

Food Allergy and Eosinophilic Esophagitis: What Do We Do?

Mirna Chehade, MD, MPH^a, Seema S. Aceves, MD, PhD^b, Glenn T. Furuta, MD^c, and David M. Fleischer, MD^d *New York, NY; San Diego, Calif; and Aurora, Colo*

Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus triggered by foods and possibly environmental allergens. Common conditions that mimic EoE include gastroesophageal reflux disease and proton pump inhibitor-responsive esophageal eosinophilia. These need to be excluded before confirming the diagnosis of EoE. Identification of food triggers for EoE using standard allergy tests remains challenging. Dietary therapy for EoE so far consists of test-directed elimination of foods, empiric elimination of common food allergens, or exclusive feeding of amino acid-based formulas, with variable success. No FDA-approved medications yet exist for EoE. Topical corticosteroids to the esophagus are being used. EoE is a chronic disease; therefore, long-term therapy seems to be necessary to avoid potential long-term complications such as esophageal remodeling and strictures. Optimal long-term therapies and follow-ups are still not established; therefore, discussion with patients and families regarding the choice of therapy is important to ensure the best possible outcomes from a medical and social standpoint. In this article, we discuss all the above issues in detail by using a hypothetical case; highlighting in a stepwise manner what is known with respect to diagnosis,

work-up, and management of EoE; and discussing gaps in knowledge that need to be addressed in the future. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:25-32)

Key words: Eosinophilic esophagitis; Dietary elimination; Topical corticosteroids; Allergy testing; Proton pump inhibitor-responsive esophageal eosinophilia; Gastroesophageal reflux disease; Endoscopy; Eosinophil

AC is a 15-year-old female with a 3-year history of intermittent epigastric abdominal pain and solid-food dysphagia that occurs daily, especially with bread and meat. Her past medical history is notable for IgE-mediated cow's milk (CM) and egg allergies, which she outgrew after she passed oral food challenges (OFCs) to CM and egg at the age of 4 and 6 years, respectively. She also experiences mild persistent asthma controlled on 2 puffs once daily of fluticasone 110 mcg with a spacer, and seasonal allergic rhinitis controlled on 10 mg once daily of cetirizine and 2 sprays once daily of fluticasone.

As an infant and toddler, she had gastroesophageal reflux disease (GERD), and was treated with a proton pump inhibitor (PPI) from the age of 2 to 15 months. Several weeks before coming to your office (allergist's office), she had an esophageal food impaction that consisted of steak that required flexible endoscopic removal performed by a pediatric surgeon. Biopsies obtained during the procedure revealed 35 eosinophils/high-powered field (hpf) in the proximal esophagus and 65 eosinophils/hpf in the distal esophagus. She was not taking PPI medication at the time of the endoscopy. The surgeon referred AC to a gastroenterologist for further evaluation of esophageal eosinophilia.

Confirmation of diagnosis:

1. AC was told that the biopsies were consistent with eosinophilic esophagitis (EoE). Does esophageal eosinophilia alone confirm a diagnosis of EoE?

It is important to differentiate EoE from esophageal eosinophilia as a descriptive finding, as the latter is not pathognomonic for EoE. Based on the most recent consensus guidelines, EoE is defined as "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."¹ Inflammation occurs only in the esophagus, and other etiologies for these features must be ruled out before assigning this diagnosis. Table 1 summarizes a list of diseases where esophageal eosinophilia can be seen.

Two common clinical conditions presenting with esophageal eosinophilia deserve particular attention: GERD and the newly

^aMount Sinai Center for Eosinophilic Disorders, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY

^bDivision of Allergy, Immunology, Department of Pediatrics, University of California, San Diego and Rady Children's Hospital, San Diego, Calif

^cDepartment of Pediatrics, Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Digestive Health Institute, Children's Hospital Colorado, Aurora, Colo

^dDepartment of Pediatrics, Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Allergy Section, Children's Hospital Colorado, Aurora, Colo

No funding was received for this work.

Conflicts of interest: M. Chehade is an unpaid Advisory Board member for APFED and has received research support from Nutricia and AGA Research Foundation. S. S. Aceves has received research support from the NIH/NIAID and TIGERS; is an unpaid board member for FARE and APFED; has a patent and received royalties for oral viscous budesonide; has stock/stock options in Meritage Pharma; and has received travel support from NIH/NIDDK. G. T. Furuta has received consultancy fees from Regeneron; has received research support from the National Institutes of Health (1K24DK100303), Morphotek, and Nutricia; has a patent and is cofounder of EnteroTrack; and receives royalties from UpToDate. D. M. Fleischer has received consultancy fees from LabCorp; is employed by University Physicians, Inc.; has received research support from Monsanto Company; has received lecture fees from Nestle Nutrition Institute; and receives royalties from UpToDate.

Received for publication June 15, 2014; revised September 27, 2014; accepted for publication November 3, 2014.

Corresponding author: Mirna Chehade, MD, MPH, Mount Sinai Center for Eosinophilic Disorders, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1198, New York, NY 10029. E-mail: mirna.chehade@mssm.edu.

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.11.009>

Abbreviations used

CM- Cow's milk
 EoE- Eosinophilic esophagitis
 GERD- Gastroesophageal reflux disease
 hpf- High-powered field
 OFC- Oral food challenge
 PPI- Proton pump inhibitor
 PPI-REE- PPI-responsive esophageal eosinophilia
 SFED- Six-food elimination diet (SFED)
 TCS- Topical corticosteroids

described entity proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE). Patients with GERD present with similar symptoms to EoE, such as heartburn and retrosternal chest pain. Patients with GERD typically have symptom relief when taking antacids and may have esophageal erosions or ulcers on gross endoscopic examination. Esophageal reflux can be assessed by pH probe monitoring.

A growing body of literature and clinical experiences identified PPI-REE as a clinicopathological entity described by symptoms, and endoscopic and histological findings consistent with EoE, which resolved with the use of PPIs.²⁻⁴ The etiology of PPI-REE is still unknown. It is not yet determined as to whether patients with PPI-REE have severe GERD that mimics EoE (though pH probe results are normal in a subset of patients with PPI-REE); GERD that triggers EoE, hence the response to PPI therapy; or EoE that is responsive to PPI therapy by some anti-inflammatory mechanism. Thus, histology alone does not confirm the diagnosis of EoE.

2. What is the best method to confirm an EoE diagnosis?

To date, the best method to confirm a diagnosis of EoE, ie, ruling out GERD and PPI-REE, is empiric therapy with high-dose PPI followed by repeat endoscopy with biopsies, documenting persistent esophageal eosinophilia. pH probe monitoring, although positive in the majority of patients with acid-induced GERD, is not always positive in those with PPI-REE. In fact, it was shown to be poorly predictive of response in those with PPI-REE, both in children and in adults.^{2,4,5}

Therefore, when symptoms of esophageal dysfunction and esophageal eosinophilia (≥ 15 eosinophils/hpf) are found, the following are recommended to confirm EoE: (1) a thorough history to rule out other potential causes of esophageal eosinophilia, (2) biopsies that demonstrate the absence of pathology in the remainder of the gastrointestinal tract, and (3) a diagnostic trial of high-dose PPI followed by clinical and histological reevaluation.¹

AC underwent a pH probe that showed no evidence of acid-induced GERD. Gastric and duodenal biopsies were normal, and she ingested wheat regularly, ruling out celiac disease. There were no clinical indicators of inflammatory bowel disease or cancer. The gastroenterologist started AC on lansoprazole 30 mg twice daily for 6 weeks. She underwent a repeat upper endoscopy that showed significant esophageal eosinophilia (32-68 eosinophils/hpf), which confirmed the diagnosis of EoE. AC's gastroenterologist refers her to you for further EoE management (see Figure 1 for management considerations). AC's family has done some research on the Internet regarding treatment of EoE with diet and/or medication, and they come to you with a list of questions.

Allergy testing and treatment:

1. My gastroenterologist gave me a choice of eliminating more foods from my diet or starting swallowed topical corticosteroids (TCS). How do we choose which treatment is best?

You explain to AC that there is evidence for successful treatment using dietary elimination, with varying success rates depending on the exact diet used (Figure 2). Dietary elimination can take the form of a targeted approach, in which the results of skin prick and patch testing are used; an empiric approach, in which the most common food allergens, consisting of CM, wheat, egg, soy, nuts (peanut/tree nuts), and seafood (fish/shellfish), therapy referred to as the six-food elimination diet (SFED), are eliminated; or an exclusive elemental formula. In children, skin prick combined with patch test-targeted elimination diets have success rates of 53-65%.^{6,7} Empiric elimination diets have success rates of 70-74% in adults and children.^{8,9} The elemental formula has success rates of >90% in almost all studies.^{7,10} Centers that utilize skin prick testing often will start by obtaining a food consumption history and test those foods commonly consumed by the patient along with the common foods that cause EoE. Skin patch tests are usually performed using single-item baby foods or dry powders to an empiric panel. Then, the combinations of positive tests on prick and patch testing are utilized to build an elimination diet.⁶ Because of the poor predictive value of patch testing to milk, some centers often eliminate milk empirically in addition to those foods to which the patient tests positive.⁶ Reports on use of targeted elimination diets have shown that CM and wheat are the most common EoE triggers in both pediatric and adult populations in the United States and Europe.^{7,11-14} Spergel et al identified the most common food combinations used in elimination diets to control EoE (Table II).⁶ The definition of the SFED varies between treating physicians; for example, in Spanish studies all legumes are avoided, whereas in U.S. studies soy is the only legume avoided. The SFED has been utilized in both children and adults with success.^{8,11-13} Because aeroallergens can also cause esophageal eosinophilia, it may be helpful to avoid these triggers.¹⁵⁻¹⁸ Based on the observations of seasonal EoE, animal models that demonstrate mold and dust mite-induced EoE,^{17,18} and new reports that specific immunotherapy for aeroallergens can help in EoE management,¹⁹ skin prick testing for aeroallergens can be justified in EoE.

TCS are also successful therapy for children and adults with EoE, with success rates in symptom reduction and histological remission ranging from 50% to >80%.²⁰⁻²⁵ Because no FDA-approved EoE therapies exist, TCS, including fluticasone and ciclesonide, have been reported to be administered with metered dose inhalers, in which the steroid is swallowed to coat the esophageal mucosa. Administration of TCS for EoE does not use a spacer, and thus thorough instructions are critical for success. Oral viscous budesonide has been developed as an alternative delivery method, in which a viscous suspension is made with sucralose and maltodextrin. Long-term side effects of esophageal TCS have not been determined to date, but esophageal deposition will allow for first-pass metabolism to occur, and hence minimal systemic absorption of corticosteroids.

You explain to AC that EoE is a chronic disease, cessation of therapy results in disease recurrence,²⁶⁻²⁸ and chronic untreated inflammation likely leads to esophageal stricture formation.^{29,30}

You further explain that choosing a dietary elimination regimen will elucidate the disease trigger(s), but will require more endoscopic procedures as opposed to TCS.¹ In either case, you recommend that she be evaluated by a dietician well versed in EoE treatment who can assist in forming a well-balanced diet to meet nutritional needs and exclusions. With these facts in mind, the decision of how to treat EoE requires consideration of personal and family considerations on the impact of the treatment on quality of life and potential for long-term adherence.

You review AC's current diet before testing. She consumes CM including yogurt, cheese, 1% milk, and baked milk; baked and scrambled egg; edamame (soy beans); peanut butter; tree nuts including almonds, cashews, and walnuts; grains including rice, corn, oat, and wheat; seafood including salmon, tuna, halibut, shrimp, and crab; meats including chicken, turkey, beef, and pork; and assorted fruits and vegetables. Skin prick tests are performed to the major food allergens, grains, and meats. They showed positive results only to CM, egg, and peanut. She has been consuming CM and egg regularly since passing OFCs previously, and she consumes peanut butter at least once weekly. Serum food-specific IgE levels were only positive to CM, egg, and peanut, but not to the other foods skin tested. AC and the family would like to see if they can control the EoE with diet alone, and you recommend the SFED. AC and her parents have further questions.

1. Can I just avoid the foods in major forms, or do I have to be completely strict? Should I see a registered dietician?

For an elimination diet to be effective, patients should strictly avoid the offending foods. Emerging data suggest, however, that certain patients may be able to tolerate CM, one of the most commonly incriminated foods in EoE in a baked form, thus possibly improving the quality of life in some patients due to easing of dietary restrictions. In a small retrospective study of children with proven CM-mediated EoE, 11 patients (73%) maintained histological remission after baked milk was added to the diet for at least 6 weeks.³¹

Because approximately 6-25% of patients with EoE have concomitant IgE-mediated food allergy,^{28,32} many patients are already well versed in strict elimination diets. With the addition of the diagnosis of EoE, a number of other challenges arise that often require the expertise of a dietician. For instance, many patients with EoE may initially present with signs or symptoms of nutritional deficiency related to poor feeding skills or maladaptive behaviors due to EoE. In these circumstances, a dietician may feel that a patient may not be an optimal candidate for an elimination diet based on the nutritional risk assessment. If an elimination diet is chosen, a dietician can provide appropriate substitutes for protein, fat, carbohydrates, vitamins, and minerals to maintain nutritional adequacy, sustain growth, and maximize adherence.³³

The elimination diet may provide symptomatic relief from EoE, but because of the centrality of food in some patients' lives, it may also have a profound negative impact. In fact, in one study, the quality of life scores were worse among patients with more restricted diets compared with those with none.³⁴ Children on elimination diets may become anxious, depressed, or oppositional, whereas teenagers may angrily disregard dietary restrictions to be able to eat favorite foods.³⁵ Parents of children with EoE worry about avoiding precipitating foods while trying

TABLE I. Diseases associated with esophageal eosinophilia¹

GERD
EoE
Eosinophilic gastrointestinal disease
Hypereosinophilic syndrome
Drug hypersensitivity
Celiac disease
Crohn's disease
Infection
Achalasia
Pemphigoid vegetans
Vasculitis
Connective tissue disease
Graft-versus-host disease

GERD, Gastroesophageal reflux disease; EoE, eosinophilic esophagitis.

to meet their children's nutritional requirements. Poor adherence to elimination diets varies according to the age of the patient and can occur due to lack of symptoms, social influences, duration of the diet, dietary boredom, and lack of school support.³³ Dieticians may be able to offer coping strategies to address some of these concerns.

2. If I start an elimination diet, does that mean I can never eat any of those foods again? How often should we test to see if it is time to introduce foods back to my diet? What happens if I "cheat" for a day for a special occasion (holiday, birthday), or if I accidentally eat one of the foods I am not supposed to eat—will I get sick?

Currently, there are no standardized guidelines on how often to retest foods being avoided. In patients with IgE-mediated food allergy, it is generally recommended to test foods being avoided on an annual basis, with serum food-specific IgE testing and/or skin testing to determine if OFCs can be performed to determine if a patient has outgrown an allergy.³⁶ However, the timing and use of repeat allergy testing in the long-term management of EoE has not been studied, and its use likely differs widely among centers.

Currently, there are no standardized guidelines on how to best reintroduce eliminated foods (eg, which foods first, at what time point after avoidance, and how many at a time before repeat clinical and histological evaluations), and reintroduction practice also widely varies among centers.³⁶ The rationale for adding foods back in any elimination diet is that some nonallergenic foods that are not triggers for the patient's EoE may have been initially eliminated and thus may be reintroduced. Some studies do provide some insight, however, into this process. Patients who are using a targeted elimination diet can have the least allergenic foods, such as fruits or vegetables, reintroduced first and then reintroduce the more allergenic, such as CM, egg, soy, or wheat, later.³⁷ In studies that use the SFED in children and adults, generally one major allergen or group of allergens (ie, nuts or seafood) at a time are reintroduced, followed by endoscopy 6-8 weeks later if no symptoms develop. By using this stepwise approach, one can identify allergenic trigger foods most commonly implicated in EoE: CM, egg, soy, and wheat.¹¹⁻¹⁴ Clinical experiences suggest that food(s) that repeatedly cause EoE symptoms may need to be eliminated indefinitely.³⁸

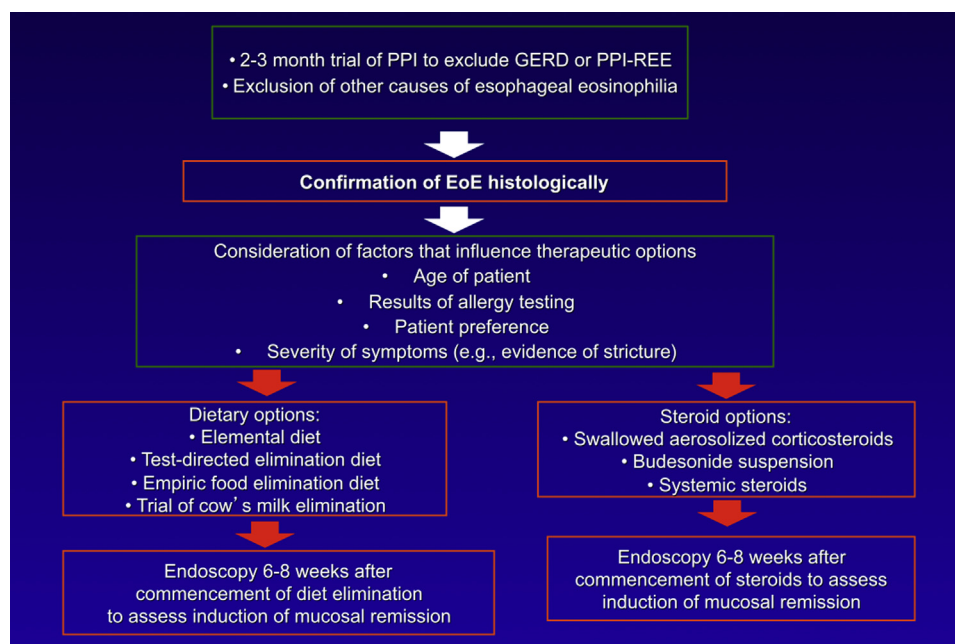


FIGURE 1. Considerations for diagnosis and treatment of EoE.

Whereas “cheating” on an elimination diet for a patient with IgE-mediated food-allergic disease can be life threatening, clinical experience suggests that exposures to an eliminated food in a patient with EoE without IgE-mediated allergy do not usually produce life-threatening immediate symptoms. Treatment for accidental exposures of non-IgE-mediated food allergens in EoE is often not necessary. Exposure to an IgE-mediated food allergen in an IgE-mediated-allergic patient with EoE should be medically managed in the same way as in any patient with IgE-mediated food allergy depending on prior allergic reaction severity and symptoms with current accidental ingestion (ie, epinephrine and possibly antihistamines).

3. *By avoiding these foods, will I become allergic to any of them (ie, in an IgE-mediated manner) and have an allergic reaction in the future? Do I need to carry an epinephrine injector again? Can I introduce the foods at home, or do I need to do this in my allergist's office (ie, observed OFC like before)?*

To date, no reports have documented patients with EoE developing an IgE-mediated food allergy to a food eliminated in their diet, but one study provides preliminary evidence that other forms of food allergy responses may coexist or develop over time. Maggadottir et al described 17 patients whose IgE-mediated food allergy resolved but later went on to develop EoE to the same outgrown IgE-mediated food allergen.³⁹ Reports have described patients with atopic dermatitis who had various foods removed from the diet for a period of time to see if the skin improved. Subsequent reintroduction of these foods resulted in IgE-mediated allergic reactions, when previously these patients were eating and tolerating these foods with no evidence of immediate IgE-mediated symptoms.⁴⁰⁻⁴² Many of these patients had documented sensitization (positive skin or serum IgE tests), but no prior history of clinical reactivity to the food to which they subsequently reacted, one reacting in a fatal manner. Although

the development of IgE-mediated food allergy to a food previously tolerated has not been reported in EoE, loss of tolerance to a food by interruption of exposure to it in the diet could potentially occur in patients with EoE with preexisting sensitization to that food.

The decision of whether a patient with EoE without documented IgE-mediated food allergy needs an epinephrine auto-injector is controversial, and there are no current guidelines with respect to this issue. In the opinions of the allergists of this article, to prescribe an autoinjector depends on the patient's specific situation: (1) the food in question (ie, is the food(s) one of the top 8 allergens); (2) the results of the allergy testing and subsequent follow-up allergy tests (ie, are the allergy tests growing larger over time vs negative); (3) whether the subject will be avoiding the food to which they are sensitized; and (4) other concurrent atopic diatheses that may place the subject at higher risk for either loss of tolerance or a severe reaction (eg, asthma, eczema). In cases where the food is one of the major allergens, allergy tests to it are increasing, or there will be prolonged elimination of it, prescribing epinephrine may be safest. Regardless of the allergen or allergy testing, we would recommend that the physician consider prescribing epinephrine and have a discussion with the family regarding the risk of losing tolerance.^{1,40-42}

The same rationale could be used in deciding whether or not to allow a patient to introduce a food that has been eliminated from the diet at home versus in an allergist-supervised OFC. If the food is not a major allergen, allergy testing is negative or reassuring, an IgE-mediated reaction is unlikely, and there have been no IgE-mediated symptoms with any potential accidental exposures, then home introduction would seem appropriate. However, given the fact that it has been documented that patients can lose tolerance to a food over time,⁴⁰⁻⁴² if the food being reintroduced is a major allergen with a history of sensitization by allergy testing, or if there are any concerns for a possible

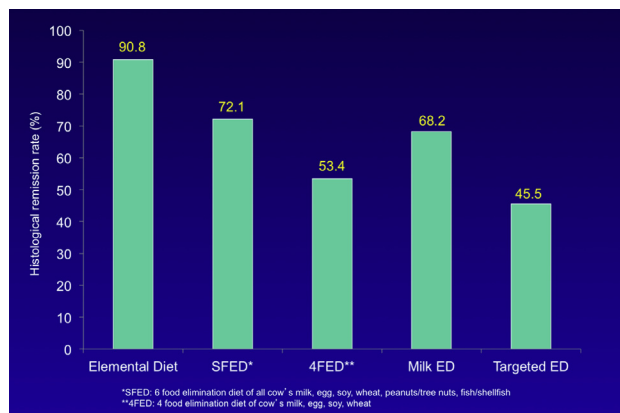


FIGURE 2. Summary of histologic remission rates for different dietary treatment options for children and adults with EoE based on meta-analysis by Arias et al. Overall effectiveness of any dietary intervention was 66.3% (95% CI, 56.9-75%).⁶³

IgE-mediated allergic reaction, then it is safest to perform an observed OFC, especially if the repeat allergy tests have increased or there is any history of possible IgE-mediated symptoms after accidental exposure.

After approximately 4 weeks on the SFED, AC no longer has abdominal pain or dysphagia. She comes back for follow-up with more questions.

Short-term follow-up:

1. All my symptoms went away after I started the elimination diet. Do I need to have a repeat endoscopy to prove that it is in remission? After how many weeks of treatment does this to be done?

In many centers, upper endoscopy with biopsy is usually performed after 6-8 weeks of treatment to assess esophageal mucosal healing, with the overall goal of reducing inflammation that may in turn reduce complications such as esophageal stricture and food impaction.^{30,43} Because symptoms do not always correlate with esophageal histology, mucosal assessment is needed to address this goal.⁴³ Endoscopy and biopsy are currently the standard of care method to assess esophageal inflammation, but other technologies are also emerging.⁴⁴

AC and the family agreed to have another endoscopy 3 months after starting the elimination diet; biopsies show normal esophageal mucosa. They ask about adding foods back to her diet now that the EoE is controlled on the SFED. AC wants to add peanut, and you recommend this be done in an observed OFC given that testing showed sensitivity to peanut. She passes the OFC in your office, and you recommend a repeat endoscopy with peanut in her diet at least 2 months from now to prove that peanut is not contributing to inflammation. You recommend follow-up after the next endoscopy to discuss further food introductions if there is no inflammation, but AC and the family are lost to follow-up until almost 2 years later.

AC now presents with abdominal pain and recurrence of solid-food dysphagia. On questioning, she admits to consuming restricted foods such as wheat and CM when she is with friends

TABLE II. Most common foods eliminated in combinations to treat patients with EoE⁶

Food	Number of subjects (total n = 319)
Milk	78
Milk, meats*	24
Milk, egg, soy, wheat	20
Milk, soy	15
Grains*	13
Milk egg, wheat, meats	11
Egg, wheat	10
Milk, egg	8
Milk, egg, wheat	8
Egg	8
Soy	7
Wheat	5

Of 319 patients, these were the most common food combinations, identified based on biopsy results, used in elimination diets to treat EoE; each food was identified by change in esophageal biopsy results from normal to >15 eosinophils/hpf when 1 food added.

*Grains: rice, oat, or wheat; meats: beef, chicken, turkey, or pork.

at school and when away from her parents. She states that she can no longer be completely adherent to the diet, and AC and the family ask about starting swallowed TCS. They have a number of questions and concerns though before starting them.

1. I am already on a nasal steroid for my seasonal allergies and take fluticasone for my asthma. If I start swallowed TCS, isn't this too much steroid? How do we know I am not taking too much?

Co-morbid problems associated with TCS for EoE have been extrapolated from long-term studies examining inhaled steroids used to treat asthma and from short-term studies on the use of swallowed TCS used to treat EoE. With respect to the former, an incremental decline in height has been reported.⁴⁵⁻⁴⁷ Swallowed TCS for EoE have been associated with side effects, including local fungal infections and cortisol suppression.^{1,48,49} Other potential problems such as cataract formation, bone demineralization, and growth disturbances have been raised as potential concerns, but the overall incidence of these problems is not certain as studies that use TCS in EoE have been limited in duration.

Balance of risk, benefits, and overall goals for the patient must be considered in making these therapeutic decisions, and monitoring for each may be indicated during the long-term use of these medications. Patients on TCS should have their height and weight monitored regularly. Given that cortisol levels can reflect the degree of adrenal suppression, it is also reasonable to check these levels in patients treated with esophageal TCS. In addition, given the potential effects of both PPIs and TCS on bone mineral density,^{50,51} it is likely reasonable to consider utilizing dual-energy X-ray absorptiometry scans. Limitations to this technique include the lack of normative pediatric data for bone density, variability in equipment read-outs, and the need for longitudinal follow-up.

2. How long do I need to take the medicine, until I feel better and then stop? Do I need to stay on a long-term treatment (ie, what are the complications if I stop), and what are the risks of being on a long-term treatment (diet vs medication)? My uncle was diagnosed with EoE, and he doesn't avoid any foods or take medicines regularly; he just undergoes dilation

approximately once a year, but in between he doesn't do any treatment.

EoE is a chronic disease that does not seem to be outgrown. In a retrospective study by Liacouras et al in which 17 children were successfully treated with TCS, symptoms recurred or worsened, and esophageal eosinophils returned, 6 months after discontinuing therapy.⁵² This demonstrates that in the presence of triggers (foods and possibly environmental allergens), esophageal eosinophilic inflammation is ongoing, and TCS need to be continually administered to be effective. This phenomenon was also seen when systemic corticosteroids were used in the form of oral methylprednisolone, where follow-up 6 months after discontinuation of therapy revealed disease relapse in children.⁵² Data on long-term use of TCS in children and adults with EoE are still scarce. One report from a randomized, double-blind, placebo-controlled, 50-week trial of low-dose oral viscous budesonide in 28 adults to maintain quiescent EoE in remission demonstrated partial effectiveness of the drug in maintaining remission compared with placebo.⁵³ In a 3-month trial with children and adults, high-dose fluticasone was effective in inducing histologic remission of EoE in 65-77% of subjects; among fluticasone responders, a 50% reduction in dose resulted in complete or partial remission in 73% and 20% of subjects, respectively.⁴⁸ Preliminary results in children with EoE also demonstrate long-term effectiveness of swallowed fluticasone.⁵⁴ In addition, signs of esophageal remodeling showed a trend toward normalization in the adult study. The latter feature is important to discuss when considering short-versus long-term therapy, because EoE is proving to be a progressive, fibrostenotic disease. Despite the limitations of its retrospective nature, a recent study by Dellon et al of a large cohort of 379 children and adults with EoE demonstrated this clearly, which showed a marked increase in the likelihood of fibrostenotic disease with age.²⁹ For every 10-year increase in age, the odds of having a fibrostenotic EoE phenotype more than doubled. This association suggests that the natural history of EoE is a progression from an inflammatory to a fibrostenotic disease. In addition, Schoepfer et al demonstrated in another retrospective study that esophageal stricture formation correlated with the duration of untreated eosinophilia.³⁰ These data point to the importance of considering long-term therapy for EoE to prevent, slow, or reverse esophageal remodeling, as it was demonstrated that esophageal fibrosis can be reversed with therapy for EoE in children, whether being treated with TCS or elimination diet.^{55,56} This has to be balanced with potential long-term complications of the therapy itself. Therefore, studies are needed to determine the optimal formulation, dose, and method of administration of TCS that would provide benefit with minimal side effects, as well as its frequency of administration; intermittent versus continuous use would be one aspect to investigate in this regard.

After answering the family's questions and providing proper instructions on how to take swallowed TCS, you start AC on fluticasone 220 mcg, 2 puffs to swallow twice daily without a spacer, and instruct her to fast for at least 30 minutes after administration. Within approximately 2 weeks, she calls to tell you that she is feeling better, with minimal abdominal pain and now rare dysphagia. She asks whether she needs to have a repeat endoscopy on fluticasone and a liberalized diet because she is feeling better. On the basis of previous discussions about

repeat endoscopy after management changes, AC agrees to have a repeat endoscopy approximately 3 months after starting swallowed TCS and consuming all foods previously avoided during the elimination diet. She does not have any symptoms at this time, and she has been adherent to the medication, as her parents state that they have refilled the prescription twice since starting it. The biopsies show 0-5 eosinophils/hpf. She calls for results of the endoscopy, and asks what the long-term follow-up plans are for EoE management.

Long-term management:

- 1. Will I ever outgrow this like I did my CM and egg allergies when I was younger?*

The natural history of EoE is not completely understood, but data support that it is a chronic disease that requires ongoing treatment. Straumann et al found no remission of untreated EoE in an 11-year follow-up of 30 adult patients.²⁶ In 87 children, Assa'ad described the chronicity of EoE.²⁷ In a longitudinal follow-up study, Menard-Katcher et al showed that dysphagia persisted from childhood to adults and that the majority of young adults continued to require pharmacological and/or dietary management. In the largest study to date, Spergel et al described 562 pediatric subjects with EoE, 330 of whom had been followed for at least 1 year; the longest follow-up was 14 years (average 3.2 years).²⁸ Of the 562 subjects, 44 (8%) developed some tolerance to foods, and only 11 (2%) had complete resolution of their EoE with reintroduction of all foods. In contrast, 24 untreated patients that returned 6.2 ± 3.6 years after initial evaluation returned with worsening symptoms of dysphagia and food impaction, with subsequent biopsies unchanged from their initial evaluation.

- 2. Now that I have a stable medication and diet, do I need to have repeat endoscopies in the future?*

The potential long-term EoE complications include esophageal narrowing, stricture, and rigidity due to remodeling,²⁹ but no data yet exist as to the long-term follow-up of adequately treated EoE beyond 1 year. Because symptoms may not correlate with esophageal histology,^{30,43} the absence of symptoms may not guarantee histological remission while on TCS. Because esophageal remodeling can occur with esophageal eosinophilia, long-term histological follow-up may be warranted until noninvasive monitoring tools (symptoms scores, blood tests) are available. In the future, esophageal function, as determined by measurements of compliance and distensibility, may provide optimal methodology to assess for the risk of food impaction and the need for esophageal dilatation.⁵⁷

- 3. There is more inflammation than my previous endoscopy on diet, but less than my original one. Should I be concerned about this, even though I am feeling well?*

The histological definition of EoE remission is not yet established, and therefore a wide range of eosinophil numbers have been reported for remission, ranging from 0 to 10/hpf.^{12,13,20,22} However, because esophageal eosinophilic inflammation has been linked to esophageal remodeling,^{58,59} it is advisable to verify a drop in esophageal eosinophil counts, until an EoE symptom assessment tool that correlates well with esophageal inflammation is developed.

4. What are the plans for future follow-up?

The degree of inflammatory control required to mitigate the risk of strictures and diminish the need for dilations is not clear.⁶⁰ No clear recommendations for long-term follow-up in terms of safety of treatments are available, but routine follow-up with an allergist, gastroenterologist, and dietician should be considered.^{45-47,50,51,61,62}

REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.
2. Molina-Infante J, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110-7.
3. Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006;101:1666-70.
4. Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr* 2009;154:96-100.
5. Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol* 2013;108:366-72.
6. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;130:461-7.
7. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;129:1570-8.
8. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097-102.
9. Doerfler B, Bryce P, Hirano I, Gonsalves N. Practical approach to implementing dietary therapy in adults with eosinophilic esophagitis: the Chicago experience. *Dis Esophagus* 2014. <http://dx.doi.org/10.1111/dote.12175> [Epub ahead of print].
10. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003;98:777-82.
11. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797-804.
12. 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* 2012;142:1451-9.
13. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;53:145-9.
14. Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2012;55:711-6.
15. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796-7.
16. Onbasi K, Sin AZ, Doganavsargil B, Onder GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy* 2005;35:1423-31.
17. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83-90.
18. Rayapudi M, Mavi P, Zhu X, Pandey AK, Abonia JP, Rothenberg ME, et al. Indoor insect allergens are potent inducers of experimental eosinophilic esophagitis in mice. *J Leukoc Biol* 2010;88:337-46.
19. Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol* 2013;132:503-4.
20. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol* 2007;102:2271-9.
21. 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* 2010;139:418-29.
22. Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381-91.
23. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012;143:321-4.
24. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526-37.
25. Schroeder S, Fleischer DM, Masterson JC, Gelfand E, Furuta GT, Atkins D. Successful treatment of eosinophilic esophagitis with ciclesonide. *J Allergy Clin Immunol* 2012;129:1419-21.
26. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660-9.
27. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731-8.
28. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;48:30-6.
29. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014;79:577-85.
30. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145:1230-6.
31. Leung J, Hundal NV, Katz AJ, Shreffler WG, Yuan Q, Butterworth CA, et al. Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis. *J Allergy Clin Immunol* 2013;132:1215-6.
32. Sugnanam KK, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy* 2007;62:1257-60.
33. Groetch M, Henry M, Feuling MB, Kim J. Guidance for the nutrition management of gastrointestinal allergy in pediatrics. *J Allergy Clin Immunol Pract* 2013;1:323-31.
34. Franciosi JP, Hommel KA, Bendo CB, King EC, Collins MH, Eby MD, et al. PedsQL eosinophilic esophagitis module: feasibility, reliability, and validity. *J Pediatr Gastroenterol Nutr* 2013;57:57-66.
35. Klennert MD. Psychological impact of eosinophilic esophagitis on children and families. *Immunol Allergy Clin N Am* 2009;29:99-107.
36. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-58.
37. Spergel JM, Shuker M. Nutritional management of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;18:179-94.
38. Papadopoulou A, Koletzko S, Heuschkel R, Dias JA, Allen KJ, Murch SH, et al. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr* 2014;58:107-18.
39. Maggadottir SM, Hill DA, Ruymann K, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. *J Allergy Clin Immunol* 2014;133:1487-9.
40. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984;59:983-6.
41. Barbi E, Gerarduzzi T, Longo G, Ventura A. Fatal allergy as a possible consequence of long-term elimination diet. *Allergy* 2004;59:668-9.
42. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 2006;61:370-4.
43. Pentiuik S, Putnam PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009;48:152-60.
44. Furuta GT, Kagalwalla AF, Lee JJ, Alumkal P, Maybruck BT, Fillon S, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut* 2013;62:1395-405.

45. Wolthers OD, Allen DB. Inhaled corticosteroids, growth, and compliance. *N Engl J Med* 2002;347:1210-1.
46. Wolthers OD, Heuck C. Assessment of the relation between short and intermediate term growth in children with asthma treated with inhaled glucocorticoids. *Allergy* 2004;59:1193-7.
47. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992;89:839-42.
48. Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology* 2014;147:324-33.
49. von Arnim U, Malfertheiner P. Eosinophilic esophagitis—treatment of eosinophilic esophagitis with drugs: corticosteroids. *Dig Dis* 2014;32:126-9.
50. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med* 2010;170:765-71.
51. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology* 2010;139:93-101.
52. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198-206.
53. Straumann A, Conus S, Degen L, Frei C, Bussmann C, Beglinger C, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400-9.
54. Andrae DA, Yershov O, Chehade M. Swallowed fluticasone is an effective maintenance therapy for children with eosinophilic esophagitis. *J Allergy Clin Immunol* 2013;131:AB180.
55. Aceves SS, Newbury RO, Chen D, Mueller J, Dohil R, Hoffman H, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010;65:109-16.
56. Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 2012;67:1299-307.
57. Nicodeme F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2013;11:1101-7.
58. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206-12.
59. Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007;45:319-28.
60. Lee J, Huprich J, Kujath C, Ravi K, Enders F, Smyrk TC, et al. Esophageal diameter is decreased in some patients with eosinophilic esophagitis and might increase with topical corticosteroid therapy. *Clin Gastroenterol Hepatol* 2012;10:481-6.
61. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343:1064-9.
62. Silverstein MD, Yunginger JW, Reed CE, Petterson T, Zimmerman D, Li JT, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.
63. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;146:1639-48.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.