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Allergic Comorbidity in Eosinophilic Esophagitis: Mechanistic Relevance and Clinical Implications

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Abstract

Allergic eosinophilic esophagitis (EoE) is a chronic, allergen-mediated inflammatory disease of the esophagus, and the most common cause of prolonged dysphagia in children and young adults in the developed world. While initially undistinguished from gastroesophageal reflux disease-associated esophageal eosinophilia, EoE is now recognized as a clinically distinct entity that shares fundamental inflammatory features of other allergic conditions, and is similarly increasing in incidence and prevalence. The clinical and epidemiologic associations between EoE and other allergic manifestations are well established. In addition to exaggerated rates of atopic dermatitis, IgE-mediated food allergy, asthma, and allergic rhinitis in EoE patients, each of these allergic manifestations imparts individual and cumulative risk for subsequent EoE diagnosis. As such, EoE may be a member of the "allergic march"—the natural history of allergic manifestations during childhood. Several determinants likely contribute to the relationship between these conditions, including shared genetic, environmental, and immunologic factors. Herein, we present a comprehensive review of allergic comorbidity in EoE. We discuss areas of the genome associated with both EoE and other allergic diseases, including the well-studied variants encoding thymic stromal lymphopoietin and calpain 14, among other "atopic" regions. We summarize ways that environment factors (such as microbiome-altering pressures and aeroallergen exposure) may predispose to multiple allergic conditions including EoE. Finally, we discuss some fundamental features of type 2 inflammation, and the resulting implications for the development of multiple allergic manifestations. We conclude with an analysis of the "type 2" biologics, and how mechanistic similarities between EoE and the other allergic manifestations have important implications for screening and treatment of the allergic patient.

Keywords

Eosinophilic esophagitis; Atopic dermatitis; Food allergy; Allergic rhinitis; Asthma

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Introduction

Allergic eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus that is thought to be caused by an allergen-specific immune response, and results in progressive esophageal dysfunction[1,2]. EoE is characterized clinically by abdominal pain, reflux, failure to thrive, odynophagia, and food impaction, and is associated histopathologically with progressive esophageal remodeling, stricture formation, and esophageal narrowing. In the 1970s-80s, early case descriptions began to distinguish the discrete characteristics of EoE from gastroesophageal reflux disease-associated esophageal eosinophilia; thought to be the predominant cause of esophagitis at the time [3–5]. In 1993, Attwood and colleagues described EoE as a clinically distinct syndrome [6], and soon thereafter EoE was found to share inflammatory features with other allergic conditions, including descriptions in early case reports [3,4,7]. EoE is now recognized as the most common cause of chronic dysphagia in children and young adults across the developed world[8–10]. Since its first description, rates of EoE diagnosis have steadily increased with current incidence estimates ranging from 5 to 10 cases per 100,000 with a prevalence of 0.5-1 cases per 1000 individuals[10,11].

Though a specific allergen is not able to be identified in every patient, it is generally thought that allergen exposure is a central feature of EoE pathogenesis. Evidence for this comes from early studies that revealed excellent response rates of esophageal inflammation to elemental diets[12,13], as well newer evidence from animal models[14]. Cohort studies from major referral centers have revealed that the most common foods associated with EoE are milk, egg, soy, and wheat—notably overlapping with foods most commonly implicated in IgE-mediated food allergy (IgE-FA). Like IgE-FA, identification and avoidance of the causative food is the primary treatment goal in EoE, when possible [15,16]. In cases where a trigger remains elusive, topical corticosteroids in various formations are highly effective therapies[17,18]. Importantly, and similar to the effects of chronic allergic inflammation seen in asthma, failure to diagnose and treat EoE can result in permanent tissue remodeling of the esophagus leading to stricture formation, odynophagia, and food impaction[19,20].

Epidemiologic associations between EoE and the other allergic manifestations have now been well established, with atopic dermatitis (AD)[1,21,22], IgE-FA, asthma[1,21–23], allergic rhinitis (AR)[1,21,22,24], and pollen food allergy syndrome[25,26] all shown to be common comorbidities in EoE patients. Conversely, patients with AD, IgE-FA, asthma, or AR are at increased risk of subsequently being diagnosed with EoE [27]. The relationship between IgE-FA and EoE seems to be particularly strong, with IgE-FA patients developing EoE almost nine-times faster than healthy peers[28]. Further, the risk relationship between EoE and AR seems to be bidirectional, with each condition imparting risk for the subsequent diagnosis of the other[27]. This final observation is consistent with data suggesting that EoE symptoms can be triggered by specific environmental allergens[7,29,30]. As a result of these various associations, EoE has been proposed as a fifth member of the allergic march[27,31]. Despite this, the recognition that EoE is associated with non-atopic diseases, such as inflammatory bowel disease and connective tissue disorders [32], speaks to the complexity of this disease and the possibility that multiple EoE endotypes exist[33].

Given the considerable allergic burden in EoE, and the relevance of shared allergic features to emerging therapeutics, we discuss the primary literature focusing on allergic comorbidity and type 2 inflammation in EoE. We focus on the shared genetic, environmental, and immunologic features that likely underlie the associations among these various allergic manifestations. We conclude with a discussion of the "type 2" biologics, and how mechanistic similarities between EoE and the other allergic manifestations have important implications for screening and treatment of the allergic patient.

Epidemiologic associations between EoE and the other allergic manifestations

In parallel with the rise in allergic diseases over the past several decades, the prevalence of EoE so too has increased both in pediatric and adult populations[34,35]. In a large pediatric cohort study at Children's Hospital of Philadelphia, a 70-fold increase in the rate of EoE was demonstrated from 1994-2011 [36]. Similarly, Straumann and Simon found an increase in EoE prevalence from 2/100,000 to 23/100,000 between 1989 and 2004 in an adult population in Switzerland[37]. While these findings may represent a true increase in the incidence of EoE over time, improved recognition and diagnostic capabilities likely also contribute to the increased diagnostic rates.

Additionally, a number of studies have associated EoE clinically with other atopic conditions, noting higher rates of comorbid asthma, AR, AD, asthma and IgE-FA in individuals with EoE compared to the general population[21,38,39]. In review of these early reports, approximately 25-50% of individuals with EoE have concurrent asthma, 30-90% have AR, and 10-25% have AD[24,40–43], with variation in these rates likely influenced by individual study populations and definition of conditions. Further, approximately 10-25% of EoE patients have concurrent or prior history of IgE-FA, compared to a rate of 8% in the general pediatric population[40–42,44]. Interestingly, patients with established IgE-FA have been found to have higher rates of subsequent EoE development compared to the general population, often secondary to the same culprit food responsible for the IgE-mediated allergy [28]. More recent studies in both children and adults within the past 5 years continue to support the association between EoE and atopy (Table 1).

To date, one large meta-analysis has also delineated the atopic burden in patients with EoE, showing significantly increased odds of AD (OR 2.85, 95% CI, 1.87-4.34), asthma (OR 3.01, 95% CI 1.96-4.62), and AR (OR 5.09, 95% CI 2.91-8.90) in those with EoE compared to healthy individuals[21]. We also performed a large analysis assessing children with and without EoE in a single large pediatric primary care network population[49]. In this study, the rates of atopic conditions were found to be significantly higher in subjects with EoE when compared to healthy children, and included AR (60% of EoE vs 17% without EoE; OR 7.1, 95% CI 5.8-8.6), asthma (60% of EoE vs 21% without EoE; OR 5.2, 95% CI 4.3-6.3) and AD (18% of EoE vs 7% without EoE; OR 3.1, 95% CI 2.4-4.0). Finally, in a large multicenter assessment of patients with EoE from the Consortium for Food Allergy Research, concomitant allergic disease was observed in 91% of the study population[50]. The overall prevalence of specific allergic diseases in EoE is depicted in Figure 1.

Given the clinical associations between EoE and the other allergic manifestations, we hypothesized that EoE might be an intrinsic member of the allergic (or atopic) march[27,31].

The allergic march refers to the natural history of allergic disease manifestations, and time course progression of these conditions throughout infancy and childhood[52]. Initial work by our group determined the peak age of diagnosis of EoE to be approximately 3 years following onset of AD, IgE-FA, and asthma (though actual EoE incidence may be earlier given the known barriers to diagnosis including presentation and histologic evaluation)[31]. Subsequently, in an analysis of over 130,000 children within a large primary care cohort, presence of AD, IgE-FA, asthma and AR were found to be both independently and cumulatively associated with subsequent diagnosis of EoE[27]. Despite these observations, it should be noted that there are varying degrees of EoE presentation, and an allergic trigger is not always identified. This fact speaks to the complexity of this disease process, and to the possible existence of multiple disease endotypes with varying degrees of allergic pathophysiology[33]. In the sections ahead, we discuss the shared genetic, environmental, and immunologic factors that may be responsible for the clinical and epidemiologic associations between EoE and the other allergic manifestations.

Genetic determinants of allergy susceptibility

Several studies, both involving human subjects and murine models, have contributed to our understanding of the immunopathogenesis of EoE[2]. Eosinophilic inflammation is generally thought to be a late-stage effector response to T helper (T_H) 2 cell-mediated inflammation, critical to other atopic diseases, and affecting select individuals with specific genetic predispositions. Many of these associations have been comprehensively reviewed previously with discrimination by genetic (disease risk variants, transcriptome) and epigenetic (histones, DNA, microRNA) disease-associated modifications[53]. Here we focus on genetic associations that may predispose to multiple allergic manifestations, including EoE.

Two widely studied genetic components involved in EoE and atopy include thymic stromal lymphopoietin (TSLP) and calpain 14 (CAPN14). Variants in the 5q22 locus encoding the gene for TSLP have been associated with EoE as well as the most common atopic diseases including, AD, asthma, and AR[54–58]. TSLP is an epithelial cell-derived cytokine that is secreted at barrier surfaces in response to allergen exposure, and is involved in the initiation and propagation of type 2 inflammation. In the esophagus, TSLP has been found to be overexpressed in biopsies from subjects with EoE, as compared to healthy individuals[59,60]. Furthermore, TSLP mediates inflammatory basophil responses in the context of experimental EoE[14]. These observations are reminiscent of the overexpression of TSLP that is observed in the skin of in patients with AD [61,62]. Notably, targeting TSLP for neutralization in murine models leads to elimination of esophageal eosinophilia, supporting a central role for TSLP in this disease process[14].

Similarly, variants in the 2p33 locus encoding the CAPN14 gene have been directly associated with EoE and atopy, with upregulation of CAPN14 in the esophagus of those with active esophagitis and following exposure to type 2 cytokines [55,63]. Previous reports have also associated CAPN14 dysregulation with epithelial barrier dysfunction[64,65]. Further, CAPN14 encodes a member of the calcium-dependent, non-lysosomal cysteine protease family and therefore may contribute to the protease hypothesis of EoE described below.

Relevant to discussion of TSLP and CAPN14, a recent study investigated the relationship between atopy, EoE, and genetic risk[66]. In this study, single nucleotide polymorphisms in 63 atopy genes were evaluated for EoE associations both in atopic and nonatopic individuals. The results suggested a mechanistic gene-gene interaction whereby atopy-related genes and EoE-specific loci (notably those for IL-4 and TSLP) synergistically cooperate to increase EoE risk. Thus, genetic susceptibility of EoE development is mediated by both EoE-specific and common atopic loci that, when present together, act synergistically to increase susceptibility to allergic disease development.

Other "atopic" regions of the genome previously identified include the 11q13 loci encoding EMSY and LRRC32 which are associated with EoE[55], AD[67,68], asthma[56,69], and AR[56]. Interestingly, this locus has also been associated with inflammatory bowel disease [70], which was recently found to be a significant comorbidity seen in children with EoE[49]. Genome-wide association studies have also identified regions contributing to susceptibility of IgE-FA onset, including the *SERPINB* gene[71]. While a direct association between *SERPINB* and EoE has not yet been established, the family of *SERPINs* genes are highly expressed in the esophagus, and so may be an important target for future exploration. Finally, 16p13 has been identified as an additional risk locus for EoE, associated with various disease including AD and asthma, and AR[56,72], among other immune and autoimmune conditions[73]. Together, these studies indicate that a shared set of genetic changes may predispose an individual to develop multiple allergic manifestations, including EoE.

Environmental factors common to the allergic manifestations

Multiple environmental factors have been associated with development of allergy [74], and the environment in which an individual is raised is a strong contributor to EoE development[54]. Common environmental factors that predispose to multiple allergic manifestations therefore likely contribute to the observed associations between EoE and its comorbidities. Here we review the major environmental considerations thought to contribute to allergy in general, and EoE specifically.

Microbiome-altering environmental pressures—Billions of microbes colonize the mucosal surfaces of mammals in a symbiotic relationship that supports normal physiology. The term microbiome describes the DNA material of these microbial communities which consists of bacteria, viruses, fungi, and protozoa. The human microbiome is both immense, and complex, with 100 trillion microbes representing multiple genera colonizing the gastrointestinal (GI) tract alone [75]. Over the past several decades, the GI microbiome has been a subject of particular focus, and research has added to our appreciation of dysbiosis (microbial imbalance or maladaptation) as an important factor in multiple human disease states [76], including allergy. Previous efforts have sought to understand the role of the microbiome in the context of allergic inflammation[77,78], and microbiome-altering environmental pressures are now thought to be important contributors to allergy risk[79].

Investigators have also focused specifically on the relationship between the esophageal microbiome and EoE. The esophagus itself is colonized by at least hundreds of bacterial

species, with members of the Firmicutes and Bacteroides phyla being among the most highly represented in both children and adults [80–83]. Initial studies of the esophageal microbiome in children with EoE have noted a few key associations. Most notably, when examining biopsy samples in children with active EoE, there is shift away from the genera *Streptococcus* and *Atopobium* in favor of *Neisseria* and *Corynebacterium* when compared with samples from patients with inactive EoE or healthy controls [83]. In another study that examined 16S rRNA from esophageal string tests from children and adults, it was observed that the total bacterial load, as well as members of the *Haemophilus* genus specifically, were enriched in patients with EoE as compared with controls[82]. In addition, approximately half of subjects with active EoE on proton-pump-inhibitor treatment had an enrichment of members of the Proteobacteria phylum when compared with controls, an enrichment that was also observed upon examination of esophageal biopsies from patients with active EoE[83]. Though preliminary, these studies have started to elucidate the microbiome of the EoE esophagus.

It is particularly useful to note that the esophageal bacterial load seems to be increased in patients with EoE irrespective of treatment status or the degree of mucosal eosinophilia, and that the microbiomes of the inflamed esophagus in patients with EoE or gastrointestinal reflux disease are distinct[82]. Together, these observations suggest that the dysbiosis observed in EoE is may be at least in part the result of a primary mucosal defect in the regulation of microbial communities, as opposed to solely the consequence of mucosal inflammation. That being said, mechanistic studies in animal models (germ-free, gnotobiotic, or otherwise) are required to establish the extent to which microbial changes are a secondary consequence of, or contributing factor to, the esophageal inflammation observed in EoE.

It is challenging to integrate microbiome data across biologic niches, as the commensals that colonize different mucosal and epithelial surfaces are distinct. However, there are a number of common environmental pressures that can impact commensal communities across the body, thereby creating dysbiosis that could contribute to allergy development or progression. Animal models have taught us that normal microbiota help control allergic responses to foods and other allergens [84,85], and antibiotic exposure, birth mode, preterm birth, and diet each dynamically restructure commensal populations [86,87], while increasing risk for allergy[79,88–90]. Similar associations exist with early-life environmental pressures and the development of EoE. For example, antibiotic exposure is associated with EoE in the majority of studies[91–95]. Similarly, cesarean delivery also increases risk of EoE[92,93]. Finally, while diet is known to influence the esophageal microbiome[83], like other allergic manifestations the association between early life breast vs. formula feeding and EoE is less clear[91,96]. Together, these studies support a role for environmental pressures that alter the microbiome as common factors that contribute to the development of EoE, and other allergic manifestations. However, future research is necessary to expand upon this work and define the most relevant microbes and immunologic mechanisms involved.

Exposure to aeroallergens as a trigger of EoE—As noted previously, there is a very high degree of comorbidity between EoE and AR[27]. However, evidence linking these two conditions extends beyond epidemiologic associations. Over the past decade, a body of

literature has emerged that describes how aeroallergens can exacerbate EoE in some individuals[97,98]. For example, a case series of 1,180 EoE patients found that 14% had a history of exacerbation by aeroallergens, and 1/5th of those had biopsy-confirmed seasonal variation of esophageal eosinophilia[30]. Several other reports have further supported an intrinsic, seasonal dependence of EoE with a decrease in the diagnosis of EoE during winter months, and increases in diagnosis during times of high pollen as the spring, summer, and fall[99–104]. One study even noted a significantly higher incidence of food bolus impactions in those with EoE during the summer and fall, compared with the winter[105].

Direct evidence for the role of aeroallergens in EoE exacerbations comes from both animal models and clinical observations. Researchers have developed models of experimental EoE in mice through exposure to perennial allergens such as cockroaches, dust mites, or molds[106,107]. Furthermore, EoE development has been seen in patients exposed to large volumes of allergens such as mold, dust, and grass following acute, large-volume accidental exposure[108] or sublingual pollen immunotherapy to trees[109] or grasses[109,110]. Interestingly, associations between aeroallergens and EoE seem to be primarily related to pollens, in contrast to the common “indoor” allergens. There is actually a small protective effect of owning a furred pet when it comes to subsequent EoE development[93,111]. It is not entirely known why pollens are particularly relevant, though it may be due to immunologic cross-reactivity with food allergen components[112].

Despite these associations, the correlation between season and rate of EoE diagnosis is not consistent across studies[113,114]. For example, a large report of over 700 patients found that EoE symptoms did not vary by season suggesting that the causal allergens are present year-round[115], and a meta-analysis of 18 studies and 16,846 patients found no statistical difference in the annual seasonal distribution of newly diagnosed EoE [116]. It is also worth pointing out that the endpoint for this meta-analysis was food bolus impaction requiring medical care—an outcome that favors specificity over sensitivity. None the less, these studies indicate that the role of aeroallergens in EoE may be nuanced, with aeroallergens being relevant in a subset of patients (for example older children where allergic rhinitis is more prevalent), or due to sensitivity to allergens characteristic of distinct seasons, geographic regions, or diets.

Oral or sublingual immunotherapy for IgE-mediated food allergy—Recently, the recognition of EoE in patients undergoing oral immunotherapy (OIT) for IgE-mediated food allergy has raised concern that OIT could trigger EoE in susceptible individuals [117–119]. This association was further explored in a meta-analysis which reported a positive correlation between OIT and EoE, with new onset of EoE occurring in 2.7% of patients undergoing OIT[119]. However, it should be noted that in this meta-analysis EoE diagnosis was defined by biopsy, excluding patients with clinical symptoms of EoE (such as abdominal pain or vomiting) alone [120]. In our previous review of studies that documented discontinuation of OIT due to EoE symptoms and/or consistent biopsy findings, we found that symptoms of EoE occur at a rate between 8 and 14%[28]. Thus, while abdominal pain and vomiting are not diagnostic for EoE, actual rate of EoE during OIT may be higher than previously appreciated.

It is unclear at this time whether OIT causes EoE, or whether OIT exacerbates mild EoE in otherwise sub-clinical individuals. We found that the prevalence of EoE in patients with IgE-mediated food allergy is higher than the rate of EoE in the general population[28], and that a history of IgE-FA to the three of the most common food allergens (milk, egg, and shellfish) was highly associated with the subsequent diagnosis of EoE [28]. In a follow-up study, we observed a hazard ratio of 9.1 for children with IgE-FA going on to develop EoE, the strongest association detected among the various allergic march relationships [27]. Finally, it has been reported that individuals who outgrow IgE-FA can go on to develop EoE to the same food[121–123]. Together, these findings suggest that a common allergen-specific T_H2 response could give rise to both IgE-FA and EoE. This body of literature also suggests that the concern for iatrogenic EoE in patients undergoing OIT is warranted, and patients undergoing OIT should be closely monitored for development of EoE symptoms.

Role of infections in EoE predisposition—In investigations into environmental factors that might influence EoE development, an interesting association was made with *Helicobacter pylori* (*H. pylori*). *H. pylori* infects about half of the global population[124], with a wide variation between regions and countries. Since it's identification as a cause of peptic ulcer disease, gastritis, and several cancers, the prevalence of *H. pylori* has dramatically decreased in westernized countries[125,126]. This occurred at the same time as an increasing recognition and diagnosis of EoE, resulting in an inverse association between EoE rates and *H. pylori* infections[127–132].

The inverse association between EoE and *H. pylori* resulted in the development of a hypothesis that *H. pylori*, by inducing both a T_H1 and T_H17 response[133], polarizes the immune system away from allergic inflammation. This hypothesis was supported by animal studies that show a protective effect of *H. pylori* infection in a model of allergic asthma[134]. However, a recent large, multicenter, case-control study directly examined the relationship between *H. pylori* and EoE in a prospective manner. A total of 808 individuals were studied, including 170 children. The study found that there was no difference in *H. pylori* prevalence between cases and controls in either children or adults [135]. Thus, despite the potential for relevant immunologic mechanisms, it is unlikely that there is a clinically-relevant protective effect of *H. pylori* infection in the setting of EoE.

Shared features of "type 2" inflammation among the allergic manifestations

The observation that most EoE patients have comorbid allergic conditions suggests that EoE is immunopathologically related to the other allergic manifestations. Additional evidence of this relationship comes from the fact that EoE shares many clinical similarities to other allergic conditions including exhibiting a "type 2" or allergic form of inflammation[136,137], and being responsive to allergen avoidance and/or topical steroid applications. For example, elemental diets have been shown to be highly effective in inducing histologic and clinical remission in children and adolescents with EoE[138–140], as have empiric elimination diets based on the most commonly identified etiologic foods[139]. Alternatively, orally administered topical steroids are an effective therapy for EoE, with resolution rates up to 80%[17,18,141–147]. A notable exception to the clinical similarities between EoE and the other allergic manifestations is that allergen testing (skin

prick or specific serum IgE) is of limited utility when attempting to determine causal foods [15,138], likely because IgE is not required for EoE pathogenesis (in animal models) [14]. There have been considerable advances over the past decade to our understanding of the immunologic mechanisms underlying EoE pathophysiology, the details of which have been reviewed previously [2,148]. We therefore focus on fundamental features of allergy development, and how they may contribute to the relationship between EoE and its comorbid conditions (Fig. 2).

The protease hypothesis—The protease hypothesis supposes that protease activity is one upstream trigger of type 2 inflammatory responses; the mammalian immune system's reaction to both parasitic and allergic stimuli. There are evolutionary advantages to mammals evolving sensors of protease activity, as many parasites utilize proteases to both aid host invasion and establish chronic infection[149]. Protease sensors of the immune system include the interleukin (IL)-1 family of cytokines, and in particular the potent T_H2 stimulus IL-33, which are directly activated by microbial and allergen-associated proteases[150,151]; direct activation of innate immune cells including basophils, eosinophils, and mast cells[152–155]; and polarization of naive T cells towards a T_H2 activation state such as that mediated upon cleavage of the protease-activated receptor 2 [156]. These innate protease sensors may be unintended targets of many of the most clinically-relevant allergens including insect venoms[157], some food allergens[158], and respiratory allergens[151,159,160], all of which can exhibit inherent protease activity. Given the fundamental role of proteases in inducing type 2 inflammatory responses, it is perhaps not surprising that the protease activity of allergens has been shown to be important for generating multiple models of allergic disease[161].

There is also building evidence to support a role for protease dysregulation in EoE pathogenesis. Clinically, a high proportion of patients with EoE display sensitivity to indoor protease allergens derived from insects[107,159,162]. Experimentally, exposure to these same indoor allergens including house dust mite (HDM), cockroach, or mold allergens, can induce EoE-like inflammation in mice[106,107,163]. For example, the major HDM allergen (Derp1) has prominent cysteine protease activity that mediates immune cell activation via cleavage of the low-affinity IgE receptor CD23, and the alpha subunit of the interleukin IL-2 receptor CD25[164,165]. In mice, exposure to HDM allergen results in significant infiltration of eosinophils and mast cells into the esophagus, which is independently dependent on eotaxin-1/2, CCR3, and IL-5.

Additional evidence of a role for proteases in EoE pathogenesis comes from genome-wide studies that have identified polymorphisms in protease inhibitors that associate with the disease. For example, EoE has been linked to polymorphisms in the CAPN14 gene[63], a calcium-activated cysteine protease that is induced by IL-13, and contributes to the esophageal epithelial barrier impairment observed in EoE [64]. Conversely, polymorphisms that interfere with potentially protective, anti-peptidases expressed by the esophageal epithelium are also associated with EoE. The *SERPIN* gene family, which encode serine and other protease inhibitors, are highly expressed in the esophagus and associated with FA on a genome-wide level[71]. Intriguingly, the SERPINs are among the most dysregulated esophagus-specific protein families in EoE[166]. Similarly, the serine protease inhibitor

Kazal-type 7 (SPINK7) is important for normal epithelial differentiation. SPINK7 is lost in the epithelium of EoE patients, and experimental manipulations of SPINK7 have shown that it plays a homeostatic role in maintaining barrier function and allergic inflammatory responses[167]. Together, these results identify mammalian-encoded proteases, and protease inhibitors, and integral components of normal esophageal epithelial barrier function and immune responses, and emphasize the role of both mechanisms in EoE pathogenesis (Fig. 2AB)[168].

A failure of barrier integrity—An additional shared feature of type 2 inflammatory diseases, whether they be of the skin, gastrointestinal (GI) tract, or airway, is an impairment of epithelial barrier integrity [169]. When this important barrier is disrupted, immune activating microorganisms and antigens can gain access to body's immune system, with resulting inflammatory responses. The GI tract is one of the best studied of the mucosal sites, and is unique in that it is one of two organ systems (along with the lungs) that has evolved to facilitate biologic interactions with the external world. Consequently, the large surface area of the GI tract is charged with absorbing essential minerals and nutrients while being simultaneously exposed to inert compounds, allergens, toxins, commensal organisms, and pathogens.

As a result of this complicated task, the GI tract has evolved physical, biochemical, and immunologic barriers between the internal and external environment[76]. Epithelial cells of the GI tract express various intercellular junctions (apical tight junctions, subjacent adherens junctions, and desmosomes) all of which control the absorption of fluid and solutes while impeding access of pathogens and other harmful molecules[170]. In addition, biochemical adaptations (such as mucus, and antimicrobial peptides) confer broad-spectrum antimicrobial properties to the epithelium[170]. Finally, the human GI tract is home to one of the highest densities of immune cells in the entire body which must identify potentially harmful stimuli and mount a protective response [171].

When these adaptations fail, the results can be catastrophic. One of the best examples of this comes from our understanding of inflammatory bowel disease where an overwhelming immune response to normally commensal microbes results in significant morbidity and mortality [172]. However, defects in barrier function are characteristic of the allergic manifestations, where microbial exposure activates the innate immune system, and subsequent T_H2 responses can develop against otherwise inert antigens. For example, AD is characterized by defects in filaggrin (a filament-associated epidermal differentiation complex protein essential for regulation of epidermal homeostasis) [173], desmosomal proteins[174,175], and tight junction proteins[176], while disruption of both epithelial tight and adherens junctions is characteristic of asthma[177].

Consistent with epithelial barrier dysfunction being a common feature of allergy, genes and molecules important for epithelial integrity (including *CRISP3*, *CLDN10*, *DSG1*, and *FLG*) have been linked to EoE in patients and disease models [167,178,179]. For example, it has been noted that patients with EoE have reduced levels of DSG1, an intercellular adhesion molecule that is important for maintaining suprabasal epithelial integrity, as compared with controls[180]—a defect which is also observed in AD[174,175]. Treatment of EoE with

topical steroids results in normalization of DSG1 expression, suggesting a central role in the barrier dysfunction observed in EoE[181]. Patients have also been identified with homozygous mutations in DSG1, and the resulting severe allergic phenotype includes eosinophilic esophageal inflammation[174,175]. Mechanistically, deletion of *DSG1* in cultured epithelial cells results in a transcriptional phenotype similar of EoE biopsies [180]. While IL-13 treatment or overexpression of calpain 14 (a protease discussed above) reduces DSG1 expression in epithelial cells and results in impaired barrier function[64,180,182]. Together, these observations identify epithelial barrier dysfunction as a central feature of EoE pathology, that is common to the other allergic manifestations (Fig. 2C).

Promiscuity of type 2 inflammatory responses—An additional mechanistic question related to the clinical associations between EoE and the other allergic manifestations is whether there is an additive effect of existing type 2 inflammation on the subsequent development of food-specific T_H2 cell responses. This effect could contribute to the progression of the allergic march in a manner that is complementary too genetic and environmental factors. Perhaps the best understood example of this phenomenon is the increased likelihood of allergic sensitization that occurs when the immune system is exposed to an antigen via inflamed skin, such as that seen in atopic dermatitis. In this case, the resulting inflammatory milieu of a primary skin defect promotes the development of specific T- and B-cell responses, and subsequent allergic disease. This mode of sensitization is certainly relevant to IgE-FA and respiratory allergy, as well as EoE (Fig. 2D)[14]

However, there is also evidence to suggest that systemic allergic inflammation could act as an adjuvant for the development of T_H2 cell responses. Basophils are one potential mechanism for this effect as they are potent innate sources of IL-4, and are recruited to lymph nodes quickly after exposure to infectious or allergic stimuli where they cooperate with DCs to promote T_H2 cell development[183]. What is particularly notable about basophils however is that their number in the blood in the steady-state, and their recruitment to lymph nodes after allergen exposure, are both directly related to serum IgE levels in an antigen-independent manner [84,184]. Thus, elevated IgE levels as a result of multiple factors could potentiate the subsequent development of basophil-facilitated T_H2 responses at other tissue sites, including the esophagus [185]. While these observations offer preliminary insights into immunologic mechanisms by which the presence of allergic inflammation at one site may potentiate the development of additional allergic manifestations, additional basic and translational research is necessary to establish its relevance.

The role of “Type 2” targeted biologics in EoE management

Given the shared features of EoE and the other allergic manifestations, it is reasonable to consider the role of new, type 2-targeted biologics in EoE management. Indeed, biologic therapies have proved to be innovative therapeutics for various allergic diseases, and several of these agents have also been evaluated for use in EoE. The possibility to treat allergic patients with a single medication that is effective against multiple allergic manifestations may represent a reality for the future of allergy care. Here we review biologics that target immunologic pathways that are common to multiple allergic manifestations including EoE.

IL-5-targeted therapies—IL-5, integral for multiple facets of eosinophil biology, and has perhaps been the most widely studied target for treatment of EoE. Studies have primarily focused on mepolizumab, a humanized monoclonal antibody currently approved for the treatment of asthma and for other hypereosinophilic syndromes including eosinophilic granulomatosis withpolyangiitis[186–188]. Initial murine studies using IL-5 targeted therapy demonstrated promising results with significant reductions in airway inflammation/ hyperresponsiveness, airway eosinophilia and reduced response to methacholine[189–191]. Use of mepolizumab for EoE was initially openly studied in a small phase 1-2 study of adults that found significant reductions in esophageal eosinophilia and clinical symptoms in the treatment group[192]. These results were not replicated, however, in prospective, randomized, double-blind placebo-controlled trials (RDBPCT) including one adult study in which both the histologic and symptom-based end points were not reached[193]. In the pediatric RDBPCT trial, only 8.8% of patients reached the pathologic primary end point, with no significant improvement in clinical symptoms [194].

Other IL-5 inhibitors studied in the treatment of EoE include Benralizumab and Reslizumab, both currently approved for use in eosinophilic asthma in adults, with additional approval for use of Benralizumab in adolescents [188]. While no specific RDBPCTs using Benralizumab (a IL-5 receptor antagonist) for EoE exist to date, significant histologic and symptomatic improvement was demonstrated in patients with hypereosinophilic syndrome involving the gastrointestinal tract, whereby depletion of gut tissue eosinophilia was demonstrated[195]. In the randomized placebo-controlled trial of Reslizumab, involving a large cohort (n=226) of children with EoE, a significant reduction in peak esophageal eosinophils was positively achieved[196]. Specifically, compared to the 24% reduction demonstrated in the placebo group, those treated with Reslizumab demonstrated a 59-67% reduction in peak eosinophil counts, however, no significant differences in patient symptoms or physician global assessment was found between groups. Given the overall mixed nature of these data, further studies using targeted IL-5 therapy are needed.

IgE-targeted therapies—Omalizumab, a humanized mouse anti-IgE monoclonal antibody currently used in the management of asthma and chronic urticaria[184,197,198], has also been studied for use in EoE with variable outcomes. In a 12-week open label study, 33% of patients who underwent omalizumab therapy achieved the study's pathologic end point in pathologic reduction of esophageal eosinophils, with nearly half of these patients experiencing symptomatic improvement[199]. Similar to the anti-IL-5 studies, results were unable to be replicated in an RDBPCT of mostly adults with EoE, where no significant difference in EoE-related symptoms or esophageal eosinophils was observed between those in the treatment vs placebo groups[200]. These negative results could indicate that IgE is not required for EoE pathogenesis. However, in the open label study, omalizumab-induced remission of EoE was limited to subjects with low peripheral blood absolute eosinophil counts, which may suggest specific utility in a subset of patients, though further studies are needed.

IL-13 and IL-4-targeted therapies—Three additional RDBPCTs involving biologic therapies targeted towards the treatment of EoE should be mentioned. These include two

studies targeting IL-13, an integral T_H2 cytokine secreted by active eosinophils and necessary for eotaxin-mediated eosinophil recruitment, among other functions[7,201]. The first study involved 23 adult patients with EoE treated with the monoclonal IgG1 anti-IL-13 antibody, QAX576[202]. Although the primary endpoint of reduced peak eosinophils was not reached, mean eosinophil count was significant reduced in the treatment group compared to controls. Additionally, in the QAX576 group, several EoE-relevant transcription markers (eotaxin-3, periostin and markers of mast cells) were improved. In the second study, adult patients who underwent 16-week treatment with RPC4046, a humanized IgG1 kappa anti-IL13 antibody showed improvement in EoE features, including improvement in clinical symptoms, clinician's global assessment of disease severity, and histology, with a significant decrease in esophageal eosinophils compared to those receiving placebo[203]. Finally, a single study evaluating the utility of Dupilumab, a human anti-IL-4 receptor alpha monoclonal antibody that inhibits signaling both of IL-4 and IL-13, and currently approved in the treatment of adult severe atopic dermatitis, was also conducted in patients with EoE. In this phase 2 RDBPCT involving multiple clinical centers, adults with EoE in the treatment group were found to have significant improvement in comprehensive histologic evaluation, including significant reduction in peak esophageal eosinophils and in symptoms, compared to the placebo group[204]. Together, these studies suggest IL-13 (and potentially IL-4) as targets for EoE therapeutics, with the potential that future studies could evaluate IL-13 as a target for atopic diseases such as asthma and AD, specifically in patients with comorbid EoE diagnosis.

Conclusions and clinical implications

In sum, evidence suggests that EoE is a primarily allergic disease, that is closely associated with AD, IgE-FA, asthma, and AR. While the relationship between these conditions is likely the result of shared genetic, environmental, and immunologic features, the details of these relationships continue to be elucidated. For example, there is likely a subset of patients who are significantly predisposed to develop EoE as a result of their genetics alone (Fig. 3A). However, others may require contributions from their environment and/or concurrent type 2 inflammation at sites other than the esophagus to potentiate EoE development (Fig. 3B,C). Future studies must focus on establishing the relative contributions of these "allergic determinants" to EoE development, with particular focus on the immunologic mechanisms that link one allergic manifestation to the development of another.

When considering the pathophysiology of EoE and the other allergic manifestations, a model emerges that can place EoE in immunologic and clinical context. In this simplified model, a foreign protein is exposed to the immune system as a result of a barrier defect such as AD (Fig. 4A). Upon exposure, there are two broad opportunities for tolerance—one at the point of the T cell, and one at the point of the B cell (Fig 4B). Should both of these checks fail, the individual develops an IgE-mediated disease such as AR, or IgE-FA (Fig. 4C). Individuals where allergen-specific T_H2 cell response form, but B cell tolerance is maintained (or develops over time such as the case with children who "outgrow" IgE-FA), may still be at risk for developing a primarily T cell-mediated disease such as EoE (Fig. 4D). There is some precedent for such discordance between allergen-specific T and B cell responses, as food allergen-specific IgE and basophil activation correlate with clinical IgE-

FA, while presence of allergen-specific T_H2 cells do not[205]. This model also provides a potential explanation for the limited utility of skin prick testing in EoE[15,138], as food-specific T cell responses can exist in the absence of circulating food-specific IgE. Further, a natural extension of this logic suggests that the ability to measure food-specific T cell responses may aid in the identification of EoE-causal foods[206]. Finally, there are mixed IgE/T cell-mediated conditions such as asthma (Fig. 4E). While this model is useful to broadly categorize the relationship between the allergic manifestations, the authors are the first to acknowledge that EoE subtypes may exist that result from a mixed, IgE/T cell-mediated mechanism. None the less, the prevailing view at this time is that IgE may contribute, but is not required for EoE pathogenesis in most cases[207].

From a clinical stand point, early diagnosis and institution of an effective treatment regimen is paramount in preventing long-term sequelae of EoE [208]. In 2018, the Updated International Consensus Criteria for EoE were published, establishing important changes in screening methods for patients suspected to have EoE [209]. Given the clinical associations between EoE and the other allergic manifestations, the use of allergic history in evaluating a patients risk for EoE is an attractive consideration[210]. It is reasonable that family or personal history of a preexisting allergic disease should increase the suspicion for EoE, as it has been reproducibly demonstrated across multiple studies that individuals with EoE have a high prevalence of allergic comorbidity. The relationship between IgE-FA and EoE seems to be particularly strong. Thus, physicians should suspect EoE in patients with chronic symptoms of esophageal dysfunction, especially in those with personal history of a significant atopic burden, and with particular emphasis on current or prior IgE-mediated food allergy. Finally, physicians should be vigilant about screening for symptoms of EoE in patients undergoing immunotherapy for IgE-FA. By continuing to elucidate the clinical and pathophysiologic relationship between these conditions, we will have the best chance of identifying and developing new preventative and therapeutic approaches that are common among EoE, and the other allergic manifestations.

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Abbreviations:

EoE	eosinophilic esophagitis
AD	atopic dermatitis
IgE-FA	IgE-mediated food allergy
AR	allergic rhinitis
GI	gastrointestinal
TSLP	thymic stromal lymphopoietin

CAPN14	calpain 14
OIT	oral immunotherapy
RDBPCT	randomized, double-blind placebo-controlled trial
H. pylori	Helicobacter pylori
T_H	T helper
IL	interleukin

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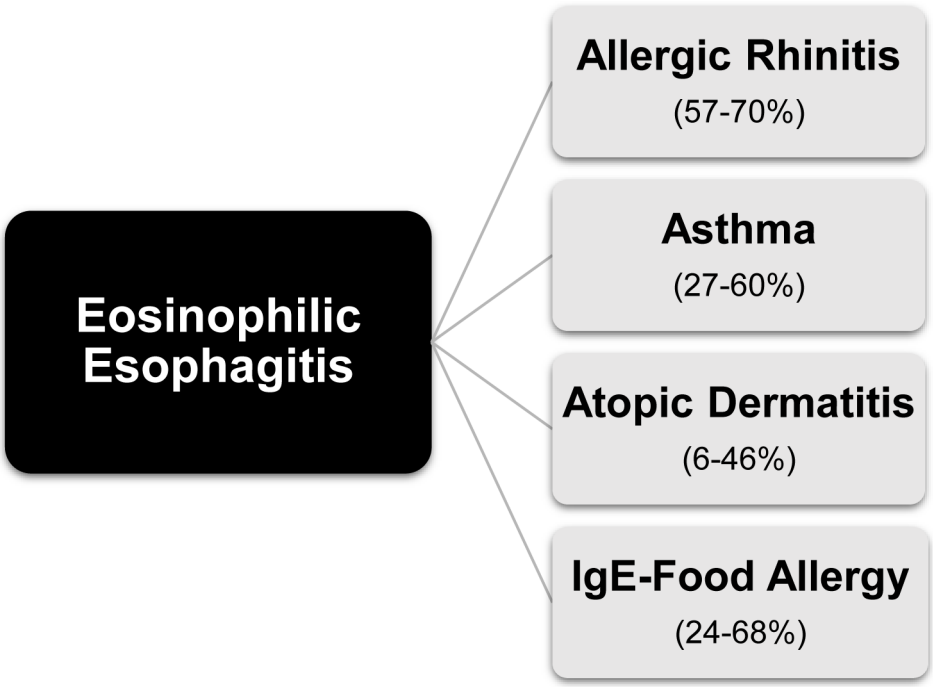

Fig 1.
Frequency of allergic diseases in patients with eosinophilic esophagitis from 2015-2019 studies. Prevalence rates shown in parentheses. [212842-48]

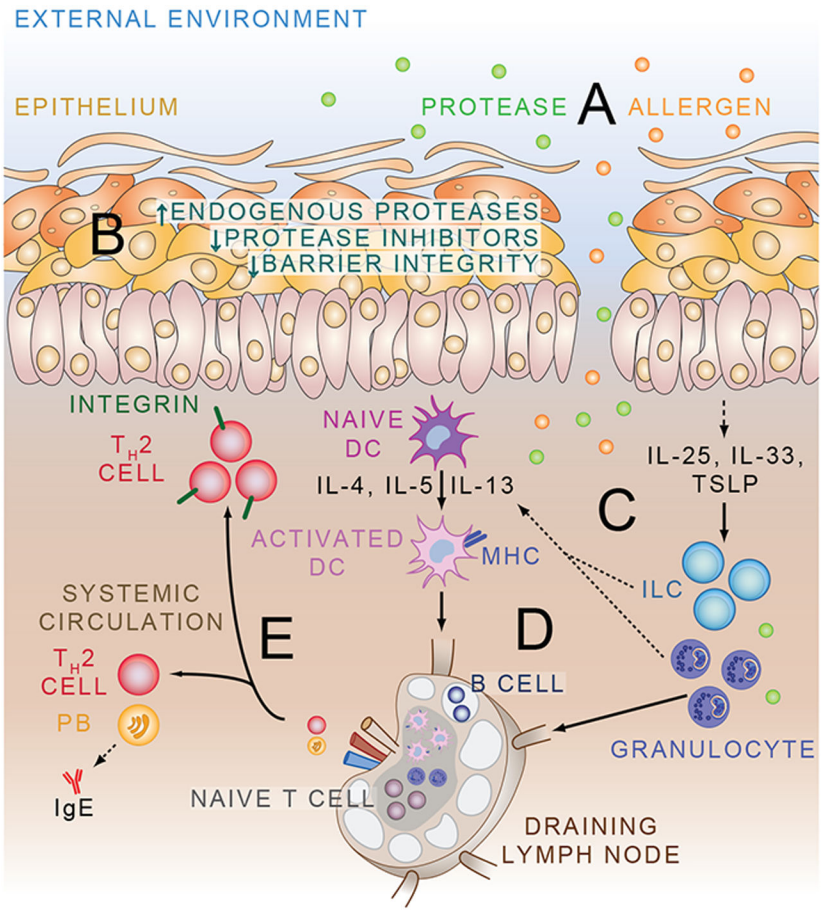

Fig 2.

Model of allergy development. The epithelium (whether it be the airway, skin, or GI tract) is constantly exposed to protease and non-protease allergens (A). Exogenous protease exposure, up-regulation of endogenous proteases, and down-regulation of protease inhibitors is associated with impaired barrier integrity (B). Breakdown of the epithelial barrier allows allergen entry, and causes secretion of alarmin cytokines including IL-25, IL-33, and TSLP that recruit and activate innate lymphoid cells (ILC) and granulocytes (C). Innate cells are potent sources of type 2 cytokines that can help to activate naive dendritic cells (DC) to process antigen, and promote development of type 2 helper T (T_H2) cell responses (D). T_H2 cells can home back to the site of inflammation via up-regulation of specific chemokine receptors and integrins, or enter the circulation along with allergen-specific IgE-producing plasma blasts to exert effects at distant tissue sites (E).

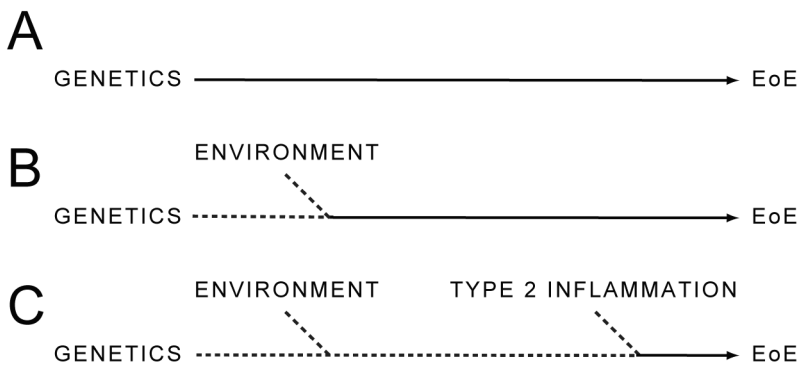

Fig 3.

Factors underlying the development of EoE. Cumulative influence of an individual's genetics (A), environment (B), and existing type 2 inflammation (C) on risk of EoE development.

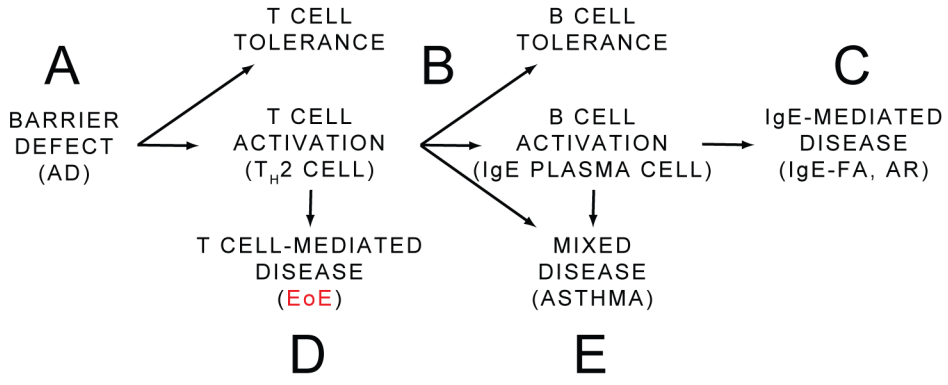

Fig 4.

Simplified model of the pathologic relationship between EoE and the other allergic manifestations. Allergy often is initiated at a site of barrier defect such as is the case in atopic dermatitis (AD) (A). There are two broad checkpoints at which antigen-specific activation or tolerance can occur: the T cell and the B cell (B). Should T and B cell tolerance fail, an IgE-mediated disease such as IgE-mediated food allergy (IgE-FA) or allergic rhinitis (AR) ensues (C). In the presence of B cell tolerance, allergen-specific T cells can cause eosinophilic esophagitis (EoE) (D). Mixed IgE/T cell-mediated disease can also occur, such as is the case with asthma (E).

Table 1.

Summary of studies showing the frequency (and odds) of allergic diseases in patients with eosinophilic esophagitis between 2015-2019.

Author/Year[Ref]	No. EoE Patients	Population	AR	Asthma	AD	IgE-FA
Dellon et al. 2015 [45]	81	Adults	62%	27%	6%	43%
Leung et al. 2015[46]	23	Children	57%	57%	30%	30%
Peterson et al. 2015[47]	4,423	Both	-	OR: 4.0	OR: 3.0	-
Duffeyet et al. 2016 [48]	4,009	Both	-	OR: 3.95	-	-
Gonzalez-Cervera et al. 2017[21]	53,542[a]	Both	OR: 5.09	OR: 3.01	OR: 2.85	-
Hill et al. 2017[28]	1,795	Children	-	-	-	68%
Capucilli et al. 2018[49]	428	Children	60% OR 7.1	60% OR: 5.2	18% OR: 3.1	-
Chehade et al. 2018[50]	705	Both	60%	45%	46%	67%, 27%[b]
Leigh et al. 2019 [51]	950	Adults	70%	36%	14%	24%

[a]Data from meta-analysis report

[b]Rate of FA-anaphylaxis, specified

Abbreviations: EoE, eosinophilic esophagitis; AR, allergic rhinitis; AD, atopic dermatitis; IgE-FA, IgE-mediated food allergy; OR, odds ratio.