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The Role of the Environment in Eosinophilic Esophagitis

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Abstract
Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease with incompletely understood pathogenesis. Though disease manifestations were initially ascribed to a delayed reaction to food allergens, emerging evidence suggests that modifiable host factors and environmental allergen exposure may also play critical roles in the pathogenesis and ongoing manifestations of EoE. As with other atopic diseases, lack of early-life exposure to microbial pathogens leads to an immune tolerance defect and reprograms the commensal gut microflora toward a type 2 T helper (Th2) phenotype; the esophageal microbiota, a rich environment consisting of diverse bacterial species, is greatly altered by inflammation. Although multiple early life microbiome-altering factors are associated with EoE development, no causative, direct relationships have been identified. Interestingly, large, cross-sectional analyses of several populations identify an inverse relationship between *Helicobacter pylori* presence and EoE, likely via virulence factors that downregulate Th2 inflammation, though causality has not been proven. In regard to environmental allergens, some studies support seasonal variation in EoE diagnosis and flares, and EoE can be generated after a large, identifiable aeroallergen exposure. Examples include mouse models of intranasal Aspergillus dosing and following initiation of oral immunotherapy to foods or environmental allergens. Conversely, treatment of allergic rhinoconjunctivitis may improve EoE symptoms, though data is limited to case reports and small series. Unfortunately, biologic therapies for atopic conditions have failed to improve EoE symptoms despite improvement in esophageal eosinophil count, though dupilumab shows promise in ongoing studies. Overall, this chapter shows that EoE pathogenesis is likely multifactorial, and the environment is a key component in our understanding of EoE.

Keywords Eosinophilic esophagitis · Microbiome · Environment · Exposure

Introduction

Eosinophilic esophagitis (EoE) is a chronic, inflammatory disease characterized by isolated esophageal eosinophilia despite high-dose proton pump inhibitor (PPI) use [1]. As EoE is a relatively new disease, its pathogenesis is not fully understood. Initial reports in children documented response to amino acid-based formula, suggesting a causal role for food allergens [2]. The rapidly increasing incidence of in EoE in developed countries, however, suggests that disparities in environment could also contribute to EoE pathogenesis [3–5]. Additionally, with emerging evidence supporting a role of the microbiome in other atopic diseases such as asthma and atopic dermatitis, focus has expanded to examine the role of non-allergic environmental exposures in EoE development [6, 7]. With ongoing exposure to inhaled and swallowed foods, drugs, and airborne pathogens, the esophagus is an ideal candidate to explore.

This paper summarizes the most recent data suggesting a role of a variety of environmental exposures in the initial pathogenesis and/or subsequent disease control of EoE. Additionally, research evaluating interventions to alter environmental exposures and possibly the microbiome will also be reviewed.

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Potential Role of Non-allergen Environmental Exposure: Hygiene Hypothesis and the Microbiome

A proposed contributory mechanism to the recently increased prevalence of EoE in developed countries is the hygiene hypothesis, which postulates that a lack of exposure to microbial pathogens early in life causes a defect in immune tolerance, leading to increased susceptibility to allergic disease [8]. The commensal microflora of the gut may be redirected toward a T helper-2 cell (Th2) phenotype by early life exposures such as Caesarian section, antibiotic exposure, lack of breastfeeding, or a stay in the neonatal intensive care unit (NICU), each of which has each been shown to increase the risk of EoE in humans [9–13]. A recent case-control study examined interactions between five EoE-associated single-nucleotide polymorphisms (SNPs) and early life factors including antibiotic use in infancy, Caesarian delivery, breastfeeding, NICU admission, and absence of a furry pet [9]. The authors found a significant protective effect of breastfeeding (aOR 0.08 [0.01–0.59]) in EoE patients possessing a SNP in the calpain 14 (CAPN14) gene, an IL-13-induced protease integral for epithelial barrier maintenance [14]. Though sample size was small (127 controls), this study yields compelling evidence that EoE pathogenesis involves an interplay of environmental and genetic factors.

In accordance with the hygiene hypothesis, alteration in commensal microbes has been shown to increase serum immunoglobulin E (IgE), serum basophils, and Th2 response in murine models [15], and antibiotic-treated mice are more likely to develop food allergen sensitization [16]. Interestingly, an inverse relationship between *Helicobacter pylori* and EoE has been established and validated in large, cross-sectional analyses of several different populations [17, 18]. *H. pylori* virulence factors promote expression of interferon gamma (IFN-χ) and interleukin 17 (IL-17) [19, 20], resulting in proliferation of Th1 and Th17 cells and a consequent downregulation in atopy-associated Th2 cells. Although the acute decline of *H. pylori* in developed countries correlates inversely with the rapid rise in EoE prevalence, there is no human data to prove a causal effect. Animal studies in other atopic diseases, however, do show a direct, protective effect of *H. pylori* [21, 22], via dendritic cell-derived regulatory T cell differentiation.

Although the esophagus was initially thought to be a conduit relatively devoid of microbes, gene sequencing has revealed a diverse environment of over 300 bacterial species [23]. An early study demonstrated that distal esophageal biopsies from healthy subjects are dominated by *Streptococcus* species, while those with active esophageal inflammation have predominantly gram-negative anaerobes or microaerophilic bacteria [24]. Benitez et al. evaluated oral and esophageal microbiome differences between children with and without EoE and aimed to determine if food-elimination resulted in a change in the EoE microbiome [25]. Proteobacteria (*Neisseria* and *Corynebacterium*) were significantly more abundant in active EoE, and gram-positive *Streptococcus* and *Atopobium* were predominant in non-EoE controls. Although dietary elimination did not significantly alter the microbiome, re-introduction led to increased *Granulicatella* and *Campylobacter* genera. Another study utilized the esophageal string test to perform ribosomal RNA sequencing in 70 children and adults (11 with untreated EoE, 26 with EoE in remission, 8 GERD controls, 25 normal controls) and found similar results, with increased Proteobacteria (*Haemophilus*) in active EoE [26]. Bacterial load was increased and diversity decreased in all EoE subjects compared with controls, not influenced by the degree of esophageal eosinophilia. Though these studies certainly show that the microbiome differs between EoE and healthy controls, sample size is small and only associations are described. Additionally, it remains unclear whether the alterations in the microbiome are due to the specific EoE disease process, or a result of esophageal inflammation in general. Further, large-scale studies are needed to help delineate these concerns. Table 1 highlights potential non-allergen environmental factors contributing to EoE pathogenesis.

Environmental Exposure to Airborne Allergens

EoE has a strong association with other atopic diseases, including allergic rhinitis, food allergy, asthma, and atopic dermatitis. Time, experience, and research have shown that food allergens are the primary trigger for this disease, and food elimination represents one of the primary EoE management strategies [27–29]. An increasing amount of evidence, however, suggests that aeroallergens play a role in the disease control of EoE. This is not surprising given that the vast majority of patients with EoE are atopic, with positive testing to foods and aeroallergens by skin and specific IgE testing [30, 31].

During pollen season, there is an influx of eosinophils into the esophageal mucosa in patients with allergic rhinitis, suggesting that post-nasal drip of patients with allergic rhinitis acts as a carrier of eosinophils from the nasal/oropharynx into the esophagus [32]. Fogg et al. were the first to postulate that aeroallergens may play a role in EoE. In 2003, they described a 21-year-old female with EoE, asthma, and seasonal allergic rhinitis, in whom EoE symptoms and esophageal eosinophil count were exacerbated in pollen seasons, with resolution during winter months [33]. A number of similar case reports and studies followed, describing patients with EoE and allergic rhinitis with seasonal variations in symptoms, and fewer cases being diagnosed in the winter months where exposure to pollens would be low [34–37]. A population study over three

Table 1 Hygiene hypothesis and the microbiome: summary of factors associated with EoE development

Factor	Proposed influence	Reference(s)
Caesarian section	T helper 2-skewed commensal gut microflora	[10, 12, 13]
Antibiotic exposure		[10, 12, 13, 16]
Bottle-fed infant		[9, 12]
NICU stay or preterm delivery		[9, 12]
Lack of a furry pet		[10]
Absence of *H. pylori*	Downregulation of interferon gamma and interleukin 17	[19–22]
Altered gut microbiome	Increased bacterial load, decreased diversity, inflammation	[24–26]

decades in Olmsted County, Minnesota, assessed the epidemiology and outcomes of EoE. Prevalence was 55/100,000 persons (higher than expected) and EoE was most frequently diagnosed in late summer/early fall [34]. Wang et al. reported seasonal distribution of EoE diagnosis and eosinophilia on biopsy in 234 children over a 6-year period [36], and similar findings have been reported in adults [37].

Findings of seasonal variation in EoE symptoms are not replicated, however, in all studies [38–42]. A retrospective chart review by Elitsur et al. found no seasonal variation in children diagnosed with EoE in rural West Virginia [38], and a 5-year retrospective review found no seasonal pattern in symptom onset, though diagnosis was made more often in the fall, in children and adolescents in suburban Michigan [39]. Another retrospective review in urban children over a 5-year period looked to see if pollen and mold played a role in the timing of an EoE diagnosis. Clinical data, biopsy reports, as well as the mold and pollen counts over this period were examined. There was no statistical association between the mold and pollens counts and diagnosis of EoE [40]. Similar findings were found when adult studies were analyzed. A retrospective case control study was done looking at adult data over a 10-year period in Australia to see if there was a correlation to massive aeroallergen exposure leading to a food bolus obstruction. Pollen records were obtained and records were reviewed of those getting biopsies. Although 85 of the 278 patients biopsied were given a diagnosis of EoE, there was no seasonality identified in food bolus obstructive events from any cause [41]. Finally, a meta- analysis by Lucendo et al. including 16,846 EoE patients did not support a clear causal role for aeroallergens [42]. Seasonal distribution of cases was homogenous, with no evidence for a clear pattern in diagnoses or clinical flares, and clinical exacerbations also occurred without any seasonal pattern. A recent analysis of the current literature by Guajardo and colleagues showed no definitive cause and effect of aeroallergens on the diagnosis or exacerbation of EoE [43]. This lack of definitive association may be due to discrepancies in tracking and notating esophageal eosinophilia, allergen season overlap, and differences in various regions, identifying EoE-inducing causative aeroallergens, and potential bias in retrospective study design.

Development of EoE Following Oral or Sublingual Immunotherapy

New-onset EoE has been reported in patients receiving food oral immunotherapy (OIT). This was initially described in OIT with peanut and milk, and a 2014 meta-analysis of 12 food OIT studies concluded that biopsy-confirmed EoE occurred in 2.7% of patients [44, 45]. A recent systematic review reported a higher prevalence of 5.3%, noting that that the true prevalence of OIT-related EoE may be under-reported as many patients with vague gastrointestinal complaints who discontinue OIT do not undergo esophageal biopsy [46]. Fortunately, this phenotype of EoE seems to resolve in the majority of patients after OIT is discontinued. Interestingly, two new-onset EoE patients who failed to respond to OIT discontinuation or to topical steroids achieved histologic remission after allergen immunotherapy to environmental allergens [45].

Case reports have also linked aeroallergen sublingual immunotherapy (SLIT) to new-onset EoE. The first association of SLIT and EoE was in an adult with allergic rhinitis treated with SLIT using hazelnut, birch, and alder. Symptoms of classic EoE developed within 4 weeks of initiation of therapy, and a peak number of 164 eosinophils/high power field were seen on biopsy. Within 4 weeks of discontinuing SLIT, EoE resolved and required no medical intervention, and follow-up at 1 year showed no signs of the disease [47]. New onset EoE has also been reported after sublingual immunotherapy with grass tablets and dust mite, which also resolved after discontinuation of OIT [48, 49].

The association between oral/sublingual immunotherapy and EoE sheds light on contributory mechanisms of EoE development. Immunotherapy causes a shift in the immune response leading to increased regulatory T cells (Tregs). Pollen SLIT reduces allergen-specific IgE levels and induces IL-10, IL-5, and Foxp3-expressing T cells [50, 51]. As IL-5 is a critical mediator in EoE, perhaps this association contributes to pathogenesis in OIT and/or SLIT.

De Novo EoE After Aeroallergen Exposure

Although timing of initial allergenic trigger(s) of EoE is often unknown, cases of EoE development after large, identifiable allergen exposure have been reported. A series by Wolf et al. reported three such cases in which PPI-responsive esophageal eosinophilia developed in a 22-year-old man with seasonal allergic rhinitis who swallowed grass clippings from a jammed lawn mower, and biopsy-proven EoE occurred in a 20-year-old non-atopic man who swallowed moldy dust and in a 39-year-old man following exposure to saw dust, mold, and dust during renovation of a home with rotted wood and drywall [52].

These human cases support the mechanism seen in murine models of EoE [53–55]. In 2001, Mishra and colleagues were able to induce esophageal eosinophilia in mice by exposing them to repeated doses of intranasal *Aspergillus fumigatus* allergens. Mice developed classic features that mimicked EoE in humans, including significant levels of esophageal eosinophils, free eosinophil granules, and epithelial cell hyperplasia. This was not seen with oral or intra-gastric allergen exposure, indicating that hypersensitivity in the esophagus occurs following development of pulmonary sensitization and inflammation [53]. These findings showed a link between hypersensitivity reactions in the esophagus and the lung and a causative role for inhaled allergens and eosinophils in gastrointestinal inflammation. The group subsequently showed that mice epicutaneously sensitized to either *A. fumigatus* or ovalbumin developed esophageal eosinophilia and marrow eosinophilopoiesis with a single intranasal challenge to allergen, via a Th2-mediated mechanism involving IL-5, -4, -13, and STAT 6 [54]. Further work by this group demonstrated esophageal remodeling and strictures similar to that seen in humans [55].

Studies of perennial aeroallergens have also provided important information in our understanding of EoE. Chapman and colleagues cloned several cysteine and serine protease allergens from house dust mites, including Der p 1, Der p 3, Der p 6, and Der p 9. Proteolytic enzymes from Der p1 were shown to break down tight junctions in lung epithelium and cause bronchial epithelial cells, mast cells, and basophils to release a variety of pro-inflammatory cytokines. Der p 1 also cleaves CD25 from T cells and CD23 from activated B cells [56]. These synergistic effects of mite enzyme allergens may promote IgE synthesis and have direct inflammatory effects on lung epithelium and could also have a similar effect on the epithelium of the esophagus. To better understand if indoor insect allergens play a role in inducing EoE, Rayapudi and colleagues delivered intranasal perennial allergens to mice. Compared to saline-challenged mice, wild-type mice exposed to dust mite and cockroach showed a marked increase in mast cells and eosinophils in the esophagus. Also seen were increased levels of total IgE, antigen-specific IgG1, and esophageal expression of IL-13 and Eotaxin-1. Further, cockroach and dust mite, but not cat or dog, were shown to be potent inducers of IL-5 and eotaxin-mediated esophageal eosinophilia [57]. A recent study report by Pesek et al. demonstrated that individuals considered 'non-responders' to EoE therapies (peak eosinophil count 25/hpf or higher) were more likely to be sensitized to mold or perennial aeroallergens, with those sensitized to cockroach or mold less likely to respond to combination diet and swallowed steroid therapy [58]. Table 2 summarizes environmental allergen factors contributing to EoE.

Environmental Interventions May Have a Role in Altering or Improving EoE Symptoms

Traditional therapeutic options for EoE include either a food elimination diet, which consists of either a 6-food elimination diet (milk, soy, wheat, egg, peanuts/tree-nuts, and shellfish) or an elemental diet consisting of an amino acid-based formula, or topical corticosteroid therapy [59]. Both of these treatment options may negatively affect the quality of life of the patient or have significant side effects. Because of the negative aspects of these treatment options, efforts are being made to determine the efficacy and side effect profile of additional or alternate therapies, including therapies traditionally used to treat other atopic conditions. Proposed EoE therapies that differ from or augment traditional therapeutic options are summarized in Table 3.

As there is a strong association between eosinophilic esophagitis and allergic rhinitis, treatment of allergic rhinitis may play a role in the treatment of EoE. Traditional therapy for environmental allergies includes antihistamines, which prevent release of histamine by antagonizing histamine receptors. The use of antihistamines in the treatment of allergies is primarily through their inhibitory action on H1 receptors, although other histamine receptors (H2, H3, and H4) also exist. Prior studies have shown that histamine, when bound to its H1 receptor, increases epithelial cytokine and chemokine secretion in the esophagus, thereby recruiting eosinophils into the mucosa. Despite this data, further evidence has done little to promote the use of antihistamines in EoE [31, 60]. Despite increased and altered histamine receptor expression in active EoE, systemic antihistamine therapy was not shown to decrease symptoms or induce clinical remission [61]. Further investigation is necessary to determine the effect of blocking other histamine receptors, including H2 and H4 receptors. H2 receptors are located on gastric parietal cells and regulate acid release, while H4 receptors are located on leukocytes to modulate cytokine production and recruitment of leukocytes. Mast-cell stabilizers, such as cromolyn sodium, which act via alteration of chloride channels in mast cell membranes, do not appear to be effective in EoE [31, 62]. Unfortunately, there is also little data to support or refute the use of steroid or antihistamine nasal sprays in EoE. Additionally, although it is possible that treatment of post-nasal drip to eliminate a

Table 2 Association between environmental allergens and EoE

Factor	Support for or evidence against factor in relationship to development of EoE	Reference(s)
Seasonal variation in EoE diagnosis	+	[32–37]
	–	[38–42]
Seasonal variation in EoE disease control	+	[32, 36]
EoE development with oral immunotherapy to food	+	[44–46]
EoE development with sublingual pollen immunotherapy	+	[47–49]
EoE development after large-volume aeroallergen exposure	+	[52]
Airway aeroallergen "priming" for development of EoE	+	[53–55]
Effect of perennial allergen sensitization on EoE control	+	[58]

possible carrier of eosinophils into the esophagus may play a role in the treatment of EoE, there is little data in support or oppose this viewpoint. Further studies are necessary to determine if nasal sprays have an effect on induction of remission, disease control, or symptom reduction in EoE.

Leukotrienes are products of arachidonic acid metabolism that increase eosinophil migration, as well as mucosal edema, mucus production, and bronchoconstriction. Montelukast is a competitive antagonist of one of the CysLT1 receptor, preventing the release of leukotrienes and reducing their downstream effects. Montelukast is traditionally used in the treatment of eosinophilic asthma, as well as eosinophilic gastritis. Investigations thus far into the potential use of montelukast in the treatment of EoE have shown limited efficacy. Initial data showed some promise in its use for symptom reduction and maintenance of disease remission in EoE; however, further studies showed mixed results [63–65]. Due to the varying results of existing studies, further investigations are needed to ascertain the efficacy of montelukast in the treatment of EoE.

Table 3 Possible therapeutic options for eosinophilic esophagitis

Treatment	Mechanism of action	Use in treatment of EoE	Reference(s)
Antihistamine	1st gen.: nonselective competitive antagonist on peripheral and central H1 receptors 2nd gen.: selective competitive antagonist of peripheral H1 receptors	Limited data supporting use in EoE	[31, 60, 61]
Cromolyn Sodium	Mast-cell stabilization (decreased release of histamine, inflammatory mediators)	Limited data supporting use in EoE	[31, 62]
Montelukast (Singulair)	Selectively antagonizes cysteine leukotriene receptors	Limited data supporting use in EoE	[63–65]
OC000459	Prostaglandin D2 chemoattractant receptor (CTRH2 antagonist)	Reduction of symptoms and eosinophils in 1 study	[66]
Immunotherapy	Alters immune response by transitioning from Th2 to Th1 response to allergens, promotes tolerance through repeated allergen-specific exposure	Few cases reports indicating reduction of symptoms of EoE with birch and dust mite immunotherapy	[67, 68]
Mepolizumab	Monoclonal antibody to IL-5	Reduction in eosinophil count but inconsistent reduction in symptoms	[69, 70]
Reslizumab	Monoclonal antibody to IL-5	Consistent reduction in eosinophils but inconsistent reduction in symptoms	[71, 72]
Omalizumab	Monoclonal antibody to IgE to prevent binding of IgE to mast cells, basophils	Reduction of symptoms but inconsistent reduction in eosinophils	[73, 74]
QAX576	Monoclonal antibody against IL-13	1 study showed reduction of eosinophil count and reduction of symptoms	[75]
RPC4046	Monoclonal antibody against Rα1 and Rα2 IL-13 receptors	Reduction of eosinophils, endoscopic improvement, non-statistically significant reduction in symptoms	[76]
Dupilumab	Monoclonal antibody against the alpha subunit of the IL-4 receptor	Reduction in dysphagia and non-statistically significant reduction of additional symptoms. Reduction in eosinophils	[77]

Like leukotrienes, prostaglandins are also derived from arachidonic acid and play a key role in the inflammatory process via increasing vascular permeability and vasodilation. Prostaglandin D2 is especially involved in eosinophilic esophagitis, as it plays a role in the chemotaxis of eosinophils and Th2 cytokines [78]. One RCT analyzed the effect of blocking Th2 cell prostaglandin D2 receptors on disease control in EoE. Following 3 weeks of treatment with OC000459, an antagonist of the prostaglandin chemoattractant receptor-homologous molecule on Th2 cells (CRTH2), patients in the treatment group demonstrated a reduction in symptoms as well as esophageal eosinophilia as compared to placebo [66]. This demonstrates promising results for treatment of EoE in the future.

Allergen immunotherapy remains a widely used and effective treatment for environmental allergies. With the observed seasonal variation in EoE development, studies have aimed to determine if treatment of allergies with aeroallergen immunotherapy affects disease control in EoE. Fahey et al. found a positive correlation between the levels of atmospheric pollen in New York City and the development of EoE, particularly in July through September, when grass pollen is at its peak [79]. This suggests that immunotherapy to grass pollen may play a role in treatment of EoE, particularly in New York City. A case report by De Swert et al. found that immunotherapy to birch pollen was helpful in improving the signs and symptoms of EoE [67]. Similarly, another case is described in which a child with treatment-refractory EoE improved dramatically with allergen immunotherapy to dust mite [68]. Though the above findings that show improvement of disease control and symptoms are possible with allergen immunotherapy to birch and dust mite, data is limited and further exploration is needed.

The Effect of Immunomodulators on EoE

As with other atopic diseases, not all patients with EoE respond similarly, or to the same degree, to traditional therapies. There is ongoing research surrounding the effects of immunomodulators designed for other atopic conditions on disease control and reduction of symptoms in EoE, including biologic drugs targeting interleukin-5 (IL-5), IgE, interleukin-13 (IL-13), and interleukin-4 (IL-4).

Mepolizumab and reslizumab are two monoclonal antibodies (mAbs) that are directed toward neutralizing the cytokine interleukin 5 (IL-5), which is involved in the recruitment of eosinophils to the esophageal mucosa [80]. Local IL-5-producing Th2 cells are increased in active EoE, and transgenic mice with esophageal over-expression of IL-5 develop an EoE-like disease [81, 82]. Mepolizumab has shown a consistent decrease in esophageal eosinophilia yet a limited improvement in symptom scores vs. placebo. A randomized, blinded, non-placebo controlled phase II trial enrolled 59 children with EoE intolerant or unresponsive to dietary or steroid therapy to receive mepolizumab dosed at 0.55, 25, or 10 mg/kg every 4 weeks for three doses. Esophageal eosinophil count was reduced in all groups, with reduction in peak count by 32.6% and mean count by 89.5% [69]. A separate placebo-controlled phase II trial in 11 adults with active EoE given mepolizumab 750 mg weekly for two doses, followed by 1500 mg weekly for two doses if not in remission, showed that mepolizumab was safe and well-tolerated, with limited, non-statistically significant improvement in EoE-related symptoms vs. placebo [70]. Reslizumab has shown some success in the treatment of EoE. A phase III randomized, double-blinded placebo controlled trial (RDBPCT) of 226 children and adolescents given placebo or 1, 2, or 3 mg/kg reslizumab intravenously every 4 weeks for four doses demonstrated a statistically significant reduction in local eosinophil count with all treatment doses compared to placebo; yet, the reduction of symptoms was not statistically significant compared to placebo [71]. A single center published subsequent open-label results of the same trial. Six patients continued to receive reslizumab 2 mg/kg every 4 weeks for 9 years; EoE-related symptoms were reduced on treatment, with zero of six patients reporting dysphagia or abdominal pain on a relatively unrestricted diet [72]. This study is limited by small sample size and lack of placebo comparator.

Unfortunately, omalizumab, an anti-IgE mAb, was shown to reduce the symptoms associated with EoE, with little effect on esophageal eosinophilia on biopsy [73]. Omalizumab may be effective in a small subset of EoE patients with mild disease and low peripheral eosinophil count [74]; yet, IgE does not appear to be a sole viable target in EoE therapy.

IL-13 is vital to the pathogenesis of EoE, via induction of eotaxin-3 secretion by esophageal cells [83]. Two anti-IL13 mAbs and one anti-IL4/13 mAb have been examined in EoE patients, with varying success. QAX576, a human anti-IL13 mAb dosed intravenously every 4 weeks, significantly improved intraepithelial esophageal counts and decreased eotaxin-3 levels compared to placebo in a phase II trial [75]. Unfortunately, the drug failed to meet the primary endpoint of the study, as not enough patients experienced a 75% reduction in peak eosinophil count. RPC4046, a humanized anti-IL3 mAb, prevents IL-13 from binding to its two receptors (Rα1 and Rα2). RPC4046 recently met its primary endpoint in a phase II trial (NCT02098473). Thus far, RPC4046 was shown to improve endoscopic features and mean eosinophil count, as compared to placebo [76]. Although not statistically significant, there was reduction in symptoms, particularly dysphagia, in the treatment groups as compared to placebo. In the study, RPC4046 was mostly well-tolerated, although there was a higher rate of adverse events, including headache, arthralgia, and upper respiratory infections in the high-dose treatment arm. Overall, RPC4046 appears promising as a treatment for EoE based on this phase II trial, and a phase III trial is planned. Dupilumab, a human mAb directed against the shared alpha subunit of the IL-4 and IL-13 receptors, was evaluated in a

recent phase II study by Hirano et al. [77]. Dosed weekly, dupilumab significantly reduced both dysphagia and peak eosinophil count at 10 to 12 weeks of therapy.

Further research regarding the treatment of EoE with biologics and immunomodulators is ongoing, and its future appears promising. However, further studies are also necessary to better determine how decreasing exposure to aeroallergens and improving control of environmental allergies and associated symptoms can affect the treatment of EoE. Specific questions include how chronic use of antihistamines and nasal corticosteroid sprays affect disease control in EoE, and to determine whether EoE has differing phenotypes that may guide a practitioner to choose a particular treatment modality.

Summary

Eosinophilic esophagitis is increasing in frequency, and pathogenesis is likely multifactorial. As this paper has summarized, the environment is a key component in our understanding of EoE. There is still much that is unknown, though progress has been made in trying to better understand the pathophysiology and genetics of this ailment. As with asthma and eczema, it is realized that researchers are just scratching the surface of the various components of EoE. Further evaluation of the roles of the environment and the microbiome will hopefully lead to a better understanding and to improvement in directed therapies for this disease.

There are some important points to remember that may prove helpful in caring for patients. First, eosinophils increase in the esophagus seasonally in patients with allergic rhinitis alone as well as those with EoE and seasonal allergies, but not in normal controls [32]. Dust mite proteases can affect the epithelial barrier in the esophagus and contribute to allergic sensitization as well as serve as potent inducers of IL-5 and eotaxin-mediated esophageal eosinophilia. Dust mite, tree, and grass SLIT can induce EoE. In some patients with EoE, traditional immunotherapy to aeroallergens resulted in remission of the disease when food elimination alone did not. Lastly, there is evidence that, in some patients, perennial allergen and mold sensitization may lead to non-responsiveness to EoE treatment. Information learned from these various studies have increased our understanding of the disease and have opened possible therapeutic windows especially for the most difficult to treat patients.

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