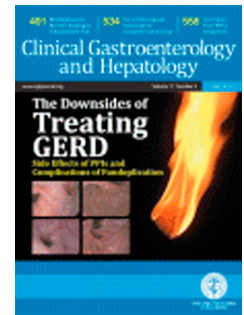


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Clinical, endoscopic, and histologic benefit with comprehensive type IV hypersensitivity patch testing in adults with eosinophilic esophagitis

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Title: Clinical, endoscopic, and histologic benefit with comprehensive type IV hypersensitivity patch testing in adults with eosinophilic esophagitis

Short Title: Type IV patch testing in eosinophilic esophagitis

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Abbreviations: atopy patch testing (APT), comprehensive type IV hypersensitivity patch testing (CPT), esophagogastroduodenoscopy (EGD), eosinophilic esophagitis (EoE), eos/HPF (eosinophils per high-power field), interquartile range (IQR), proton pump inhibitor (PPI)

Keywords: hypersensitivity patch testing; eosinophilic esophagitis; type IV allergy skin testing

Introduction:

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder of increasing incidence¹. While empiric elimination diets are commonly used EoE therapies, adoption of allergy testing to guide elimination diets has been more limited^{2,3}. This likely stems from testing which has often focused on immediate type I hypersensitivity (i.e. skin-prick or serum-specific IgE testing) rather than comprehensive type IV hypersensitivity patch tests (CPT) which identify delayed type allergens⁴. While atopy patch tests have been less successful for food triggers, CPTs can evaluate the potential role of additives and aeroallergens in EoE⁵. Our study aimed to determine if avoiding aeroallergens and additives to everyday products based on a CPT would lead to symptomatic and histologic improvement in patients with EoE who had not responded to proton pump inhibitors (PPIs) alone.

Methods:

In this retrospective cohort study at our tertiary academic medical center, we identified adults with EoE, based upon histologic criteria, who had undergone CPT (American Contact Dermatitis Society standard patch test series and additional series of allergens established at Weill Cornell) with subsequent diet/lifestyle modifications (Supp. Methods). Patients had completed an 8-week course of high dose PPI therapy without relief of symptoms, such as dysphagia or food impactions, prior to CPT referral. We collected information from medical records on demographics, atopic background, patch testing results, as well as pre- and post-CPT symptoms, endoscopy findings, and histologic features. Bivariate analyses were performed using a Wilcoxon Sign-Rank test to analyze pre-and post-CPT patient symptoms, endoscopic severity

measured by Composite EoE Endoscopic Reference Scores (EREFS), and histologic outcomes (improvement in mean eosinophils per high-power field [eos/HPF]) 6 to 12 months after avoiding allergens identified on CPT.

Results:

We identified 18 adults with EoE who underwent patch testing after non-response to PPI therapy; 67% were men, 67% were atopic, and only 11% with history of unsuccessful elimination diets. Pre-CPT, 94% of all patients were symptomatic (67% dysphagia, 50% heartburn, 33% food impactions), mean eos/HPF was 31 ± 21.8 , and EREFS 1.8 ± 1.1 (Supp. Table 1).

16 (88.9%) patients had positive CPT, with 61.1% positive for chemicals/dyes/preservatives, 55.6% for food additives, and 38.9% for aeroallergens (Supp. Table 2). The most commonly positive allergens were Fragrance Mix 1 (including cinnamic aldehyde) [25%], cinnamic aldehyde [25%], gold sodium thiosulfate [18.8%], carmine [18.8%], and balsam of peru [12.5%].

Post-CPT, 12 patients followed up and 92% reported adherence to the provided diet and food avoidance strategies with 8/11 (72.7%) reporting improved symptoms. Seven adherent patients followed up for EGD (Fig. 1, Supp. Table 1), 71% had symptomatic improvement and 57% had histologic remission (<15 eos/hpf). Composite EREFS improved in all but one patient, and thus was not a statistically significant improvement (median score 1 [IQR 0-1]; $p = 0.10$). However,

mean eosinophil counts showed a statistically significant decrease post-CPT (median count 5 [IQR 5-20] eos/hpf; $p=0.04$).

Discussion:

We found that use of type IV hypersensitivity allergy skin testing is a viable method to identify food additives and aeroallergens, and avoidance of these allergens with diet/lifestyle modifications can lead to clinical, endoscopic, and histologic improvement in adults with EoE who did not respond to PPIs alone. We evaluated patients who did not respond clinically to PPI therapy, as this may represent a more “allergic phenotype” of EoE which may respond to the addition of CPT-guided elimination diet. While our analysis focused on those who reported adherence to the CPT-guided diet and had subsequent endoscopy, many patients who did not follow up for endoscopy also reported symptomatic improvement.

Limitations of this study include a small sample size at one medical center and retrospective study design. The majority of patients were continued on PPI therapy (a minority also started topical steroids) in conjunction with CPT-guided diet/lifestyle modifications, which limits attribution of improvement solely to CPT-associated intervention. However, the strength of this hypothesis-generating study is that there were improved symptoms and histologic remission identified in a PPI-resistant EoE population when using a more comprehensive hypersensitivity patch testing than previously reported.

Recent guidelines have suggested a potential role for aeroallergen testing and treatment in EoE⁶. Our findings show that aeroallergen testing provides actionable targets for lifestyle modification in patients with EoE with resulting clinical and histologic improvement. Additionally, our findings suggest that food additives may be overlooked triggers of EoE. Prospective studies are necessary to confirm these results, but more comprehensive type IV hypersensitivity patch testing may help patients who have not responded to initial therapies and would prefer to avoid long-term topical steroids.

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Figure 1. Clinical, endoscopic, and histologic changes pre- and post-type IV patch testing

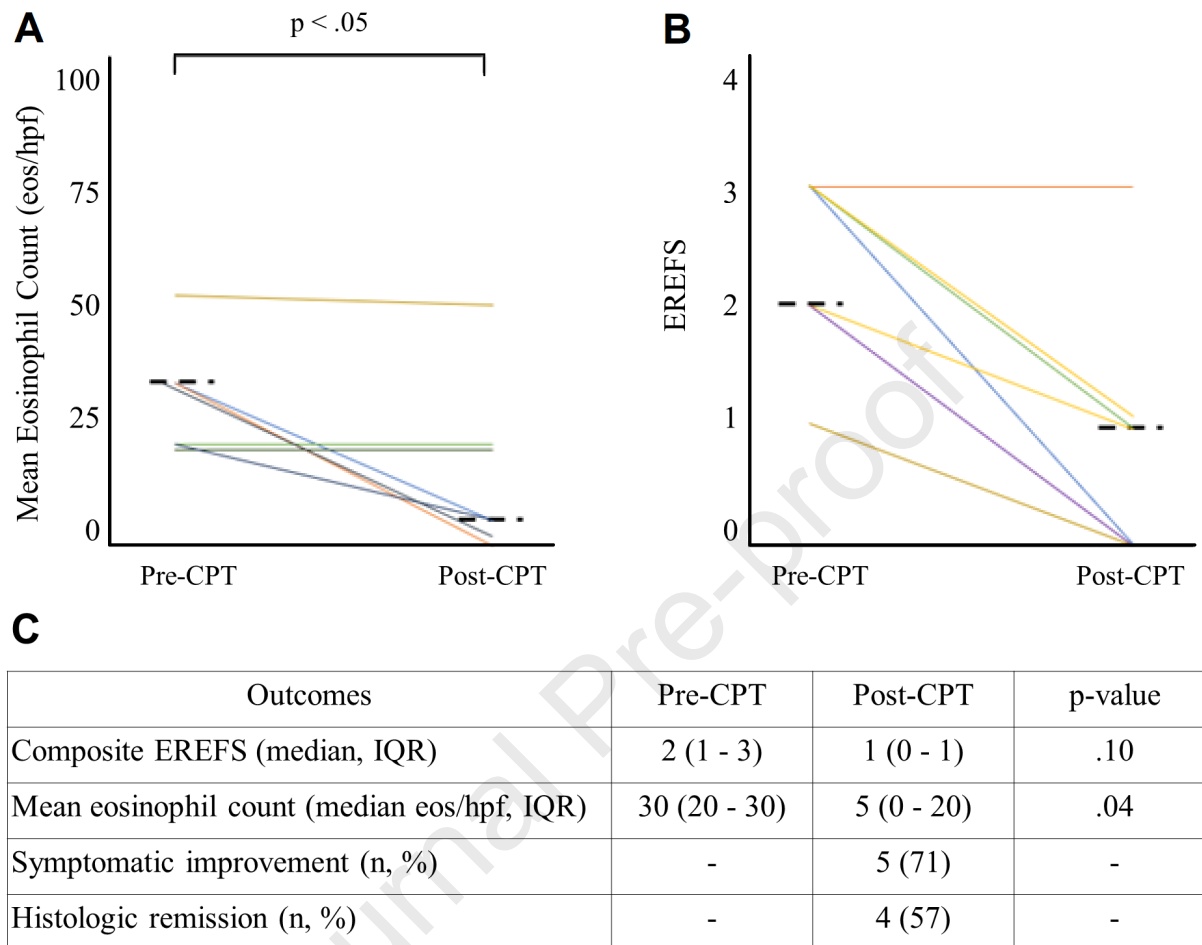


Figure 1. (A) Statistically significant improvement in mean eosinophil count after adhering to type IV hypersensitivity patch testing (CPT) guided diet/lifestyle modifications. Dashed lines reflect median value. (B) Improvement in Eosinophilic Esophagitis Endoscopy Reference Score (EREFs) after CPT-guided diet/lifestyle modification, not statistically significant. Dashed lines reflect median value. (C) Quantified outcomes for EREFs, mean eosinophil count, symptomatic improvement, and histologic response with comparisons made using Wilcoxon signed-rank test; IQR (interquartile range), eos/hpf (eosinophils per high-power field)

Supplementary Methods:

Comprehensive type IV hypersensitivity patch testing is a provocation test designed to instigate allergic contact dermatitis through the use of haptens (small chemically reactive molecules with low molecular weight). The hapten preparation and vehicle is loaded into chambers, which provides a defined area in which the skin is exposed to the particular hapten. The patch test chamber also ensures that the hapten remains in direct contact with the skin for the required time (48h) to create a standardized controlled reaction. We performed testing on non-lesional skin on the back with the American Contact Dermatitis Society standard patch test series and additional series of allergens established at Weill Cornell to test for consumed allergens¹. The occlusion time took place for 48 hours and the patch test reading occurred in the dermatology clinic at 48 and 96 hours after placement, according to standards set forth by a multi-society contact dermatitis practice guideline². The patch test results are graded according to the International Contact Dermatitis Research Group descriptive scoring system: no reaction or erythema without infiltration (–), erythema and infiltration (+), erythema and few papules (++), erythema and many or spreading papules (+++), erythema, papules and vesicles (++++), or patchy erythema without infiltration (IR). Tests that are at least + or higher after 48 and 96 hours are considered positive tests. Tests that are positive after 48 hours but negative after 96 hours are considered irritants and therefore not considered positive findings for hypersensitivity. Subsequent reading at 96 hours is necessary, because up to 30% of patients with negative tests at 48 hours can have an eventual positive test. The readouts of all the patch testing results were performed by a single expert (senior author/principal investigator) in order to minimize errors. Based upon the patch testing findings, the patient was counselled on lifestyle modifications to avoid chemicals/dyes/aeroallergens by the dermatologist and/or diet modifications to avoid food additives by the nutritionist.

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Supplementary Table 1. Characteristics of patients undergoing patch testing

	All patients (n = 18)	CPT-adherent with follow up EGD (n = 7)
Age at CPT	34.1 ± 11.1	31.6 ± 11.0
Male	12 (66.7)	3 (42.9)
Allergic background	12 (66.7)	5 (71.4)
History of esophageal dilation	1 (5.6)	0 (100)
History of elimination diets	2 (11.1)	1 (14.3)
Symptoms in clinic	17 (94.4)	7 (100)
Dysphagia	12 (66.7)	4 (66.7)
Regurgitation	1 (5.6)	0
Food impaction	6 (33.3)	1 (14.3)
Heartburn	9 (50.0)	4 (57.1)
Mean number of eos/hpf on initial EGD	31.1 ± 21.8	28.7 ± 12.4
Mean EREFS score	1.8 ± 1.1	2.1 ± 0.9
Mean Inflammatory EREFS score ^a	1.2 ± 1.0	1.7 ± 0.8
Patients with Edema	4 (23.5)	3 (42.9)
Patients with Rings	8 (47.1)	2 (28.6)
Patients with Exudates	7 (41.2)	4 (57.1)
Patients with Furrows	9 (52.9)	5 (71.4)
Patients with Stricture	2 (11.8)	1 (14.3)
Completed PPI 8 weeks after EGD	18 (100)	7 (100)
Started on steroids after EGD ^b	7 (38.9)	2 (28.6)
Positive on patch exam	16 (88.9)	7 (100)
Patch test positive for chemicals/dyes/preservatives	11 (61.1)	4 (57.1)
Patch test positive for food products	10 (55.6)	5 (71.4)
Patch test positive for aeroallergens	7 (38.9)	3 (42.9)
Had follow up appointment	12 (66.7)	7 (100)

Adherence to diet	11/12 (91.7)	7 (100)
Improved symptoms	8/11 (72.7)	7 (100)

Values are mean $\pm$ standard deviation or n (%)

CPT – comprehensive type IV hypersensitivity patch testing, EGD – esophagogastroduodenoscopy, eos/hpf – eosinophils per high-power field, EREFS - Eosinophilic Esophagitis Endoscopy Reference Score, PPI – proton pump inhibitor

^a Inflammatory EREFS – scored 1 for each of edema, exudates, furrow

^b Patients with especially high mean eos/HPF on initial EGD were often started on topical steroids with CPT-guided diet/lifestyle. Of the patients compliant with CPT-guided diet/lifestyle, one improved clinically and histologically, while the other did not.

Supplementary Table 2. Frequency of allergen identified on patch testing

Number of patients with allergen identified n (% of 16 positive patch tests)	Allergens
1 (6.3)	hydroperoxides of limonene; iodopropynyl butylcarbamate; cetylstearylalcohol; benzoic acid/benzocaine; ethanol; formaldehyde; mixed dialkyl thiourea; fragrance mix II; kathon CG; amerchol L-101; lanolin alcohol; 4,4- diaminodiphenyl methane; methyl methacrylate; ethyl acrylate; dodecyl gallate; emidoamine; black rubber mix IPPD; cocamidopropyl betaine
2 (12.5)	propylene glycol, shellac, balsalm of peru
3 (18.8)	carmine 2.5%, gold (I) sodium thiosulfate dihydrate
4 (25)	fragrance mix I (includes cinnamic aldehyde, cinnamal, geraniol, eugenol, oakmoss absolute); cinnamic aldehyde alone

Supplementary Table 3. Pre- and post-CPT outcomes data for adherent patients

Patient Number	Pre-CPT eos/hpf	Pre-CPT Composite EREFS	Post-CPT symptoms improved	Post-CPT eos/hpf	Post-CPT Composite EREFS	Allergens identified on CPT and eliminated
1	30	3	Yes	5	1	benzoic acid, shellac, carmine 2.5%
2	30	1	Yes	3	0	sodium thiosulfoaurate (gold), cinnamic aldehyde
3	52	3	Yes	50	3	propylene glycol
4	20	3	Yes	5	0	sodium thiosulfoaurate (gold), balsam of peru, fragrance Mix I, carmine 2.5%, dodecyl gallate
5	20	2	No	20	1	emidoamine (stearamidopropyl dimethylamine), black rubber mix, cocamidopropyl betaine
6	20	3	No	20	1	shellac
7	30	2	yes	0	0	sodium thiosulfoaurate (gold), cinnamic aldehyde, fragrance mix I, carmine 2.5%

CPT – comprehensive type IV hypersensitivity patch testing, EGD – esophagogastroduodenoscopy, eos/hpf – eosinophils per high-power field, EREFS - Eosinophilic Esophagitis Endoscopy Reference Score