

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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## An Overview of Dietary Therapies for the Treatment of Eosinophilic Esophagitis



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### **G&H** What is the connection between food and eosinophilic esophagitis?

**IH** The connection between food and eosinophilic esophagitis (EoE) was first described in a 1995 study from an allergy group at Johns Hopkins. The study, which was published just 2 years after the initial characterization of EoE, identified a group of 10 pediatric patients who were thought to have gastroesophageal reflux disease (GERD) owing to eosinophilic inflammation in the esophagus. At the time, it was thought that esophageal eosinophils were a marker for GERD. However, the children's symptoms and histopathology did not improve with therapy directed at acid reflux, including acid suppression and surgical fundoplication. The investigators then placed the children on an elemental formula that removed dietary protein, and noted marked improvement both in terms of symptoms and eosinophilic inflammation. This landmark study provided evidence for a connection between dietary protein and EoE. Because food allergies are generally a response to dietary protein, the observation led to the concept that EoE is a form of food allergy. Since this initial report, additional large studies from several pediatric centers and smaller, prospective studies in adults have confirmed the effectiveness of elemental formula diets to heal esophageal eosinophilic inflammation in the majority of patients with EoE.

### **G&H** How have food triggers for EoE traditionally been identified?

**IH** An early approach to identify specific food triggers was to perform allergy tests (eg, skin prick test, serum immuno-

globulin E [IgE] test, atopy patch tests) and eliminate the foods for which patients tested positive. This approach was led by investigators at the Children's Hospital of Philadelphia and has remained an effective diet option within the pediatric population with EoE; however, this strategy has not worked as effectively within the adult population. Currently, standardized allergy tests are based on IgE-mediated immune reactions, but the available literature indicates that EoE is a Th2-mediated disease that is not IgE-mediated. Moreover, prospective adult studies have shown that the predictive value for IgE-based allergy tests is poor, with both false-negative and false-positive results. Thus, clinical practice has moved away from the reliance on available allergy tests. The current standard approach to diet therapy is an empiric elimination diet that involves an induction phase with strict avoidance of the most common food allergens (ie, milk, wheat, soy, egg, nuts, seafood). In the 50% to 75% of patients demonstrating a histologic response, food groups are sequentially reintroduced to identify one or more specific food triggers. Fortunately, most adult patients with EoE have only a single identified food trigger. Unfortunately, symptoms are not a reliable indicator of disease activity, leading to the need for repeated upper endoscopies with biopsies during the reintroduction protocol. The time and cost necessitated by repeated endoscopies are major drawbacks to this approach.

### **G&H** What dietary therapies are available to treat EoE, and how do they compare?

**IH** The dietary treatments for EoE are broken down into 3 categories. One approach is the elemental diet, discussed

previously, that utilizes a formula diet to remove all dietary protein. Once inflammation subsides, foods are then reintroduced, starting with the least likely suspects and progressing to the most likely suspects. While this approach is the most effective form of diet therapy, there are many downsides. Formula diets are often not well tolerated in the long term. It can take years to reintroduce all eliminated food types back into a patient's diet when starting from scratch. Pediatric patients undergoing this approach have had nasogastric feeding tubes or percutaneous gastrostomy tubes placed to help administer the formula, with gradual reintroduction to more table foods over time guided by repeated upper endoscopies with biopsies. Adult studies examining the elemental diet approach have relied upon the oral administration of the elemental formula.

Another diet approach is allergy testing–directed diets, which utilize a combination of skin-prick testing and atopy-patch testing to predict specific foods that may be responsible for an individual patient's disease. Unfortunately, patch testing has not been well standardized, and the success of this approach has been limited by poor to modest predictive values of the available tests. Better methods to detect specific food triggers are needed and under development.

The third approach, considered the current standard of dietary treatment for EoE, is the empiric elimination diet, also known as the six-food elimination diet (SFED), described above. The SFED has emerged as the most popular form of diet therapy for EoE owing to the practical benefit of allowing patients to remain on commonly ingested table foods (eg, meat, poultry, rice, beans, vegetables, fruits, quinoa, oats) during the induction of response with a limited period of food reintroduction.

### **G&H** What are the short- and long-term efficacies of these treatment approaches?

**IH** The most effective diet treatment for EoE is the elemental formula diet with reported response rates of over 90% in both pediatric and adult studies. The SFED has shown response rates of 50% to 75% in pediatric and adult studies from the United States, Western Europe, and Australia. Allergy testing–directed diets have response rates that are similar to the SFED, although lower response rates were observed in the adult patient population.

### **G&H** Is dietary therapy considered a first-line treatment for patients with EoE?

**IH** A 2011 survey of pediatric and adult gastroenterologists and allergists found that the majority of clinicians used topical corticosteroids as the first-line therapy for EoE. I believe that diet therapy should be viewed as a highly effective, front-line treatment option for EoE that should not be relegated to patients who do not respond

to corticosteroids. Many of my patients are reluctant to rely on long-term corticosteroid use, although available data support their safety in EoE. Moreover, diet therapy has appeal to patients as a form of maintenance therapy. Many patients are already using various forms of diet therapy, not only for accepted medical indications but also for weight control, food intolerance, or perceived health benefits, which speaks to the attractiveness of this alternative approach. Conceptually, diet therapy has the advantage of preventing the initiation of the immune disease rather than using medications to suppress the downstream inflammatory response.

### **G&H** Are medical interventions necessary? Should dietary therapy and corticosteroids be used in combination?

**IH** Medical interventions such as corticosteroids and esophageal dilation of strictures are highly effective therapeutic options for patients with EoE. Not every patient finds diet therapy practical or feasible due to eating preferences, inability to adhere to diets while traveling or at college, and the need for multiple endoscopies. In general, the combined use of corticosteroids with diet therapy for EoE should be avoided, as the histologic response to corticosteroids masks the effect of the elimination diet, making it difficult, if not impossible, to identify a food trigger during the food reintroduction process.

### **G&H** What challenges are associated with adopting dietary modifications as a treatment approach?

**IH** There are several important limitations to dietary therapy, with the major one being the reintroduction process. The SFED eliminates 6 to 8 food groups and reintroduces one every 2 to 4 weeks. During this reintroduction, an endoscopy with biopsy is repeated, leading to 4 to 6 endoscopies, which is costly and time-consuming. Patient adherence can also pose a major challenge. Avoiding common food groups such as milk, soy, or wheat can be socially difficult, especially when dining out. The need for vigilance to avoid an identified or potential food trigger can create significant anxiety. Involvement of a dietitian can facilitate implementation of diet therapy but is a resource that may not be readily available in certain practice settings. Furthermore, the response rate of the SFED is 50% to 75%, translating to 25% to 50% of patients who do not respond and require an alternative approach.

### **G&H** Has any research been conducted to evaluate why certain foods trigger EoE?

**IH** Certainly, this is a fundamental question that is being intensively investigated. Why have patients increasingly

developed immune reactions to commonly ingested foods over the past few decades? The question applies not only to EoE, but to the marked rise in the prevalence of all forms of food allergy and atopy in general. Many hypotheses exist regarding the emergence of food allergies, including chemical additives, genetic modification of food, widespread use of acid suppression, and early life exposures. The hygiene hypothesis remains a popular concept, linking the development of autoimmune and allergic conditions to the decline in exposure to infectious pathogens. This concept fits with the epidemiologic observation of high prevalence of EoE in developed countries, with the exception being parts of Asia, such as Japan, in which a low prevalence has been reported. Interestingly, a diet study from Spain reported that many patients were reacting to beans, legumes, and rice, foods that are more commonly ingested in a Spanish diet compared to a US diet. Therefore, the reactivity may be related to how frequently susceptible individuals are exposed to specific foods.

### G&H Are food allergies more common in certain patient populations than others?

**IH** For reasons still unknown, EoE is most commonly found in white men. In addition, the majority of patients have other forms of atopy, including a history of allergic rhinitis, asthma, or atopic dermatitis. The median age at diagnosis is 30 to 40 years, although an initial presentation has been described in infants to patients age 90 years.

### G&H Has any treatment for EoE been approved by the US Food and Drug Administration?

**IH** To date, no pharmacologic agent has received approval from the US Food and Drug Administration or European regulatory agencies. The current, widespread use of topical corticosteroids with asthma delivery systems is being done off-label. There are an increasing number of phase 1, 2, and 3 studies in the United States and Europe that are investigating systems that optimize esophageal delivery for topical corticosteroids as well as novel therapeutic agents that target specific allergic pathways in EoE.

### G&H What follow-up is needed for allergy-related EoE?

**IH** The major consequence of EoE is fibrostenosis that can be quite severe in some patients, leading to intolerance of solid foods and risks of food impaction. Available data have identified the duration of untreated disease as the biggest predictor of esophageal stricture formation.

Clinical follow-up of symptoms and esophageal luminal compromise via endoscopy or barium esophagram seems appropriate, although the interval for such assessment is not defined. Limited data support the long-term effectiveness of elimination diets in EoE. Given the paucity of data on the durability of the avoidance of food triggers, however, clinical follow-up for potential loss of initial response is reasonable.

### G&H What are the top priorities of research in this field?

**IH** Short-term priorities for diet therapy relate to the development of less invasive methods to assess disease activity that obviate the need for repeated upper endoscopies with biopsy during food reintroduction. Examples include office-based capsule technologies (Esophageal String Test, EnteroTrack; Cytosponge, University of Cambridge) that can be used to detect inflammatory activity in a patient in the office setting. Transnasal endoscopy is being examined to reduce cost and the need for sedation. A more intermediate-term goal is the development of allergy tests that can identify food triggers in individual patients without the use of elimination diets. Long-term investigations are ongoing to better understand the pathogenesis of EoE and reasons for the rapid emergence of this increasingly recognized esophageal disorder.

*Dr Hirano serves as a consultant for Adare Pharmaceuticals, Receptos, Regeneron Pharmaceuticals, and Shire, and has received research funding from Receptos, Regeneron Pharmaceuticals, and Shire.*

### Suggested Reading

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