

Emerging concepts of dietary therapy for pediatric and adult eosinophilic esophagitis

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“Several studies published in the past year, of both adult and pediatric patients with eosinophilic esophagitis, have compared skin test-directed diet therapy with six-food elimination diet therapy as well as attempted to identify causative foods.”

Eosinophilic esophagitis (EoE) is a disease of the esophagus distinguished by pronounced esophageal eosinophilia, and for which dietary antigen appears to be an important driving factor of the disease process. Multiple studies have demonstrated that food elimination diets are an effective therapy [1–4]. In addition, food reintroduction triggers relapse of the disease, suggesting an allergic mechanism to ingested foods [5–7].

Predictive values for both skin prick test (SPT) and atopy patch test (APT) have been reported [3,5,8]. However, APTs have not been standardized in an EoE population [9–11], and both SPT and APT may not be widely applicable [12]. Thus, SPTs, serum IgE tests and APTs may be adjunctive in identifying a causative food in EoE, but food triggers can only be identified by disease remission, after a specific food elimination, followed by EoE relapse upon reintroduction of that food [13]. Several studies published in the past year, of both adult and pediatric patients with EoE, have compared skin test-directed diet therapy with six-food elimination diet (SFED) therapy as well as attempted to identify causative foods [14–16]. Herein, we summarize the results of these studies and suggest a clinical approach based on collective data.

Overview of the 2012 studies

Gonsalves *et al.* [14] reported a prospective, nonrandomized, uncontrolled study of 50

adult patients (>18 years) with EoE, which assessed the effects of the SFED followed by food reintroduction on histologic response, symptoms and quality of life. All patients underwent esophagogastroduodenoscopies (EGDs), biopsies and SPTs for food and aeroallergens and then underwent an elimination diet for 6 weeks followed by EGD and biopsy. Patients were not on any swallowed or systemic steroids but were allowed to be on proton pump-inhibitor therapy. Histologic responders, defined by <5 eosinophils/high-power field (hpf; n = 32), underwent systematic reintroduction of foods followed by EGD and biopsies (n = 20).

The SFED significantly reduced esophageal eosinophilia. In total, 74% of patients had <15 eosinophils/hpf with 64% of patients having <5 eosinophils/hpf post-SFED therapy. Endoscopic features were also shown to improve but recurred upon specific food reintroduction. All patients who underwent reintroduction had a causative food identified by biopsy. The most common food triggers in this adult cohort were wheat (60%), milk (50%), soy (10%), nuts (10%) and eggs (5%). A total of 67% of patients who had a causative food identified by biopsy had negative SPTs for all foods tested, and SPTs accurately predicted only 13% of food triggers. This study demonstrated that similar to that in children, food allergens have a causative role in the majority of adults with EoE.

KEYWORDS: atopy patch test • dietary therapy • directed diet • elemental diet • elimination diet • eosinophilic esophagitis • skin prick test

Henderson *et al.* [15] reported a retrospective study of pediatric patients (≤ 21 years) with EoE and compared the remission rates among three dietary therapies: elemental diet, SFED and a skin test-directed elimination diet. Patients were not on swallowed or systemic steroids for 2 months prior to or during the study. All diets showed a significant histological response. The elemental diet had a peak eosinophils/hpf drop from 51 to 1, SFED had a peak eosinophils/hpf drop from 77 to 2.5 and skin test-directed diet had a peak eosinophils/hpf drop from 38 to 7. There was a trend of greater remission rate, but there was not a significant difference, when comparing the elemental diet to SFED or SFED to the skin test-directed diet. There were significant differences between the elemental diet and skin test-directed diet therapy. The negative predictive values (NPVs) of skin test for the four most commonly introduced foods (milk, egg, soy and wheat) were low, ranging from 40 to 67%. These poor NPVs are in agreement with Gonsalves *et al.* [14]. Thus, skin test (prick and patch) directed elimination diets showed no superiority compared with the empiric SFED for the treatment of pediatric EoE. Notably, both of these diet plans were inferior at inducing remission compared with an elemental diet.

Spergel *et al.* [16] reported a pediatric (≤ 18 years) retrospective study and analyzed the effectiveness of skin test-directed diets. The study attempted to identify causative foods, calculate predictive values for skin testing and compare various elimination diets. As above, patients were excluded if they were treated with swallowed steroids. Causative foods were identified by biopsy with the four main contributors being milk (35%), egg (13%), wheat (12%) and soy (9%). Causative foods were defined using a strict, gold-standard definition, that is biopsy-proven foods were either: foods that, when removed, decreased eosinophils/hpf from >15 to 0 or foods that, when reintroduced, increased eosinophils/hpf from 0 to >15 . In addition, this study reported much higher NPVs for SPT and APT than were reported by the other two reports discussed above. It also reported the effect of an empiric elimination diet different from the original SFED (seafood and nuts allowed and meats eliminated) and that this modified SFED was as effective as skin test-directed diets and more successful than the original SFED. In addition, skin test-directed diets allowed for fewer foods being removed from the diet compared with the original SFED (by one food group on average).

The NPVs reported in this study were significantly higher than those reported in the other two aforementioned studies. We see at least two possible explanations for the higher NPVs in the Spergel *et al.* study. The first is a stricter, gold-standard definition of what constituted food responsiveness in patients with EoE. As outlined above, the authors required a biopsy to change from >15 eosinophils/hpf down to 0 with food removal or vice versa with food reintroduction to definitively identify a food as causative. Patients who meet these stringent criteria are more likely to have a phenotype that is driven by food (or a particular food) than the general EoE population and may be more likely to have a positive SPT/APT, thus yielding more true positives and fewer false negatives. The effect of this decrease of false negatives would be a drop in the denominator of the NPV calculation, thus increasing NPV. By contrast, those that do not meet these criteria, or the disease-negative group, are more likely to have negative SPT/APTs or true negatives. True negatives contribute to both the nominator and denominator in the NPV calculation, but contribute more to the nominator, thus also increasing the NPV. A second possible cause for the higher NPVs reported for this study is that the authors used a lower threshold for a positive APT result. It has been suggested that in atopic individuals, a higher threshold for positive APTs (the equivalent of a 2+) needs to be used for appropriate diagnostic accuracy [10]. The lower APT threshold (1+) used in the Spergel *et al.* study may have increased NPV by shifting false negatives to true positives, thus decreasing the denominator of the NPV calculation [16]. Therefore, the predictive values reported in this study may not extrapolate to the general EoE population.

Summary

Each of these three studies has its own strengths and weaknesses, but collectively they highlight a broader picture of the role of food in EoE disease and management.

Overall conclusions that can be drawn from these studies include: the elemental diet is superior to the SFED and skin test-directed diet; the SFED is similar to skin test-directed diet therapy in response rate and nearly similar in the number of foods eliminated in pediatric EoE; and the SFED is an effective therapy in adult EoE.

Specifically with regards to the SFED, all three studies showed similar effectiveness of the SFED (based on histology), in agreement with previous reports. Gonsalves *et al.* [14] demonstrated a 74% success rate and identified causative foods in 40% of patients studied. Henderson *et al.* [15] demonstrated a 75% success rate with the SFED. Spergel *et al.* [16] reported an 81% success rate with a modified SFED and identified causative foods in 34% of patients (TABLE 1). Multiple studies have reported a response rate to swallowed steroids in both adult and pediatric EoE populations with response rates ranging from 50 to 87% [17–20], similar to the response rate of the empiric elimination diets reported above (including modified

Table 1. Comparison of elimination diet success rates and percentage of patients with causative foods identified for eosinophilic esophagitis.

Study (year)	Elimination diet success rate (%)	Patients with causative foods identified (%)	Ref.
Gonsalves <i>et al.</i> (2012)	74	40 [†]	[14]
Henderson <i>et al.</i> (2012)	75	NA	[15]
Spergel <i>et al.</i> (2012)	81	34 [‡]	[16]

[†]Identified by confirming disease remission after a specific food elimination and by EoE relapse on reintroduction of that food.

[‡]Identified by confirming disease remission after a specific food elimination or by EoE relapse on reintroduction of that food.

EoE: Eosinophilic esophagitis; NA: Not available.

SFED). In addition, there appears to be potential to identify causative foods in 35–40% of patients. On the basis of these data, we propose a method for clinical management. It may be reasonable to begin therapy with an empiric elimination diet and reintroduce the foods least likely to be causative (based both on history and published data) first, thus allowing the quickest identification of the majority of foods. On the basis of the above studies, this would suggest reintroduction of seafood/nuts first, followed sequentially by soy, wheat, egg and finally milk for pediatric patients with EoE. For adults with EoE, the current data imply reintroduction of seafood first, followed sequentially by egg, nuts/soy, milk and finally wheat (TABLE 2). The value of this approach should ultimately be evaluated with controlled clinical trials.

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Table 2. Suggested order of food reintroductions following a six-food elimination diet.

Order	Pediatric EoE	Adult EoE
First	Seafood/nuts	Seafood
Second	Soy	Egg
Third	Wheat	Nuts/soy
Fourth	Egg	Milk
Fifth	Milk	Wheat
EoE: Eosinophilic esophagitis.		

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References

- Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 109(5), 1503–1512 (1995).
- Liacouras CA, Spergel JM, Ruchelli E *et al.* Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin. Gastroenterol. Hepatol.* 3(12), 1198–1206 (2005).
- Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann. Allergy Asthma Immunol.* 95(4), 336–343 (2005).
- Kagalwalla AF, Sentongo TA, Ritz S *et al.* Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 4(9), 1097–1102 (2006).
- Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 109(2), 363–368 (2002).
- Wang FY, Gupta SK, Fitzgerald JF. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? *J. Clin. Gastroenterol.* 41(5), 451–453 (2007).
- Nielsen RG, Husby S. Eosinophilic oesophagitis: epidemiology, clinical aspects, and association to allergy. *J. Pediatr. Gastroenterol. Nutr.* 45(3), 281–289 (2007).
- Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 119(2), 509–511 (2007).
- Hong S, Vogel NM. Food allergy and eosinophilic esophagitis: learning what to avoid. *Cleve. Clin. J. Med.* 77(1), 51–59 (2010).
- Heine RG, Verstege A, Mehl A, Staden U, Rolinck-Werninghaus C, Niggemann B. Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatr. Allergy Immunol.* 17(3), 213–217 (2006).
- Furuta GT, Liacouras CA, Collins MH *et al.*; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 133(4), 1342–1363 (2007).
- Assa'ad A. Detection of causative foods by skin prick and atopy patch tests in patients with eosinophilic esophagitis: things are not what they seem. *Ann. Allergy Asthma Immunol.* 95(4), 309–311 (2005).
- Liacouras CA, Furuta GT, Hirano I *et al.* Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J. Allergy Clin. Immunol.* 128(1), 3–20.e6; quiz 21–22 (2011).
- Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 142(7), 1451–1459.e1; quiz e14–e15 (2012).
- Henderson CJ, Abonia JP, King EC *et al.* Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 129(6), 1570–1578 (2012).
- Spergel JM, Brown-Whitehorn TF, Cianferoni A *et al.* Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J. Allergy Clin. Immunol.* 130(2), 461–467.e5 (2012).
- Konikoff MR, Noel RJ, Blanchard C *et al.* A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 131(5), 1381–1391 (2006).
- Straumann A, Conus S, Degen L *et al.* Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 139(5), 1526–1537.e1 (2010).
- Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 139(2), 418–429 (2010).
- Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin. Proc.* 78(7), 830–835 (2003).