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

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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 suppression¹. 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 diseases². 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 µg/day of fluticasone or 1000 µg/day of budesonide/beclomethasone)³. The prevalence of adrenal insufficiency in patients with EoE treated with STS has been estimated to be anywhere from 0–65%^{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.

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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 Jan 1, 2016 and October 1, 2018 were contacted with the recommendation for adrenal insufficiency screening. New patients seen after October 1st 2018 who were placed on STS were contacted on a rolling basis, through September 2019. High-dose STS exposure was defined as 500 µg/day of fluticasone or 1000 µg/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 the online repository text.

Three hundred and ten patients were identified via 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 two 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 one demonstrated adrenal insufficiency (4% of those tested) (detailed in Table E1). Five (10%) received a recommendation to repeat the screen but declined to do so (three had an AM cortisol level greater than 9 µg/dL and 2 were drawn at the incorrect time). Of the 17 patients with normal adrenal function, 6 (35%) required repeat testing or ACTH stimulation to demonstrate a normal HPA 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. Though the sample sizes for the other groups were small, no other patient in any other group reported using four 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 one screen. 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 one step but not the second and 6 (26%) required repeat AM cortisol or ACTH stimulation testing but ultimately demonstrated a normal HPA 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 this data does 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 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 five 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, while 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical implications box:

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.

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Figure 1: Flowchart of Quality Improvement Project

*Declined testing defined as no result within 60 days of the original order, or refusal at the time of the recommendation

EHR: Electronic health record, STS: Swallowed topical steroids, JHH: Johns Hopkins Hospital, ACTH: Adrenocorticotrophic hormone

Table 1:

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
Number 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 (%)						
Beclomethasone	0	0	20		4	4
Budesonide	27	50	40		12	23
Fluticasone	64	50	40	100	84	71
Mometasone	9	0	0		0	2
STS dose in pg/day (median, IQR)	440 (440 – 940)	940 (880 – 1188)	880 (880 – 1000)	440	440 (440 – 880)	440 (440 – 880)
Duration of STS therapy (months, median, IQR)	41 (27 – 66)	48 (27 – 69)	27 (12 – 60)	9	45 (24 – 60)	44 (24 – 60)
Cumulative steroid dose in µg/day (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
% on inhaled steroids	27	0	40	100	16	23

AR: Allergic Rhinitis, STS: Swallowed topical steroid, IQR: interquartile range, ICS: inhaled