



Efficacy of Atopy Patch Testing in Directed Dietary Therapy of Eosinophilic Esophagitis: A Pilot Study

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Abstract

Background Atopy patch testing (APT) has shown potential for predicting dietary food triggers in studies of children and adolescents with eosinophilic esophagitis (EoE).

Aims To assess the efficacy of APT in adults with EoE.

Methods We conducted a prospective open-label pilot study of patients ≥ 18 years old with diagnosis of EoE at Mayo Clinic in Rochester, Minnesota, from November 2014 to January 2016. All patients underwent patch testing using intact food products, followed by a six food elimination diet and stepwise food reintroduction. Response to elimination diet was assessed with serial endoscopy with biopsies as well as clinical symptoms. APT results were directly compared to elimination diet results for assessment of efficacy. Correlation between clinical symptoms, endoscopic score, and histology was also qualitatively evaluated.

Results Fifty percent of the patients had a positive APT, while only 16% had an APT result confirmed histologically during food reintroduction. Sensitivity of APT was calculated to be 5.9%, with specificity of 92.0%. Furthermore, we found significant qualitative inter-patient heterogeneity in the correlation between clinical symptoms, EREFS score, and histology.

Conclusions APT does not reliably predict food triggers identified by food elimination diet in adult patients with EoE. As a result, APT does not have a clear role in the evaluation of patients with EoE.

Keywords Eosinophilic esophagitis (EoE) · Atopy patch testing (APT) · Elimination diet · Six food elimination diet (SFED) · EREFS score

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease characterized by esophageal eosinophilia leading to inflammation and fibrosis of the esophagus, along with symptoms of esophageal dysfunction. One of the postulated mechanisms of pathogenesis is food antigen recognition by dendritic

cells in the esophagus leading to generation of a Th2 allergic response [1, 2]. This mechanism is supported by the resolution of esophageal eosinophilia in most patients upon treatment with an elemental diet [3–6]. However, elemental diets are difficult to comply with and expensive, significantly limiting their clinical utility [6]. Consequently, the six food elimination diet (SFED) emerged as a more viable option for patients. This diet eliminates the six most common food triggers in EoE, specifically milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish, followed by gradual reintroduction of food until the culprit food is identified histologically [7–9]. In the absence of an easily applied noninvasive test, this approach is a lengthy and cumbersome process, requiring numerous esophagogastroduodenoscopies (EGDs) taking place over several months [8]. Recent studies have proposed more focused empiric food elimination diets (FEDs), such as the four-FED and step-up two-four-six FED, which reduce

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the burden of endoscopies but do not completely eliminate the need altogether [10–12].

If noninvasive food antigen testing could predict dietary triggers of EoE, this would obviate the need for repeated endoscopic testing and broad dietary restrictions, thereby saving significant time, cost, and patient burden. Skin prick testing (SPT) and serum IgE testing have been evaluated in several adult studies and have not been found to be predictive of food triggers [8, 9]. A meta-analysis of 14 studies utilizing these methods demonstrated only 45% efficacy in inducing remission, with poorer performance in adults as compared to children [13]. This is potentially related to the fact that these modalities evaluate an immediate IgE-mediated hypersensitivity pathway, whereas EoE is more likely mediated by delayed hypersensitivity [1, 9, 14].

Atopy patch testing (APT) measures the delayed hypersensitivity pathway [15], and therefore should be more useful in directing elimination diets in EoE. APT has already shown success in identifying non-IgE-mediated food allergies in children with atopic dermatitis [15, 16] and has also been investigated in children with EoE in multiple studies [5, 17–20]. In a large pediatric EoE study, combined SPT and APT were shown to be predictive of EoE food triggers, with a complete histologic response seen in 49% of pediatric patients with allergen-test-directed elimination diet, and a 77% response when including patients who were placed on an elemental diet after multiple triggers were identified by APT and SPT [21]. However, there has been limited investigation of APT in adult patients with EoE, and for unclear reasons the data overall have not suggested the more robust effect seen in the pediatric literature [6, 22, 23]. Notably, APT is not a standardized process, with variance in both methods and timing of application, and can be performed using food antigens or wet or dry fresh foods, which can lead to significant heterogeneity in results across studies. The studies in the adult population reflect this lack of standardization, using varying methods, trial designs, and food preparations.

In this study, we prospectively enrolled patients and directly compared food triggers identified by APT using real food products to triggers identified by elimination diet and food reintroduction with serial esophageal histologic sampling. Our aim was to determine whether performing APT in this manner proved to be a reliable method for predicting food triggers in adults with EoE.

Methods

Study Design and Participants

The pilot study was a prospective open-label design. The managing esophageal physicians were blinded to the

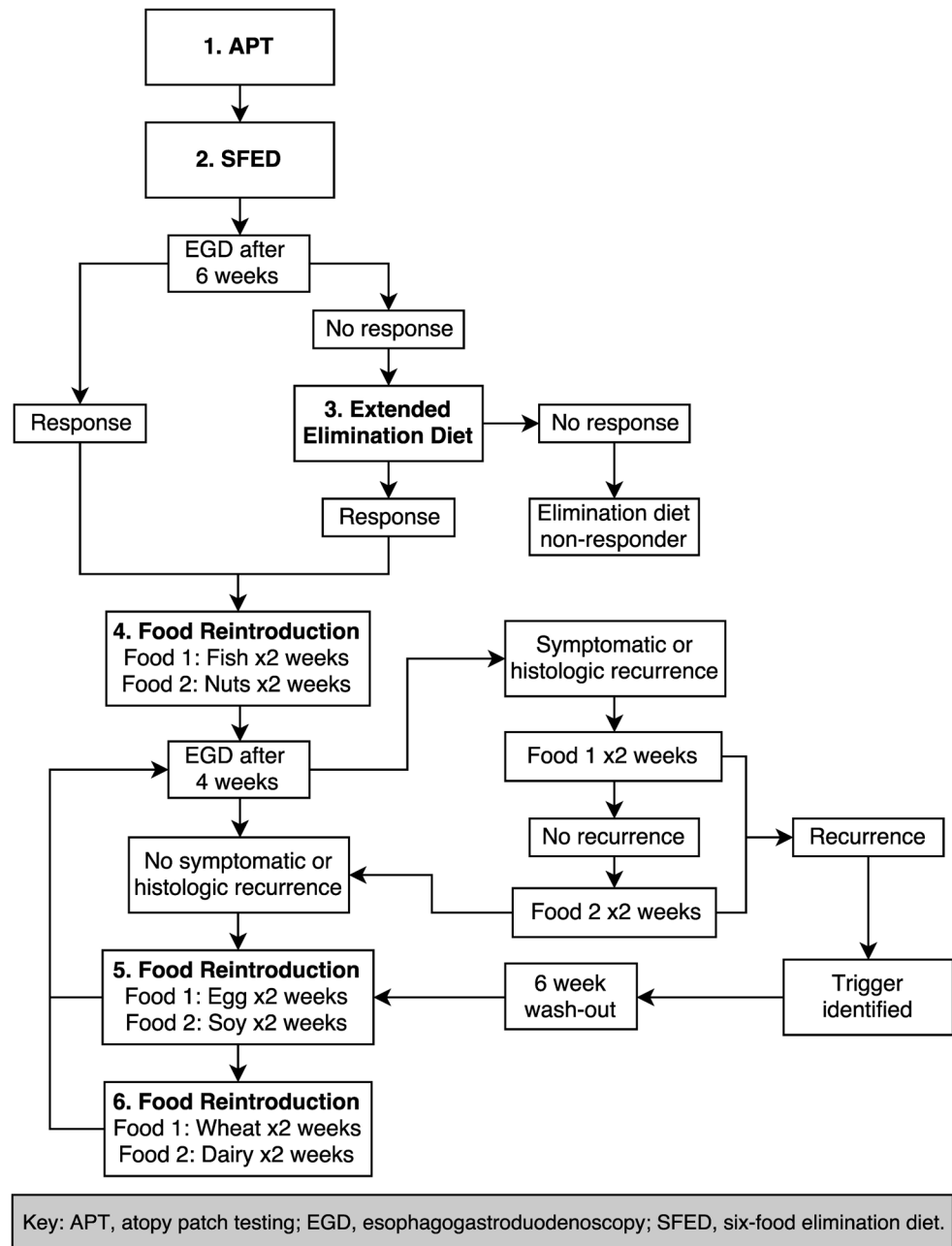
patch test results. The study was approved by the Mayo Clinic Foundation Institutional Review Board on July 13, 2014. The study was registered with ClinicalTrials.gov: #NCT02227836. All subjects provided written informed consent. All authors had access to the study data and approved the final manuscript.

Patients ≥ 18 years of age seen in the outpatient Esophageal Clinic at Mayo Clinic, Rochester, were prospectively identified. All patients had a consensus diagnosis of EoE, with esophageal mucosal biopsies demonstrating ≥ 15 eosinophils per high-powered field (eos/hpf) after at least 8 weeks of twice daily proton pump inhibitor (PPI) therapy [24]. All subjects were required to have symptomatic solid food dysphagia prior to study enrollment as determined by the 30-day Mayo Dysphagia Questionnaire (MDQ-30). This was defined as an answer of “yes” to the question of “In the past thirty days, have you had trouble swallowing not associated with other cold symptoms?”, a severity of at least “moderate”, and a frequency of at least “ $\geq$ once per week”. Patients were excluded from the study if they suffered from conditions known to cause secondary esophageal eosinophilia, including Crohn’s disease, achalasia, and hypereosinophilic syndrome; if they had taken topical or systemic steroids within the last 8 weeks; or if they suffered from underlying dermatologic conditions precluding allergy patch testing.

Study Flow

Patients meeting inclusion criteria for our study were evaluated by a gastroenterologist (KR, JAA, DAK) for a baseline clinical assessment and asked to fill out a baseline validated 30-day Mayo Dysphagia Questionnaire (MDQ-30) [25]. Study participants then underwent APT as described below, followed by standard SFED with serial EGD for assessment of response. Patients were asked to eliminate dairy, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish for 6 weeks, and to keep a dietary diary throughout the process. Participants met with a dietitian trained in management of EoE before initiating the SFED and immediately after completion, and completed a telephone interview 2 and 4 weeks into the diet to ensure compliance. After completion of the diet, patients again met with one of the three gastroenterologists, who were blinded to the results of APT testing, for repeat clinical assessment. The patients then underwent EGD with esophageal biopsies to assess for clinical response, defined as < 15 eos/hpf. Non-responders to the SFED were started on an extended elimination diet, which also removed corn and legumes (peas, chickpeas, beans, lentils) with follow-up EGD and biopsy in 6 weeks.

Responders underwent stepwise reintroduction of the eliminated foods with periodic endoscopies with biopsies, as shown in Fig. 1. Based on previous studies suggesting an

Fig. 1 Study flow

increase of approximately 5 eos/hpf/day upon food trigger reintroduction, foods were reintroduced at 2 week intervals in the following order: fish, nuts, egg, soy, wheat, and dairy. All foods were reintroduced except in the setting of previously recognized food allergy. Patients ate the reintroduced foods at a minimum of three times per week. Per the protocol developed by Gonsalves et al. [8] one food was introduced every 2 weeks and an EGD with esophageal biopsy was performed every 4 weeks or if symptoms developed. If a histologic flare of disease developed, each food was eliminated from the diet independently with endoscopy after 2 weeks to identify the causative food. When a trigger was identified,

that food was removed from the diet and the next food was introduced after a 6 week washout period and endoscopic confirmation of histologic remission. Patients taking a PPI for symptomatic treatment of GERD were allowed to continue the medication at the same dose.

Atopy Patch Testing

APT was performed in the Department of Dermatology at Mayo Clinic Rochester, a group with extensive experience using APT (approximately 300 series per year) in the evaluation of dermatologic disease. APT was performed using both

dry and wet fresh foods. Milk, egg white, soy, corn, barley, rice, rye, wheat, garbanzo bean, potato, and almond were all tested in dried form. Two grams of dry food product was mixed into 2 mL of isotonic saline solution, and the mixture was then placed into aluminum Finn chambers on Scanpor tape (SmartPractice, Phoenix, AZ). Wet foods (applesauce, tomato paste, peanut butter, fish, shrimp, beef, and turkey) were placed directly into the Finn chambers. The aluminum chambers were then applied to a clean, dry area of the skin, usually the upper back. The patches were removed 48 h after application, and results were read at 72 and 120 h. Results were classified based on degree of reaction: 0 for negative; 1 for macular erythema; 2 for raised erythema; 3 for raised, spreading erythema; and 4 for blistering or ulceration. Any reaction was considered a positive result. Patients in this study did not alter their diet based on APT findings.

Assessment of Clinical and Histologic Response

All endoscopies were performed with a staff physician in attendance as part of the patient's clinical evaluation. Eosinophilic Esophagitis Endoscopic Reference Scores (EREFS) were calculated based on endoscopic appearance of the esophagus [26] and were independently calculated by a single gastroenterologist upon review of the endoscopic images and reports to maximize uniformity between patients. Exudates were classified as grade 0 (absent), grade 1 (mild, involving < 10% of the esophageal surface area), or grade 2 (severe, involving $\geq$ 10% of the esophageal mucosa). Rings were classified as grade 0 (absent), grade 1 (mild, circumferential ridges), grade 2 (moderate, distinct rings that did not impair passage of a standard adult endoscope), or grade 3 (severe, distinct rings that impaired passage of standard adult endoscope). Edema was classified as grade 0 (absent) or grade 1 (present, with loss of vascular markings). Furrows were classified as grade 0 (absent), grade 1 (mild, present but without visible depth), or grade 2 (severe, visible depth or mucosal indentation). Strictures were classified as grade 0 (absent) or grade 1 (present). A total EREFS score was calculated by totaling the numeric grades from each category. This score was calculated at baseline and with each subsequent endoscopy performed throughout the food reintroduction process.

During endoscopy, biopsies were obtained with standard size biopsy cables, with 8 biopsies taken from the entire esophagus. Biopsy specimens were stained with hematoxylin and eosin and then read by one of four experienced gastrointestinal pathologists using a Nikon E600 microscope with a 10 X 25 ultra-wide eyepiece. The area of greatest eosinophil density was initially determined by low powered review of all slides. Eosinophil count was then determined using a 40X objective, a field diameter of 0.625 mm, and

a field area of 0.307 mm². The peak eosinophil count per high-power field was reported.

Clinical response was assessed using the MDQ-30. All subjects were required to have symptomatic solid food dysphagia prior to study enrollment as noted previously, with symptoms $\geq$ once per week. Partial response was defined as continued symptoms, but with a frequency < once per week. Symptom remission was defined as an answer of "no" to the question of "Have you had trouble swallowing unrelated to a sore throat or cold over the last 2 weeks?"

Data Collection and Statistical Analysis

Clinical data were collected from patient questionnaires, and histologic data were collected from pathology reports. Both endoscopic data and APT results were collected by the performing staff and entered into standardized report forms. The data from these sources were entered into a database for analysis by staff trained in clinical and translational research. The data were cross-referenced to the original clinical reports and questionnaires by one of the physician investigators to ensure accuracy prior to data analysis. APT results were compared to histologic findings to determine the sensitivity and specificity of APT, which were calculated comparing only foods tested by both elimination diet and APT. Only patients who fully completed testing were included in this analysis. Data were also qualitatively analyzed in graphical form to evaluate the correlation between clinical symptoms, endoscopic findings, and histologic characteristics.

Results

Baseline Patient Characteristics and Study Course

Eight patients met inclusion criteria and were enrolled into the pilot study. Baseline characteristics of the patients are shown in Table 1. The average age was 43 years old, with even gender distribution. Seven of the eight patients had an allergic history, and seven had history of reflux symptoms. All eight patients described clinically significant dysphagia at baseline as previously defined. At baseline endoscopy, the average number of eos/hpf for all eight patients was 87 (range 55–120). The average EREFS score was 4.3 (range 3–5). Rings and furrows were the most common finding on endoscopic examination, seen in seven patients each. Four patients had small caliber esophagus, and one had erosive esophagitis. One patient underwent patch testing and initial SFED, but withdrew from the study prior to food reintroduction, preferring therapy with topical corticosteroids instead. Another patient did not respond to either SFED or extended elimination diet, but did undergo patch testing.

Table 1 Baseline patient characteristics

General characteristics	<i>n</i> = 8
Age in years (SEM)	43 (11)
Male gender (%)	4 (50)
Any allergic history	7
History of seasonal allergy	4
History of asthma	2
History of allergic dermatitis	3
History of other allergy	4
Reflux symptoms	7
Heartburn	4
Regurgitation	5
History of food impaction	4
Dysphagia	8
Current PPI use	4
Histologic characteristics	
Peak eosinophils/hpf (SEM)	87 (7.8)
Endoscopic characteristics	
Edema	5
Rings	7
Exudates	6
Furrows	7
Strictures	3
Average EREFS score (SEM)	4.3 (0.36)
Erosive esophagitis	1
Small caliber esophagus* (< 15 mm)	4

* As determined by barium esophagram or endoscopy

SFED Results

Six of the eight patients (75%) showed complete histologic response to SFED, and one additional patient responded to the extended elimination diet, for a total of seven of eight patients (82.5%) showing complete histologic remission after dietary intervention. The average number of eosinophils/HPF after diet completion in this group was 4.2 (SEM 2.3, range 0–15). The last patient withdrew from the study after initial elimination diet, without follow-up endoscopy. Stepwise food reintroduction with serial endoscopy identified specific food triggers in all seven patients (100%) who had responded to the elimination diet, with sixteen food triggers identified histologically in total (Table 2).

APT Results

APT results are shown in Table 2. Four patients (50%) showed a positive APT to at least one food, with a total of eight positive reactions. The remaining four patients showed no reaction to any food. The most commonly identified positive foods were fish in two patients, followed by wheat, egg, rye, potato, apple, and milk in one patient each. In only one of six patients (17%) was a food trigger identified by APT found to correlate to one of the foods identified by food withdrawal and reintroduction on biopsy (bolded in Table 2). In contrast, of the 16 positive foods identified on elimination diet, only one correlated to positive findings on APT. Only one of eight (12.5%) total positive APT reactions correlated to histologic findings. Using these results, the sensitivity

Table 2 Comparison of response to SFED with food reintroduction versus APT

Patient	Modality	Fish	Nuts	Eggs	Soy	Wheat	Dairy	Legumes	Other
1	Histology	–	–	–	+	–	+	+	
	APT	–	–	–	–	–	–	–	
2*	Histology								
	APT	–	–	+	–	+	–	–	Rye
3	Histology	–	+	+	+	+	–	–	
	APT	–	+	–	–	–	–	–	Apple, potato
4	Histology	–	–	–	–	+	–	–	
	APT	+	–	–	–	–	–	–	
5	Histology	–	–	–	–	+	+	–	
	APT	+	–	–	–	–	–	–	
6**	Histology								
	APT	–	–	–	–	–	–	–	
7	Histology	–	+	+	–	+	+	–	
	APT	–	–	–	–	–	–	–	
8	Histology	–	–	–	+	+	+	–	
	APT	–	–	–	–	–	–	–	

*SFED and extended diet non-responder did not undergo food reintroduction

**Responder to SFED, patient opted for topical steroid therapy instead

of APT in identifying food triggers as determined by histology on food reintroduction was 5.88% (95% confidence interval (CI) 0.31–30.76%), while the specificity was 92% (95% CI 72.49–98.60%). Three other foods, specifically rye, apple, and potato, produced a positive APT in two of the patients, but were not tested for as part of the standard elimination diets, and therefore were not included in these calculations. One of these patients, who reacted to rye, was a non-responder to both the SFED and the extended elimination diet, suggesting rye as a potential trigger although this was not investigated endoscopically. The second patient responded fully to the SFED despite positive APT to apple and potato, indicating false positive reactions.

Correlation Between Clinical Symptoms, Histologic Findings, and Endoscopic Findings

All patients reported clinical improvement after elimination diet; seven (82.5%) experienced complete resolution of their dysphagia, while one exhibited a partial clinical response as previously defined. Strong correlation between improvement in histologic eosinophilia and clinical symptoms was noted in five of the patients, with resolution of symptoms occurring at the same visit as endoscopically obtained biopsies showed resolution of esophageal eosinophilia. A sixth patient had clinical symptoms despite resolution of endoscopic findings after finishing the elimination diet, but complete response by the time of the first food reintroduction. Another patient did not show histologic evidence of response despite clinical improvement, while the last experienced clinical response but withdrew from the study as noted previously, prior to post-elimination diet endoscopy.

Overall, EREFS score had a varying qualitative degree of correlation with esophageal eosinophilia and clinical symptoms, as is demonstrated in Fig. 2. In three of the patients, EREFS score and histology were closely correlated, but were not representative of the patient's clinical symptoms. In another patient, all three parameters were divergent at various times during their treatment course. Only in two patients did EREFS scores, symptoms, and histology all have a generally concordant response to dietary therapy. The last two patients did not have enough testing performed to make meaningful correlations.

Discussion

Food allergens are a significant contributor to the pathogenesis of EoE. Unfortunately, the current gold standard for identification of causative food allergens, SFED followed by dietary reintroduction with serial endoscopy, is a time-consuming and expensive process for many patients. If effective at determining specific food triggers, APT would be an

ideal noninvasive alternative to this current method. Our pilot study explored the ability of APT to identify causative food allergens in adult patients with EoE, and to our knowledge is the first that prospectively analyzes adult patients in whom APT is performed using fresh foods and directly compares these results to SFED with serial EGD.

Previous studies using APT in adults have had limited success and have been performed with varying techniques and study designs. In one adult study in which APT was compared to SFED using eleven commercially prepared food antigens, no food triggers were identified correctly, with only 5/23 (22%) of patients reacting to APT [22]. In another series using dried food and baby food, multimodality allergy testing including APT was used to direct a selective elimination diet [23]. Only 23% of patients reacted to the food antigens tested using APT, and the study did not directly compare the food triggers detected by APT to the results of an elimination diet. In yet another study, patients underwent elemental diet with comparison to APT using fresh foods, with only 7% showing APT reactivity [6]. In our study, APT showed poor performance in predicting food triggers in adult patients with EoE; of the eight patients in our study, only one had a food trigger successfully identified, resulting in a sensitivity of only approximately 6%.

Notably, in our cohort we had a significantly higher percentage of patients with positive reactions using APT (50%), approximately double that observed in previous adult studies. One explanation for this may be the utilization of food that is comparable to that ingested by the patient, which may increase the sensitivity of the patch testing, as opposed to food antigens manufactured for the patch testing process [27]. Furthermore, in our study patients were evaluated twice for reactions, once on Day 3 and once on Day 5. In two of these four patients who reacted, positive results appeared only on the second assessment. Other studies did not appear to reassess patients after initial evaluation at 72 h, and therefore may have missed these delayed reactions. Regardless, despite our higher rate of positive results using APT, there does not seem to be an accompanying improvement in the identification of food triggers.

There are several explanations for why APT may not successfully identify food triggers. First, it may be that the predominant immunologic driver behind EoE is not purely the delayed type hypersensitivity tested for by APT, but instead a combination of multiple allergic processes acting together to promote the disease such as IgG4, rendering single modality testing inaccurate and incomplete [14]. Secondly, it could be that the process of mastication and digestion releases allergens from food that are not present when merely applied to the skin. Finally, the immunologic sensitization of the esophagus may be different than that of the skin, whether due to different exposures, compartmentalization of the immune system, or other factors. In

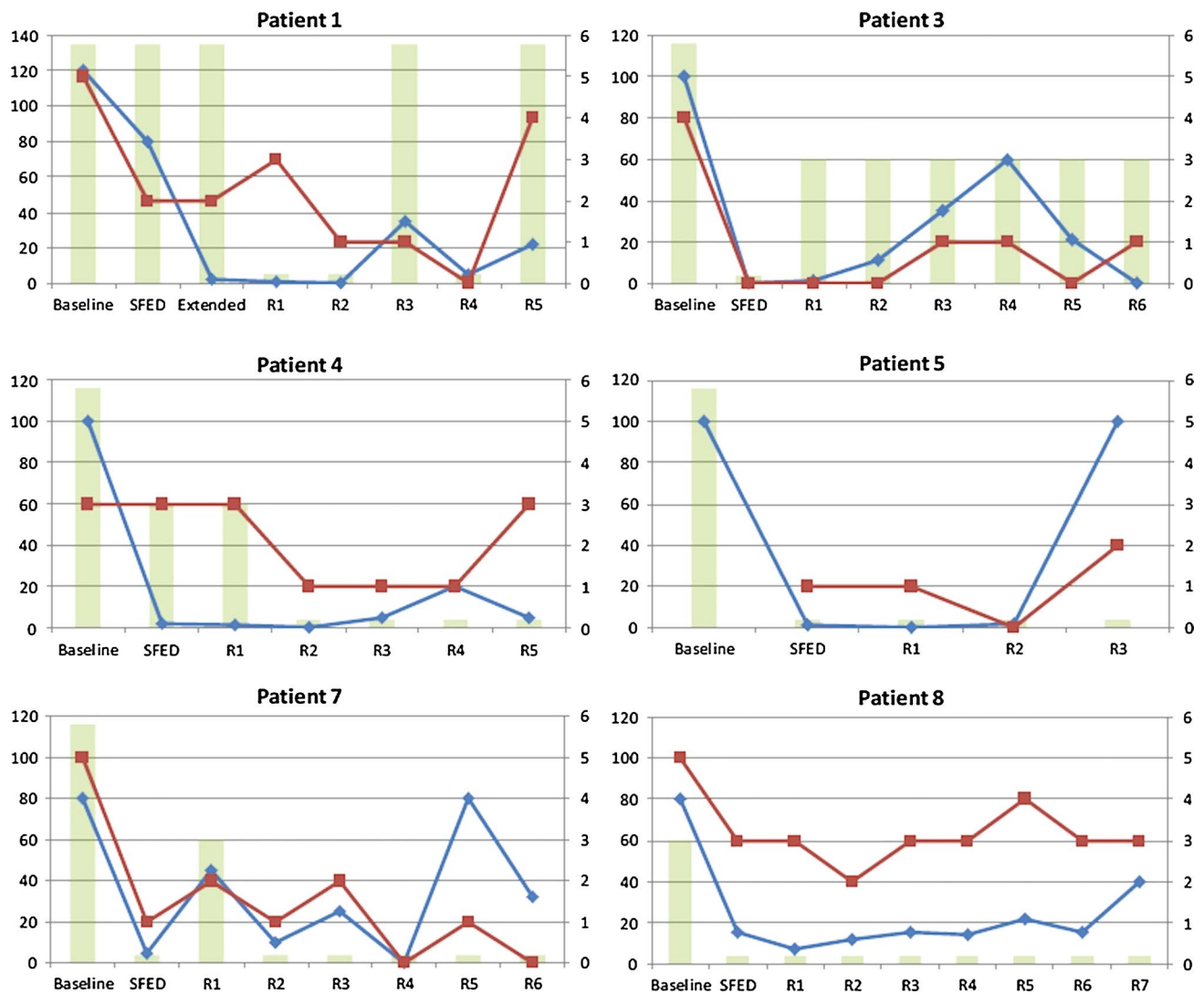


Fig. 2 Correlation between clinical symptoms, histology, and EREFS scores in select patients. Left vertical axis: number of eosinophils per high-power field (blue line). Right vertical axis: total EREFS score (red line). Horizontal axis: endoscopy (R = reintroduction). Vertical

green bars represent clinical symptoms (full bar = persistent dysphagia, middle bar = partial clinical response, bottom bar = full clinical response)

this scenario, an allergen triggering a positive skin reaction identified by APT may not trigger a corresponding allergic response in the esophagus, and vice versa. Regardless of the reason, our study shows that APT does not successfully identify causative food allergens in EoE.

Seven of the eight patients experienced clinical remission after the elimination diet, with food triggers identified for each of these patients during the food reintroduction phase, indicating the continued utility of this method despite the cumbersome and involved process. Interestingly, within the cohort there was considerable heterogeneity in the correlation between clinical symptoms, histologic response, and endoscopic characteristics as quantified by EREFS scores. A recent study evaluated the use of the EREFS score in

diagnosing EoE and determining response to treatment and found it to be highly accurate, with an area under the receiver operator characteristic curve of 0.934 [28]. However, this analysis compared EREFS scores before and after treatment alone, and did not evaluate the utility of serial EREFS scores in guiding a food elimination diet. The significant variation within our small cohort of patients would indicate that EREFS scoring is not accurate alone in assessing response to treatment in these patients, suggesting substantial variability in the esophageal mucosal response to food elimination and reintroduction.

Furthermore, we also noted significant discrepancies between clinical, histologic, and endoscopic responses. Each patient in our study had at least one instance in which they

either experienced no clinical symptoms despite continued esophageal eosinophilia, or vice versa. While this is a small study with a limited number of patients, two recent larger studies have demonstrated a similar discrepancy between clinical symptoms, histologic results, and endoscopic findings as measured by the EREFS score [29, 30]. This confirms the importance of endoscopic evaluation in patients with EoE, as clinical symptoms alone may not be sufficient to monitor disease progress.

A limitation to our study is the number of participants, which is a reflection of the complexity of the testing process, with many patients opting instead for therapy with topical steroids in order to avoid the time-intensive food elimination therapy and patch testing process. This limits the power of the study to identify statistically significant results, but also emphasizes the importance of finding a less cumbersome and time-consuming method of identifying food triggers in these patients. Furthermore, the study did not test for aeroallergens in the APT process, which may play a role in the pathogenesis of EoE, although the purpose of our study was to identify food triggers. Finally, there was not 100% overlap between foods tested for by elimination diet and those tested by APT, although only those foods tested for by both were included in statistical analysis.

There are also several strengths to our study. The first is that we used real food in the patch testing process, as opposed to commercially prepared food antigens that have been used in many other studies, which may have increased the response rate of APT. Secondly, we put the patients through an extensive patch testing process with a large number of foods at a facility with decades of experience in this process. Furthermore, we performed both APT and elimination diet with food reintroduction and serial endoscopy, and then directly compared the two. This is preferable to a directed elimination diet based on results of allergy testing, which does not compare APT results to a gold standard, and therefore makes it difficult to interpret the effectiveness of APT in food allergen identification.

In conclusion, our study prospectively confirms that there is no clinical utility in using APT to direct dietary therapy in adult patients with EoE. Although allergy testing for the purpose of identifying extra-esophageal atopic factors is important, this study limits their use in guiding EoE therapy. Further investigation into less invasive and less costly techniques to predict dietary triggers in EoE continues to be needed.

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Compliance with ethical standards

Conflict of interests Jeffrey A. Alexander: Meritage Pharmacia; financial interest. Jason D. Eckmann, Karthik Ravi, Dawn R. Davis, Jacalyn A. See, Debra R. Geno, and Lori A. Kryzer have no disclosures

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