

Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients

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Purpose of review

Eosinophilic esophagitis is a recently recognized disorder receiving increasing attention. Patients present with symptoms of gastroesophageal reflux and are not responsive to standard or aggressive reflux medications. This article reviews all literature published in English from December 2005 to November 2006 from PubMed on the topic of eosinophilic esophagitis.

Recent findings

Three articles have confirmed that food allergies are causative in more than 90% of patients. Three different diet strategies were used: elemental, elimination diet based on the prick-skin test, and the atopy patch test or removal of the six most common foods. The elemental diet had the highest success rate (> 95%), whereas the testing-based elimination diet (> 75%) and six-food elimination diet (> 70%) had lower success rates. There are no organized dietary trials in adults.

Summary

Recent literature on pediatric patients with eosinophilic esophagitis confirms that nearly all patients respond to an elemental diet with resolution of symptoms and normalization of biopsies. Although diets based on testing or removal of the most common allergens showed success, they were less successful than a complete elimination diet. Unfortunately, there are very limited studies in adults that address this issue.

Keywords

atopy patch test, elemental diet, eosinophilic esophagitis, food allergies, prick-skin test

Introduction

Eosinophilic esophagitis is characterized by infiltration of the esophagus with eosinophils, without infiltration in other parts of the gastrointestinal tract [1,2[•]]. The first case of eosinophilic esophagitis was described in 1978 [3], with increasing incidence as well as publications on the subject in the past year. The symptoms of eosinophilic esophagitis are similar to those of gastro-intestinal reflux disease (GERD) and include vomiting, pain, regurgitation, food impaction and dysphagia. Patients with eosinophilic esophagitis are, however, unresponsive to standard GERD treatment and have normal pH probes [4].

The prevalence of eosinophilic esophagitis is unknown, but two studies found an estimated prevalence of $4.3/10^5$ in children and $2.5/10^5$ in adults in the United States [5,6]. Several studies have suggested that approximately 6–10% of patients with GERD do not actually have GERD but eosinophilic esophagitis [2[•]]. A study in western Australia [7] found an increase in eosinophilic esophagitis over the decade 1995–2004, rising from 0.05 to 0.89 per 10 000 children. As GERD has a prevalence of 1–8% [8], the prevalence would range from $6/10^5$ to $8/10^4$, making it more common than inflammatory bowel disease. A recent population study of 1000 random adults in the Swedish general population found a prevalence of up to 1% [9]. Many of the patients were asymptomatic, suggesting a significantly higher incidence of eosinophilic esophagitis than was originally thought.

Patients with eosinophilic esophagitis are typically male (~60–70%) with an allergic background, such as an elevated IgE level, peripheral eosinophilia, allergic disease (including asthma, atopic dermatitis, or allergic rhinitis), and sensitization as demonstrated by a positive prick-skin test (PST) result [10,11]. Eosinophilic esophagitis has primarily been studied in children, with far fewer studies in adults. There are significant differences in the presentation. Young children typically present with GERD symptoms or food refusal and failure to thrive, whereas adolescents can present with dysphagia, and adults present with dysphagia, food impaction and strictures, suggesting a potential natural history of untreated disease [12,13].

The diagnosis of eosinophilic esophagitis depends on the clinical-histopathological definition. Eosinophils are not normally found in the esophagus, whereas they can

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Abbreviations

APT atopy patch test
GERD gastrointestinal reflux disease
PST prick-skin test

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been seen normally in other locations in the gastrointestinal tract [14]. The standard definition of eosinophilic esophagitis is based on the finding of more than 20 eosinophils per high-power field [15]. Some studies have, however, used 15 and others have used 24 eosinophils per high-power field as the cutoff [16]. Also, the disease is patchy, and multiple biopsies are needed to confirm the diagnosis, with five biopsies being optimal for the highest sensitivity [13]. Another histological finding is severe basal cell hyperplasia found in the esophagus in patients with eosinophilic esophagitis compared with normal individuals or patients with GERD [17].

Eosinophils can, however, occur in the esophagus in other conditions. GERD typically causes 0–5 eosinophils per high-power field, but there are case reports on patients having up to 50 eosinophils per high-power field with GERD [18]. In addition, allergic rhinitis can contribute to eosinophils in the esophagus. Fogg *et al.* [19] found a single case of pollen sensitization causing eosinophilic esophagitis with up to 40 eosinophils per high-power field. Onbasi and colleagues [20] examined three populations (normal controls, patients with GERD and no atopy, and patients with no GERD and allergic rhinitis) and performed biopsies in and out of the pollen season. They found that normal patients had no eosinophils in the biopsy compared with an average of 3 eosinophils per high-power field in the GERD patients and 5 eosinophils per high-power field in allergic rhinitis patients during the pollen season and no eosinophils per high-power field out of the pollen season. Therefore, when a diagnosis of eosinophilic esophagitis is made, it is important to ensure that GERD and pollinosis are under control with proton pump inhibitors and nasal steroids.

Pathogenesis

The pathogenesis of eosinophilic esophagitis is unknown; however, an examination of inflamed esophageal tissue shows an elevated expression of IL-5 with a similar expression of IL-4 and IL-13. As IL-5 is a potent eosinophilic growth factor, it might maintain eosinophils at the tissue level [21]. Recent work by the Rothenberg laboratory [22•] found a marked elevation of eotaxin-3 on gene-chip analysis. Eotaxin-3 levels correlated with tissue eosinophilia and mast cell counts. Eotaxin-3 is a chemokine for eosinophils, suggesting that eotaxin-3 is an important molecule in the pathogenesis of eosinophilic esophagitis. Interestingly, Blanchard and colleagues [22•] also found a single-nucleotide polymorphism in patients with eosinophilic esophagitis on the eotaxin-3 gene implicating eosinophilic esophagitis to a particular genetic polymorphism in 14% of the eosinophilic esophagitis population studied.

Role of food in eosinophilic esophagitis: new results

Food allergy has been examined in eosinophilic esophagitis with the first case in 1977 in adults [23] and the first case in children in 1995 [24]. The next sections will explore the role of food allergy in pediatric and adult patients, with emphasis on articles published in the past year.

Pediatric patients

The first evidence for food allergies causing eosinophilic esophagitis was 11 years ago in a study by Kelly *et al.* [24], which used an elemental diet in 10 children with intractable GERD and eosinophilic esophagitis, with partial or complete resolution of symptoms in all 10 children on symptoms and biopsies. Markowitz *et al.* [25] confirmed this result in a study in 346 children with chronic GERD, of whom 51 were eventually diagnosed with eosinophilic esophagitis. The 51 eosinophilic esophagitis patients were then given an elemental formula; 49 of the 51 patients improved symptomatically within 8 days, and there was a significant decrease in the number of eosinophils in the distal esophagus to normal levels within one month.

The largest study of eosinophilic esophagitis was conducted by Liacouras *et al.* [1] at the Children's Hospital of Philadelphia, in which they reviewed the last 389 patients with eosinophilic esophagitis over a 10-year period. A total of 160 patients were treated with an elemental diet, and 75 patients were treated with an elimination diet based on the PST and atopy patch test (APT). The authors found a 97% response rate to the elemental diet, with a complete resolution of symptoms and normalization of biopsies to 1.1 eosinophils per high-power field compared with treatment with swallowed fluticasone propionate 220 µg twice a day, which improved histological counts to 11 eosinophils per high-power field. The study indicated that an elemental diet is superior to pharmacological trials (also the use of cromolyn resulted in no change in symptoms or biopsy results). The dramatic improvement with the elemental diet with either neocate or elecare shows that food allergies are causing eosinophilic esophagitis in pediatric patients. Unfortunately, 80% of the patients requiring elemental diets required a nasogastric tube to get sufficient calories. In those patients, after the normalization of esophageal biopsies, individual foods were reintroduced. A new food was reintroduced approximately every 5 days. Patients were subsequently followed for clinical symptoms and the recurrence of esophageal eosinophilia. An esophagogastroduodenoscopy with biopsy was performed in all cases approximately 4–8 weeks after the reintroduction of the last food. An average of 5.6 ± 2.9 allergic foods per patient were directly linked to the development of esophageal eosinophilia. The elimination of foods leading to the normalization of symptoms and biopsies and the reintroduction of foods causing

symptoms to occur and esophageal eosinophilia to return is definitive proof that foods are the cause of eosinophilic esophagitis in pediatric patients.

As a result of the unpalatable nature of the elemental formulae and their high cost, we have developed elimination diets based on PSTs and APTs to identify the foods that are causative in eosinophilic esophagitis [26]. In our most recent publication on the use of PSTs and APTs to guide dietary management in eosinophilic esophagitis, we examined the results in 146 patients with eosinophilic esophagitis [10,27]. All patients had eosinophilic esophagitis based on histological findings of more than 20 eosinophils per high-power field after failing therapy with proton pump inhibitors and treatment for allergic rhinitis. Seventy-seven per cent (112 patients) showed a marked improvement of their biopsies down to near normal levels of 1.1 eosinophils per high-power field. Forty out of 112 patients needed an elemental diet because of the severe nutritional deficits resulting from their elimination diet. The patients who failed on the elimination diet did improve and had a resolution of tissue eosinophilia on the elemental diet. We found 3.2 ± 4.3 foods on PST results, with egg, milk, soy, peanut, chicken, wheat, and beef being the most common foods identified. For the positive APT results, we found an average of 3.1 ± 2.6 foods, with corn, soy, wheat, milk, rice, chicken, beef, and potato being the most common foods found on APT. On average, our patients were allergic to (or needed to eliminate) five foods for the resolution of eosinophilic esophagitis and symptoms.

We were able to identify the definitive food(s) that caused symptoms by examining the subpopulation with single food reintroduction leading to symptoms of esophageal eosinophilia. It is hard to identify individual foods because a biopsy pre and post single food reintroduction is the gold standard to identify a food definitively. On the basis of the results in 39 patients, the most common foods identified were milk, egg, soy, chicken, wheat, beef, corn and peanuts [10]. It appears that a combination of SPTs and APTs is necessary to identify the foods correctly. For example, SPTs were able to identify the reactions caused by milk, egg, soy and chicken but missed six, five, one and four patients, respectively, which APT was able to identify. These results suggest that the combination of SPTs and APTs are ideal for the identification of foods causing eosinophilic esophagitis in children.

Kagalwalla *et al.* [28**] took a different approach to the unpalatable elemental formulae by just removing the most common food allergies. They examined two different diet plans (elemental diet versus six-food elimination diet) in 60 children. All patients had eosinophilic esophagitis with at least 20 eosinophils per high-power field isolated in the

esophagus without eosinophils in the stomach or duodenum. Twenty-five children were treated with an elemental diet from January to September 2001. Thirty-five children were treated with a 6-week course of selective food elimination from October 2003 to June 2005, with the removal of milk, egg, wheat, soy, peanuts, and seafood. The children treated with the elemental diet all had complete normalization of their biopsies as counts improved from 58.8 ± 31.9 to 3.6 ± 6.5 ($P < 0.001$). The children treated with the six-food elimination diet also had an improvement in the biopsies, but not as low as the elemental diet (pre 80.2 ± 44.0 , post 13.6 ± 23.8). Kagalwalla *et al.* [28**] also examined treatment failures and improvement rates based on counts of less than 10 eosinophils per high-power field, 10–20 and more than 20 eosinophils per high-power field. Eighty-eight per cent of patients on the elemental diet and 74% of patients on the six-food diet had an improvement to less than 10 eosinophils per high-power field. One patient on the elemental diet did not improve compared with four patients on the six-food elimination diet. The study confirms that food allergies are causative of eosinophilic esophagitis in a majority of patients and most of the patients have allergies to the most common allergens.

Several other centers have also found that food elimination leads to an improvement of symptoms and resolution of histological abnormalities. De Angelis *et al.* [29] studied 11 patients with eosinophilic esophagitis. In the nine patients with follow-up, five improved on milk elimination, two on elemental elimination, and one patient improved on milk, egg and wheat elimination. This was an improvement in 89% with diets similar to the other results discussed above. In addition, Martin-Munoz *et al.* [30] found that food elimination in two adolescents led to the resolution of their symptoms and normalization of biopsies with the elimination of chicken, egg and legumes.

Adults

Adults with eosinophilic esophagitis often present with different symptoms to children. Adults typically present with esophageal strictures, food impaction, chest pain and severe dysphagia [31*]. In contrast to the several studies examining diet therapy in children, there are very limited studies in adults. Simon *et al.* [32] examined in-vitro specific IgE to foods (wheat and rye) in six adults with eosinophilic esophagitis. Wheat and rye were removed from the diet without any changes in biopsies, but with one patient reporting improvement in symptoms. The authors concluded that skin tests to wheat and rye were not relevant for eosinophilic esophagitis because wheat and rye extracts crossreacted with grass pollen extracts in these patients with known grass pollen allergies. It is also possible that they did not eliminate enough foods to cause any improvement in symptoms or biopsy findings. We have, however, also found that in-vitro specific IgE

had a very low predictive value for causative foods in eosinophilic esophagitis (data not shown).

One study indicated that foods may cause reactions in adults. Yamazaki *et al.* [33] examined 15 adult patients with eosinophilic esophagitis and examined IL-5 and IL-13 expression. They found that dust mite, ragweed, *Aspergillus*, milk, and soy induced significantly higher IL-5 production in eosinophilic esophagitis patients compared with atopic controls. Also, peripheral blood monocytes produce more IL-13 after stimulation with dust mite. The study does not have direct evidence that food causes eosinophilic esophagitis in adults, but the enhanced IL-5 expression to foods and aeroallergens suggest that both types of allergens may play a role in the pathogenesis of eosinophilic esophagitis in adults. One case report by Anton Ramirez *et al.* [34] found the removal of egg from the diet of a 37-year-old man led to an improvement of symptoms and a decrease in peripheral blood eosinophilia, indicating that foods can be causative in some adults.

Most of the studies examining treatments in adults have involved medical intervention [35]. This potential bias is caused by the difficulty of adults accepting strict diets of only a few foods, and compliance with a restricted diet. Remedios *et al.* [36] examined 26 adult patients with eosinophilic esophagitis, 19 given swallowed fluticasone propionate 250 µg two puffs twice a day for 4 weeks; seven patients refused therapy. All treated patients showed an improvement of symptoms, a histological improvement in the distal esophagus, and complete normalization in four patients. The treatment was well tolerated except for three patients who developed mild esophageal candidiasis. A randomized placebo-controlled trial on the treatment of eosinophilic esophagitis was recently performed in children with fluticasone propionate 220 µg two puffs twice a day in 36 patients (aged 3–18 years) for 3 months, with 21 patients on active therapy and 15 patients on placebo [37]. Fifty per cent of patients on fluticasone propionate had a histological improvement to normal levels compared with 9% on placebo. Also, in that trial two patients had complete clearing on an elimination diet before randomization. The improvement with fluticasone propionate compares poorly with the greater than 90% improvement in pediatric patients with diet therapy, indicating that diet therapy is the optimal therapy for pediatric eosinophilic esophagitis at present, and should be further explored in adults.

Conclusion

Eosinophilic esophagitis is a rapidly more recognized and diagnosed disorder, with increasing numbers of papers being published in the past 5 years. The role of food allergies has been debated in this field over the past few

years. In pediatrics, however, it has become clear that the majority of patients (88–100%) show complete normalization on an elemental diet. If all the patients are summed up, 97% improve on an elemental diet indicating that food allergies are contributing to eosinophilic esophagitis in the majority of pediatric patients, but we cannot currently confirm that adults will be the same. Young adults (15–18 years) appear to respond to diet in an identical manner to younger children, suggesting that older adults would be the same.

The identification of the individual foods causing symptoms has not, however, been perfected. Removal of the six most common foods in eosinophilic esophagitis led to a 74% improvement in patients with pediatric eosinophilic esophagitis compared with 77% of patients who resolved on diet, based on the elimination of the foods found on PSTs and APTs. The elimination diet based on foods had a much lower endpoint for tissue eosinophilia (1.1 eosinophils per high-power field) compared with the six-food elimination diet (13.6 eosinophils per high-power field). In addition, in the patients who showed a marked improvement in eosinophil counts to less than 20 eosinophils per high-power field, six-food elimination improved to 83 and 90% on the PST and APT elimination diet.

In conclusion, dietary therapy is the optimal therapy for eosinophilic esophagitis in pediatric populations. Palatability, however, and the need for sufficient calories remain major obstacles in dietary therapy. Limited information is available in adults.

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 (p. 292).

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