

Low detection of adrenal suppression secondary to swallowed steroids for eosinophilic esophagitis in a quality improvement project

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Clinical Implications

- Screening of patients prescribed swallowed topical steroids for eosinophilic esophagitis was a time-intensive quality improvement project. The outcomes support the recommendation for screening those on multiple forms of topical steroids but also suggest that widespread screening may be difficult and create unintended consequences.

The 2011 eosinophilic esophagitis (EoE) consensus recommendations recognized the need for further research regarding consequences of prolonged use of swallowed topical steroids (STS), including adrenal suppression.¹ Guidelines published in 2017 from the United European Gastroenterology (UEG), the European Academy of Allergy and Clinical Immunology (EAACI), the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Society of Eosinophilic Oesophagitis (EUREOS) recommend monitoring for adrenal insufficiency for children with EoE in the setting of high doses of STS for long periods, or concomitant use of other corticosteroids for atopic diseases.² Adrenal insufficiency secondary to inhaled corticosteroids (ICS) for asthma has been more extensively studied and appears dose-dependent (though cases on low-dose ICS have also been reported).³ Consensus guidelines have not been developed, but it has been recommended that screening of children with asthma on ICS include those who present with symptoms of adrenal insufficiency and those on high-dose inhaled steroids (≥ 500 $\mu\text{g/day}$ of fluticasone or ≥ 1000 $\mu\text{g/day}$ of budesonide/beclomethasone).³ The prevalence of adrenal insufficiency in patients with EoE treated with STS has been estimated to be anywhere from 0% to 65%.⁴⁻⁸ Given the somewhat vague recommendations to screen and uncertainty about the prevalence of adrenal insufficiency, we instituted a quality improvement project with the goal of screening all patients with EoE on STS for more than 3 months at our institution. Here we describe the feasibility and outcomes of that screening program.

Through electronic health record (EHR) review, all patients with EoE treated with STS for at least 3 months who were active patients in our pediatric allergy clinic between January 1, 2016, and October 1, 2018, were contacted with the recommendation for adrenal insufficiency screening. New patients seen after October 1, 2018, who were placed on STS were contacted on a rolling basis, through September 2019. High-dose STS exposure was defined as ≥ 500 $\mu\text{g/day}$ of fluticasone or ≥ 1000 $\mu\text{g/day}$ of

budesonide/beclomethasone. Patients who did not complete the recommended testing within 60 days of the original order were considered to have declined testing. Further details of the project methods are provided in this article's Online Repository text at www.jaci-inpractice.org.

Three hundred and ten patients were identified via the EHR query. After medication review, 137 patients on STS for EoE were identified, of whom 121 (88%) were eligible to be contacted (Figure 1). Of the 121 patients eligible for screening, 27 (22%) had stopped their STS without discussion with our practice, 14 were no longer being treated at Johns Hopkins, and 30 (25%) were unable to be reached after 2 attempts. We recommended screening for 48 patients, of whom 23 complied. Of the 48, the majority were male, had allergic comorbidities, and were treated with fluticasone or budesonide (Table 1). Thirty-three (69%) were on high-dose STS treated for prolonged periods and/or were treated with concomitant inhaled, nasal, or topical steroids, thus meeting UEG/EAACI/ESPGHAN/EUREOS criteria for screening. Of the 23 screened, only 1 demonstrated adrenal insufficiency (4% of those tested) (detailed in Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Five (10%) received a recommendation to repeat the screening but declined to do so (3 had an morning cortisol level greater than 9 $\mu\text{g/dL}$ and 2 were drawn at the incorrect time). Of the 17 patients with normal adrenal function, 6 (35%) required repeat testing or adrenocorticotrophic hormone (ACTH) stimulation to demonstrate a normal hypothalamic-pituitary-adrenal axis. In addition to high-dose STS, the patient with adrenal insufficiency was also on nasal, inhaled, and cutaneous steroids and appeared adherent to all. Although the sample sizes for the other groups were small, no other patient in any other group reported using 4 modalities simultaneously. Two patients reported stopping the prescribed STS after the recommendation for screening was made and a third patient requested an immediate appointment to discuss alternative treatment due to concern about this side effect. Overall, completion of this project required more than 150 phone calls with completion of the screening in only 23 of 121 contacted patients (19%).

In summary, of the 121 patients eligible to be contacted for screening based on the quality improvement project protocol, 48 (40%) received the recommendation for screening and 23 (48%) completed 1 screening. Of these 23 patients, 17 (74%) ultimately demonstrated normal adrenal function, though only 11 (48%) had normal testing on the first test. One patient (4%) was diagnosed with adrenal suppression, 5 (22%) completed 1 step but not the second, and 6 (26%) required repeat AM cortisol or ACTH stimulation testing but ultimately demonstrated a normal hypothalamic-pituitary-adrenal axis. The remainder of the eligible patients had stopped their steroids, could not be contacted, were treated with systemic steroids, had a previously normal cortisol level, or had left our practice. In this time-intensive quality improvement project, 12 patients (52% of those tested) required repeat or ACTH stimulation testing and the rate of adrenal insufficiency detection was low.

Although these data do not provide strong evidence for or against screening, this study shows that large-scale screening of all patients prescribed STS for EoE is time-intensive and has a low yield, with less than 50% of patients following the

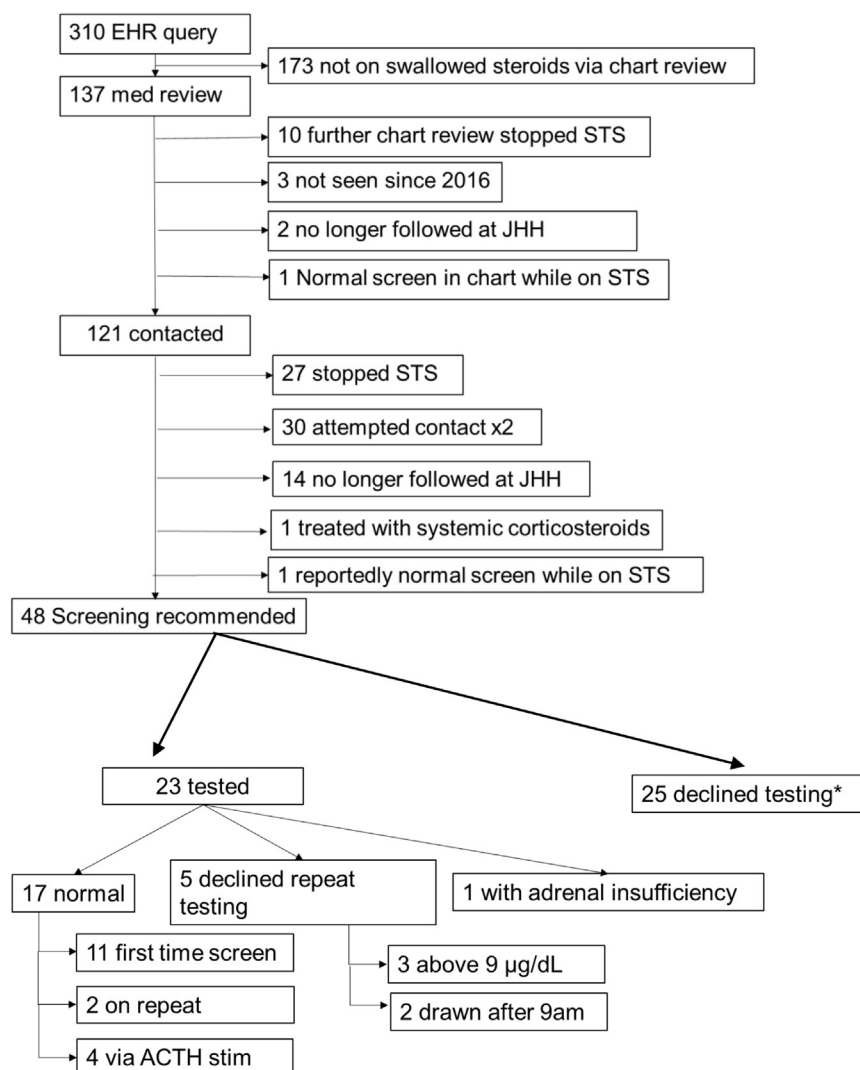


FIGURE 1. Flowchart of the quality improvement project. EHR, Electronic health record; STS, Swallowed topical steroids; JHH, Johns Hopkins Hospital; ACTH, Adrenocorticotropic hormone. *Declined testing defined as no result within 60 days of the original order, or refusal at the time of the recommendation.

recommendation. Major limitations of this screening modality include the need for a timed blood draw and low specificity of the initial test. The low incidence of adrenal insufficiency in this tested population may reflect low medication adherence among patients treated with STS, which is supported by the outcome of 22% of patients who reported stopping their medication without discussion with our practice. This also suggests that there might be a dose-dependent response to the occurrence of adrenal insufficiency in EoE due to STS, as has been shown for inhaled steroids in asthma.³

It is also difficult to know the true rate of adrenal insufficiency in this population, as 5 patients with abnormal morning cortisol levels declined further testing. Recommendations for screening should consider patient adherence, total steroid dose, symptoms of adrenal insufficiency, and the risks and benefits of screening. However, calculating a total steroid dose can be challenging because conversion among the different steroids is not straightforward. For example, budesonide has a higher bioavailability than fluticasone but a lower binding affinity and shorter plasma half-life, whereas beclomethasone has a lower binding affinity but

its metabolite has a high binding affinity.⁹ This project may support the recommendation for screening for those on multiple forms of topical steroids but also shows that widespread screening is difficult and may create unintended consequences, such as discontinuation of the medication and frustration with testing and therapy. More research is necessary to determine the true prevalence of adrenal suppression in patients on STS for EoE and the major risk factors for this adverse effect so that patients who may most benefit from screening can be identified and followed closely.

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TABLE I. Characteristics of patient population for whom testing was recommended

	Normal screen	Abnormal screen but normal HPA axis	Declined repeat screen	Abnormal cortisol result	Declined screening	Overall
No. of patients	11	6	5	1	25	48
Male, %	82	67	60	100	68	71
Age, median (IQR)	13 (11-16)	14 (9-17)	15 (7-15)	15	10 (8-13)	12 (8-15)
Comorbidities (%)						
AR	64	50	80	100	68	67
Asthma	45	33	60	100	36	42
Eczema	55	17	40	100	44	44
Type of STS (%)				100		
Beclomethasone	0	0	20		4	4
Budesonide	27	50	40		12	23
Fluticasone	64	50	40		84	71
Mometasone	9	0	0		0	2
STS dose (μg/d), median (IQR)	440 (440-940)	940 (880-1188)	880 (880-1000)	440	440 (440-880)	440 (440-880)
Duration of STS therapy (mo), median (IQR)	41 (27-66)	48 (27-69)	27 (12-60)	9	45 (24-60)	44 (24-60)
Cumulative steroid dose (μg/d) (swallowed, inhaled, nasal), median (IQR)	660 (440-940)	940 (880-1188)	1000 (880-1000)	1100	540 (440-880)	688 (440-985)
Range of number of steroid modalities, N (including STS, ICS, nasal and topical steroids)	1-3	1	1-2	4	1-3	1-4
% on more than 1 steroid modality (including STS, ICS, nasal and topical steroids)	36	0	40	100	40	35
Percentage on inhaled steroids	27	0	40	100	16	23

AR, Allergic rhinitis; HPA, hypothalamic-pituitary-adrenal; ICS, inhaled corticosteroids; IQR, interquartile range; STS, swallowed topical steroid.

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ADDITIONAL METHODS

Patients treated with less than 1 week of systemic steroids at the time of the recommendation delayed screening until 1 week after completion of systemic steroids. Patients treated for more than 1 week were excluded. Fasting morning cortisol was obtained at the patient's local lab and was considered normal if the result was greater than 10 µg/dL. If the result was between 5 and 10 µg/dL, the decision was made to either repeat a morning cortisol or pursue adrenocorticotropic hormone (ACTH) stimulation testing based on the circumstances of the original test and in consultation with pediatric endocrinology. If the result was less than 5 µg/dL, ACTH stimulation testing was pursued.

ACTH stimulation testing was done using 250 µg of cosyntropin. ACTH stimulation testing was considered abnormal if the cortisol level was less than 14.5 µg/dL at 30 and 60 minutes. For the analysis, although fluticasone, beclomethasone, mometasone, triamcinolone, and budesonide do not have the same bioequivalence, the total daily steroid dose was combined to compare across patients (Table E1). From the inhaled steroid literature, budesonide has a higher oral bioavailability than fluticasone propionate, but a lower binding affinity and shorter plasma half-life.^{E1} The quality improvement study was acknowledged by the Johns Hopkins IRB, as IRB00185578. The retrospective chart review aspect was acknowledged by the IRB as IRB00203775.

TABLE E1. Characteristics of patient population who were tested

ID	Swallowed steroid type and dose	Inhaled steroid type and dose	Intranasal steroid type and dose	Topical steroid type and dose*	Total steroid dose (mcg/d)	Duration of STS therapy (mo)	Comorbidity	Age Sex	Screening Category
1	Fluticasone 110 mcg 2 puffs BID	N/A	N/A	N/A	440	60	AR	12 M	Normal screen
2	Fluticasone 220 mcg 1 puff BID	N/A	Fluticasone 50 mcg 2 sprays daily	N/A	540	24	AR and asthma	10 M	Normal screen
3	Budesonide 0.5 mg (500 mcg) BID	N/A	N/A	HC 1%	1000	96	AR, asthma, and eczema	12 M	Normal screen
4	Fluticasone 44 mcg 2 puff BID	N/A	N/A	N/A	176	30	Eczema	5 M	Normal screen
5	Budesonide 1 mg (1000 mcg) daily	N/A	N/A	N/A	1000	72	Eczema	13 M	Normal screen
6	Fluticasone 220 mcg 1 puff BID	Fluticasone 110 mcg 1 puff BID	Fluticasone 27.5 mcg 2 sprays daily	N/A	715	96	AR, asthma, and eczema	20 F	Normal screen
7	Fluticasone 220 mcg 2 puffs BID	N/A	N/A	N/A	880	54	N/A	19 M	Normal screen
8	Budesonide 0.5 mg (500 mcg) BID	N/A	N/A	N/A	1000	7	AR	13 M	Normal screen
9	Fluticasone 220 mcg 1 puff BID	Mometasone 110 mcg 1 puff BID	N/A	N/A	660	39	AR and asthma	8 F	Normal screen
10	Fluticasone 220 mcg 1 puff BID	N/A	N/A	N/A	440	41	AR, asthma and eczema	13 M	Normal screen
11	Mometasone 200 mcg 1 puff BID	N/A	N/A	N/A	400	20	Eczema	18 M	Normal screen
12	Budesonide 1.250 mg (1250 mcg) daily	N/A	N/A	N/A	1250	72	AR and eczema	8 M	Normal screen on repeat
13	Fluticasone 110 mcg 2 puffs BID	N/A	N/A	N/A	440	12	N/A	15 M	Normal screen on repeat
14	Fluticasone 220 mcg 2 puffs BID	N/A	N/A	N/A	880	60	Asthma	13 M	Normal ACTH stimulation
15	Budesonide 0.5 mg (500 mcg) BID	N/A	N/A	N/A	1000	36	AR	5 F	Normal ACTH stim
16	Fluticasone 220 mcg 2 puffs BID	N/A	N/A	N/A	880	150	AR and asthma	18 M	Normal ACTH stimulation
17	Budesonide 1 mg (1000 mcg) BID	N/A	N/A	N/A	2000	24	N/A	17 F	Normal ACTH stimulation
18	Beclomethasone 80 mcg 1 puff daily	Fluticasone 45 mcg 2 puffs BID	N/A	N/A	260	27	AR and asthma	7 M	Needs repeat
19	Fluticasone 220 mcg 2 puffs BID	N/A	N/A	N/A	880	60	AR, asthma, and eczema	15 F	Needs repeat
20	Budesonide 1 mg (1000 mcg) daily	N/A	N/A	N/A	1000	12	AR and eczema	4 F	Needs repeat
21	Fluticasone 220 mcg 2 puffs BID	Fluticasone 115 mcg 2 puffs BID	N/A	N/A	1340	120	AR and asthma	15 M	Needs repeat
22	Budesonide 0.5 mg (500 mcg) BID	N/A	N/A	N/A	1000	7	N/A	16 M	Needs repeat
23	Fluticasone 110 mcg 2 puffs BID	Fluticasone 110 mcg 2 puffs BID	Triamcinolone 55 mcg 2 sprays BID	HC 2.5%	1100	9	AR, asthma, and eczema	15 M	Adrenal insufficiency

ACTH, Adrenocorticotropic hormone; AR, allergic rhinitis; BID, bis in die; HC, hydrocortisone; N/A, not applicable; mcg, microgram; mg, milligram; STS, swallowed topical steroid.

*Topical steroid not included in total daily dose calculation.

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