
Correspondence

AUTHORS' RESPONSE TO DETECTION OF CAUSATIVE FOODS BY SKIN PRICK AND ATOPY PATCH TESTS IN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS: THINGS ARE NOT WHAT THEY SEEM

To the Editor:

We appreciate Dr Assa'ad's comments about our article; however, there are many inaccuracies that need to be addressed in a point-point fashion.

1. Dr Assa'ad's first comment is about the diagnosis of eosinophilic esophagitis (EoE). Dr Assa'ad is concerned about cutoff for the diagnosis being set at 15 eosinophils per high-power field (HPF) instead of 20 or 24 eosinophils per HPF. If we switch to her most strict definition of 24 eosinophils per HPF, we would only lose 6 of 146 patients. A biopsy specimen with 5 eosinophils per HPF or less is typical of gastroesophageal reflux disease (GERD) and 5 to 15 or 24 eosinophils per HPF is either GERD or EoE. It is rare to have more than 15 eosinophils per HPF after using a proton pump inhibitor for 1 month and not to have EoE. Furthermore, we did not see failure of dietary elimination more frequently in patients with these borderline values.

2. Dr Assa'ad commented that we should have the same criteria for pre-evaluation and postevaluation. We do. We used the cutoff of 15 eosinophils per HPF at both points. We reported improvement in terms of mean number of eosinophils per HPF to take into account partial responders. All patients whom we considered responders had less than 15 eosinophils per HPF and, in fact, had less than 5 eosinophils per HPF.

3. Dr Assa'ad's breakdown of the patients is incorrect. Twenty-five patients from the original 171 are not included in the analysis, because they did not undergo subsequent biopsy or were lost to follow-up. The 26 patients were prescribed an elemental diet based on multiple positive foods not lack of food sensitization. Nineteen patients with partial response and 15 patients had no response to dietary elimination based on skin test and atopy patch test (APT) of 146 patients with EoE. We do not know the response to elemental diet in these 36 patients, because they refused to follow an elemental diet. These patients are NOT evidence that foods do not cause EoE, because they have not tried an elemental diet. These patients are evidence that the combination of skin testing and patch testing is not helpful for all patients.

4. The comment that the 3 populations are the same and that the detection of food sensitization by skin prick testing or APT does not predict who will respond to dietary intervention is correct. The advantage of testing is to attempt to identify specific foods and eliminate them rather than immediately

institute an elemental diet. By using these allergy tests, we avoided an elemental diet in 72 patients.

5. Other centers^{1,2} have also found that diet is effective in treating EoE. We believe the failure of other studies to show that food allergy is the cause of EoE is because they did not try an elemental diet.^{3,4} Even data at Dr Assa'ad's own institution show a significant response to diet; 13 of 16 patients with EoE responded to dietary elimination.⁵ If patients had eosinophilic gastroenteritis and not esophagitis, the response rates are significantly lower. EoE is a different disease than eosinophilic gastroenteritis. Their response rate of 81% (13/16) is remarkably similar to our response rate of 78%.

6. Although Dr Assa'ad agrees with our skin testing reaction rate, she has had technical issues with APT. We have helped several other investigators with this. If she or other investigators have trouble with APT staying on, or other technical issues, we would be glad to provide assistance.

7. To answer her question regarding the degree of food elimination, all patients were instructed to have complete avoidance.

8. In our experience, the least likely foods to cause EoE are lettuce, berries, celery, melons, other green vegetables, and other fruits. The high-protein foods have been the most problematic.

9. Her analysis of the 39 patients who fulfill the Koch postulate is wrong. These patients fulfill the basic tenets of science. Elimination of the item, in this case food, leads to a resolution of symptoms and normalization of the biopsy results. Reintroduction of the food led to a recurrence of symptoms and abnormal biopsy results. For the patients with single food elimination, only one food was identified on skin testing or APT. Furthermore, to clarify how a single food was identified, these patients had normalization of biopsy results on food elimination. For the patients with multiple food allergies, we reintroduced foods one at a time based on our preliminary results of the most likely foods that cause EoE, with the foods least likely to cause EoE being reintroduced first. It would not take 10 to 15 biopsies to prove 5 foods that cause EoE in a patient, for example, first biopsy—diagnosis of EoE; second biopsy—elimination of 5 foods (normal biopsy result); third biopsy—introduction of food A—positive biopsy result; fourth biopsy—introduction of food B—positive biopsy result; fifth biopsy—introduction of food C—positive biopsy result; sixth biopsy—introduction of food D—positive biopsy result; seventh biopsy—introduction of food E—positive biopsy result; and eighth biopsy—back to 5 food elimination—normal biopsy results. It is not necessary to have normal biopsy results between the third and seventh biopsies, since we know that elimination of the foods lead to normal biopsy results. Furthermore, in many instances patients added

several (up to 5) lower-risk foods between biopsies. If the biopsy result was normal, we were then able to rule out several food allergies with a single procedure.

10. Yes, we have no control group in this study. When we remove the incorrect foods (failures), biopsy results do not improve. We believe there would be ethical issues in using a nonintervention pediatric group with repeated biopsies. In studies that use other treatment options, montelukast showed no improvement in biopsy results⁶; oral corticosteroids provided a temporary resolution of eosinophils in the biopsy results, with return of eosinophils and symptoms with discontinuation of systemic steroids,⁷ and the use of swallowed, topical treatment with inhaled corticosteroids led to an incomplete response in many patients.^{4,8} These 2 studies indicate that failure to remove causative foods provides no improvement. These 3 scenarios compared with the success of removing the correct food indicate that proper diet elimination is the only effective way to treat the cause of EoE, rather than the symptoms of EoE.

11. Dr Assa'ad's criticism that we cannot monitor the patient's diet is correct. Some of the failures to improve on diet were due to noncompliance. In general, we believe that our patients had relatively good compliance with the elimination diet, since the other option we presented was no foods with a strict elemental diet. Patients preferred to lose multiple foods rather than all foods. Nevertheless, it is possible that with better compliance our results of dietary elimination based on skin prick testing and APT would be even better.

12. The relevance of positive skin test results is a criticism of most studies on food allergies that examine skin testing or in vitro testing. In most studies on food allergies, no control population is used. We used the standard and classic criteria of a positive skin test result of a 3-mm wheal.⁹ Although we know that we had false-positive results on skin testing, we thought it was better to initially eliminate all *potential* foods, since the other option was an elemental diet. The false-positive results were eventually weeded out by challenges during the reintroduction phase.

13. Dr Assa'ad's criticism of the esophagus not being an absorptive organ is true. However, we know that ingestion of food can cause hives in the skin or flaring of atopic dermatitis. The skin is not an absorptive tissue either. The most likely scenario for both of these cases is that food is absorbed systemically and food-specific cells (CLA⁺ T cells for the skin and unknown for esophagus) exist to mediate the local reaction.

14. Yes, APT is not standardized, since reagents are freshly prepared in concentrations previously reported by others. Our technique is the standard technique used in Europe.¹⁰ Future studies are needed to develop predictive values for individual foods and standardized testing reagents as has been done with skin prick testing.

15. The sensitivity of APT varies in studies. Dr Assa'ad has picked the lowest specificity at 34%. The sensitivity ranges from 35% to 97%, with most studies showing the specificity in atopic dermatitis in the high 80% to low 90%.¹¹

16. We agree that the exact mechanism of how APT correlates with the gastrointestinal tract is unknown. However, the same argument can be made for standard skin tests. How does allergen specific IgE on mast cells in the skin correlate with bronchospasm with the same allergen in the lung? No evidence exists that mast cells in the skin move to the lung. Allergy is a systemic disease. Years of clinical experience have shown that this is true.

This article¹² along with our other articles,^{13,14} including one in press,¹⁵ have now shown that patients with EoE respond to the removal of dietary antigens based on biopsy findings and resolution of symptoms. Furthermore, no significant nutritional complications have been reported.

The conclusion of the article is that diet eliminates symptoms and normalizes biopsy results in 78% of patients with EoE (nearly identical to Dr Assa'ad's own results of 81%). The remaining 22% may respond to diet, but this is still unknown. In our larger study, we have a 97% response rate to an elemental diet.¹⁵ The combination of skin testing and APT can identify the correct foods in 49% of the patients, not counting the patients given elemental formula for multiple foods. If these patients are included, the percentage of specific diet success improves to 77%.

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