RESEARCH LETTER

Esophageal Candidiasis Is Strongly Associated With Treatment Response to Topical Steroids in Eosinophilic Esophagitis and Could Be a Marker of Adherence

Eosinophilic esophagitis (EoE) is a chronic atopic disease characterized by eosinophilia and esophageal dysfunction.[1] Pharmacologic management of EoE commonly includes topical corticosteroids (tCS) such as fluticasone in a multidose inhaler or aqueous budesonide in a slurry.[2] These asthma medications are used because there have been no Food and Drug Administration–approved steroids for EoE. The tCS are swallowed to coat the esophagus and successfully achieve an anti-inflammatory effect leading to remission in 60%–70% of patients.[3,4] Still, markers to assess treatment response are needed. One known side effect of tCS is esophageal candidiasis. In a previous clinical trial, 12% of patients on oral viscous budesonide and 16% of fluticasone multidose inhaler patients reported esophageal candidiasis and it was the most common adverse event.[2] Although rates vary in EoE, patients are often quoted a 5%–10% risk of associated oral candidiasis with oral/swallowed steroid use.[5] Still, it is unknown if candidiasis is associated with or impacts treatment response. Therefore, this study aimed to determine whether treatment outcomes to tCS in EoE patients vary by the presence of candidal esophagitis.

We conducted a retrospective cohort study of the University of North Carolina EoE Clinicopathologic database, the details of which have been published.[6] This database includes

Table 1. Comparison of Baseline Characteristics of Patients With and Without Esophageal Candidiasis After Treatment With Topical Steroids

Baseline characteristic	No candidiasis (n = 466)	Candidiasis (n = 34)	P[a]
Age at diagnosis (mean years ± SD)	27.4 ± 18.1	38.6 ± 17.3	<.001
Male (n, %)	315 (68)	25 (74)	.47
White (n, %)	411 (88)	32 (94)	.36
BMI (mean kg/m^2 ± SD)	24.0 ± 7.0	26.3 ± 1.8	.09
Any atopic condition (n, %)	292 (63)	23 (68)	.64
Allergic rhinitis	226 (48)	20 (59)	.26
Asthma	127 (27)	10 (29)	.80
Eczema	73 (16)	5 (15)	.93
Food allergy	147 (32)	14 (41)	.17
Symptom length prior to diagnosis (mean years ± SD)	10.3 ± 9.9	14.3 ± 11.5	.04
Symptoms (n, %)			
Dysphagia	352 (76)	30 (88)	.10
Food impaction	163 (35)	11 (32)	.74
Heartburn	169 (36)	15 (44)	.38
Chest pain	52 (11)	3 (9)	.66
Abdominal pain	78 (17)	6 (18)	.90
Nausea	44 (9)	3 (9)	.89
Vomiting	113 (24)	5 (15)	.20
Endoscopic findings (n, %)			
Exudates	231 (50)	21 (62)	.18
Rings	258 (55)	24 (71)	.09
Edema	227 (49)	22 (65)	.08
Furrows	352 (76)	25 (74)	.76
Stricture	145 (31)	16 (47)	.06
Narrowing	96 (21)	9 (26)	.43
Crepe-paper mucosa	24 (5)	1 (3)	.57
Dilation	152 (33)	13 (38)	.52
Total EREFS (mean ± SD)[b]	4.1 ± 2.0	4.8 ± 2.0	.16
Total ESS (mean ± SD)[b]	2.6 ± 1.5	3.2 ± 1.7	.04
Peak eosinophil count (mean eos/hpf ± SD)	70.1 ± 46.8	72.5 ± 38.1	.77

[a]Means compared with 2-sample *t*-test; proportions compared with chi-squared.
[b]EREFS, data available for n = 256; ESS, Endoscopic Severity Score, for which all data available; EREFS, EoE Endoscopic Reference Score.

patients of any age with a new diagnosis of EoE as per guidelines.[1] For the present study, we included those who also had documented treatment with a tCS and a follow-up endoscopy with biopsy.[7,8] At our center, either fluticasone (usually dose 880-1760 mc/d) or budesonide (1–2 mg/day) are commonly used, at the discretion of the provider, for 8–12 weeks, and an endoscopy is performed to assess treatment response. Demographic, symptom, endoscopic, and histologic data, as well as atopic comorbidities and steroid treatment details, were extracted from the electronic medical record. On the post-treatment endoscopy, we assessed for esophageal candidiasis, defined as the presence of candida either endoscopically or histologically.

For outcomes, histological response was defined as $<$ 15 eosinophils per high-power field (eos/hpf), with additional assessment of $\leq$ 6 and $<$ 1 eos/hpf.[9] We also recorded a global symptomatic response (as reported in the chart), and an endoscopic response (as reported by the endoscopist). Endoscopic findings were also quantified by the EoE Endoscopic Reference Score (EREFS), and by an endoscopic severity score (ESS). EREFS ranged from 0–9, and ESS ranged from 0–5 (one point for each finding of edema, rings, exudates, furrows, and stricture, as these data were available for all patients, including those in the database prior to the description of EREFS).[10]

For statistical analysis, we compared the baseline characteristics of patients with and without esophageal candidiasis and assessed responses after tCS therapy. Means between groups were compared with 2-sample *t*-tests, means before/after treatment were compared with paired *t*-tests, and proportions were compared with chi-squared. We performed logistic regression to adjust for potential confounders of the relationship between histologic response and candidiasis. This study was approved by the University of North Carolina Institutional Review Board.

Of 500 EoE patients eligible for inclusion, 34 (7%) had esophageal candidiasis following initial treatment. At baseline, patients with candida were older (38.6 ± 17.3 vs 27.4 ± 18.1 years; $P < .001$) and had longer symptom duration prior to diagnosis (14.3 ± 11.5 vs 10.3 ± 9.9 years; $P = .04$) compared to those without candida; characteristics were otherwise generally similar (Table 1). More patients in the candidiasis group used fluticasone (50% vs 30%; $P = .05$) but overall doses were similar (Table 2).

Table 2. Comparison of Treatment and Response Outcomes for Patients With and Without Esophageal Candidiasis

Treament characteristic	No candidiasis (n = 466)	Candidiasis (n = 34)	P[a]
Type of steroid used (n, %)			.05
Fluticasone	140 (30)	17 (50)	
Budesonide	325 (70)	17 (50)	
Ciclesonide	1 (< 1)	0 (0)	
Mean steroid dose (mcg ± SD)	1688 ± 724	1849 ± 505	.20
Symptom response (n, %)[b]	122 (75)	20 (87)	.22
Post-treatment peak eosinophil count (mean eos/hpf ± SD)	26.2 ± 38.1	8.8 ± 20.0	.009
P value vs baseline	<.001	<.001	
Histologic response (n, %)			
< 15 eos/hpf	252 (54)	29 (85)	<.001
≤ 6 eos/hpf	222 (48)	25 (74)	.004
< 1 eos/hpf	133 (29)	14 (41)	.12
Post-treatment endoscopic findings (n, %)			
Exudates	113 (24)	11 (32)	.30
Rings	205 (44)	15 (44)	.99
Edema	138 (30)	7 (21)	.26
Furrows	220 (47)	9 (26)	.02
Stricture	141 (30)	14 (41)	.18
Narrowing	77 (17)	5 (15)	.78
Crepe-paper mucosa	4 (1)	0 (0)	.59
Dilation	139 (30)	13 (38)	.30
Endoscopic response (n, %)	324 (70)	31 (91)	.008
Post-treatment endoscopic severity (mean scores ± SD)			
EREFS[c]	2.3 ± 1.9	1.7 ± 1.4	.14
P value vs baseline	<.001	<.001	
ESS[c]	1.76 ± 1.5	1.65 ± 1.4	.67
P value vs baseline	<.001	<.001	

[a]Means between compared with 2-sample *t*-test; means among groups compared with a paired *t*-test; proportions compared with chi-squared.
[b]Available for 162 without candidiasis and 23 with candidiasis; EREFS, EoE endoscopic reference score.
[c]Available for 261 without candidiasis and 24 with candidiasis; ESS, Endoscopic Severity Score, for which all data available.

Following tCS treatment, 85% of patients with candida were histologic responders (< 15 eos/hpf) compared to 54% of patients without candida ($P < .001$), and post-tCS peak eosinophil count was significantly higher in patients without candida (26.2 ± 38.1 eos/hpf vs 8.8 ± 20.0; $P < .009$) (Table 2). Endoscopic response occurred in 91% of candida patients and 70% of patients without candida ($P = .008$), although EREFS, ESS, and symptom response were similar. After adjusting for potentially confounding clinical factors including age, body mass index, and strictures, patients with candida remained > 6 times more likely to be histologic responders than patients without candida (adjusted odds ratio 6.43, 95% confidence intervals: 2.07–20.0); type of steroid and steroid dose were not significant in the model.

Esophageal candidiasis is a known side effect of tCS treatment for EoE but information on its role as a marker of treatment response or adherence has not been previously available. This study analyzed the proportion of patients who developed candidiasis after their initial tCS course and the impact of the candidiasis on treatment outcomes. Notably, we found that histologic and provider-reported endoscopic responses were significantly higher in individuals with esophageal candidiasis, although symptom response remained similar. This suggests that candida may not only be an indicator of treatment response but that perhaps it is a sign of good adherence as well. Moreover, the relationship between histologic response and the presence of candida remained significant after adjusting for potential confounding factors.

Limitations of this study include the retrospective and single-center design. We were only able to record the presence of absence of candida and cannot comment on the extent of candida found on endoscopy, as this was not routinely documented. While we assessed several known confounders of candida, future studies could include others not available in our database. Similarly, patient adherence to tCS therapy is not routinely recorded in the chart, so we are unable to relate that directly to the presence of candidiasis. Our study also has strengths. We analyzed a large cohort of subjects, data were extracted in detailed and standardized fashion, and outcomes across symptoms, endoscopy, and histology were assessed, although given the study design, validated patient-reported outcomes were not available.

In conclusion, esophageal candidiasis is strongly and independently associated with treatment response to tCS in EoE. Patients with candida are more than 6 times as likely to have a histologic response, after adjusting for potential confounding factors. The presence of candida is likely not only a marker of local tCS effect and esophageal coverage by tCS but also potentially a marker of medication adherence, which would need to be confirmed in future prospective studies.

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Abbreviations used in this paper: **EoE, eosinophilic esophagitis; EREFS, EoE Endoscopic Reference Score; ESS, endoscopic severity score; OVB, oral viscous budesonide; tCS, topical corticosteroids**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2024.03.003

Received February 16, 2024. Accepted March 1, 2024.

Conflicts of Interest:
These authors disclose the following: Evan S. Dellon is a consultant for Abbott, Abbvie, Adare/Ellodi, Aimmune, Akesobio, Alfasigma, ALK, Allakos, Amgen, Aqilion, Arena/Pfizer, Aslan, AstraZeneca, Avir, Biorasi, Calypso, Celgene/Receptos/BMS, Celldex, Eli Lilly, EsoCap, Eupraxia, Dr Falk Pharma, Ferring, GSK, Gossamer Bio, Holoclara, Invea, Knightpoint, Landos, LucidDx, Morphic, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Salix, Sanofi, Shire/Takeda, Target RWE, and Upstream Bio; receives research funding from Adare/Ellodi, Allakos, Arena/Pfizer, AstraZeneca, Eupraxia, Ferring, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Revolo, and Shire/Takeda; and has received an educational grant from Allakos, Aqilion, Holoclara, and Invea. The remaining authors disclose no conflicts.

Funding:
This study was supported by NIH T35 DK007386 and T32 DK007634.

Ethical Statement:
This study was approved by the UNC Institutional Review Board (#13-2623).

Data Transparency Statement:
To protect patient confidentiality, data and study materials are not available; however, analytic methods will be available upon request.

Reporting Guidelines:
STROBE.