Journal of

Gastroenterology and Hepatology Research

Online Submissions: http://www.ghrnet.org/index./joghr/
doi:10.17554/j.issn.2224-3992.2015.04.562

Journal of GHR 2015 October 21 4(10): 1780-1787
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

ORIGINAL ARTICLE

Evaluation of Histologic Cutpoints for Treatment Response in Eosinophilic Esophagitis

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Received: August 15, 2015 Revised: Setember 28, 2015

Accepted: Setember 30, 2015

Published online: October 21, 2015

ABSTRACT

AIM: No consensus exists on the definition of successful treatment in eosinophilic esophagitis (EoE). The aim of this study was to identify the optimal histologic cutpoint to define successful treatment of EoE by assessing rates of symptomatic and endoscopic improvement.

MATERIALS AND METHODS: We performed a retrospective cohort study utilizing the University of North Carolina EoE Clinicopathologic Database between 2006 and 2013. Rates of symptomatic and endoscopic improvement were determined, as were post-treatment eosinophil counts. The area under the receiver operator characteristic curve (AUC) was calculated for symptomatic and endoscopic response at several possible eosinophil count cutpoints (eos/hpf). Predictors of response were also assessed.

RESULTS: Of 224 treatments in 199 patients, 76% were associated with symptomatic improvement, 68% with endoscopic improvement, and 60% with both. Of treatments that resulted in a post-treatment count of <15 eos/hpf, 90% were associated with an endoscopic response, 88% with a symptomatic response, and 81% with both symptomatic and endoscopic responses. Using a <15 eos/hpf threshold, the area under the curves (AUCs) were 0.70, 0.78, and 0.75 for symptomatic, endoscopic, and symptomatic/endoscopic responses, respectively. Lower histologic cut-points did not result in a substantial gain in response, but decreased the AUC.

CONCLUSION: In this large cohort of EoE patients, rates of symptomatic and endoscopic improvement were generally associated with histologic improvement. A histologic cutoff for treatment response of <15 eos/hpf may balance clinical outcomes and test performance.

Key words: Eosinophilic esophagitis; Treatment; Cutpoint; Corticosteroids; Dietary therapy

Wolf WA, Cotton CC, Green DJ, Hughes JT, Woosley JT, Shaheen NJ, Dellon ES. Evaluation of Histologic Cutpoints for Treatment Response in Eosinophilic Esophagitis. *Journal of Gastroenterology and Hepatology Research* 2015; 4(10): 1780-1787 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/1337

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder of the esophagus defined by ⩾15 eosinophils per high powered field (eos/hpf) on esophageal biopsy accompanied by esophageal dysfunction in the absence of competing causes of

eosinophilia[1-3]. While the adoption of diagnostic criteria have brought a measure of consistency to patient identification and research subject selection[4,5], a similar consensus definition of successful treatment has not been reached.

There are few data informing the most appropriate histologic outcome after EoE treatment[3,6]. For example, it is not known if complete histologic normalization of the esophageal mucosa is the most clinically relevant outcome, or whether lower levels of inflammation are acceptable, and if so, what level. Previous studies have used variable cutpoints (from <15 eos/hpf to 0 eos/hpf) or have relied on percentage change in eosinophil counts[3,7,8]. Other researchers have proposed endoscopic end points such as the eosinophilic esophagitis endoscopic reference score (EREFS) or have used symptomatic improvement as the target[9-11]. These diverse outcomes hamper interpretation and synthesis of the literature. Adding to this confusion, the degree of concordance between symptomatic, endoscopic, and histologic outcomes is unknown. However, these data are required to make informed decisions about the most appropriate histologic response metric after treatment.

The aim of this study was to explore the optimal histologic cutpoint for treatment response in EoE by assessing rates of symptomatic and endoscopic improvement. We also aimed to assess the frequency and predictors of concordant symptomatic, endoscopic, and histologic response.

METHODS

Patients, data sources, and outcomes

We performed a retrospective cohort analysis of patients at University of North Carolina (UNC) Hospitals from 2006-2013. Patients of any age with EoE were identified from the UNC EoE Clinicopathologic Database[12,13]. For inclusion, patients had to have EoE by consensus guidelines, including failure to respond to a PPI trial[1-3]; undergo treatment with swallowed topical corticosteroids (tCS) or dietary therapy; and have a follow up endoscopy with biopsy. Treatment with tCS consisted of either budesonide (0.5-1 mg twice daily, depending on patient age)[14,15] or fluticasone (440-880 mcg twice daily, depending on patient age)[16-18]. Dietary therapy consisted of six food elimination diets or targeted elimination diets[19-21]. Patients were treated with either tCS or dietary elimination for approximately 8 weeks prior to reassessment with esophagogastroduodenoscopy (EGD). For patients undergoing serial therapeutic trials of pharmacologic treatment modalities (for example fluticasone followed by budesonide), the results from the trial resulting in the lowest post-treatment eosinophil count were used for analysis. For patients undergoing sequential trials of dietary and steroid therapy (for example, dietary therapy after steroid therapy had failed), each therapeutic outcome was included. When a patient had outcomes for both dietary and steroid therapy, the eosinophil count from the diagnostic pre-treatment EGD was used to determine the percentage change in eosinophils.

Data were abstracted from the UNC electronic medical record. Using standardized data collection tools, we recorded patient demographics, symptoms, comorbidities, baseline and follow-up endoscopy findings, baseline and follow-up eosinophil counts on esophageal biopsy, and therapeutic regimen. Pre- and post-treatment eosinophil counts were recorded as the maximum number of eosinophils per high-power field (eos/hpf; hpf size = 0.24mm^2) from pathologist review. Treatment outcomes were defined as follows: symptom response (dichotomous patient-reported subjective improvement [yes/no]); endoscopic response (dichotomous endoscopist-reported assessment of improvement [yes/no]), and both symptom and endoscopic response.

Data Analysis

All data were analyzed using SAS version 9.3 (Cary, NC). Bivariate analyses were performed with chi-square testing for categorical variables. Because all continuous variables were not normally distributed, the Wilcoxon two-tailed t approximation (rank-sum) was used. For evaluation of treatment outcomes, a per-treatment analysis was performed, allowing inclusion of both outcomes for patients who underwent separate courses of steroid and dietary therapy. Receiver operator characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated for multiple values of the post-treatment eosinophil count (eos/hpf) as well as for the percentage change in the eosinophil count compared to baseline. Because dilation can produce symptomatic improvement without endoscopic or histologic improvement, we conducted a subgroup analysis among patients not undergoing dilation at baseline (prior to treatment) to evaluate outcomes. For patients treated with tCS, those with concordant symptomatic, endoscopic, and histologic response (<15 eos/hpf) were compared to those without using a bivariate analysis. For inclusion in this portion of the analysis, patients had to have recorded symptomatic and endoscopic response variables and pre- and post- treatment eosinophil counts. A logistic regression model was constructed to assess predictors of concordant response by including all variables significant at the $p<0.2$ level and then reducing until all factors were significant at the $p<0.05$ level. This study was approved by the UNC Institutional Review Board.

RESULTS

We identified 199 patients with EoE meeting inclusion criteria. The mean age was 27, and they were predominately white (84%), male (68%), and had a history of atopic disease (52%) (Table 1). Eighty-three percent were adults (⩾18 years old) at the time of diagnosis. The predominant baseline symptom was dysphagia (72%). Baseline endoscopies demonstrated features typical of EoE with furrows (56%), rings (49%), decreased vascularity (32%), and narrowing (20%). Twenty-seven percent required dilation at the time of diagnosis. Mean baseline eosinophil count was 74 ± 56 eos/hpf.

The majority of patients received tCS therapy alone (n=165, 83%), while a small number were prescribed dietary elimination (n=9, 5%). The remainder underwent separate trials of each therapy (n= 25, 13%), resulting in a total of 224 treatment outcomes that were used for the per-treatment analyses.

Concordance of Symptomatic, Endoscopic, and Histologic Outcomes and Determination of Histologic Cut-Points

Of 224 sets of treatment outcomes, 125 (56%) resulted in post-treatment eosinophil counts meeting a response threshold of <15 eos/hpf (Figure 1a), while only 64 (29%) met the most stringent criteria of 0 eos/hpf (Table 2). There were 154 (69%) treatment courses that decreased eosinophil counts from baseline by ⩾50% (Figure 1b), while 85 (38%) had a decrease in counts by ⩾97.5%. Of 223 treatment courses with endoscopist-reported global assessment, 152 (68%) demonstrated improvement. Among the 193 treatment courses with symptom outcome data, 146 (76%) reported improvement. Of 192 outcomes where both symptoms and endoscopic outcomes were available, 115 (60%) had improvement in both and 89 (46%) achieved symptom, endoscopic, and histologic response at the <15 eos/hpf level. Endoscopic response was associated with low

eosinophil counts, regardless of whether there was an associated symptomatic response or not (Figure 1c).

Among patients achieving <15 eos/hpf, 90% had endoscopic response, 88% had symptomatic response, and 81% had both symptomatic and endoscopic response. Using a cutpoint of <15 eos/hpf, the AUCs for symptomatic, endoscopic and concordant responses were 0.70, 0.78, and 0.75, respectively (Table 2; Figure 2a-c). At a cutpoint of 0 eos/hpf, 92% had EGD response, 93% had symptomatic response, and 85% had both. Here, the AUCs for symptomatic, endoscopic, and concordant responses were 0.64, 0.66, and 0.65, respectively. Excluding patients who had undergone dilation did not alter rates of symptomatic, endoscopic or concordant response (data not shown). On logistic regression, a post-treatment eosinophil count decrease of 1 eo/hpf increased the odds of symptomatic response by 2% [OR 1.02 (1.01-1.02)], endoscopic response by 4% [OR 1.04 (1.03-1.06)], and concordant endoscopic and symptomatic response by 5% [OR 1.05 (1.03-1.07)] (Figure 3a-c).

Results were similar using a percentage change in the post-treatment eosinophil count. For example, a decrease of 50% was associated with both an endoscopic and a symptom response rate of 84%, and concordant symptomatic and endoscopic response in 75%. Endoscopic response was associated with large percentage decreases in eos regardless of whether there was a symptomatic response, while symptomatic response in the absence of an endoscopic response was not associated with a clear pattern (Figure 1d). Using a 50% decrease in post-treatment eosinophil count, the AUCs for symptomatic, endoscopic, and concordant response were 0.66, 0.76, and 0.72, respectively (Figure 2a-c). For a decrease of 97.5%, the symptomatic response rate was 89%, the endoscopic response rate was 93%, and concordant response occurred in 84%. Here, the AUCs for symptomatic, endoscopic, and concordant responses were 0.64, 0.71, and 0.69, respectively. Excluding patients who had undergone dilation did not alter rates of symptomatic, endoscopic or concordant response (data not shown). On logistic regression, a post-treatment decrease in the eosinophil count of 1% increased the odds of symptomatic response by 1% [OR 1.01 (1.01-1.01)], endoscopic response by 2% [OR 1.02 (1.01-1.02)], and concordant endoscopic and symptomatic response by 2% [OR 1.02 (1.01-1.02)] (Figure 3d-f).

Table 1 Demographics and Baseline Characteristics (*n* = 199).

Age, mean years ± SD	**27 ± 18**
White Race, *n* (%)	166 (84)
Male, *n* (%)	136 (68)
Adult ⩾ 18 years, *n* (%)	125 (63)
Atopic Disease, *n* (%)	102 (52)
Asthma, *n* (%)	50 (25)
Food Allergy, *n* (%)	65 (36)
Baseline maximum eosinophil counts (eos/hpf, mean ± SD)	74 ± 56
Baseline symptoms	
Abdominal Pain, *n* (%)	35 (18)
Chest Pain, *n* (%)	27 (14)
Dysphagia, *n* (%)	141 (72)
Heartburn, *n* (%)	81 (41)
Nausea, *n* (%)	22 (11)
Vomiting, *n* (%)	53 (27)
Food Impaction, *n* (%)	68 (35)
Baseline Endoscopy Findings	
Normal, *n* (%)	15 (8)
Rings, *n* (%)	98 (49)
Narrowing, *n* (%)	39 (20)
Stricture, *n* (%)	41 (21)
Furrows, *n* (%)	111 (56)
White Plaques, *n* (%)	63 (32)
Decreased Vascularity, *n* (%)	63 (32)
Crepe Paper, *n* (%)	13 (7)
Hiatal Hernia, *n* (%)	18 (9)
Dilation Performed, *n* (%)	53 (27)
Steroid Therapy Only, *n* (%)	165 (83)
Diet Therapy Only, *n* (%)	9 (5)
Both Steroid and Dietary Therapy, *n* (%)	25 (13)

Factors Associated with Concordant Outcomes in Patients Treated with tCS

To assess factors associated with concordant symptomatic, endoscopic, and histologic outcomes, we compared patients treated with tCS who had <15 eos/hpf on follow up biopsy accompanied by symptomatic and endoscopic improvement (*n*=77, 44%) to patients who did not achieve improvement in all three categories (*n*=98 56%). Patients with concordant results did not differ from those with discordant or non-response on demographic features, and had similar baseline eosinophil counts and rates of atopy and food allergies (Table 3). Patients with concordant response were more likely to present with abdominal pain (24% *vs* 11, $p = 0.03$) and nausea (16% vs 6, $p = 0.04$). Endoscopy of patients with concordant response was less likely to show narrowing (13% *vs* 26, $p = 0.04$) or require dilation (19% *vs* 34, $p = 0.03$). On multivariate logistic regression, non-white race [OR 2.6 (1.1-6.4)] and the absence of dilation [OR 2.5 (1.2-5.1)] predicted concordant response. After adjustment for atopic status, baseline eos/hpf, and age, only absence of dilation [OR 3.1 (1.4-6.6)] was a significant predictor of concordance.

Table 2 Treatment Response, ROC-derived AUC, and Outcome Concordance by Histologic Response Threshold.

		Endoscopic Response		Symptomatic Response		Endoscopic and Symptomatic Response	
Eosinophil Cutoff	Histologic Response *N* = 224, n (%)	Frequency at Given Histologic Threshold (%)	AUC [95% CI]	Frequency at Given Histologic Threshold (%)	AUC [95% CI]	Frequency at Given Histologic Threshold (%)	AUC [95% CI]
<30 eos/hpf	144 (64)	90	0.82 [0.76, 0.87]	87	0.70 [0.62, 0.77]	79	0.77 [0.70, 0.83]
<20 eos/hpf	132 (59)	90	0.80 [0.74, 0.85]	88	0.70 [0.63, 0.78]	81	0.77 [0.70, 0.83]
<15 eos/hpf	125 (56)	90	0.78 [0.73, 0.84]	88	0.70 [0.62, 0.77]	81	0.75 [0.69, 0.81]
<10 eos/hpf	115 (51)	91	0.77 [0.72, 0.83]	87	0.66 [0.59, 0.74]	81	0.73 [0.66, 0.79]
<5 eos/hpf	106 (47)	90	0.74 [0.69, 0.80]	86	0.64 [0.56, 0.71]	79	0.69 [0.63, 0.76]
<3 eos/hpf	88 (39)	92	0.71 [0.66, 0.77]	91	0.66 [0.60, 0.73]	84	0.70 [0.63, 0.76]
≤1 eo/hpf	84 (38)	92	0.70 [0.65, 0.75]	92	0.66 [0.60, 0.73]	85	0.69 [0.63, 0.75]
0 eos/hpf	64 (29)	92	0.66 [0.61, 0.70]	93	0.64 [0.58, 0.69]	85	0.65 [0.60, 0.71]
Eosinophil Count Percentage Decrease from Pre- to Post-Treatment							
-50%	154 (69)	84	0.76 [0.69, 0.82]	84	0.66 [0.58, 0.74]	75	0.72 [0.66, 0.79]
-75%	134 (60)	90	0.80 [0.75, 0.86]	88	0.71 [0.63, 0.79]	80	0.76 [0.70, 0.82]
-90%	105 (47)	91	0.75 [0.69, 0.80]	87	0.65 [0.57, 0.72]	80	0.70 [0.64, 0.77]
-95%	95 (42)	93	0.74 [0.68, 0.79]	89	0.65 [0.58, 0.72]	83	0.70 [0.64, 0.76]
-97.5%	85 (38)	93	0.71 [0.66, 0.77]	89	0.64 [0.57, 0.71]	84	0.69 [0.63, 0.75]

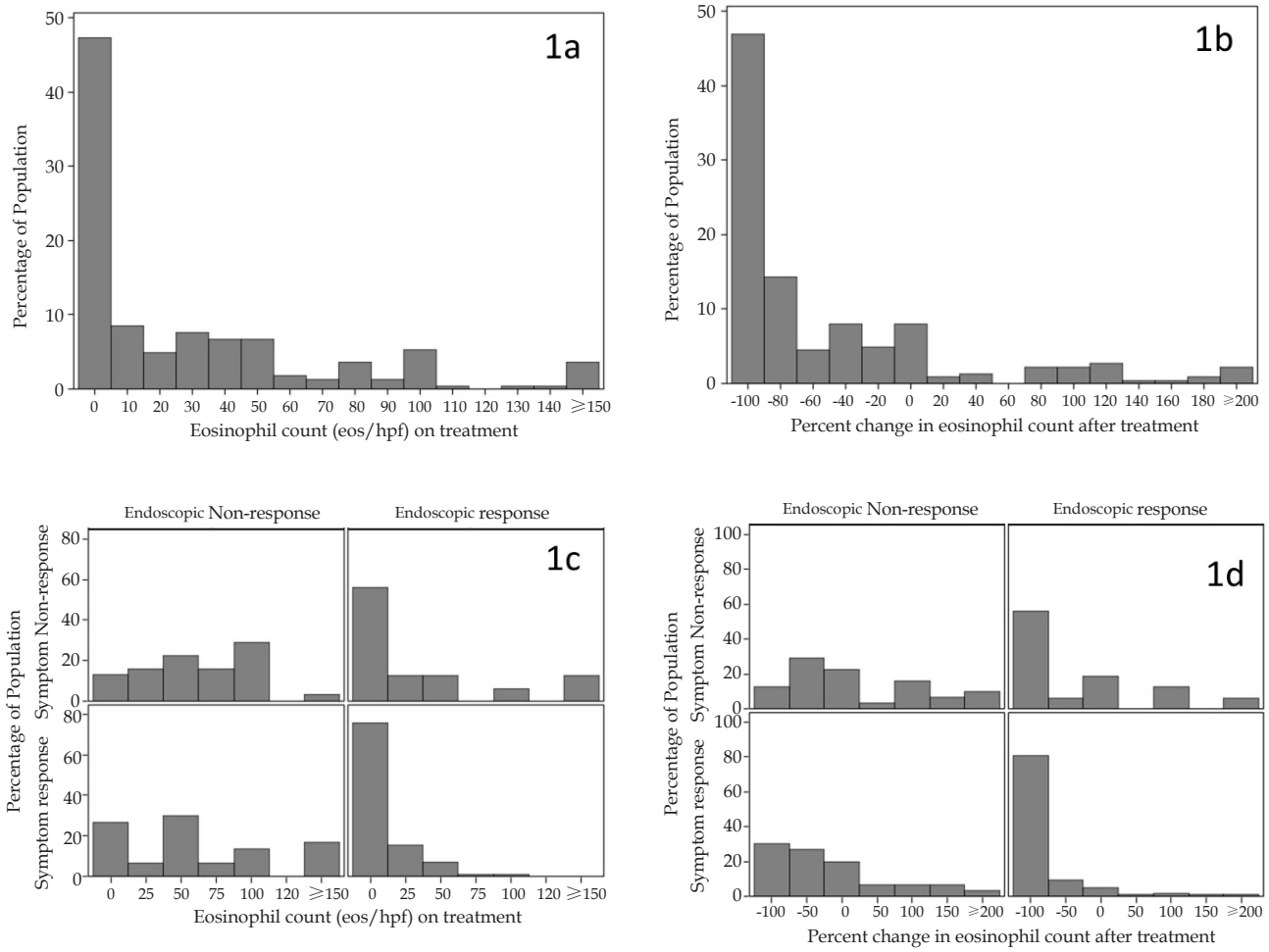

Figure 1 Histogram of proportion of patients by eosinophil count (eos/hpf) after treatment (1a) and the percentage change in eosinophil count after treatment (1b). Histogram of post-treatment eosinophil counts (eos/hpf) stratified by endoscopic and symptom response (1c) and of the percentage change in eosinophil counts after treatment, also stratified by endoscopic and symptom response (1d).

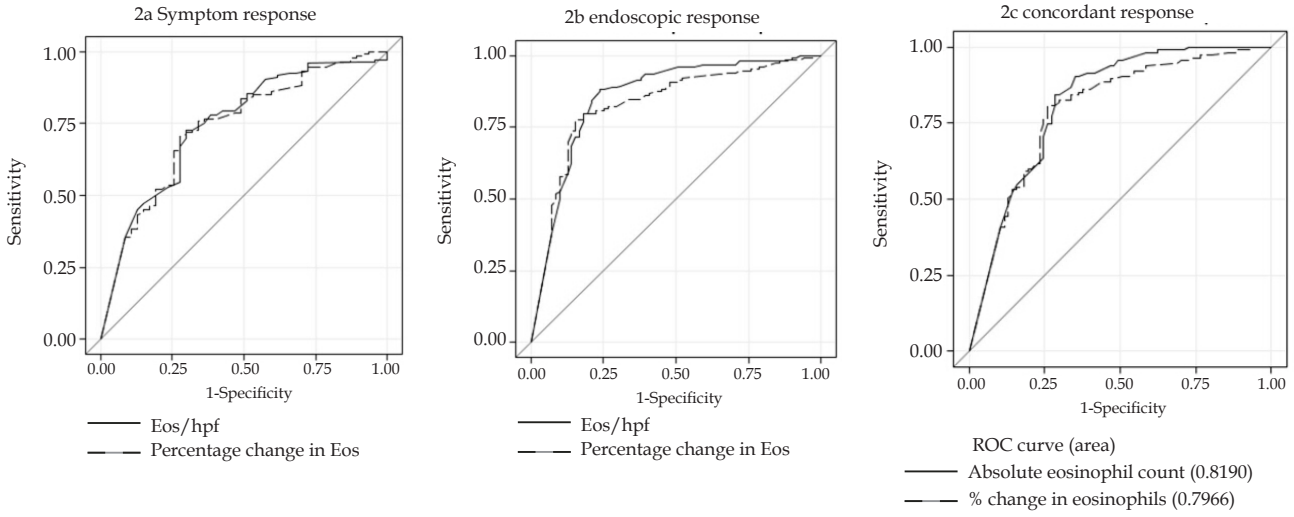

Figure 2 ROC curves comparing the post-treatment eosinophil count (eos/hpf) and percentage change in eosinophil count after treatment as a test for symptom response (2a), endoscopic response (2b), and concurrent endoscopic and symptom response (2c).

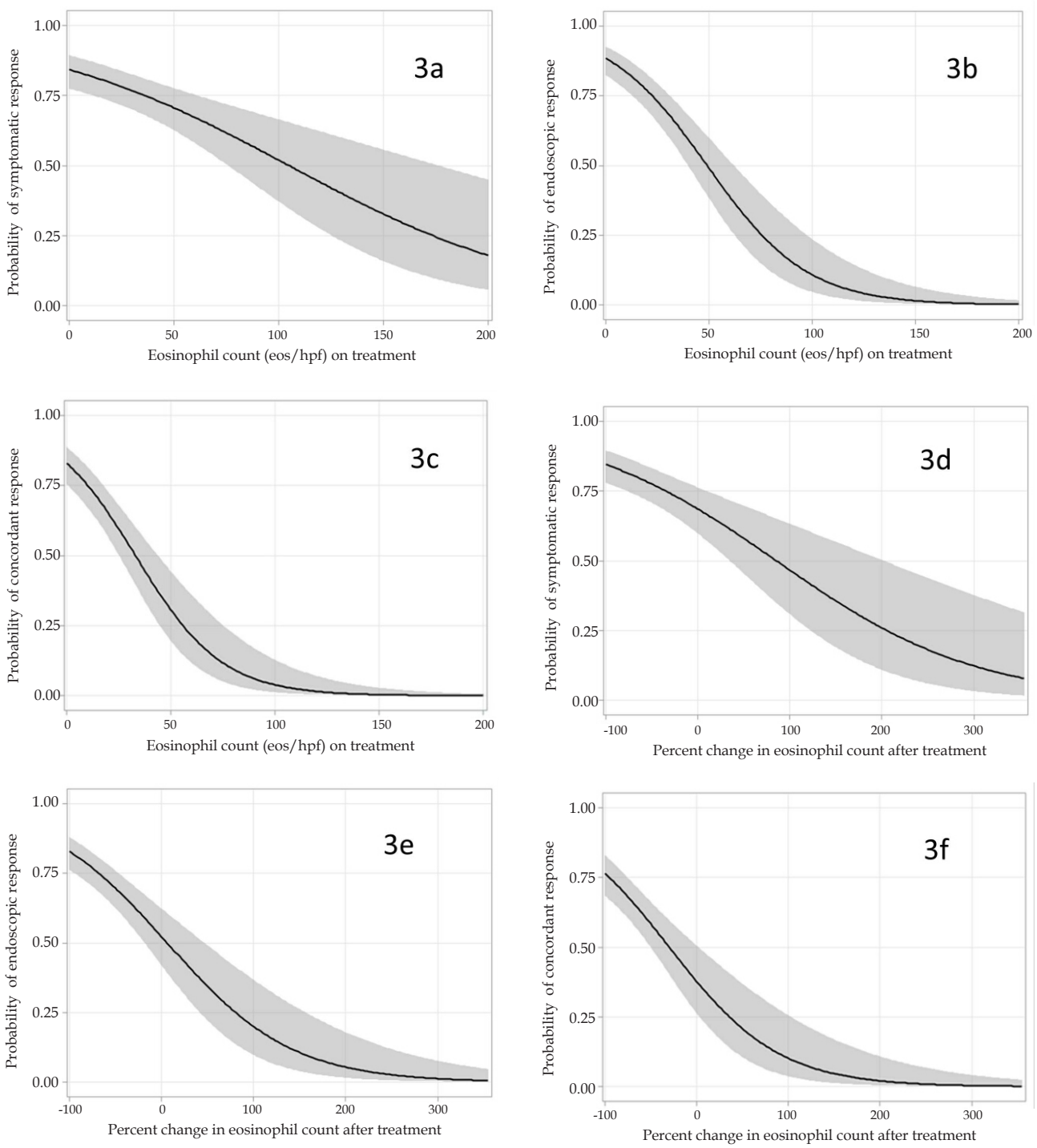

Figure 3 Predicted probability (with 95% confidence intervals) of symptomatic response (3a), endoscopic response (3b), concordant symptomatic and endoscopic response (3c) based on the post-treatment eosinophil count (eos/hpf) and of symptomatic response (3d), endoscopic response (3e), and concordant symptomatic and endoscopic response (3f) based on percentage change in eosinophil count after treatment.

DISCUSSION

Limited data exist describing the relationship of symptomatic, endoscopic, and histologic outcomes in EoE, and no consensus exists on the optimal post-treatment histologic cut-points for eosinophil counts. In this study of a large cohort of EoE patients treated with tCS and diet, we examined the frequency of concordant improvement in these three clinical outcomes and explored the implications of using different eosinophil counts as the threshold for successfully treated disease. Importantly, we found that among patients achieving histologic response, concordant response was relatively frequent, with over 80% of those with <15 eos/hpf also achieving symptomatic and endoscopic response.

Previous studies have not shown consistent results with respect to concordance of histologic, endoscopic, and symptomatic outcomes. For example, two studies by the same group had conflicting results. In one, a symptom score showed dissociation with histologic severity as measured by the eosinophil count in children with EoE[22]. In the other, there was a correlation between the presence of dysphagia and increasing eosinophil counts[23]. In clinical trials, however, this inconsistency may be attributable to variable histologic endpoints. For example, among studies where treatment achieved mean

eosinophil counts of <15 eos/hpf (regardless of the stated primary histologic outcome), concordant symptomatic and endoscopic response was actually common (though some trials did not include both outcomes)[16,18,24-27]. Only one trial achieved <15 eos/hpf without demonstrating improvement in symptoms or endoscopy, though there was a trend towards both symptomatic and endoscopic improvement that may not have reached significance due to sample size[17]. In contrast, trials that failed to lower eosinophil counts to <15, even those demonstrating statistically significant decreases in eos/hpf, had inconsistent symptomatic and endoscopic outcomes[14,24,25].

We also explored factors which were associated with concordant outcomes in steroid therapy, but found that few clinical, endoscopic, or histologic factors predicted concordant response. While several factors appeared to different on bivariate analysis, only the lack of dilation at baseline remained significant after multivariate logistic regression. Our previous research has indicated that the need for dilation is a marker of refractory disease[26], making histologic response less likely in this population and potentially contributing to a decrease in concordant response. The need for dilation may also represent a more advanced or treatment-resistant clinical phenotype, which could also contribute to discordant responses.

If a histologic response outcome were to be used as a measure of treatment efficacy, based on our data we favor using the absolute eosinophil count over the percentage change. This is because the ongoing presence of large numbers of eosinophils, which would occur in patients with high baseline counts treated to an endpoint of 50 or 75% reduction, may result in ongoing risk for fibrotic remodeling of the esophagus based on new natural history data[27,28]. Based on exploration of our data, a threshold of <15 eos/hpf could be considered a reasonable threshold. Our analysis demonstrates that the rate of endoscopic and symptomatic response increases with decreasing eosinophil counts. Notably, though, pushing the response threshold lower than <15 eos/hpf results in only small further gains in symptom and endoscopic improvement. For example, by decreasing the eosinophil cutpoint from <15 eos/hpf to 0, the symptomatic response rate increases 5%, the endoscopic response rate 2%, and the concordant response rate 4%. These improvements are offset by a decline in the test performance which is substantial.

Table 3 Factors Associated with Concordant Histologic, Endoscopic, and Symptom Response to Steroid Therapy.

	Discordant (*n* = 98)	Concordant (*n* = 77)	*p*-value
Age, mean years ± SD	24 ± 17	29 ± 18	0.06
White Race, *n* (%)	77 (79)	69 (90)	0.05
Male, *n* (%)	71 (72)	51 (66)	0.37
Adult ⩾ 18 years, *n* (%)	60 (61)	50 (65)	0.61
Atopic Disease, *n* (%)	47 (48)	37 (48)	0.96
Asthma, *n* (%)	26 (27)	19 (25)	0.75
Food Allergy, *n* (%)	25 (27)	24 (34)	0.34
Baseline maximum eosinophil count (eos/hpf, mean ± SD)	75 ± 63	78 ± 62	0.35
Baseline symptoms			
Abdominal Pain, *n* (%)	11 (11)	18 (24)	0.03
Chest Pain, *n* (%)	8 (8)	13 (17)	0.08
Dysphagia, *n* (%)	70 (73)	55 (72)	0.94
Heartburn, *n* (%)	41 (43)	26 (34)	0.26
Nausea, *n* (%)	6 (6)	12 (16)	0.04
Vomiting, *n* (%)	25 (26)	22 (29)	0.67
Food Impaction, *n* (%)	30 (31)	28 (37)	0.44
Baseline EGD Findings			
Normal, *n* (%)	7 (7)	6 (8)	0.85
Rings, *n* (%)	52 (53)	37 (49)	0.57
Narrowing, *n* (%)	25 (26)	10 (13)	0.04
Stricture, *n* (%)	23 (23)	15 (20)	0.55
Furrows, *n* (%)	58 (59)	41 (54)	0.49
White Plaques, *n* (%)	33 (34)	22 (29)	0.51
Decreased Vascularity, *n* (%)	33 (34)	23 (30)	0.63
Crepe Paper, *n* (%)	8 (8)	4 (5)	0.45
Hiatal Hernia, *n* (%)	9 (9)	6 (8)	0.74
Dilation Performed, *n* (%)	33 (34)	14 (19)	0.03
Steroid Therapy Details			
Budesonide, *n* (%)	69 (70)	60 (78)	0.26
Fluticasone, *n* (%)	29 (30)	17 (22)	
Budesonide dose, mean mcg ± SD	1641 ± 673	1792 ± 709	0.18
Fluticasone dose, mean mcg ± SD	1244 ± 620	1310 ± 579	0.71

This study has several potential limitations. First, it is retrospective, resulting in the possibility of non-differential classification bias. In addition, we rely on non-validated, binary (yes/no) measures of symptom and endoscopic response. Though a necessity due to the retrospective design, we are unable to assess the specific components of patients' symptoms and endoscopy which may (or may not) have responded to therapy. We have utilized this method because no validated measures of symptomatic or endoscopic response existed during the study time frame, we have employed similar measures in other studies[19,26], and it has the benefit of reflecting the patient's global status – did they feel better and did their endoscopy look better? We acknowledge that validated symptom and endoscopic assessments for evaluating EoE have recently been published[9-11,29], and these should be applied in future prospective studies to help answer this question more definitively. However, such symptom metrics may not come to be used in routine practice, and some clinicians may continue to use a clinical outcome measure more akin to what we employed during this study. We also note that our outcomes are assessed only after an initial 8 week treatment course. Therefore, we are unable to comment on whether this histologic threshold might decrease long-term complications such as fibrosis and strictures of the esophagus, important issues that would need to be assessed in long-term prospective studies.

This study also has multiple strengths. This is one of the largest cohorts reported to date with follow-up data on patients treated both with tCS and dietary therapy. This allowed both a per-patient, and per-treatment analysis. Additionally, because these results were found outside of a clinical trial, we believe they represent "real-world" response rates which could be typical of clinical practice, giving them broad applicability. The analyses linking specific histologic treatment outcomes to symptomatic and endoscopic responses are also unique in the EoE literature.

In conclusion, we have identified a high degree of concordance between symptomatic endoscopic improvement in EoE patients who also have histologic response to treatment, though note that many patients still fail to respond to treatment. In exploring potential histologic outcome thresholds, we favor an eosinophil cut-point of <15 eos/hpf as this optimizes the tradeoffs between improved outcomes and losses in test performance. It also provides conceptual symmetry, mirroring the current diagnostic threshold of ⩾15 eos/hpf, which has recently been supported by empiric data[30]. While these findings should be interpreted in the context of a retrospective study, they provide a starting point for furture investigations where the merits of this response threshold in a prospectively followed cohort of EoE, as well as the long-term outcomes and treatment options for patients failing to achieving this <15 eos/hpf, can be assessed.

ACKNOWLEDGMENTS

Financial Support: This research was supported, in part, by NIH awards T32DK007634 (WAW), P30DK034987 (WAW), K24DK100548 (NJS), and K23DK090073 (ESD).

Specific author contributions: Wolf: Manuscript drafting, data

analysis/interpretation; critical revision; Cotton: Data extraction, critical revision; Green: Data extraction, critical revision; Hughes: Data extraction, critical revision; Woosley: Pathology supervision, critical revision; Shaheen: Data interpretation, critical revision; Dellon: Project conception, supervision; data analysis/interpretation, critical revision.

Competing interests: Dr. Dellon has received research funding from AstraZeneca, Meritage, Receptos, and Regeneron, an educational grant from Diagnovus, and is a consultant for Aptalsis, Novartis, Receptos, Regeneron, and Roche. None of the other authors have any relevant conflicts of interest to disclose.

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