involves a high cost to families and staff manpower for the testing and teaching.

Our study is different from others in that the 3-tiered testing methodology of screening with 2 morning cortisols and then performing ACTH stimulation testing likely identifies those with profound, clinically relevant deficiency. When this study was designed in 2012, we felt that the pretest probability of AI was low, and therefore designed the study to ensure that those proceeding to an ACTH stimulation test had a higher probability of being abnormal. Future multicentered studies will need to decide whether morning cortisol levels, 24-h urinary cortisol quantification or ACTH stimulation testing is most appropriate for screening of large heterogeneous populations of EoE patients.

When considering the wide range of reported risk for AI in STS-treated EoE patients alongside the financial and practical aspects related to screening, the question of whom and how to screen deserves further study. Although the number of patients identified with AI here is low, we did not find an association of a particular type or dose of the STS with AI, suggesting that additional individual factors contribute to AI. In addition, no clinical signs such as growth failure or fractures predicted AI. Although no molecular biomarkers exist to detect patients who may be more prone to develop AI, one study determined that patients with active EoE may have altered metabolism based on measurements of cytochrome P450 3A (CYP3A) enzymes.²⁴ Whether this holds true in inactive disease, or is a reflection of the inflammatory state will require further study. Thus, screening of EoE patients treated with STS remains an important consideration, especially for those on higher doses or those who take multiple forms of steroid products, because of the potential clinical impact of AI on patients undergoing stressful procedures like endoscopies. We anticipate that future studies using multiple metrics will provide more insights into the impact of STS in the generation of AI in children and adults with EoE.

In this study, we report that the use of STS led to AI in only a few asymptomatic children with EoE. AI was only found in those with concomitant use of additional topical steroids for comorbid allergic diseases. We anticipate that expanded screening/testing may lead to increased awareness of AI and elucidation of risk factors. The identification of patients with AI will allow providers to provide stress dose

steroid precautions to prevent life-threatening adrenal crisis. Increased awareness of the possibility of iatrogenic AI among pediatric providers and implementation of appropriate screening protocols will improve patient safety.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Stephanie Hsu, MD, PhD
Pediatric Endocrinology
University of Colorado School of Medicine
13123 E. 16th Avenue
Mailstop B265
Aurora, CO 80045

E-mail: stephanie.hsu@childrenscolorado.org

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