Adrenal Insufficiency in Children With Eosinophilic Esophagitis Treated With Topical Corticosteroids

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See "Swallowed Steroids and Adrenal Insufficiency in Eosinophilic Esophagitis: Should We Screen and How to Screen" by Wershil and Wechsler on page 277.

ABSTRACT

Objectives: The aim of the study was to identify practices of gastroenterologists screening for adrenal insufficiency (AI) and report prevalence of AI in children with eosinophilic esophagitis (EoE) treated with topical corticosteroids (TCS); compare serum dehydroepiandrosterone sulfate (DHEA-S) levels to morning serum cortisol (MSC) levels as screening tool for AI.

Methods: A multipart study was conducted. In part 1, a survey about screening practices for AI in children with EoE on TCS was sent to gastroenterologists belonging to a PedsGI listserv and to EoE consortia. In part 2, children with EoE on TCS for ≥6 months were prospectively screened for AI with MSC levels. For subjects with a MSC level of <10 μg/dL, a repeat MSC level and/or confirmatory adrenocorticotropic hormone (ACTH) stimulation testing was offered. AI was defined by peak serum cortisol level <18 μg/dL. In part 3, DHEA-S levels were drawn with MSC levels.

Results: Seven percent (16/238) of gastroenterologists screened for AI. Providers in EoE consortia were more likely to screen than nonconsortia providers [9/21(43%) vs 7/217(3%); $P = 0.0001$]. Thirty-seven children were prospectively screened for AI, and 51% (19/37) had a low MSC level. Ten patients had a low-dose ACTH stimulation test (LDST) after 1 or more low MSC levels. Five percent (2/37) of patients were diagnosed with AI. DHEA-S and MSC levels had a moderate correlation ($r_s = 0.44$, $P = 0.03$).

Conclusions: Gastroenterologists belonging to EoE consortia were more likely to screen for AI. Prevalence of AI in our prospective cohort was 5%. DHEA-S has a moderate correlation with MSC levels, but more data is required to assess utility as a screening tool for AI.

Key Words: adrenal insufficiency, adrenal suppression, corticosteroids, eosinophilic esophagitis

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What Is Known

- Data on screening for adrenal insufficiency and the prevalence of adrenal insufficiency with swallowed topical corticosteroids for treatment of eosinophilic esophagitis is variable and unclear.
- Serum cortisol is used to screen for adrenal insufficiency but has a diurnal rhythm that may affect accuracy.

What Is New

- Only 7% of pediatric gastroenterologists screen for adrenal insufficiency, and providers belonging to an eosinophilic esophagitis consortia are more likely to screen.
- Five percent of children with eosinophilic esophagitis on topical corticosteroids have adrenal insufficiency based on a morning serum cortisol level followed by confirmatory low-dose adrenocorticotropic hormone stimulation testing.
- Dehydroepiandrosterone sulfate has a moderate correlation with serum cortisol.

Chronic use of corticosteroids can disrupt the hypothalamic-pituitary-adrenal (HPA) axis and lead to adrenal insufficiency (AI) (1). Secondary AI may occur regardless of administration form, dose, and duration of corticosteroid use (2,3). Clinical presentation of AI is nonspecific and may include fatigue, altered mental status, hypoglycemia, electrolyte disturbances, and hypotension (1). AI can be life-threatening in times of stress or acute illness if untreated.

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Testing for AI is cumbersome. Many centers use morning serum cortisol (MSC) levels, which must be drawn early to correspond to its peak and diurnal rhythm. Definitive testing, like an insulin tolerance test, metyrapone testing, or adrenocorticotropic hormone (ACTH) stimulation, involves precise measurements by trained personnel, and can be costly and lead to errors (4). These tests can also have serious side effects, like hypoglycemia (5). Other markers for adrenal function exist, like dehydroepiandrosterone sulfate (DHEA-S) which does not have a diurnal variation, but have been minimally explored as replacements for these tests (6).

Eosinophilic esophagitis (EoE) is a chronic immune-mediated gastrointestinal disease associated with atopic diseases like asthma, food allergies, allergic rhinitis, and eczema. Although not yet approved by the Food and Drug Administration (FDA) for use in EoE, swallowed topical corticosteroids (TCS) are a known treatment option (7). Data on the prevalence of AI with TCS for treatment of EoE is variable and unclear (8–10). Reported prevalence has ranged from 5% to 43% (8,11). There is little guidance regarding utility of screening and optimal testing to screen for AI in this patient population.

We conducted a multipart study to address the following questions:

1. Part 1, Survey: What are the practice patterns of gastroenterologists screening for AI in patients with EoE on chronic TCS?
2. Part 2, Prospective Study: What is the prevalence of AI in pediatric patients with EoE treated with TCS?
3. Part 3, Alternative Screening: Is DHEA-S a screening tool for AI that can be used in place of a MSC level?

METHODS

All studies were conducted through Riley Hospital for Children at IU Health and approved by the Institutional Review Board at Indiana University.

Part 1, Survey

To assess the practice patterns for AI screening in EoE patients on TCS, an online survey with 20 multiple choice questions was sent via email to adult and pediatric gastroenterologists. SurveyMonkey Inc. and SurveyMonkey Inc. analytics software were used to collect and collate data. The survey was distributed to the Pediatric GI bulletin board listserv (*PEDGI@list.uvm.edu*), which includes pediatric gastroenterologists worldwide who sign up (nonconsortia or NC group). The survey was also sent to gastroenterologists in the following EoE consortia (consortia or C group): Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), The International Gastrointestinal Eosinophil Researchers (TIGERS), and American Partnership for Eosinophilic Disorders (APFED). EoE consortia consisted of adult and pediatric providers. A survey request was sent once, followed by 3 additional reminders over a period of 2 months. Data was collected over the 2-month period in early 2016. Survey participants were asked questions regarding motivations for screening, time at which screening begins, and screening modality (Supplemental Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B736*).

Part 2, Prospective Study

Simultaneously, we implemented a protocol (Fig. 1) within the Division of Pediatric Gastroenterology to screen for AI in EoE patients on TCS. Children ≤18 years with EoE treated with TCS between January to September 2016 were enrolled. Medical records were reviewed for age, sex, body mass index (BMI), BMI percentile, symptoms, TCS type, dose, indication(s), duration of therapy, and use of other corticosteroids. They were not prescreened for primary adrenal dysfunction before starting TCS, as treatment strategies were decided by their pediatric gastroenterologist before the study. Patients were screened for AI with a MSC level after ≥6 months of TCS therapy. For those patients with a MSC level of <10 μg/dL, a repeat MSC level and/or confirmatory ACTH stimulation testing was offered (12).

A modified low-dose ACTH stimulation test (LDST) with 10 μg of synthetic ACTH (cosyntropin) was used. A baseline serum cortisol level was measured before ACTH administration. ACTH was given intravenously, and serum cortisol levels were measured serially at 20, 40, and 60 minutes. Patients with a cortisol level of >18 μg/dL at any time point were considered normal responders and did not have AI. Patients with a peak cortisol <18 μg/dL by 60 minutes were considered to have an abnormal response to LDST consistent with AI (13) and were referred to pediatric endocrinology for evaluation. A pediatric endocrinologist confirmed diagnosis of AI and recommended therapy.

Part 3, Alternative Screening

DHEA-S levels were concurrently drawn with MSC levels based on the ordering physician's discretion.

Statistical Analysis

Descriptive data were reported as means with ranges for continuous variables and frequencies for categorical data. One-way analysis of variance (ANOVA) was conducted to determine statistically significant differences between the means of clinical data in children with and without AI. A Spearman's rank-order correlation was done to evaluate the relationship between standardized DHEA-S and MSC levels. A multiple regression analysis was used to test if age, sex, BMI percentile, and MSC levels significantly predicted DHEA-S levels.

RESULTS

Part 1, Survey

The survey was sent to 2567 pediatric gastroenterologists belonging to the NC group and 26 providers belonging to the C group. Two hundred thirty-eight respondents completed the survey, with a response rate of 9%. Two hundred seventeen (91%) respondents were in the NC group, and 21 (9%) were in the C group.

Overall, 7% (16/238) of respondents screened for AI in patients on TCS therapy. The C group was statistically more likely to screen for AI compared with NC group (43% [9/21] vs 3% [7/217]; $P = 0.0001$). Eighty-eight percent (14/16) were pediatric specialists in academic institutions (13 gastroenterologists, 1 allergist). The other 2 screeners were adult gastroenterologists. Seventy-five percent (12/16) used a MSC level as their screening tool, and 83% (13/16) screened after at least 6 months of TCS therapy. One respondent used DHEA-S as a screen. If the initial screen was abnormal, 25% (4/16) proceeded with ACTH stimulation testing, 25% (4/16) repeated a MSC level instead, and 50% (8/16) referred to an endocrinologist. Sixty-three percent (10/16) had at least 1 confirmed case of AI. Seventy-five percent (12/16) continued to screen every 6 to 12 months if the initial screening was negative.

Fifteen percent (35/238) of the respondents planned to screen for AI, but had not incorporated it into practice yet. Eighty-six

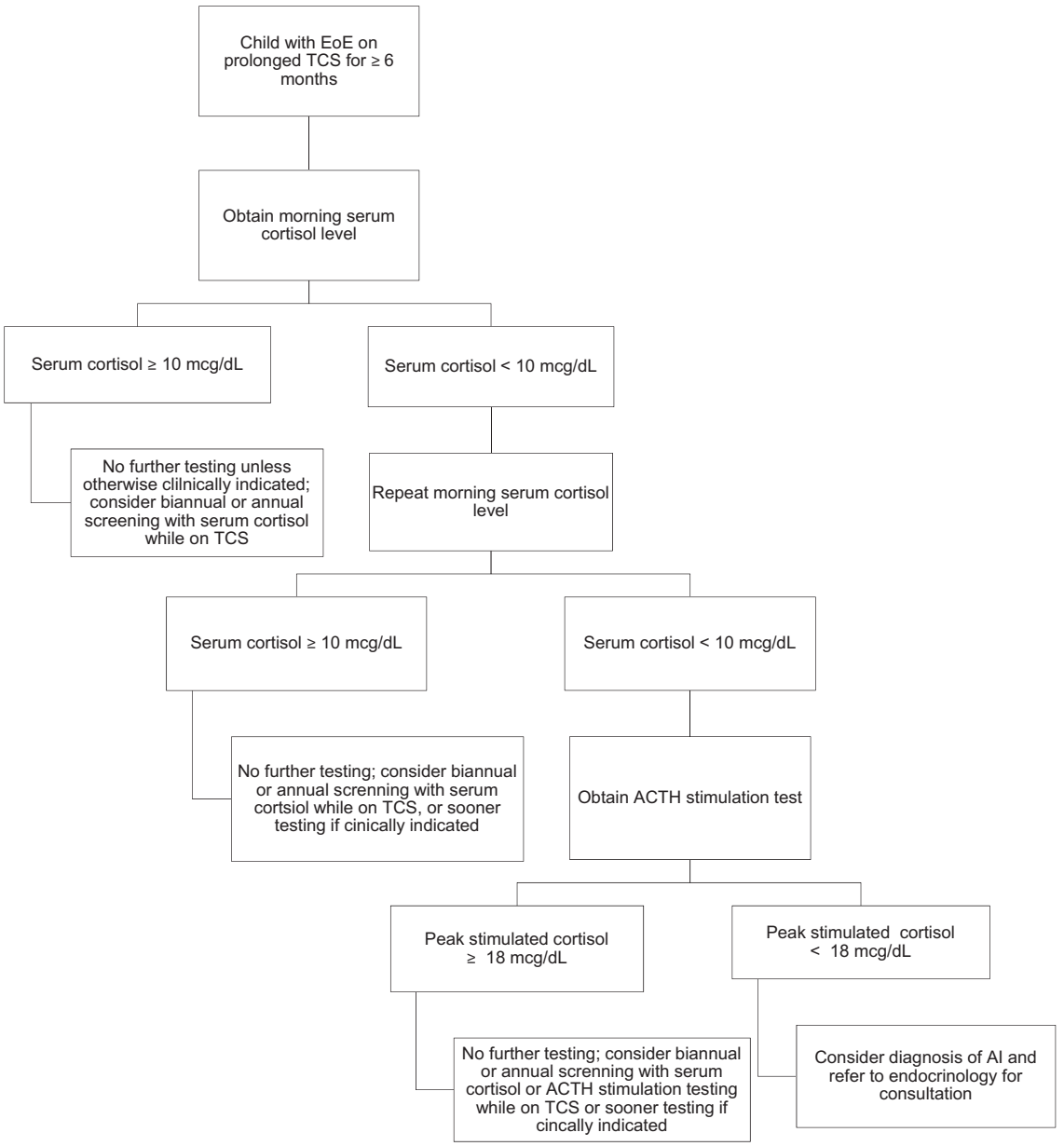

FIGURE 1. Adrenal insufficiency diagnostic algorithm for Part 2, Prospective Study.

percent (30/35) of the respondents planned to use MSC levels as a screening test. Eighty-nine percent (31/35) planned to screen after 6 months of TCS therapy, and 74% (26/35) would continue to screen annually if the initial screen was normal (Table 1).

Part 2, Prospective Study

Thirty-seven children with EoE treated with TCS (budesonide [68%] or fluticasone [32%]) were included. The study group had a male predominance (78%) as seen with EoE population. Clinical characteristics are listed in Table 2. One patient treated with TCS for $\geq$5 months was included. The remaining patients were treated with TCS for $\geq$6 months. Thirteen patients (35%) were using intranasal (8 patients), topical (4 patients), and inhaled (8 patients) concomitantly (Table 2). No patients were on systemic corticosteroids at the time of testing. Fifty-one percent (19/37) had a MSC level of less than 10 μg/dL.

A total of 10 patients had LDST after 1 or 2 abnormal MSC levels. Among those 10 children, 7/10 had a serum cortisol less than 18 μg/dL at 20 minutes, 4/10 had a serum cortisol $<$18 μg/dL at 40 minutes, and 3 patients had a serum cortisol $<$18 μg/dL (range 13.9–17.9 μg/dL) at 60 minutes. After confirmation with a pediatric endocrinology consultation, 2 patients (patient A and patient B) were diagnosed with AI, yielding a prevalence of 5% (2/37) in this cohort. The third patient with a peak serum cortisol of 17.9 μg/dL during LDST was considered adrenally sufficient as peak neared a normal response of 18 μg/dL.

Patient A was a 6-year-old boy with BMI of 15.2 kg/m^2 (42nd percentile). He was on swallowed budesonide (750 μg daily) for

TABLE 1. Online survey responses

	n (%)
Total number of respondents	238
Respondents who screen for AI	16/238 (7%)
Pediatric gastroenterologists	14/16 (88%)
Inspired to screen by recent literature	10/16 (63%)
Use MSC to screen for AI	12/16 (75%)
Initiate screening after at least 6 months of TCS use	13/16 (83%)
Repeat MSC if initial screen is abnormal	4/16 (25%)
Use ACTH stimulation testing if initial screen is abnormal	4/16 (25%)
Refer to endocrinology if initial screen is abnormal	8/16 (50%)
Have at least 1 confirmed case of AI	10/16 (63%)
Continue to screen at least every 12 months if screen is normal	12/16 (75%)
Respondents who will consider screening for AI	35 (15%)
Pediatric gastroenterologists	35/35 (100%)
Inspired to screen by recent literature	24/35 (69%)
Use MSC to screen for AI	30/35 (86%)
Initiate screening after at least 6 months of TCS use	31/35 (89%)
Screen at least every 12 months if initial screen is normal	26/35 (74%)

ACTH = adrenocorticotropic hormone; AI = adrenal insufficiency; MSC = morning serum cortisol; TCS = topical corticosteroids.

21 months before his diagnosis. He also took inhaled fluticasone 110 μg/dL 1 puff twice daily for asthma, and applied topical triamcinolone 0.1% twice daily for eczema. His baseline MSC level was 2.6 μg/dL, and his peak cortisol during LDST was 14.7 μg/dL. Following the diagnosis of AI, he was slowly weaned off budesonide. The inhaled fluticasone dose was decreased by 50%, and he was switched to low-potency hydrocortisone 1% for eczema. His family was instructed to administer stress-dose corticosteroids during acute illnesses. He underwent a repeat LDST 11 months later (3 months after discontinuing the TCS) and continued to demonstrate AI with a peak cortisol of 9.9 μg/dL despite reduction in his total corticosteroid exposure.

Patient B was an 11-year-old girl with a BMI of 17.7 kg/m^2 (48th percentile). She was on swallowed fluticasone (880 μg daily) for 7 months before testing. She was on a 2-week course of topical corticosteroids for psoriasis at the time of testing. Her baseline MSC level was 0.4 μg/dL, and her peak cortisol during LDST was 13.9 μg/dL. Her TCS dose was reduced by 50% after the low MSC level. She was lost to follow-up and did not have repeat testing.

TABLE 2. Clinical characteristics from part 2, prospective study

	n = 37 (range)
Mean age in years (range)	9.4 (2–18)
Sex	29 (78%) male 8 (21%) female
Mean BMI in kg/m^2 (range)	19.9 (13.8–36.6)
Mean BMI percentile (range)	57.48 (1.11–99.60)
Type of TCS (budesonide/fluticasone)	25 (68%) budesonide 12 (32%) fluticasone
Mean total daily dose, μg (range)	840 (220–1760)
Budesonide	720 (500–1000)
Fluticasone	900 (220–1760)
Mean duration of therapy in months (range)	20.9 (5–95)
Number of patients with other corticosteroid use	13 (35%) with other use
Inhaled	8
Intranasal	8
Topical	4

BMI = body mass index; TCS = topical corticosteroids.

Clinical factors of age, sex, BMI, duration of therapy, type of corticosteroid, total daily dose of TCS, daily dose per kg of weight, and exposure to other corticosteroids were similar between patients with and without AI. BMI and BMI percentile were significantly lower in children with MSC levels less than 10 μg/dL. Mean BMI was 17.8 kg/m^2 in children with MSC levels <10 μg/dL versus 22.0 kg/m^2 in children with MSC levels ≥10 μg/dL ($P = 0.04$). Mean BMI percentile was 44.3 in children with MSC levels <10 μg/dL versus 71.4 in children with MSC levels ≥10 μg/dL ($P = 0.02$).

Part 3, Alternative Screening

Twenty-six patients had DHEA-S levels drawn with their MSC level. DHEA-S ranged from 1 to 274.6 μg/dL (mean 48.2 μg/dL). There was a moderate correlation between DHEA-S and MSC levels ($r_s = 0.44$, $P = 0.025$). Results of the multiple regression analysis showed that age (B = 0.50, $P = 0.001$) and BMI percentile (B = 0.32, $P = 0.02$) significantly predicted DHEA-S levels. MSC levels trended towards significance in predicting DHEA-S levels (B = 0.24, $P = 0.06$). Sex did not predict DHEA-S levels (B = 0.16, $P = 0.23$).

DISCUSSION

We present a multipart study that encompasses an online survey, a prospective study, and examination of alternate methods to evaluate for AI in children with EoE on TCS.

In the online survey, 7% of all gastroenterologists screened for AI in their patients with EoE on TCS. Gastroenterologists belonging to an EoE consortia were more likely to screen (43% in C group vs 3% in NC group). The difference in screening practice is likely because of increased EoE expertise and familiarity with the current literature in the consortia group regarding potential risk of AI in chronic TCS use. An additional 15% of gastroenterologists considered adding AI screening to their clinical practice within 6 to 12 months, which highlights increasing awareness. In this study, we did note remarkable variability in the process of screening for and

diagnosing AI. Sixty-three percent of gastroenterologists who screen reported finding at least 1 case of AI in their practice. This raises concern that many cases of AI are underdiagnosed by providers who do not routinely screen for AI. The absence of symptoms to suggest AI in many of these patients may play a role in the lack of widespread screening.

In our prospective study, after 9 months of routine screening for AI at a single institution, we found an AI prevalence of 5% in children with EoE treated with TCS for ≥6 months. We also demonstrated that lower BMI and BMI percentiles were associated with lower MSC levels. The significance of this finding in our study remains unclear, though BMI may be a marker for increased risk of development of AI in EoE, as has been observed in children with asthma treated with inhaled corticosteroids (3).

Testing for AI can be accomplished with cortisol measurements or dynamic testing that examines the integrity of the HPA axis. Our results show that the majority of pediatric gastroenterologists prefer a MSC level. A MSC level was used as a screening tool in our protocol, and LDST was done for confirmatory testing. This protocol was influenced by suggestions from Ahmet et al (12) regarding screening for AI while on inhaled corticosteroids. Although a MSC level has a poor sensitivity of 60%, they proposed screening with a MSC level as it is easier to obtain, and less expensive when compared with ACTH stimulation testing (12,14). Sensitivity of a MSC level increases with higher cutoff values; however, specificity decreases concurrently (14). Both sensitivity and specificity of ACTH stimulation testing approach 90% but the test is technically difficult and expensive (15,16). On the basis of a low MSC level alone, 51% of our patients would have been classified as having AI. With LDST, we were able to narrow to 5% of children diagnosed with AI.

A key aspect of our protocol differentiates our study from others using LDST. We used a modified LDST with 10 μg of ACTH (cosyntropin), instead of the standard LDST where the dose of ACTH is 1 μg. Studies have suggested that the high-dose 250 μg ACTH stimulation test provides a pharmacologic dose to which even patients with secondary AI can mount an appropriate response (15). Studies have shown that the 1 μg ACTH test is sensitive at detecting AI and mimics physiologic response to stress (16). However, the 1 μg LDST involves a difficult dilution that may adhere to the IV tubing during testing (17). If children receive a subphysiologic dose of ACTH, their peak cortisol levels will be lower, leading to an erroneous diagnosis of AI. Additional research suggests that testing outcomes may not differ between a 1 and 10 μg dose (18). To avoid incorrectly diagnosing AI, we used the modified LDST.

Our study suggests that AI in patients with EoE on swallowed TCS is less common than previously described. This difference may be because of the timing of cortisol measurements during LDST. Harel et al (8) suggested an AI prevalence of 43% using LDST in patients on swallowed budesonide for ≥3 months, but cortisol was only measured at 20 and 30 minutes after ACTH administration. Another study, which showed a 10% prevalence of AI in children on swallowed corticosteroids for 6 months, measured cortisol levels only at 20 minutes (9). Cortisol concentrations not only can peak at 20 and 30 minutes, but can also peak later up to 60 minutes post-ACTH administration (19,20). Our results demonstrate that 19% (7/37) of patients would have been incorrectly diagnosed with AI based on a cortisol level at 20 minutes alone. With multiple time-point measurements in our study, only 5% (2/37) were diagnosed with AI.

Our results are consistent with a recent study published by Hsu et al (11). They tested children with EoE on TCS for ≥3 months with a MSC level followed by a repeat MSC level if the initial value was low. If both MSC levels were low, referral to an endocrinologist for LDST was made. They found that 30% of their patients had a low MSC level, compared with 51% in our study. Nine patients underwent LDST where cortisol levels were measured at 30 and 60 minutes. Five patients were diagnosed with AI, giving a similar prevalence of 5%. It is reassuring that the study design and results are similar, which demonstrates reproducibility of the results.

Although a MSC level is a useful screening tool in identifying patients at risk for AI (21), the test must be carefully timed. DHEA-S has been suggested as an alternative screening test for AI in children on inhaled corticosteroids for asthma (6). The half-life of DHEA-S is much longer than cortisol, allowing for measurements at any time of day, which may lead to improved adherence in getting the level drawn (6). We attempted to evaluate DHEA-S as a screening tool for AI in children with EoE. DHEA-S and MSC levels had a moderate correlation of 0.44 ($P = 0.03$). We used a multiple linear regression model as DHEA-S is an androgen precursor that can change with age, sex, and pubertal status. Age and BMI percentile were significant predictors of DHEA-S levels. A MSC level trended towards significance in predicting DHEA-S level ($P = 0.06$). On the basis of our study, it is difficult to determine whether DHEA-S is an appropriate substitute for a MSC level, and further studies comparing MSC levels and DHEA-S levels to gold standard testing are necessary.

This multipart study did have some limitations. Part 1 of our study was limited by response and recall bias as providers estimated their own practice patterns. We did not obtain data regarding what cortisol level was considered abnormal and requirements for definitively diagnosing AI. Parts 2 and 3 were constrained by a limited sample size though the AI prevalence of 5% is the same as that in a similar study by Hsu et al (11). Clinical risk factors that contribute to the development of AI may be undetected because of sample size limitation. On the basis of review of medical records, we were unable to uncover if children were on systemic corticosteroids in the months preceding the clinic visit where AI testing was ordered. We do know that no children were taking systemic corticosteroids at the time of their testing for AI. We identified that 13 children were also using inhaled, intranasal, or topical corticosteroids. Use of multiple corticosteroid modalities is common in this population as children with EoE often have other atopic conditions.

In summary, we sought to evaluate screening practices to detect AI in children with EoE on TCS, determine the prevalence of AI in this population, and investigate DHEA-S as a screening method for AI. Only 7% of providers currently screen for AI, but a higher percentage of gastroenterologists who are members of an EoE consortia routinely screen. Following a structured diagnostic algorithm, our prospective study showed a 5% prevalence of AI in our cohort of EoE patients on TCS. As testing for AI is a challenging process with timed MSC levels and stimulation testing, we propose a diagnostic algorithm (Fig. 1) to detect asymptomatic AI in EoE patients treated with chronic TCS. More convenient substitutes for these cumbersome tests, like DHEA-S, should be further investigated. We hope for continued investigation on a multicenter level into the relationship between TCS and development of AI to improve patient care and outcomes.

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