

Food allergy and eosinophilic esophagitis

Mirna Chehade^a and Seema S. Aceves^b

^aDivisions of Allergy/Immunology and Gastroenterology, Departments of Pediatrics and Medicine, Mount Sinai Center for Eosinophilic Disorders, Mount Sinai School of Medicine, New York and ^bDivision of Allergy/Immunology, Departments of Pediatrics and Medicine, University of California, San Diego, Rady Children's Hospital, San Diego, California, USA

Correspondence to Mirna Chehade, MD, MPH, Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA
Tel: +1 212 241 0830; fax: +1 212 426 1902;
e-mail: mirna.chehade@mssm.edu

Current Opinion in Allergy and Clinical Immunology 2010, 10:231–237

Purpose of review

Eosinophilic esophagitis (EoE) is a chronic allergic disease of the esophagus. A mix of immediate, IgE-mediated and delayed, non-IgE-mediated immunological reactions to foods is thought to play a role in EoE. Our purpose is to review available clinical and research evidence for this link between food allergy and EoE.

Recent findings

Various food elimination trials resulted in various rates of disease remission. Exclusive amino acid formula-based dietary trials resulted in more than 90% remission in children with EoE. Empiric elimination diets consisting of avoidance of foods commonly known to cause hypersensitivity reactions resulted in 50–74% disease remission. When diets were tailored based on results from skin prick and atopy patch tests, remission rates were comparable. Translational research studies performed on esophageal tissues and peripheral blood of patients with EoE demonstrated an allergic T-helper type 2 phenotype, though mechanisms linking the disease to food allergens are not fully addressed.

Summary

Foods appear to be important allergic triggers in EoE. Identification of these triggers, however, remains a challenge. Research is needed to elucidate at which point in the pathogenesis of EoE foods become important so that their role can be better understood, and develop better tests to identify these foods.

Keywords

diet, eosinophilic esophagitis, food allergy, lymphocyte, skin test

Curr Opin Allergy Clin Immunol 10:231–237
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus characterized by eosinophilic infiltration of the esophageal mucosa, the latter serving as its diagnostic hallmark. Finding 15 or more eosinophils/high power field (HPF) in the maximally infiltrated areas of the esophageal epithelium upon biopsy is considered diagnostic for EoE in the absence of acid-induced reflux disease [1]. EoE has become more prevalent over the past decade [2,3]. Patients with the disease present with a variety of symptoms including abdominal pain, emesis, gastroesophageal reflux symptoms, dysphagia with solid foods, and failure to thrive in children [4]. Serious complications of EoE such as esophageal food impactions necessitating urgent endoscopic removal of the food and esophageal strictures requiring endoscopic balloon dilations are also seen [5]. Age-related differences in presenting symptoms are noticed. Whereas infants and young children present mostly with feeding refusal, abdominal pain and vomiting, adolescents and adults often complain of dysphagia and food impactions [3,6] (Table 1). This difference may be secondary to the fact

that young children cannot relate the feeling of dysphagia. EoE spanning generations has been observed [7], but this subset of patients was found to have similar features and genetics to those with sporadic EoE [8]. EoE is thought to be an allergic disease, caused by multiple food allergens and possibly by environmental allergens as well.

Generally, we can classify food hypersensitivity reactions into immediate, IgE-mediated and delayed, non-IgE-mediated ones. IgE-mediated reactions develop when food-specific IgE antibodies residing on mast cells and basophils come in contact with and bind circulating food antigens and activate the cells to release potent mediators and cytokines. In non-IgE-mediated food allergic reactions, multiple inflammatory cells and their mediators play a role in immunopathogenesis. Activation of lymphocytes and recruitment of eosinophils and mast cells are cardinal features of many of the diseases involving such reactions. IgE-mediated reactions are typically rapid in onset, predominantly involve the skin, and may lead to anaphylaxis. By contrast, non-IgE-mediated reactions become evident hours to days after allergen

Table 1 Most common age-related clinical manifestations of EoE

Infants	Feeding refusal or intolerance, irritability, vomiting, failure to thrive
Children	Abdominal pain, vomiting, GERD-like symptoms, difficulty swallowing, food aversion/self-limited diet, failure to thrive
Adolescents	Dysphagia, esophageal food impactions, nausea, GERD-like symptoms, self-limited diet
Adults	Dysphagia, esophageal food impactions

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

ingestion, and often manifest in the gastrointestinal tract and skin (e.g. contact dermatitis), causing chronic inflammation and eosinophilia. Whereas skin prick tests (SPTs) and food-specific IgE levels in the serum are accepted standardized tests for immediate IgE-mediated food allergic reactions, skin patch tests are being used to detect delayed, cell-mediated reactions. It is important to note that the presence of food-specific IgE in the serum or a positive skin test demonstrate sensitization but not necessarily clinical allergy. For example, 50% of patients with food sensitization are tolerant (i.e. do not develop a clinical reaction) to the food when ingested. Atopy patch tests (APT) are utilized for detection of delayed, T-cell-mediated hypersensitivity reactions and have been standardized for conditions such as contact dermatitis. However, the use of APT for foods remains a research tool that has yet to be standardized and validated.

The link between food allergies and EoE has been made so far through a number of clinical studies that implicate foods as disease triggers, and through a very small number of translational studies consistent with, but not proving a causative link. A mix of IgE-mediated and non-IgE-mediated immunological reactions to foods is thought to play a role in EoE. In this article, available clinical and research evidence for this likely link between food allergies and EoE will be discussed.

Link between food allergens and eosinophilic esophagitis: clinical evidence

Studies using various dietary elimination therapies, empiric or allergen test-based, resulted in disease remission in some patients with EoE, indicating a link between food allergens and the disease.

Results from empiric food allergen elimination trials

Although the immunopathogenesis of food-induced EoE is poorly understood, there is substantial evidence from short-term clinical studies that implicates dietary antigens as EoE triggers. Recently performed clinical trials and retrospective reports of food eliminations have documented varying clinical response and esophageal

histological improvement in EoE. Often, re-introduction of the foods resulted in re-occurrence of EoE symptoms and histology, proving a causative relationship of EoE with dietary antigens.

The first study to shed light on the potential causation of EoE by dietary allergens was reported by Kelly *et al.* [9] in 1995. In this study, 10 children with EoE had refractory gastroesophageal reflux symptoms and had persistent esophageal eosinophilia on biopsy despite acid blocking medications and/or fundoplication. A dietary trial consisting of an amino acid-based formula for a minimum of 6 weeks (in addition to corn and apples in those old enough to eat solid foods) resulted in EoE symptom improvement and histological resolution. Symptoms completely resolved in eight of the 10 children, and improved in the remaining two patients. Maximal esophageal intraepithelial eosinophils decreased from a median of 41/HPF (range 15–100) to 0.5/HPF (range 0–22). Re-challenge with various foods resulted in re-creation of symptoms identical to those experienced before the dietary trial, suggesting a link of the patients' disease to a possible immunological reaction to foods. Patients showed symptomatic responses to a median of two foods per patient (range one to six foods). Commonly implicated foods were cow's milk, soy, wheat, peanut and egg. Avoidance of the offending foods allowed eight of the 10 patients to remain asymptomatic without antireflux medications.

Markowitz *et al.* [10] confirmed Kelly's findings on a larger group of 51 children with EoE. Dietary intervention for these children consisted of an amino acid-based formula and one food, grape or apple, for a month. All but two patients experienced clinical improvement on the dietary intervention and distal esophageal eosinophils decreased from 33.7 ± 10.3 to 1.0 ± 0.6 /HPF.

Kagalwalla *et al.* [11] reported their clinical experience with a less restricted dietary trial in 35 pediatric EoE patients. Empiric dietary removal of the six most common foods that drive immediate hypersensitivity reactions was done for 6 weeks. These foods consisted of cow's milk, soy, wheat, egg, peanut, and seafood. Clinical and histological improvement, though not complete resolution of the disease, occurred in 74% of the patients. Overall, esophageal intraepithelial eosinophils decreased from 80.2 ± 44.0 to 13.6 ± 23.8 /HPF.

In adults with EoE, a potential role for food allergy in EoE has been more controversial, due to the scarcity of clinical trials involving dietary restriction in adults with the disease. Gonsalves *et al.* [12] prospectively implemented the same dietary elimination done by Kagalwalla and colleagues in 18 adult EoE patients. Histologic (defined as less than 15 eosinophils/HPF in the maximally involved areas upon esophageal biopsies) and

symptomatic improvement occurred in 50 and 94% of patients, respectively, following 6 weeks of therapy. Overall, peak intraepithelial eosinophils decreased from 41 ± 26 to 9 ± 17 /HPF in the proximal esophagus and from 43 ± 28 to 20 ± 24 /HPF in the distal esophagus.

In all the above studies, patients with EoE responded clinically and histologically to a dietary restriction, pointing to food antigens as potential triggers for the disease.

Results from test-based food allergen elimination trials

Since foods triggering EoE are thought to be mediated by IgE and non-IgE mechanisms, studies from Spergel and colleagues have investigated skin testing (both SPT and APT) as tools for identification of food triggers in EoE for the purpose of tailoring elimination trials, with reported success rates similar to empiric dietary eliminations. By contrast, the data for serum food-specific IgE and SPT-based elimination diets in EoE have had fewer reported successes.

The first such study in children was conducted by Spergel *et al.* [13], who performed a combination of SPT and APT on 26 children with EoE. Patients were positive to an average of 2.7 ± 3.3 foods (range 0–13) by SPT, and an average of 2.7 ± 1.8 foods (range 0–7) by APT. Foods most commonly identified by SPT were cow's milk, egg, peanut, shellfish, peas, beef, fish, rye, tomato and wheat. Foods most commonly identified on APT were wheat, corn, beef, cow's milk, soy, rye, egg, chicken, oats and potato. These children were instructed to avoid all foods that tested positive by SPT and/or APT for a minimum of 6 weeks. Eighteen children (69%) had resolution of their symptoms. Overall, esophageal intraepithelial eosinophil counts improved from 55.8 ± 24.6 to 8.4 ± 8.4 /HPF following this directed dietary therapy. Although treatment for co-existing atopic diseases was concomitantly initiated, which may have potentially contributed to the high response rate, their approach in dietary therapy demonstrated a role for both immediate, IgE-mediated food reactions and delayed, cell-mediated reactions in EoE.

However, when Spergel *et al.* [14] went further and tested the predictive value of SPT and APT in identifying food triggers, by checking for histological disease remission/relapse following removal/introduction of a triggering food, positive and negative predictive values for either SPT or APT proved to be highly variable, ranging from 30 to 90%. Those foods with higher predictive power were common allergens. Since APT is currently not standardized for the type of foods used (extracts versus fresh) for its interpretation and for proof of a local cutaneous immunologic at the testing site, it remains a research

tool that would benefit from additional data from multiple centers.

In adults with EoE, Gonsalves *et al.* [12] found a low predictive value of SPT to foods when patients were treated with dietary elimination of the six common food allergens. In their study of 18 patients, SPT predicted only 22% of the causative foods found on eliminations followed by single food re-introduction to cause disease relapse. The most common food triggers in these patients, as judged by recurrence of symptoms and esophageal eosinophilia, were cow's milk and wheat (50%), followed by soy and egg (17%).

Simon *et al.* [15] prospectively examined six adult patients with EoE who had evidence of sensitization to grass pollen, wheat and rye, but not to cow's milk, egg or fish, as determined by SPT and/or serum allergen-specific IgE levels. Elimination of wheat, rye and barley from the diet of these patients for 6 weeks failed to reduce clinical disease activity. Although one patient noticed some improvement of symptoms, endoscopic and histological findings remained unchanged. It is important to note, however, that standard allergy tests to grains, especially wheat, have poor predictive value even for immediate hypersensitivity reactions, likely due to the preparation of the antigen.

In conclusion, the above studies demonstrate that although food sensitizations in patients with EoE are common, the utility in using allergen skin testing (SPT and/or APT) for identifying food triggers still requires further research. There have been no reported clinical studies that document APT in adults. In addition, adults overall have a lower response rate to dietary interventions than children, whether an empiric approach or a skin test approach is followed. This difference in results may be simply the result of lack of enough studies to allow adequate comparisons, lower adherence to the restrictive diets by adults due to severe lifestyle limitations, or a prominent role for aeroallergens as triggers for EoE in the adult population.

In fact, aeroallergen sensitization has been proposed as a potential cause of EoE in adults. This stems from murine studies of EoE when intranasal instillation of antigen resulted in esophageal eosinophilia [16], reports of seasonal variations in disease activity [17,18], as well as reports that aeroallergens can drive esophageal eosinophilia in adult patients, though not to the extent seen in EoE [19]. A recent study by Sugnam *et al.* [20] on 45 Australian children with EoE demonstrates a positive relationship between increasing age and degree of aeroallergen sensitization and a negative relationship between increasing patient age and degree of food allergen sensitization. In the study, allergen sensitization

profiles were prospectively analyzed by SPT to common food allergens and environmental allergens in Australia. A subset of those patients also had APT to common food allergens. Sensitization to inhalant allergens increased with age, pointing to a possibly larger role for aeroallergens in older children and adults compared with younger children. It is important to note that loss of food allergies and accumulation of aeroallergen sensitization reflect the natural history of allergies in general and as such, these observations are likely not to be specific for EoE. More conclusive studies are needed to establish whether aeroallergens are at all potential triggers for EoE.

Link between food allergens and eosinophilic esophagitis: translational research evidence

To date, research studies on EoE uncovered an allergic phenotype for the disease, consistent with clinical findings. However, the link of food allergens to EoE has not been thoroughly studied.

Histopathological examination of esophageal tissue from patients with EoE has revealed an inflammatory phenotype similar to that of other atopic diseases. Intraepithelial T-lymphocytes, mast cells, and eosinophils were shown to be increased in the esophageal epithelium [21]; and tissue remodeling is increased in the subepithelium [22,23]. Basophils were also found in the esophagus of patients with EoE, whereas they were absent in the normal esophagus [24]. Many of these inflammatory cells appear to be activated, as evidenced by degranulation of mast cells, basophils and eosinophils [21]. Eosinophil granule products such as major basic protein (MBP) can increase fibroblast growth factor 9 (FGF9) to promote esophageal epithelial hyperplasia [25], and eosinophilic secretion of pro-fibrotic factors such as TGF- β 1 can cause subepithelial fibrosis [22]. As for T-lymphocytes in EoE, both CD4 (T-helper) and CD8 (T-suppressor) subsets of T-lymphocytes were found to be increased in the esophageal epithelium, with maintenance of CD8 predominance over CD4 cells [26]. Whether this CD8 predominance is also true in the deeper, subepithelial lamina propria of the esophagus is unknown.

Despite a predominance of CD8 cells in the esophageal epithelium of EoE patients, CD4 cells seem to be important in EoE pathogenesis. In a mouse model of EoE, CD4-deficient mice were partially protected from EoE [27]; and in EoE patients, a T-helper type 2 (Th2) phenotype has been found. Evidence for this allergic phenotype stems from various studies of T-cells in the esophagus and in the peripheral blood of patients with EoE, although not definitive.

In the esophagus, increased levels of the Th2 cytokines IL-5 and IL-13 have been reported in patients with EoE

[28–30], although identification of the specific inflammatory cells producing these cytokines remains to be studied. Both IL-5 and IL-13 have been shown to potentially play an important role in EoE pathogenesis. In a mouse model of EoE, IL-5 was shown to promote eosinophil trafficking to the esophagus [31]. When stimulated with IL-13 *in vitro*, esophageal epithelial cells produced high levels of eotaxin-3 [30], a highly induced chemokine in EoE that was shown to regulate eosinophil responses *in vitro* [32] and to correlate with the severity of esophageal eosinophilia in EoE [33].

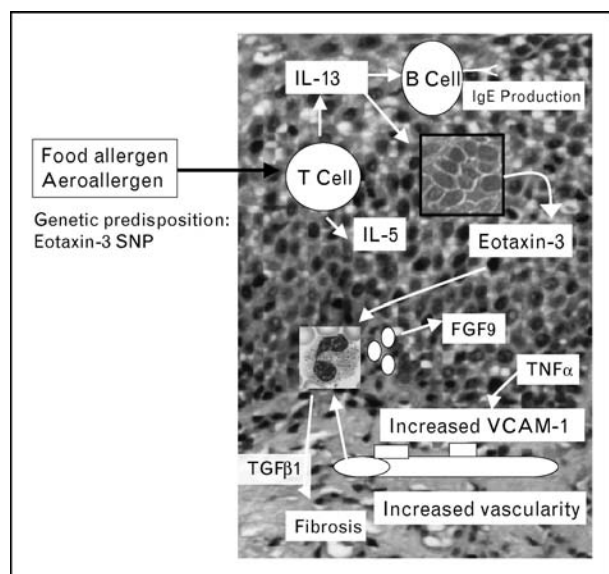
Since the identification of the specific inflammatory cells in the esophagus producing the Th2 cytokines has not been analyzed, we do not know the exact extent of the esophageal lymphocytes' contribution to the production of these Th2 cytokines, especially given the esophageal infiltration by other immune cells, such as eosinophils and mast cells, capable of secreting these cytokines. For example, 60% of esophageal eosinophils of patients with EoE were found to express IL-4 and IL-13 upon immunohistochemical staining [34]. Further studies addressing the specific contribution of esophageal lymphocytes into the production of Th2 cytokines, especially in response to specific dietary allergens, need to be performed.

A recent study by Vicario *et al.* [35•] established that the esophageal mucosa is a site for initiation and development of humoral responses and local IgE production. Increased B-lymphocytes and expression of molecular immunoglobulin machinery in the esophagus of patients with EoE was found, regardless of their atopic status. These results may explain the dissociation between food sensitization on skin testing (SPT) and the results of food elimination diets in EoE.

The immune mechanisms that explain why all EoE patients with IgE to food do not anaphylax remain unclear. A recent study by Prussin and colleagues [36•] demonstrated that patients with eosinophilic gastrointestinal disease have a predominance of IL-5+ CD4+ cells to peanut antigens as compared with patients with peanut anaphylaxis who have predominantly IL-5 negative CD4+ cells. Further studies will be important in defining mechanisms that underlie distinct immunologic reactions to foods.

In the peripheral circulation, Bullock *et al.* [37] examined cytokine expression by peripheral blood mononuclear cells (PBMCs), and found that children with active EoE had an increased percentage of CD4+ T-cells expressing IL-5 compared with nonatopic controls. This percentage was lower in EoE patients in remission than in patients with active disease. However, this study was cross-sectional rather than longitudinal to show that

Figure 1 Eosinophilic esophagitis pathogenesis: food allergens and aeroallergens cause a presumed T cell activation and production of the key interleukins 5 and 13 to promote eosinophil trafficking, activation, and survival, IgE production, and eotaxin-3 production by activated epithelium. Eotaxin-3 together with VCAM-1 activated vessels allow eosinophil recruitment via increased blood vessels. TNF- α can increase VCAM-1 production. Eosinophil granule products such as MBP increase FGF9 to promote epithelial hyperplasia; and eosinophilic secretion of pro-fibrotic factors such as TGF- β 1 cause sub-epithelial fibrosis



an individual patient has changes in Th2 cytokines. Straumann *et al.* [28] measured cytokine production by PBMCs of EoE patients in response to in-vitro stimulation with phytohemagglutinin (PHA), a CD3 stimulant. Increased release of the Th2 cytokine IL-13 was found in 40% of the patients studied. Yamazaki *et al.* [38] conducted similar experiments using stimulation with specific allergens. PBMCs from 15 adult patients with EoE were incubated *in vitro* with food allergen extracts and aeroallergen extracts. Food extracts consisted of cow's milk, egg, soy, wheat and peanut. Compared with healthy controls, PBMCs from EoE patients secreted significantly more IL-5 and/or IL-13 in response to various allergens, even in the absence of clear-cut sensitization to the allergens when serum allergen-specific IgE levels were measured. A limitation to the study is the high prevalence of concurrent allergic diseases in the EoE population studied, which could have accounted for the Th2 response by the PBMCs. Comparison of these results to those of allergic controls is needed to confirm these findings.

In conclusion, the above studies demonstrate tissue and peripheral blood immune cell profiles in EoE to be consistent with an allergic phenotype, though the mechanisms that link EoE to food allergens are still not fully

addressed. A proposed mechanism for EoE pathogenesis and its relation to food allergens is illustrated in Fig. 1.

Conclusion

Foods appear to be important allergic triggers in patients with EoE, whether in children or adults. Studies are needed to elucidate at which point in the pathogenesis of EoE foods become important, so that their role can be better understood. Until more studies are performed, we may conclude that a link between food antigens and EoE exists, since the disease can be driven into remission by dietary restrictions alone. Identification of these food triggers remains a challenge. Current consensus recommendations published in 2007 by a task force of physicians who participated in the First International Gastrointestinal Eosinophil Research Symposium point to a moderate evidence against recommending measurement of serum food-specific IgE levels in patients with EoE, and weak evidence to suggest skin testing to foods in patients with EoE [1]. Multiple studies published since these consensus guidelines demonstrate that further research is required to identify the best tests to determine antigenic foods in EoE. In addition, since EoE is characterized clinically by a high degree of concurrent allergic disease, it is important to consider a full allergic evaluation in order to treat the multiple atopic diatheses present in the individual. In addition, some studies suggest that allergic sensitization may predict response to therapy [39].

Given the limitations above, we believe that an empiric elimination of common food allergens is the simplest dietary intervention in patients with EoE regardless of their age due to its reasonable remission rate (at least 50%). However, in some centers the rates of response to a directed dietary elimination using skin testing are similar to those of empiric dietary elimination, and can be considered. It is essential when choosing a therapeutic modality for a patient with EoE to consider the impact on the patient's lifestyle and ability to adhere to the recommended therapy. Dietary manipulation therapy appears to have similar response rates to other therapeutic interventions such as topical esophageal corticosteroids (Table 2) [40–49]. Potential problems with dietary manipulation include nutritional deficiencies and decreased quality of life. Therefore, it is critical to perform dietary eliminations under the guidance and monitoring of a dietician with expertise in food allergies to avoid these consequences. SPT to foods and physician monitored oral challenges may have an important role during food introductions following prolonged dietary restrictions, to ensure safety of these re-introductions in the rare event of increased sensitization to these foods especially in individuals with elevated serum food-specific IgE levels.

Table 2 Reported treatment modalities for EoE

Treatment modality	Population studied	Remission ^a rate
Diet		
Amino acid-based formula	Children	96–100% [9,10]
Empiric elimination diet (6-food elimination diet)	Children, adults	50–74% [11,12]
Directed elimination diet (SPT and APT-based)	Children	69% [13]
Corticosteroids		
Systemic	Children	93–95% [40,41]
Topical (fluticasone, budesonide)	Children, adults	50–95% [39,41–43]
Others (limited data)		
Montelukast	Adults	No histological remission but 75% clinical response [44]
Cromolyn sodium	Children	No remission [45]
6-mercaptopurine	Adults	Some clinical response [46]
Mepolizumab (anti-IL-5)	Adults	Significant histological response but no significant clinical response [47,48]
Infliximab (anti-TNF- α)	Adults	No remission [49]

APT, atopy patch test; EoE, eosinophilic esophagitis; SPT, skin prick test.

^a Clinical and histological remission (significant symptom improvement and decrease in esophageal eosinophilia to <10–15/HPF).

Acknowledgements

M. Chehade receives funding from the NIH/NIAID-AI 44236 and the Buckeye Foundation. S. Aceves receives funding from the AAAAI Women in Allergy Junior Faculty Development Award. Both authors have no conflicts of interest to disclose.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 269–270).

- 1 Furuta GT, Liacouras CA, Collins MH, *et al.* Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; 133:1342–1363.
- 2 Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; 115:418–419.
- 3 Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004; 351:940–941.
- 4 Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000; 30 (Suppl):S87–S94.
- 5 Straumann A, Spichtin HP, Grize L, *et al.* Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003; 125:1660–1669.
- 6 Assa'ad AH, Putnam PE, Collins MH, *et al.* Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007; 119:731–738.
- 7 Zink DA, Amin M, Gebara S, Desai TK. Familial dysphagia and eosinophilia. *Gastrointest Endosc* 2007; 65:330–334.
- 8 Collins MH, Blanchard C, Abonia JP, *et al.* Clinical, pathologic, and molecular characterization of familial eosinophilic esophagitis compared with sporadic cases. *Clin Gastroenterol Hepatol* 2008; 6:621–629.
- 9 Kelly KJ, Lazenby AJ, Rowe PC, *et al.* Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995; 109:1503–1512.
- 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; 98:777–782.
- 11 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* 2006; 4:1097–1102.
- 12 Gonsalves N, Ritz S, Yang G, *et al.* A prospective clinical trial of allergy testing and food elimination diet in adults with eosinophilic esophagitis (EE). *Gastroenterology* 2007; 132:A6.
- 13 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* 2002; 109:363–368.
- 14 Spergel JM, Brown-Whitehorn T, Beausoleil JL, *et al.* Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007; 119:509–511.
- 15 Simon D, Straumann A, Wenk A, *et al.* Eosinophilic esophagitis in adults: no clinical relevance of wheat and rye sensitizations. *Allergy* 2006; 61:1480–1483.
- 16 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.
- 17 Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003; 112:796–797.
- 18 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* 2007; 41:451–453.
- 19 Onbasi K, Sin AZ, Doganavsargil B, *et al.* Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy* 2005; 35:1423–1431.
- 20 Sugnam KK, Collins JT, Smith PK, *et al.* Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy* 2007; 62:1257–1260.
- 21 Chehade M. Translational research on the pathogenesis of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008; 18:145–156.
- 22 Aceves SS, Newbury RO, Dohil R, *et al.* Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007; 119:206–212.
- 23 Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007; 45:319–328.
- 24 Chehade M, Yershov O, Shreffler W, *et al.* Basophils are present in the esophagus of children with eosinophilic esophagitis. *J Allergy Clin Immunol* 2008; 121:S105.
- 25 Mulder DJ, Pacheco I, Hurlbut DJ, *et al.* FGF9-induced proliferative response to eosinophilic inflammation in esophagitis. *Gut* 2009; 58:166–173.
- 26 Lucendo AJ, Navarro M, Comas C, *et al.* Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* 2007; 31:598–606.
- 27 Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. *J Leukoc Biol* 2007; 81:916–924.
- 28 Straumann A, Bauer M, Fischer B, *et al.* Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001; 108:954–961.
- 29 Gupta SK, Fitzgerald JF, Kondratyuk T, HogenEsch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2006; 42:22–26.

- 30 Blanchard C, Mingler MK, Vicario M, *et al*. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007; 120:1292–1300.
- 31 Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002; 168:2464–2469.
- 32 Kitaoura M, Suzuki N, Imai T, *et al*. Molecular cloning of a novel human CC chemokine (Eotaxin-3) that is a functional ligand of CC chemokine receptor 3. *J Biol Chem* 1999; 274:27975–27980.
- 33 Blanchard C, Wang N, Stringer KF, *et al*. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; 116:536–547.
- 34 Straumann A, Kristl J, Conus S, *et al*. Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. *Inflamm Bowel Dis* 2005; 11:720–726.
- 35 Vicario M, Blanchard C, Stringer KF, *et al*. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010; 59:12–20.
- Novel study demonstrating evidence for local IgE class switching in the esophagus of patients with eosinophilic esophagitis.
- 36 Prussin C, Lee J, Foster B. Eosinophilic gastrointestinal disease and peanut allergy are alternatively associated with IL-5+ and IL-5(–) T(H)2 responses. *J Allergy Clin Immunol* 2009; 124:1326–1332.
- Novel study demonstrating phenotypic differences in T-helper type 2 lymphocytes in response to food antigen stimulation.
- 37 Bullock JZ, Villanueva JM, Blanchard C, *et al*. Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007; 45:22–31.
- 38 Yamazaki K, Murray JA, Arora AS, *et al*. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. *Dig Dis Sci* 2006; 51:1934–1941.
- 39 Konikoff MR, Noel RJ, Blanchard C, *et al*. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006; 131:1381–1391.
- 40 Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998; 26:380–385.
- 41 Schaefer ET, Fitzgerald JF, Molleston JP, *et al*. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008; 6:165–173.
- 42 Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol* 2007; 102:2271–2279.
- 43 Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* 2006; 63:3–12.
- 44 Attwood SE, Lewis CJ, Bronder CS, *et al*. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003; 52:181–185.
- 45 Liacouras CA, Spergel JM, Ruchelli E, *et al*. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005; 3:1198–1206.
- 46 Netzer P, Gschossmann JM, Straumann A, *et al*. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* 2007; 19:865–869.
- 47 Stein ML, Collins MH, Villanueva JM, *et al*. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006; 118:1312–1319.
- 48 Straumann A, Conus S, Grzonka P, *et al*. Antiinterleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2009; 58:21–30.
- 49 Straumann A, Bussmann C, Conus S, *et al*. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008; 122:425–427.