Eosinophilic Esophagitis: Is It All Allergies?

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Eosinophilic esophagitis (EE) is an increasingly recognized disorder in the adult population, most often manifested by symptoms of dysphagia and food impaction. Mechanisms involving eotaxin-3, interleukin 5, and signal transducer and activator of transcription 6 have been studied and may represent future therapeutic targets. Patients commonly have a personal and family history of atopy, and both food allergies and aeroallergens have also been investigated as triggers of EE. Traditional allergy-testing methods, including skin prick testing and specific IgE testing, have been used to identify food and environmental allergies. However, new studies suggest that patch testing could add to diagnostic accuracy in EE because the disorder might not be a classic type I allergic response. Although studies of treatment of adults with EE have thus far focused on swallowed fluticasone proprionate, many trials in children have assessed the efficacy of food elimination and elemental diets. These diets, which have been extremely successful in reducing symptoms, have also been shown to induce histological improvement and remission. No similar studies have been conducted in adults; the tolerability of such an intervention may prove more difficult in this population. This article reviews the underlying pathophysiology of EE and describes evolving options for more accurately identifying food and environmental allergies. We also discuss the pediatric trials using food elimination and avoidance diets and suggest that this type of intervention may be an important area of future research in the adult population.

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EE = eosinophilic esophagitis; EGD = esophagogastroduodenoscopy; IL = interleukin; PPV = positive predictive value; RAST = radioallergosorbent test; STAT-6 = signal transducer and activator of transcription 6; T_H2 = T helper type 2

Eosinophilic esophagitis (EE) is a relatively recently described disorder characterized by an eosinophilic infiltration of the esophagus. The underlying etiology of this disorder is poorly understood, as is its natural history. There is debate over whether the disease is an allergic or immunologic condition or whether it is a manifestation of gastroesophageal reflux disease.[1] The prevalence of this disorder has been difficult to define and seems to be increasing as EE becomes more recognized. The prevalence of EE in Hamilton County, OH, was estimated to be 4 cases per 10,000 children at the end of 2003.[2] A population-based study from Switzerland suggested an increase in prevalence of EE among adults from 2 per 100,000 in 1989 to 23 per 100,000 in 2004.[3]

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Most adult patients with EE who are seen by internists are white middle-aged men.[4] However, this disorder was first described in the pediatric population, and many treatment recommendations have been influenced by studies in children. The differences in symptoms and treatments between adults and children remain a subject of debate.

Although EE is seen in both pediatric and adult populations, it remains unclear whether EE is a single entity or whether children and adults are affected by different subtypes of the disorder. The natural history of EE may also differ in these 2 populations. Symptoms in adults with EE include solid food dysphagia, chest pain, and food impaction. Dysphagia is less frequent in children, who instead tend to present with nausea and vomiting, weight loss, anemia, and failure to thrive.[4,5]

Patients in both groups often have a history of inhalant allergies, food allergies, eczema, or atopic dermatitis. Up to 80% of children have been reported to have a coexisting allergic disorder[5-8] vs 40% to 60% of adults.[7,9] A strong family history of atopic diseases has been reported in up to 60% of pediatric patients.[8]

The association between a history of atopy and EE has sparked interest in the role of allergies in the pathogenesis of the disease. Elegant studies have implicated both food allergies and aeroallergens in the development of EE. Whereas the usual treatment of EE in adults has been either topical or systemic corticosteroids, studies in children have shown impressive results in treating this condition using both restrictive and elemental diets. Dietary manipulation has not yet been evaluated in adults but represents an important area for future EE research.

We review the underlying immunology of EE, along with the evidence for the role of food allergies and aeroallergens in its development. We also discuss advances in the diagnosis of allergic disorders and review the successes of dietary restriction in treating children with EE.

PATHOPHYSIOLOGY

Role of Eosinophils in the Esophagus

The esophageal mucosa is unique in the gut because it is normally devoid of any resident eosinophils. However, eosinophils accumulate in disease states, in lower levels in gastroesophageal reflux disease, and in greater numbers in EE. Further, adult patients with EE usually do not have elevated eosinophils or IgE levels in peripheral blood specimens.[10]

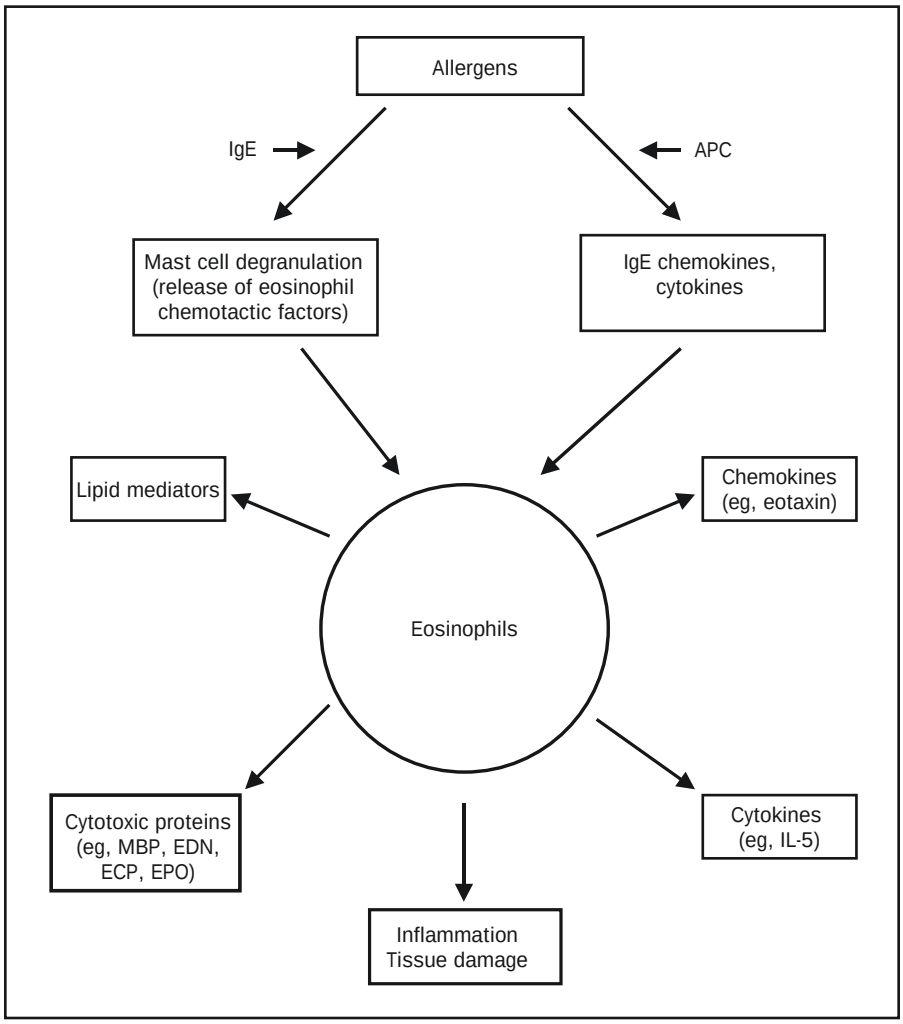

FIGURE 1. Basic pathway of eosinophilic activation and degranulation. In a sensitized individual, allergens react with IgE, causing mast cells to migrate to the esophagus. Mast cell degranulation occurs, causing release of eosinophil chemotactic factors, which induce eosinophil migration and degranulation. Eosinophilic granules release a variety of chemokines, cytokines, and cytotoxic proteins, which ultimately cause inflammation and tissue damage. In addition, the toxic granule proteins cause further mast cell degranulation, which perpetuates the cycle. APC = antigen-presenting cell; ECP = eosinophil cationic protein; EDN = eosinophil-derived neurotoxin; EPO = eosinophil peroxidase; IL = interleukin; MBP = major basic protein

In previously sensitized individuals, IgE interacts with a food allergen or aeroallergen, leading to resident mast cell degranulation. Chemokines, histamine, and eosinophilic chemotactic factors are released from the mast cells.[11,12] These factors induce eosinophil migration and degranulation. Among the products released by eosinophil granules are major basic protein, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin[13] (Figure 1).

Effect of Eosinophils on the Esophagus

In general, eosinophils have proinflammatory effects, upregulating adhesion systems, mediating cell trafficking, and releasing cytokines, chemokines, and lipid mediators.[13,14] The cationic proteins that are released cause tissue damage and dysfunction and can ultimately result in fibrosis. The toxic granule proteins also induce further mast cell degranulation, and the cycle of inflammation and tissue damage continues.

When released from eosinophils, major basic protein has been found to induce smooth muscle contraction through actions on muscarinic M_2 receptors.[13] This contraction may lead to the sensation of dysphagia in EE, as well as cause episodes of food impaction. These constrictive symptoms from smooth muscle contraction in the esophagus may be mechanistically similar to the bronchoconstriction responsible for symptoms in asthma.[15]

Eosinophil Recruitment to the Esophagus

Given that the normal esophagus is usually devoid of eosinophils, a possible mechanism of their recruitment to the esophagus involving interleukin (IL) 5 has been proposed. A cytokine produced by T helper type 2 (T_H2) lymphocytes,[16] IL-5 primes eosinophils to react to chemoattractants (eg, eotaxin) and promotes their development, activation, migration, and effector functions.[6,14,17] Furthermore, IL-5 increases levels of eotaxin, resulting in a perpetuating cycle of chemoattraction. In patients with EE, esophageal IL-5 is overexpressed, and systemic IL-5 overexpression may promote eosinophil migration to the esophagus.[17] Increases in mast cells and T cells in the esophagus of patients with EE have also been documented.[15]

Eotaxin is a specific eosinophilic chemotactic factor that has a role in promoting eosinophil accumulation and adhesion.[13] It is thought to be involved in the recruitment of eosinophils to the gastrointestinal tract. It promotes adhesion of eosinophils to vascular cell adhesion molecule 1, an adhesion molecule that is expressed on endothelial tissues. Eotaxin, specifically eotaxin-3, has been found to be overexpressed in patients with EE.[18]

The cytokine IL-13 upregulates IgE, is important for eosinophil recruitment and survival, and activates adhesion systems.[13] Studies have shown IL-13 dysregulation in allergic disorders such as asthma, atopic dermatitis, and allergic rhinitis. Further, after direct delivery of IL-13 to the lung, an eosinophilic infiltration, as well as epithelial hyperplasia, developed in the esophagus.[17] Mishra and Rothenberg[17] showed the crucial role that IL-5 and signal transducer and activator of transcription 6 (STAT-6) play in the development of EE. When STAT-6 and IL-5 transgenic knockout mice were then studied, EE did not develop after the intratracheal administration of IL-13 in these strains.

FOOD ALLERGIES IN PATIENTS WITH EE

Rothenberg et al[6] reported that approximately 80% of their pediatric patients with EE had a positive skin test result to a panel of food allergens and aeroallergens. Food allergies can be identified by skin prick testing, skin patch testing, specific IgE testing, and oral challenge. However, a direct correlation does not always exist between a positive food allergy test result and the development of EE or its response to treatment. Some patients continue to have symptoms even after foods that were positive on traditional allergy testing are eliminated, perhaps because of either sensitization to the food or allergies to multiple foods.

Food allergies, which have been noted in a number (19%-73%) of children with EE, are less prominently reported in adults (13%-25%).[9] In one study, skin prick tests or specific IgE tests were positive in 53% to 73% of children and 40% of adults,[9] with high-protein foods being most problematic and fruits and green vegetables less likely to cause symptoms.[19] Foods that have been commonly implicated in food allergies include milk, eggs, soybeans, corn, wheat, chicken, and nuts.

Food reactions come in different forms, including intolerances and true hypersensitivity reactions.[20] Intolerances, which include reactions to toxins or poisons, can be due to metabolic or pharmacological reactions. Allergies can be immediate or delayed in onset and either systemic or localized.

An IgE-mediated allergic reaction (such as that which occurs with peanuts) induces systemic symptoms (eg, anaphylaxis), and patients with such a reaction will have positive skin prick and specific IgE test results. These type I reactions are histamine mediated and usually occur within minutes after exposure to the allergen. The symptoms seen during a type I allergic reaction may include rash, pruritus, hives, swelling, angioedema, or anaphylaxis. However, the food allergy in EE may not be a pure IgE-mediated reaction, explaining why allergies in EE are not always identified by traditional skin prick or specific IgE testing.[9]

Alternatively, the food allergy in EE may be a delayed hypersensitivity reaction, which is an immunologically mediated reaction to a food unrelated to any physiologic effect.[20] It is thought that EE is a type IV cell-mediated allergic reaction, not a type I IgE-dependent reaction. Mishra et al[16] used a mouse process to show the involvement of T cells of the T_H2 $CD4^+$ phenotype. T helper type 2 reactions can occur hours to days after antigen exposure, making identification of the culprit food even more difficult.[12] On the basis of allergy testing results, EE is thought to be a polygenic allergic disorder, characterized by a mixed IgE- and non–IgE-mediated reaction.[21,22]

FOOD ALLERGY TESTING METHODS

The presence of food allergies can be detected by specific IgE testing (including radioallergosorbent testing [RAST], skin prick testing, and skin patch testing. Skin prick and specific IgE tests, which tend to denote type I allergic reactions, are difficult to correlate with EE in adults. More recently, Spergel and Brown-Whitehorn[23] reported the use of skin patch testing of food allergies in the evaluation for EE. Atopy patch testing is useful in the diagnosis of non–IgE-mediated immune responses, of which T cells are the major mediators. Eosinophilic esophagitis may be a combined IgE-mediated and non–IgE-mediated reaction, and further research is needed to identify the most effective allergy testing method for this condition (Table 1).

TABLE 1. **Types of Allergies in Eosinophilic Esophagitis and Their Corresponding Testing Methods***

Predominant mediator	Type of reaction	Specific IgE	Skin prick testing	Atopy patch testing
IgE	Type I, immediate	+	+	+
T_H2	T_H2, delayed	–	–	+

*T_H2 = T helper type 2.

Specific IgE Testing

Specific IgE testing is performed in vitro on a sample of a patient's blood. The test is designed to measure the number of specific IgE antibodies to a panel of various allergens. Because the antibodies in this case are IgE, specific IgE testing detects allergens against which a patient would have a type I (IgE-mediated) allergic reaction. Specific IgE testing can be performed while the patient is taking antihistamines.

Skin Prick Testing

Skin prick testing involves placing a drop of a commercial extract of a specific allergen on the skin, then pricking the skin through the drop with a bifurcated needle to absorb the extract.[24] Reactions are recorded by measuring a wheal-and-flare reaction after 15 minutes. A positive test result shows a wheal of greater than 3 mm. Dauer et al[25] reported positive skin prick or RAST test results in 28 (60%) of 47 patients with EE, most commonly to milk, peanuts, and soybeans. Of their patients, 52% had elevated IgE levels, with only 32% having peripheral blood eosinophilia.

Skin Patch Testing

Skin patch testing ensures prolonged contact of the allergen to the skin. This established method has only relatively recently been applied to the diagnosis of food allergies. The concentration of food in the skin patch test should be similar to the concentration that is ingested. Spergel and Brown-Whitehorn[23] diluted 2 g of dry food with 2 mL of isotonic saline; however, concentrations may differ with type of food. They placed the food in a 12-mm Finn chamber (Allerderm Laboratories Inc, Petaluma, CA), occluding for 48 hours and reading at 72 hours. Findings can be described as erythema, erythema and infiltration, erythema and a few papules, erythema and many papules, or erythema and vesicles. The most commonly positive foods in skin patch testing in patients with EE include milk, beef, chicken, potatoes, eggs, corn, soybeans, barley, oats, and wheat, although any food may be tested.[22]

The criterion standard for food allergy testing is the double-blind placebo-controlled food challenge; neither the usual skin patch test nor skin prick testing has been compared to this method in patients with EE.

Testing for Food Allergies in Patients With EE

Of the 31 patients with EE who underwent skin prick testing and determination of specific IgE levels to aeroallergens in a study by Simon et al,[7] 68% reported a history of allergic diseases. After IgE testing, only 16% of the patients were considered to be nonatopic. Overall, specific IgE antibodies to food allergens, aeroallergens, or both were found in 80% of patients. Skin prick testing was positive in 84% of patients for food, aeroallergens, or both. Twelve of the 19 patients with positive skin prick test results for food allergens were also found to be sensitized to an aeroallergen, such as wheat or rye, plus grass pollen.

Spergel et al[26] showed that most pediatric patients with EE had a positive skin prick test (73%) and a positive patch test (81%), suggesting a role for both IgE-mediated and non–IgE-mediated reactions.[26] In both types of reactions, test results were positive for approximately 3 foods. Interestingly, 19% of patients had a negative skin prick test result but a positive skin patch test result, suggesting that these patients may have a pure non–IgE-mediated response. Together, these data support a dual immune response in EE, with both IgE-mediated and non–IgE-dependent mechanisms.[9,12]

Spergel et al[22] recently reported on the sensitivity, specificity, and predictive values of these testing methods in a subgroup of patients for whom the individual foods causing their symptoms were identified. Biopsy specimens were evaluated after removal of individual foods and again after their reintroduction. The diagnostic accuracy of these methods depended on the particular food being tested. For skin prick testing, the positive predictive value (PPV) ranged from 33% to 96%; the specificity, from 10% to 78%; and the sensitivity, which was excellent, from 89.5% to 97.6%. Skin patch testing in patients with EE had a similar PPV (47.4%-94.4%), with specificity ranging from 43% to 89%. The sensitivity in patients with EE was 78% to 99%. Because EE is likely a mixed IgE- and non–IgE-mediated reaction, a combination of the 2 testing methods was also evaluated. The negative predictive value for the combination of skin prick testing and skin patch testing was 88% to 100% (excluding milk), and the PPV was more than 74% for the 3 most common foods. The sensitivity ranged from 77% to 97% for the combination of testing methods.

AEROALLERGENS, ATOPIC DERMATITIS, AND EE: A SYNERGISTIC ROLE

Because the esophagus might not be the primary site of allergen exposure in EE, several studies have investigated aeroallergens as possible provoking agents. The pattern of inflammatory cells and cytokine expression in EE is similar to that seen in allergic airway and skin disorders.[7,15] Pulmo-

TABLE 2. **Summary of Dietary Manipulation Trials in Children**

Study	No. of patients	Mean ± SD age (y)	Type of dietary intervention	Symptomatic response, No. (%)	No. of eosinophils (mean/high-power field ± SD)	
					Pretreatment	Posttreatment
Kelly et al[28]	10	5*	Elemental	8/10 (80)†	41 (15-100)‡	0.5 (0-22)‡
Markowitz et al[29]	51	8.3±3.1	Elemental	49/51 (96)	33.7±10.3	1.0±0.6
Spergel et al[26]	24	6.9±3.5	Elimination or elemental	18/24 (75)† 6/24 (25)§	55.8±24.6	8.4±8.4
Spergel et al[24]	146	6.5±4.5	Elimination or elemental	109/112 (97)// 19/19 (100)¶	48.4±24.2 68.8±25.7§	1.1±2.1// 12.0±3.2¶
Kagalwalla et al[30]	35	6.2*	Elimination	34/35 (97)	80.2±44	13.6±23.8
	25	6.4*	Elemental	25/25 (100)	58.8 ±31.9	3.6±6.5
Teitelbaum et al[8]	11	8±0.9	Restriction	0/11 (0)	22.5±4.9	8±0.9
Liacouras et al[31]	172	8.1±4.3	Elemental	160/164 (97)	38.7±10.3	1.1±0.6
	75	10.4±5.2	Elimination	72/75 (96)	47.5±12.1	5.3±2.7

*SD not provided in study.
†Complete symptomatic resolution.
‡Reported as mean (confidence interval) in original study.
§Symptomatic improvement.
//Responders based on biopsy analysis
¶Partial responders based on biopsy analysis

nary exposure to these inhaled antigens has been hypothesized to result in mast cell activation in the esophagus, resulting in cytokine release.[10] Additionally, the aeroallergens may be swallowed, possibly after being transported from the lung to the oropharynx by a ciliary mechanism, provoking cytokine production in the esophagus.[1,10]

Mishra et al[27] carried out an elegant series of experiments, in which they exposed mice to *Aspergillus fumigatus*, using both intragastric and intranasal approaches. Only the intranasal approach elicited EE and increased the number of eosinophils in the lungs. This finding strengthens the argument that initial allergen sensitization occurs in the respiratory tract, with symptoms occurring after delivery of the antigen to the esophagus. Aeroallergens, which can contribute to the development of EE in sensitized, atopic patients, can be deposited in the oropharynx and subsequently swallowed.[6] Because the immune system has been primed by the initial lung sensitization, exposure of the gastrointestinal tract to the inciting allergen then provokes a hypersensitivity response in the esophagus, accompanied by eosinophilic infiltration.[6] A connection between the bronchus and the esophagus might also exist because delivery of IL-13 to the airway promoted the development of EE, as aforementioned.[12]

Fogg et al[5] reported a case of a 21-year-old woman whose symptoms worsened only during pollen season; esophageal biopsy specimens also showed increased numbers of eosinophils during these periods. Skin prick and patch testing to foods was negative, but she did have positive skin prick test results to multiple seasonal and environmental allergens. Interestingly, the patient tested positive for *A fumigatus*, the fungus used in establishing the EE mouse model described in Rothenberg's laboratory.[13]

Akei et al[21] used an epicutaneous exposure to induce EE in mice, followed by an airway challenge. The antigens used were ovalbumin and *A fumigatus*. The epicutaneous exposure induced a strong systemic T_H2 response via an IL-5–dependent pathway. Mice developed EE after intranasal exposure to the same antigen. This finding shows that a skin allergen can prime atopic individuals for further respiratory challenge, which can induce EE.[21]

Taken together, the data on food allergies and aeroallergens suggest 2 possible mechanisms of disease in EE. There might be initial esophageal sensitization due to a food antigen, with EE occurring on esophageal re-challenge with the same antigen. Alternatively, there might be initial bronchial sensitization followed by esophageal rechallenge, as suggested by the data using inhaled *A fumigatus* and the presence of IL-13.

TREATMENT

Currently, 2 treatment modalities are available for EE. The first is avoidance of the inciting antigen, best established by an elemental amino acid diet. The second modality is pharmacologic, in which anti-inflammatory medications and biological agents have been used.

Elimination and Elemental Diets—Lessons From Studies in Children

Elimination diets have resulted in impressive clinical and histological improvement (Table 2).[20] Further, advances in the diagnosis of food allergies, along with an improved understanding of the underlying allergic mechanisms of this disease, could lead to even more success in the future.

These diets remove all antigenic stimuli, thereby reducing inflammation.

Kelly et al[28] were the first to report the successful treatment of children with EE using an elemental diet. They used Neocate (Nutrica, Gaithersburg, MD), a 1-crystalline amino acid–based formula that removes all intact complex proteins. Rapid, complete symptomatic resolution occurred in all 10 patients. After follow-up endoscopy, histological improvement was noted in all 10 subjects, with complete resolution documented in 5.

When rechallenged with foods, 9 of 10 patients had recurrent symptoms. In this study, milk, soybeans, wheat, peanuts, and eggs were the most common inciting foods, as determined by open food challenges, which were carried out at home after the initial treatment period. Once the offending food was again eliminated, patients remained asymptomatic for a 6-month follow-up period. Notably, none of the foods that were identified on open challenge to be causative of symptoms were found on skin prick testing. This finding suggests a more complex or mixed allergic mechanism, pointing to the need to evaluate for non–IgE-mediated allergies.

Markowitz et al[29] treated 51 pediatric patients with EE with an elemental diet for 1 month. The diet consisted of free amino acids, corn syrup solids, and medium-chain triglyceride oil; the patients were also allowed water. Of the 51 patients, 48 (94%) required nasogastric tube placement for delivery of this elemental diet. Symptomatic improvement occurred in nearly all patients, and follow-up endoscopy documented a marked decrease in esophageal eosinophilic infiltration. After symptomatic and histological improvement, foods were slowly reintroduced, allowing for evaluation of reactions to each specific food. On the basis on their results, these authors concluded that an elemental diet was the best treatment option for children with EE.

In a study of 24 patients with EE, Spergel et al[26] found that skin prick and patch testing determined the offending food in 75% of patients. Removal of the offending foods led to symptomatic improvement in all patients, with complete resolution of symptoms in 18 of 24. Follow-up biopsy specimens showed histological improvement and, after rechallenge, an increase in eosinophils. Eggs, milk, soybeans, and peanuts were the allergens most commonly identified by skin prick testing, whereas corn, wheat, soybeans, and chicken were the most often identified by skin patch testing.

In a study by Spergel et al[24] of 146 pediatric patients with EE who were evaluated using skin prick and patch testing, 77% showed histological improvement after following an elimination diet for 6 weeks. An additional 13% had symptomatic improvement, but biopsy specimens obtained after the intervention showed a persistent elevation in eosinophils. Esophageal eosinophilia returned after food reintroduction in 39 of 112 patients with EE who had responded to the elimination diet. Ten percent of patients did not respond; these patients tended to be older. Notably, all but 3 of the 15 patients who did not respond to an elimination diet improved when treated with an elemental diet. Overall, these authors reported a greater than 75% treatment success rate for symptomatic and histological improvement through a combination of skin prick and patch testing.

These large reports have led others to treat children with EE using both elemental and elimination diets, with good responses.[30] Liacouras et al[31,32] found symptomatic improvement in 247 of 381 pediatric patients with EE after dietary manipulation. Of these 247 patients, 75 improved with restriction alone and 172 with an elemental diet, as determined by allergy testing and a combination of skin patch and prick testing. The elemental diet was continued for approximately 6 months, including the reintroduction phase.

In contrast, Teitelbaum et al[8] performed allergy tests on 15 children with EE and identified specific food allergies in 11. These patients were then given restrictive diets (on the basisof skin prick testing and RAST testing results) for 8 weeks, and no symptomatic improvement was noted. Patients without an identified allergy received medical therapy, and 9 of the 11 patients responded to fluticasone propionate. This study suggests that the simple restriction of foods might not be sufficient for treatment and that elemental diets might be necessary. However, these authors did not use skin patch testing and might not have identified accurately all food allergies contributing to the disorder, evaluating only IgE-mediated allergic reactions.

Medical Therapy

Anti-inflammatory therapies, which include fluticasone propionate or budesonide that is swallowed by the patient, have been shown to improve the symptoms caused by EE.[33] The goal is to swallow approximately 80% of the medication, aiming for topical delivery of the medication to the affected areas of the esophagus. Treatment with prednisone or montelukast can improve symptoms but often only temporarily. Symptoms often tend to recur with cessation of treatment,[12] leading to multiple courses of therapy. These therapies, which can be costly, require patients to take medications, possibly on a long-term basis, and may lead to adverse effects. Adverse effects of fluticasone propionate include oral thrush and esophageal candidiasis.[25] However, patients who require systemic corticosteroids are exposed to the multiple, often severe adverse effects associated with the long-term use of these agents.

Recently, an open-label phase 1/2 study evaluated mepolizumab, a monoclonal antibody against IL-5, for patients with severe EE.[34] This medication may reduce the proliferation, maturation, production, activation, and tissue recruitment of eosinophils into the esophagus.[1] Stein et al[34] reported on 4 patients with EE who underwent 16 weeks of treatment with mepolizumab, with follow-up esophageal biopsies at week 20. Results showed improvement in clinical symptoms, enhancement in quality of life, and a decrease in eosinophils on biopsy. Endoscopic findings improved in 3 of 4 patients. The medication was well tolerated overall. Because aeroallergens are a suggested trigger in the development and exacerbation of EE, mepolizumab could be especially effective in patients with an aeroallergen trigger.

Esophageal dilation has been used to address the complications of EE, such as strictures, but provides only a transient improvement.[35] Symptomatic treatment does not address the underlying etiology of the disorder, which, if altered, could ultimately provide a lasting cure. These medications treat the final manifestation of the eosinophilic infiltration without addressing the primary cause.[29] We do not know the long-term prognosis of patients with EE and whether any complications, such as stricture, food impaction, or even esophageal cancer, could be related to a protracted course or to a longer history of active disease. Straumann et al[36] followed up 30 adult patients over a mean of 7.2 years and noted that 97% had persistent dysphagia and 71% an episode of food impaction. This study also suggested that chronic inflammation might lead to permanent structural changes, with a long-term and progressive risk of impairment in function.

Food Elimination Diets

Treatment algorithms for addressing food allergies in patients with EE have been developed[20,29] (Figure 2). Whereas some recommend patch testing as the method of choice for identifying "culprit foods," recent studies suggest that a combination of skin prick and patch testing might be the most effective approach.[26] If offending foods are identified, they should be eliminated, and esophagogastroduodenoscopy (EGD), also known as upper endoscopy, with biopsy should be undertaken in 6 to 8 weeks to document a decrease in eosinophils. If 15 or more eosinophils per high-power field are present, the patient should then be given an elemental diet. If no food allergens are identified on patch testing, an elemental diet is recommended at the time of diagnosis, with EGD 4 weeks later to document resolution. If fewer than 15 eosinophils per high-power field are seen, a food allergy would be confirmed as the etiology of the disorder, and a slow reintroduction diet can be undertaken. Foods should be reintroduced every 5 to 7 days, with endoscopy and biopsies performed after a group of 5 foods has been reintroduced.[20] Markowitz and Liacouras[20] have constructed a food chart, which suggests the order in which foods should be reintroduced. The foods most likely to cause a reaction, such as milk, eggs, soybeans, wheat, nuts, and corn, are reintroduced last.

If food allergies are identified to multiple foods (up to 6 or more in some reports), a large number of foods might need to be eliminated. Adherence to such food avoidance diets for the weeks to months necessary for full effect can be difficult in adults who might consider them unpalatable. In many children, successful delivery of the diet requires placement of nasogastric tubes. The most definitive elimination diet is an elemental amino acid diet, which is unpalatable to most adults. However, such a diet could indicate whether a less stringent elimination might be successful. In addition, frequent EGDs with biopsies might not be readily available in some areas, and the cost of the frequent procedures could be prohibitive.

CONCLUSION

Multiple studies have shown the role of food allergies and aeroallergens in the development of EE. Studies in children have shown successful treatment of this disorder using elimination and elemental diets. Although these diets have been shown to be successful in adolescents and young adults, this approach has yet to be addressed in the adult population. Elemental diets and food restriction could likely be used successfully to treat adults with EE. A multidisciplinary approach to treating EE is needed, with contributions from internists, gastroenterologists, and allergists. Nutritionists would also be valuable to ensure that patients receive the required number of calories, fluids, vitamins, and other nutritional requirements.

This approach is not a simple one to undertake in an adult population. Some studies have shown atopy to be more common in children than in adults, which may affect response to an elemental or restricted diet in adults. If adults do not respond in a similar manner to children, then that would be evidence for the existence of different subtypes of this disorder in the pediatric vs adult populations.

In both adults and pediatric patients with EE, referral to an allergist at the time of diagnosis may be valuable in identifying the antigenic trigger of the disease. Prior studies have not shown any of the tests for food allergies—specific IgE testing, prick testing, or patch testing—to be superior to the others. However, the studies by Spergel and colleagues suggest that a combination of testing for both IgE-mediated and non–IgE-mediated reactions using both skin prick and patch testing might be most effective. If specific foods are identified through allergy testing, elimi-

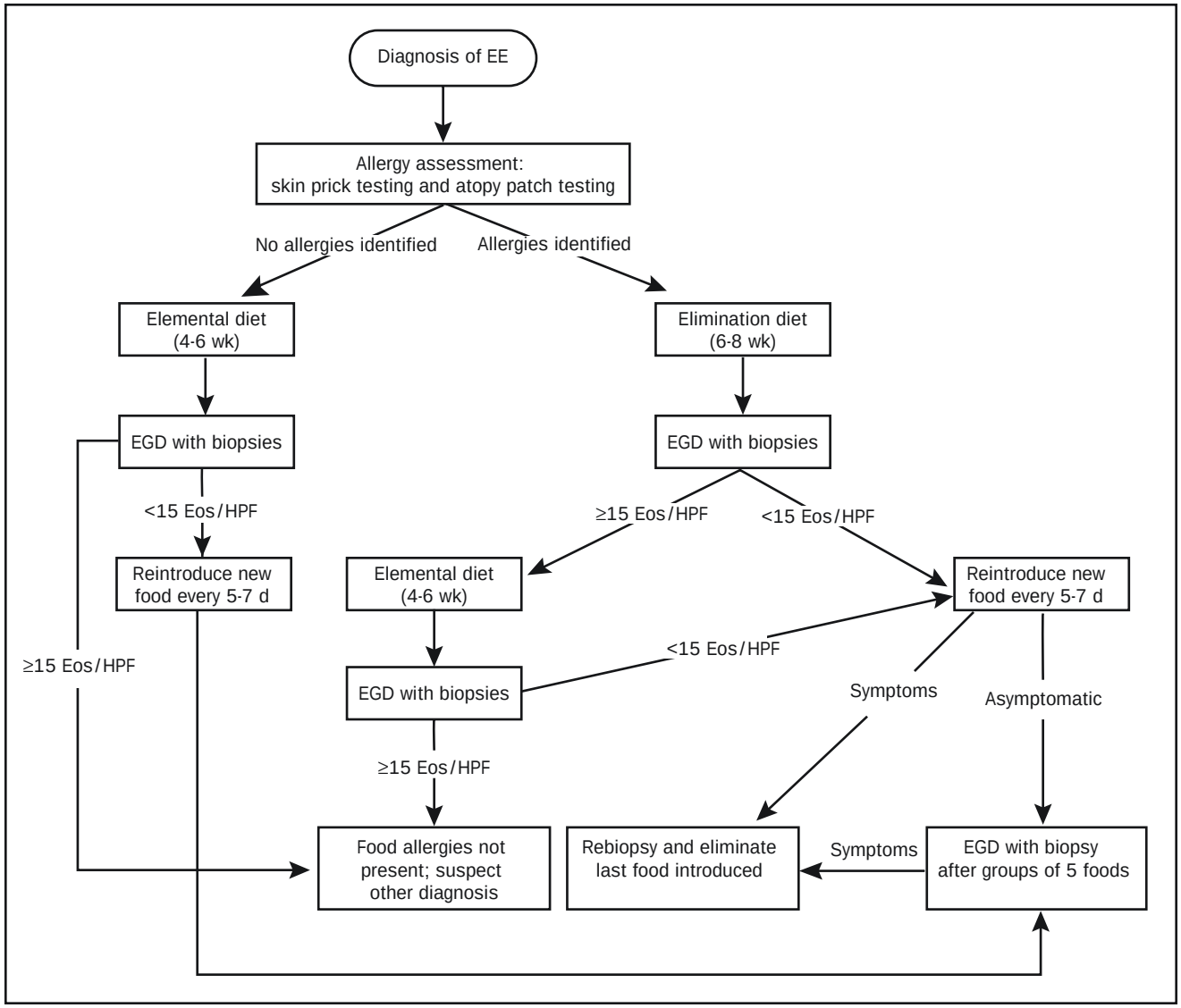

FIGURE 2. Possible diagnostic and treatment algorithm for dietary intervention alone in adults with eosinophilic esophagitis (EE). EGD = esophagogastroduodenoscopy; Eos = eosinophils; HPF = high-power field. Adapted from *Ann Allergy Asthma Immunol*,[24] with permission.

nation diets would be a reasonable approach, along with follow-up endoscopy to document changes in eosinophilic infiltration. An algorithm similar to that used in children, using elimination and gradual reintroduction of food, or even an elemental diet in some cases, could help provide a lasting cure for this disorder in adults. Although it might be unreasonable to expect dietary modification to lead to results that are as impressive in adults as in children, identification of patients with food allergies could save them from long-term medication use and the resultant adverse effects, along with the possible long-term complications of stricture and food impaction.

A subgroup of patients could benefit from control of aeroallergen sensitization as well as exposure. The work of Mishra et al[27] in describing the critical role of IL-5 in the development of EE after aeroallergen exposure provides a rationale for the use of anti–IL-5 therapy. Other novel therapeutic agents, such as those that target STAT-6 and eotaxin, should also be evaluated as potential treatments.[31]

Further research on EE should focus on the role of allergens, both food and environmental, in triggering esophageal symptoms in adults. Diet elimination and allergen avoidance are the only current methods for treating the underlying cause of the disorder and not just the symptoms.

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