Published in final edited form as:

Curr Gastroenterol Rep. 2016 November ; 18(11): 58. doi:10.1007/s11894-016-0531-z.

Eosinophilic Esophagitis From an Allergy Perspective: How to Optimally Pursue Allergy Testing & Dietary Modification in the Adult Population

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Abstract

Eosinophilic esophagitis (EoE) is a clinicopathologic condition characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation. In adults, the three most common treatment options are swallowed steroids, elimination diets, and periodic esophageal dilations. Many different elimination diets have been studied in adults, including elemental diets, allergy testing-directed diets, and empiric elimination diets. This article will review the existing data on these dietary therapies and will propose an approach to dietary management in adult EoE.

Keywords

Eosinophilic esophagitis; Six-food elimination diet; Skin prick testing; Food-specific IgE

Introduction

Eosinophilic esophagitis (EoE) is defined by consensus guidelines as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Similar to other allergic conditions, the prevalence of EoE appears to be increasing [2] and is now estimated to affect 10–57 per 100,000 individuals in the USA and Europe [2–5], and recent reports demonstrate emerging cases in other areas of the world [6–10]. This condition affects both children and adults, and while the underlying histopathology appears to be similar, adults present more frequently with dysphagia, food impaction, and fibrostenotic disease than children [11]. Furthermore, while both children and adults are frequently diagnosed with other comorbid allergic conditions, early studies suggested that pediatric and adult EoE were driven by food and aeroallergen exposure, respectively [11]. While most initial dietary

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This article is part of the Topical Collection on *Esophagus*

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

studies were thus first performed in children, recent publications have similarly demonstrated the effectiveness of food elimination diets in adult EoE (Table 1).

For adults with EoE, the current treatment options are proton pump inhibitors, swallowed steroids, elimination diets, and periodic esophageal dilations. There are benefits and limitations to each of these therapies, which are extensively reviewed elsewhere [12–16], and this review will focus on the recent evidence for pursuing dietary elimination in adults. In comparison to the other available treatment options, dietary therapy has the potential to eliminate the underlying cause of inflammation, which has been shown to lead to long-term remission in patients when trigger foods are identified [17•]. Furthermore, it is not associated with the potential side effect profile of chronic steroid use, such as adrenal suppression [18], the development of cataracts [19], and esophageal candidiasis [20, 21]. As there are also limitations to this therapy, which will be discussed, the ultimate decision should be tailored to the patient's background and preferences, provider experience, and the availability of local resources.

The Role of Allergy in Eosinophilic Esophagitis

Since the time of its initial description, EoE has been considered an allergic disease. The majority of patients with EoE have been found to have concomitant allergic conditions, such as asthma, rhinitis, IgE-mediated food allergy, urticaria, and/or atopic dermatitis [22–24]. Previous studies have further demonstrated seasonal variation in EoE diagnosis [25–27], suggesting a role for aeroallergen exposure in the underlying pathogenesis in some patients. In addition, most EoE patients have high levels of total IgE and the presence of aeroallergen-specific and food-specific IgE [11, 28–30], an immunoglobulin that cross-links receptors on mast cells and basophils and is intricately involved in the manifestations of allergic disease. The inflammation characteristic of EoE is dominated by eosinophils, mast cells, and Th2 cytokines, such as IL-4, IL-5, and IL-13, which are characteristics of allergic inflammation [31–33]. Furthermore, EoE appears to be associated with epithelial barrier defects [31, 34] and perturbations in innate immunity [35, 36], which are important features of atopic dermatitis [37]. Finally, many studies over the past 20 years, which will be described, have demonstrated a role for food antigens in the development of this allergic inflammation. Although IgE may not be the relevant mechanism underlying EoE, there is strong evidence that this disease is primarily caused by exposure to foreign antigens, most of which are allergens.

Dietary Therapy in Eosinophilic Esophagitis

Elemental Diet

The role of food antigens in the pathogenesis of EoE was first suggested in a seminal study by Kelly et al. in 1995, in which ten children with esophageal eosinophilia resistant to proton pump inhibitor (PPI) therapy were treated with an elemental diet for a minimum of 6 weeks [38]. The authors found that all of the treated children reported an improvement in their symptoms, and 90 % had histologic improvement as well (< 15 eosinophils/high-powered field [hpf]). Since this time, additional studies have confirmed this high rate of

improvement on elemental diet in children [39–41], and this therapy is now considered an accepted, albeit cumbersome, means of treatment for pediatric EoE.

The role of elemental diets in treating adults with EoE was first examined in 2013 by Peterson et al. [42•]. In that study, 18 adults with confirmed EoE were given EleCare (30 kcal/oz dilution) for 2–4 weeks. While there was not a significant decrease in symptoms on the elemental diet, histologic findings improved in 17/18 patients (92 %). The authors of this study, however, noted that compliance of the elemental diet was very low in this population (33 % dropped out), and many patients lost a significant amount of weight.

While elemental diets have been shown to be an effective treatment in adults with EoE, many considerations limit their long-term use. First, the formulas are costly and are not universally reimbursed by health insurance companies. Furthermore, they are unpalatable, and their use requires significant lifestyle modifications in adults. The use of elemental diets may thus be limited to achieving disease remission prior to food reintroduction or when other treatment options have failed [14].

Allergy Testing-Directed Diets

The recognition that food antigens may drive the allergic inflammation seen in EoE prompted many investigators, mainly allergists, to examine whether conventional allergy testing could identify trigger foods for this condition. These studies involved the use of skin prick testing (SPT), atopy patch testing (APT), serum food-specific IgE testing (sIgE), and component-resolved diagnostics (CRD), which will be described.

Overview of Allergy Testing—Allergy testing is used to assess two distinct types of hypersensitivity reactions: (1) IgE-mediated (immediate) and (2) non-IgE cell-mediated (delayed). The presence of IgE can be detected through either SPT or the quantification of sIgE. The presence of IgE to an allergen is referred to as “allergic sensitization.” Prick testing assesses both the presence and the function of IgE antibodies that are bound to mast cells in the skin. These tests can be performed using commercially available food extracts or fresh food. Serum IgE testing, in contrast, assesses the presence and quantity of sIgE that is circulating in the blood. As IgE is typically bound to receptors on mast cells and basophils, only a fraction of the total IgE is found in circulation. Serum IgE antibodies were previously assessed by RAST (radioimmunoassay), but this method has been replaced by a non-radioactive sandwich immunoassay. While there are different manufacturers who perform this newer assay, the results between the various systems are not comparable [43], and published predictive values for immediate food reactions have been based on the Phadia ImmunoCAP system (Thermo-Fisher/Phadia, Kalamazoo, MI). For food allergy, both of these tests are validated in assessing immediate reactions, such as hives, angioedema, and anaphylaxis. It is important to note that false-positive tests are common with both of these testing modalities, so they should be used only in combination with a careful clinical history, preferably under the care of a specialist.

A more recent technique used to assess the presence of IgE antibodies is called CRD. Allergen extracts are complex mixtures of proteins and glycoproteins, and the individual proteins, which are the targets for IgE antibodies, are often referred to as components. In

recent years, CRD, which relies on purified native or recombinant allergens, has enabled the assessment of sensitization to these individual proteins [44]. This technique is now frequently used in the diagnosis of IgE-mediated peanut allergy [45–47] and has also been studied in EoE, as described below.

Assessment of cell-mediated (delayed) reactions can be done through the use of atopy patch testing (APT). This testing has been most rigorously studied in chemical and allergic contact dermatitis, as well as food involvement in atopic dermatitis [48–50]. As opposed to commercially available patch tests for chemicals, APT to foods involves setting fresh foods in aluminum Finn chambers and placing them on a patient's back for 48 h. The skin is then examined at 48 and 72 h for evidence of erythema and vesicles. As the inflammation associated with EoE typically occurs within days, rather than within minutes or hours, after food reintroduction [51•, 52], many investigators have assessed the utility of APT in EoE.

Skin Prick Testing -and Atopy Patch Testing-Based Diets—In 2002, Spergel et al. performed the first prospective study examining allergy testing-directed diets in children. In this study, 26 children underwent SPT and APT and were then placed on either testing-directed diets or elemental formula for at least 6 weeks [24]. Of the 24 children who were followed, 75 % had symptom improvement, and all had significant improvement in their esophageal biopsies (>50 % decrease in eosinophils/hpf). This same group updated their findings in subsequent publications, and their most recent study in 2012 demonstrated a success rate of 53 % for testing-directed diets [53, 54]. These authors further found a low specificity and low negative predictive value (NPV) for SPT and APT to milk [55], and they found that the success rate increased to 77 % when empiric milk elimination was added to the dietary regimen [54]. While these results were encouraging, other groups have demonstrated variable success with testing-directed diets in children [56–58].

Studies examining SPT- and APT-directed diets in adults are more limited. In 2006, Simon et al. described six adults with EoE who were sensitized to grass, rye, and wheat. These individuals avoided rye and wheat for 6 weeks, and only one patient had improvement in their clinical symptoms [59]. In 2012, Molina-Infante et al. performed a prospective study in which 22 consecutive adults with EOE underwent SPT, APT, and prick-prick testing to 26 different foods [60•]. Seventeen of these patients then followed an allergy testing-directed diet for 6 weeks, and only five (29 %) achieved histologic remission (< 15 eosinophils/hpf). Finally, in 2014, Wolf et al. performed a retrospective review of their adult EoE clinic population and similarly found that only 32 % of patients following an elimination diet based on SPT and clinical history achieved histologic remission (< 15 eosinophils/hpf) [61]. These last two studies were included in a recent systematic review, which demonstrated a remission rate of only 32.2 % (95 % CI 17.8–48.7 %) for this therapy in adults [62]. Taken together, these studies demonstrate that SPT- and APT-directed diets appear to have limited utility for achieving remission in adults with EoE.

Serum-Specific IgE Diets—Patients with EoE have been shown to be sensitized to a larger number of foods when assessed by sIgE than by conventional SPT [29, 63•], and early studies suggested that elimination diets based on sIgE were effective in achieving disease remission in adults with EoE [64, 65]. In 2014, Rodriguez-Sánchez et al. assessed the

efficacy of sIgE-directed diets in a prospective study of 43 adults with EoE [66•]. Those patients with positive sIgE results ($n = 26$, defined as ≥ 0.10 kU/L) were started on a targeted elimination diet, whereas those with negative sIgE results were started on the six-food elimination diet (SFED, discussed). The authors found that 73.1 % of adults achieved histologic remission with the sIgE-directed diet, as compared to 52.9 % on the SFED, and this was associated with fewer endoscopies and fewer eliminated foods. The authors further found that sIgE testing had a high accuracy in identifying cow's milk as a trigger food. While these results have not yet been replicated, the findings suggest that in those with food sensitization identified by sIgE, a targeted elimination diet may be a viable treatment option.

Component-Resolved Diagnostic Diets—Many allergenic molecules are cross-reactive between foods and aeroallergens, and previous studies have suggested that food sensitization in adults with EoE may be due to aeroallergen (particularly birch) cross-reactivity [64, 67]. A prospective study assessing CRD-guided diets in adults with EoE was thus initiated, but the trial was prematurely terminated due to a low response rate (7 %) at the interim analysis [68•]. Recent studies have demonstrated poor correlation between food CRD and sIgE assessment (ImmunoCAP) in patients with EoE [63•], possibly because of assay inhibition by IgG4 blocking antibodies [69], which further limits its use in designing elimination diets for EoE. These studies, however, were all based on one particular method of CRD (Immuno Solid-phase Allergen Chip, Thermo-Fisher/Phadia), and it is unclear if other methodologies would have similar limitations.

Limitations of Allergy Testing-Directed Diets—Recent studies, as previously demonstrated, have consistently reported the low efficacy of allergy testing-directed diets. These testing modalities may be limited in EoE because they are based on the presence of IgE, which now appears to have little role in the pathophysiology of EoE. This concept was best demonstrated in recent studies using omalizumab (a monoclonal antibody blocking IgE), which was found to be ineffective in improving clinical symptoms or histology in both children and adults with EoE [70, 71•]. Recent studies have further suggested that EoE may be an IgG4-associated disorder, as total [71•] and food-specific [72] IgG4 levels are higher in esophageal homogenates in patients with EoE compared to controls. Furthermore, dense infiltrates of IgG4-producing plasma cells have been identified in the deep lamina propria of the esophagus in patients with EoE [71•]. In this model, IgE may be produced in parallel with IgG4, as B cells that produce IgG4 can switch to producing IgE, but not vice versa [69]. These data recently prompted several authors to state that EoE is not an IgE-mediated food hypersensitivity [37], though the underlying immunologic pathophysiology remains unclear.

Empiric Elimination Diets

Given the limited efficacy of allergy testing-directed diets, many groups have examined the use of empiric elimination diets, in which the foods most commonly associated with childhood food allergy and EoE are avoided without reliance on allergy testing. In these protocols, patients undergo a baseline endoscopy and biopsy and then follow a strict elimination diet for 6 weeks. The endoscopy and biopsies are then repeated, and histologic remission is assessed. If the patients are in remission, they begin a systematic reintroduction

of foods for 2–6 weeks, depending on the study, with repeat endoscopies to determine the trigger food(s).

Six-Food Elimination Diet—The first elimination diet was proposed in 2006 by Kagalwalla et al. [73]. This diet was developed to eliminate the six most common foods associated with IgE-mediated food allergy [74] and EoE (milk, soy, egg, wheat, peanut/tree nuts, and seafood). In this study, 35 children with EoE were prescribed the SFED, and 26 (74 %) achieved histologic and clinical remission (< 10 eosinophils/hpf). Given the success of this study, two groups proceeded to examine the efficacy of the SFED in adults. In 2012, Gonsalves et al. reported the results of the first prospective study, in which 50 adults with EoE were treated with the SFED for 6 weeks [51••]. Similar to the pediatric study, the authors found that 70 % of patients had histologic remission (< 10 eosinophils/hpf), and 94 % had symptom improvement. Twenty patients then underwent food reintroduction, with confirmatory histologic assessment, and wheat and milk were identified as the most common triggers.

Shortly thereafter, the second prospective study was published by Lucendo et al. in Spain, in which 67 adults with EoE were treated with a SFED [17•]. In contrast to the previous study, this group also eliminated rice, corn, and all legumes. The authors found that 73 % of patients had improvement in their symptoms and histology (< 15 eosinophils/hpf) with this diet, and wheat and milk were identified as the most common food triggers. Allergy testing (SPT and sIgE) was also performed and was not found to be predictive of the food trigger in this study. After 2 years, 30 % of responders maintained long-term remission.

Since this time, three additional comparison studies have demonstrated lower success rates with the SFED (52–56 %) in adults [61, 75, 66•]. These studies, however, differed from the those previously mentioned in a number of ways. In the first study, Rodriguez-Sanchez et al. only prescribed the SFED to adults who were negative on sIgE testing, which may have led to selection bias [66•]. In the remaining two studies [61, 75], consultation with a registered dietician was not part of the study protocol, which may have influenced compliance with the elimination diet. While these results are not as encouraging as the initial studies of the SFED, they may be more indicative of real-world implementation.

Four-Food Elimination Diet—Based on the initial studies of the SFED in adults, in which milk, wheat, egg, and soy/legumes were the most common triggers [17•, 51••], Molina-Infante et al. prospectively examined the efficacy of eliminating solely these four foods in adults [76•]. In this study, 52 patients with EoE avoided these four foods for 6 weeks and underwent repeat endoscopies. The authors found that 28 patients (54 %) achieved histologic remission (< 15 eosinophils/hpf). Among the non-responders, 19 patients subsequently underwent the SFED, and 31 % achieved histologic remission. While not as effective as the SFED, the FFED has the advantages of eliminating fewer foods, shortening the duration of treatment to identify the causative food, and minimizing the number of endoscopies needed during the food reintroduction phase.

Milk Elimination Diet—As milk has been persistently identified as the most frequent food associated with EoE in both children [52, 54] and adults [17•, 76•], recent studies have

examined whether solely milk elimination could be an effective treatment for EoE. In 2012, Kagalwalla et al. performed a retrospective review of their clinic population, in which 17 children were prescribed a cow's milk elimination diet [77]. Clinical and histologic remission (< 15 eosinophils/hpf) was achieved in 11 (65 %) of these children. Similarly, a recent study comparing empiric cow's milk elimination to swallowed fluticasone demonstrated clinical and histologic improvement in 64 % of children, though this study was limited by the fact that all patients were treated with a PPI [78]. Interestingly, individuals with confirmed cow's milk-mediated EoE have been shown to tolerate cow's milk-based hydrolyzed formula [79] and baked milk [80], and recent studies indicate that children who have histologic improvement with milk elimination have lower levels of IgE to milk than those who did not respond (0.50 versus 2.6 IU/mL, $p = 0.002$) [81]. These findings may improve adherence and nutritional intake in these patients and raise further questions about the underlying pathophysiology of this disease. To our knowledge, no studies have yet evaluated empiric milk elimination diets in adults.

Limitations of Empiric Elimination Diets—Initial studies of empiric elimination diets, in particular the SFED, demonstrated higher efficacy rates in achieving histologic remission than allergy testing-directed diets. However, recent studies have not been as successful. These diets are further limited by the long duration required for both food avoidance and then subsequent reintroduction and the high number of endoscopies required to verify the trigger foods. Furthermore, while previous authors have stated that their success rates are not dependent on support from a registered dietician [14], other authors assert that guidance from a nutritionist is a necessary practice in their patients following an elimination diet [15], which may limit the widespread use of this practice.

Our Approach to Implementing Allergy Testing and Dietary Modification in Adult Eosinophilic Esophagitis

In motivated patients who meet the criteria for EoE, we offer dietary modification as an alternative to swallowed steroids and periodic endoscopic dilations (Fig. 1). While we recognize that the following approach is different than that which has been previously reported at other centers [14, 15], this approach incorporates findings from recent studies on sIgE testing and has shown initial promise in our patient populations. After a thorough dietary history to elucidate common exposures, we measure sIgE to the foods most commonly associated with EoE (milk, wheat, egg, soy/legumes, peanut, tree nuts, fish, and shellfish), as well as those that are frequently consumed in the patient's diet. In patients found to have positive sIgE (> 0.10 kU/L) to foods, we initiate a targeted elimination diet for 6 weeks, under the guidance of a registered dietician. In those who have either negative sIgE testing or ≤ 8 positive tests, we recommend the SFED for 6 weeks, similarly under the guidance of a nutritionist.

After 6 weeks, the patients undergo repeat endoscopies with biopsies. If they have achieved clinical and histologic remission (< 15 eosinophils/hpf), then foods are reintroduced every 2 weeks, with repeat endoscopies every 4 weeks to identify the trigger foods, as has been previously described [15]. If patients continue to have symptoms or have not achieved

histologic remission, it is possible that the continued inflammation is a result of (a) dietary non-compliance, (b) cross-contamination of allergens in consumed foods, (c) consumption of a trigger food that has not been identified, or (d) persistent exposure to potential aeroallergen triggers. After a careful discussion about dietary non-compliance and cross-contamination with a nutritionist, motivated patients may elect to pursue either the SFED (if previously on a sIgE-directed diet), empirically eliminate other potential allergenic foods that are regularly consumed, or switch to elemental formula. At this time, other therapeutic options are also discussed, and some patients elect to switch to swallowed topical steroids or periodic endoscopic dilations.

Conclusions

Recent studies have demonstrated that dietary modification is a viable treatment option for adults with EoE. Whereas diets based on SPT and APT do not appear to be as efficacious in adults as they are in children, both sIgE-directed and empiric food elimination diets currently show promise. Dietary therapy has the benefit of addressing the underlying cause of allergic inflammation, which can lead to long-term remission in many patients, and limiting long-term exposure to corticosteroids and PPIs. This therapy is currently hindered, however, by the limited efficacy of allergy testing, the need for repeat endoscopies to determine the causative food(s), and the difficulty of practically implementing dietary modifications in adults. Future research aimed at improving the use of IgE, and possibly IgG4, assays to identify food triggers and developing non-invasive techniques to monitor disease activity and optimize therapy are thus clearly needed.

Acknowledgments

Conflict of Interest ECM reports grants from the National Institutes of Health (grant number 1KL2TR001077) and receipt of the AAAAI/ARTrust/FARE/Howard Gittis Junior Faculty Research Award during the conduct of the study. TPM reports grants from the National Institutes of Health and non-financial support from Phadia/Thermo-Fischer during the conduct of the study.

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Fig. 1.

Proposed approach to dietary management of EoE in adults

Table 1

Studies examining dietary interventions in adults with EOE

Study (year)	No. of subjects (age range)	Duration of diet	Histologic response [<i>n</i> (%)]	Additional findings
Elemental diet				
Peterson KA et al.(2013) [42••]	29 (19–58)	2–4 weeks	17/18 (94 %) ^a	<ul style="list-style-type: none"> High dropout rate (33 %) 8 patients lost >3 kg
Skin testing directed				
Simon D et al. (2006) [59]	6 (19–43)	6 weeks	N/A	<ul style="list-style-type: none"> Diet eliminating wheat, barley, and rye, based on allergy testing Symptomatic improvement in 1 patient Did not look at histology
Dominguez-Ortega J et al. (2009) [64]	1 (32)	4 months		<ul style="list-style-type: none"> Case report of a patient with EOE, found to be triggered by cross-reactive profilins in fruits and vegetables.
Gonzalez-Cervera J et al. (2012) [65]	3 (27–37)	6 weeks	3/3 (100 %)	<ul style="list-style-type: none"> Case series of 3 patients who were successfully treated with food elimination (1 SFED, 2 allergy testing directed)
Molina-Infante J et al. (2012) [60•]	22 (18–62)	6 weeks	5/15 (33 %) ^b	<ul style="list-style-type: none"> Diet based on SPT, APT, and prick-prick testing
Component directed				
Van Rhijn BD et al. (2015) [68•]	95 (27–47)	6 weeks	1/15 (7 %) ^c	<ul style="list-style-type: none"> Trial was prematurely terminated because only 1/15 patients showed improvement in the interim analysis
Six-food elimination diet (SFED)				
Gonsalves N et al. (2012) [51••]	50 (19–76)	6 weeks	39/50 (78 %) ^a	<ul style="list-style-type: none"> First study of SFED in adults. 94 % of patients had clinical remission. Most common triggers: wheat and milk SPT only predicted trigger foods in 13 %
Lucendo AJ et al. (2013) [17•]	67 (17–60)	6 weeks	49/67 (73 %) ^d	<ul style="list-style-type: none"> Also excluded rice, corn, and legumes 15 patients demonstrated remission at 2 years Most common triggers: milk, wheat, eggs, and legumes Minimal weight loss noted
Four-food elimination diet (FFED)				
Molina-Infante J et al. (2014) [76•]	52 (16–68)	6 weeks	28/52 (54 %) ^d	<ul style="list-style-type: none"> SFED successful in 31 % of non-responders

Study (year)	No. of subjects (age range)	Duration of diet	Histologic response [<i>n</i> (%)]	Additional findings
Diet comparisons				<ul style="list-style-type: none"> Milk was the most common trigger (50 %)
Rodriguez-Sanchez J et al. (2014) [66•]	43 (mean 33)	6 weeks	SFED: 9/17 (52.9 %) ^b +sIgE: 19/26 (73.1 %) ^b	<ul style="list-style-type: none"> Compared SFED to sIgE-targeted diets. Fewer foods were removed, and fewer EGDs were required in sIgE-directed diet. Most common triggers: milk, wheat, egg, and legumes
Wolf WA et al. (2014) [61]	31 (mean 36)	6 weeks	SFED: 5/9 (56 %) ^d +SPT: 6/22 (27 %) ^d	<ul style="list-style-type: none"> Retrospective study of clinic cohort Milk, egg, and wheat were most common trigger foods No predictors of response to dietary intervention identified
Philpott H et al. (2016) [75]	82 (mean 34)	3 months	SFED: 29/56 (52 %) ^d Budesonide: 23/25 (92 %) ^d	<ul style="list-style-type: none"> Prospective, observational study in Australia comparing SFED to swallowed budesonide

+sIgE food-specific IgE, *SPT* skin prick testing, *APT* atopy patch testing

^a Histologic response defined as <50 % of pretreatment eosinophils

^b Histologic response defined as <14 eosinophils/hpf and clinical improvement

^c Histologic response defined as <10 eosinophils/hpf

^d Histologic response defined as <15 eosinophils/hpf