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# From genetics to treatment of eosinophilic esophagitis

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## Abstract

**Purpose of review—**Eosinophilic Esophagitis (EoE) is an emerging chronic atopic disease. Recent advances in understanding its genetic and molecular biology pathogenesis may lead to a better management of the disease

**Recent findings—**EoE is an atopic disease. Most of the patients affected by EoE have other atopic diseases such as allergic rhinitis, asthma, IgE-mediated food allergies and/or atopic dermatitis. The local inflammation is a T helper type 2 (Th2) flogosis, which most likely is driven by a mixed IgE and n-IgE-mediated reaction to food and/or environmental allergens. Epidemiological studies show that EoE is an atopic disease with a strong genetic component. Genetic studies have shown that EoE is associated with single nucleotide polymorphism on genes, which are released by the epithelium and important in atopic inflammation such as thymic stromal lymphopoietin located (TSLP) close to the Th2 cytokine cluster [interleukin (IL)-4, IL-5, IL-13] on chromosome 5q22, Calpain 14, EMSY, and Eotaxin3. When the EoE diagnosis is made, it is imperative to control the local eosinophilic inflammation not only to give symptomatic relief to the patient, but also to prevent complications such as esophageal stricture and food impaction.

**Summary—**EoE is treated like many other atopic diseases with a combination of topical steroids and/or food antigen avoidance. The new understanding of EoE may lead to more specific and definitive treatments of EoE.

### Keywords

eosinophilic esophagitis; genome wide association study; T helper type 2 inflammation

## INTRODUCTION

Eosinophilic Esophagitis (EoE) is a chronic atopic clinical-pathologic disease affecting both children and adults [1,2]. It is defined by a significant pathological eosinophil infiltration limited to the esophagus that causes esophageal dysfunction and, if left untreated, fibrosis [1,2]. As the esophageal gastro-duodenal endoscopy has become readily available at the

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**Conflicts of interest**

There are no conflicts of interest.

beginning of the 21st century, EoE has been exponentially more recognized in western countries, with a yearly incidence now estimated to be similar to Crohn's disease [3–8].

In the last few year, using traditional epidemiology, a novel genetics study approach and traditional molecular biology, there has been great progress in understanding EoE pathogenesis [9▪]. This progress has led to establish a well defined globally accepted management of the EoE and a search for more specific treatments that will hopefully result in the cure of this puzzling and ever more prevalent disease [10–13].

## EPIDEMIOLOGY

Several epidemiological studies [5–7,14▪,15,16] have revealed that EoE is a highly hereditable atopic disease that affect mainly Caucasian men regardless of their age. EoE affects children and adults from all continents [5–7,14▪,15,17]; however, the western world has a highest prevalence, with a north–south and west–east gradients similar to the one described for the incidence of atopic diseases [5–7,14▪,15,16]. In children in the Unite States, EoE has prevalence of 50.5/10000, equivalent to pediatric inflammatory bowel disease [18].

The epidemiological data suggest both atopic and genetic components in patients with EoE:

1. Patients with EoE are highly atopic [19,20] (Table 1). The most common comorbidity is the allergic rhinitis, but also the rate of IgE-mediated food allergy is 10 times higher than the general population [19–22]. Unlike classic food allergy that typically involves a limited set of foods, EoE patients are often sensitized to a myriad of foods, often including food groups not typically considered to elicit IgE-mediated food allergy [23].
2. EoE affects predominantly men with a male to female ratio of 3 : 1 in both children and adults [2,6,18].
3. Family history, especially in men, is very frequent with nearly 10% of parents of EoE patients having a history of esophageal strictures and about 8% having biopsy-proven EoE [24]. EoE also shows a sibling-risk ratio of 80, meaning that having a sibling with the disease increase 80 times the risk of developing a similar disease in other siblings. This is extremely high compared with the one for related atopic diseases such as asthma that has a sibling-risk ratio of about 2 [4,25,26].

All together, the epidemiological data suggest a strong atopic and genetic component in EoE development.

## GENETICS BASIS OF EOSINOPHILIC ESOPHAGITIS

The epidemiological data show that EoE is an atopic, multifactorial, and complex disease with a strong genetic component, whose inheritance does not follow the classical Mendelian patterns [26,27,28▪▪, 29,30]. It is believed that multiple interacting genes, some having a protective effect and other a causative one, act together with each gene having its own tendency to be influenced by the environment [26,27,28▪▪,29,30]. Two study designs are

commonly used to determine the genetic contributions in complex diseases candidate gene association studies and genome-wide association studies (GWAS) [30]. Genome-wide linkage study design can be also used in large families affected by complex multifactorial diseases, but it will not be discussed as this approach has not been used to study EoE.

The candidate gene association studies allow the identification of genes and pathways suspected of contributing to the disease based on its biological plausibility, and the incidence of small gene variations such as single nucleotide polymorphysim (SNP) in the suspected gene or sets of genes are compared between a population affected by the disease (cases) and a group of controls [30]. The main limitations of such a design are its inability to identify novel or unsuspected genes and pathways contributing to the pathogenesis of a disorder [30].

The availability of microarray technology has made possible the high-throughput genotyping of hundreds of thousands SNPs on the entire genome and has allowed the development of like GWAS [30]. In this design many SNPs are compared across the entire genome between cases and controls. As shown in the candidate gene association study [30], the larger the number of cases and controls for analysis, the better the statistical power. GWAS allows also performing a hypothesis-free search for gene variants associated with a certain disease and this has been a powerful tool to unveil new targets for researchers [30]. Moreover, independent replication of genes identified through GWAS is much more common than those identified with the single gene approach association [30].

The first candidate gene for EoE identified was *CCL-26 (Eotaxin 3)*, after a genome-wide profiling revealed that CCL-26 was overexpressed about 50-fold compared with normal controls or patients with gastroesophageal acid reflux [31]. This study highlighted the important role of CCL-26 in EoE pathogenesis. A potential proposed mechanism is that T helper type 2 (Th2) cell activation leads to overexpression of CCL-26 from the esophageal epithelial cells, especially if genetically predisposed, and to the migration of eosinophils to the esophagus [29,31–40].

Aceves *et al.* [41–43] examined how SNP could influence the response to topical corticosteroids in patients with EoE. The patients who responded to the topical therapy were more likely to have a CC genotype at the −509 position in the TGF-β promoter than were nonresponders. These data suggest that response to therapy may be influenced by the genetic background.

More recently, GWAS analysis has identified three genes as important candidate gene in the pathogenesis of EoE: the thymic stromal lymphopoietin (*TSLP*) gene, at 5q22, the Calpain 14 one on chr2p23.1, and the *c11orf30/EMSY* gene one on chr11q13.5 [27,28▪▪,44▪▪,45] (Table 2).

TSLP is a cytokine that belongs to the interleukin (IL)-7 family, it is secreted by epithelial cells in response danger stimuli (i.e. infectious agent, stimulation of toll-like receptor, allergens) and it is elevated in EoE patients [27,46,47]. TSLP is a major driver of atopic inflammation and tissue remodeling, as it strongly promotes Th2 inflammation by: activating professional antigen-presenting cells (APC to prime naive T-cell to initiate Th2-type allergic responses; inhibiting Tregs; directly promoting Th2-cytokine secretion from T

cells, basophils, eosinophils, mast cells, and invariant natural killer cells [46,48–59]. The first ever GWAS conducted in EoE showed an association between a SNP in TSLP gene and risk for EoE in a relative small population of 500 EoE children, confirming the strong influence of genetics in EoE [27]. Those who were homozygous for the EoE risk allele (AA) had increased TSLP expression and basophil infiltration in the esophageal epithelium compared with those carrying heterozygous (AG) risk allele and homozygous (GG) protective minor alleles [27]. In addition, Sherrill *et al.* [45] not only confirmed TSLP protective SNP but also found that male patients with EoE had more often a SNP in the TSLP receptor (TSLPR) gene, which is encoded by a pseudoautosomal region on Xp22.3 and Yp11.3 [45]. This finding could explain the epidemiological data that EoE is more common in men by a 3 : 1 ratio [15].

Subsequent molecular biology studies [52,53,60] conducted by our group with collaboration with Dr Artis's group showed that TSLP may promote Th2 inflammation in EoE through basophils. Basophils are known to secrete histamine and Th2 cytokine (IL-4 and IL-13) if stimulated through their high affinity receptor for immunoglobulin (Ig)E (FcεRI) [61]. However, Siracusa *et al.* [53] have described that TSLP may act as an independent growth factor for a subpopulation of basophils, which is overexpressed in EoE patients and is able to produce significant Th2 cytokines (IL-4, IL-6, CCL3, CCL4, and CCL12). Even more interestingly Noti *et al.* [52] recently described a novel mouse model of EoE in which the development of EoE-like features was dependent upon both TSLP and basophils, but independent of IgE responses. In his mouse model, blocking of TSLP or basophil by monoclonal antibodies prevented the development of EoE.

Together, these studies show how a GWAS identified in TSLP and subsequent studies confirmed its role in EoE making it a promising therapeutic target.

Th2 cytokines are responsible of the inflammation observed in EoE [9▪]. The Th2 cytokines appear to exert redundant functions, as they have many similar and overlapping effects; therefore, treatment strategies that are based on abolishing a single cytokine are probably not going to be sufficient to treat EoE. Indeed, anti-IL-5 administration in patients with EoE has resulted to partial reduction of esophageal inflammation and minimal symptomatic relief [62,63]. But, targets against TSLP would may be a better option, as they would abolish more globally the Th2 response.

Building on the success of our first GWAS, we performed an expanded GWAS 936 cases and 4312 controls to identify additional targets worthy of further biological study. In addition to confirming the relevance of our previously reported *TSLP* locus [27], we discovered three novel loci on *c110rf30*, Calpain 14 (*CAPN14*), [28▪▪] (Table 2). A summary of the findings is shown in Table 2.

Variants at the *c11orf30* locus (EMSY) have been associated with seasonal allergic rhinitis [64], ulcerative colitis [65], Crohn's disease [66], atopic dermatitis [67,68], asthma [69], and allergic sensitization [70], albeit with much lower odds ratios (range 1.09 in asthma to 1.22 in atopic dermatitis). *EMSY* has been identified as a central component in a novel Akt-dependent mechanism by which interferon and other growth factors regulate the expression

of interferon-stimulated genes (ISGs) [71]. Interferon and ISGs play a central role in Th1 inflammation and Th2 suppression; consequently, a dysregulation in EMSY expression could lead to allergic diseases [71–73].

SNPs in *CAPN14* has been shown as a risk factor for EoE independently by Kottyan *et al.* [44▪▪], hence it is the second locus that has been replicated linked to EoE to date. *CAPN14* belongs to the calpain family of intracellular $Ca^{2+}$-regulated cysteine proteases known to function in diverse biological processes including the cell cycle, tight junction protein, cytokine regulation, and human fibroblast biology [74–78]. Calpains include both ubiquitous and tissue- specific members. The Genotype-Tissue Expression project [79], the Human Protein Atlas [80], and Kottyan *et al.* [44▪▪] demonstrated that CAPN14 is highly and selectively expressed in the esophagus. Moreover, we and others also demonstrated that *CAPN14* is overexpressed in EoE esophageal epithelial cells compared with controls [28▪▪, 44▪▪] and is dynamically upregulated after exposure of epithelial cells to Th2 cytokines (i.e. IL-13 [44▪▪] and IL-4 [81]).

The role of CAPN14 in esophageal biology or in EoE is not known but is a gene selective expressed in the epihelium and like TSLP points to an epithelial dysfunction as a driving force of local immune Th2 response in genetically predisposed patients. Other molecular biology studies have also shown an impaired epithelial barrier function, using gene expression profiling [82] and immunolocalization studies [83], which may contribute enhanced permeability of the epithelium to local food and environmental allergens and subsequent local inflammation [84].

## POTENTIAL PATHWAYS FOR TREATMENT

The current understanding of the pathobiology of EoE is incomplete, but evolving it seems to point to three factors leading to the development of EoE: atopy, genetic predisposition, and a local Th2 inflammation driven by a dysfunctional esophageal epithelium.

Current EoE management is based on current knowledge of the disease and is mainly based on two main clinically accepted clinical treatment strategies like any other atopic disease: allergen avoidance and corticosteroid treatment (Table 3).

The new genetic studies that are pointing to the esophageal dysfunction are shaping the treatment for tomorrow that will be based on antigen tolerance induction and specific biological treatments.

### Steroid treatment

Steroids are a very effective treatment of EoE. Oral steroids are very effective, but not recommended as a long-term therapy for the well known side-effects [85] (Table 3). Swallowed inhaled corticosteroids are effective in 50–80% of patients and can be considered as first-line therapies for initial and maintenance management of EoE, as they have low bioavailability and fewer systemic side-effects. Fluticasone is administered by spraying in the mouth with a metered dose inhaler without a spacer, and swallowed twice daily [86,87]. Budesonide is used as an oral viscous slurry once or twice daily [88,89]. Swallowed inhaled

corticosteroids appear to be well tolerated when used in the short term, but they can lead to increased risk of localized yeast infections and have potential long-term side-effects, including growth suppression and osteopenia (low-bone density) [87,89]. Although steroids are effective for treatment, clinical, and histologic features of EoE return upon discontinuation [1,2]. Steroids may reverse the esophageal fibrosis in children [90–92] but not in adults [93] with EoE.

### Dietary intervention

The majority of patients with EoE are allergic to food allergens and aeroallergens [1,2] (Table 3). Dietary elimination therapy should be considered in all children and motivated adults diagnosed with EoE. Dietary elimination approaches include a strictly elemental diet, specific antigen avoidance based on allergy testing, and empiric food elimination based on the most common food antigens [1,2]. All three methods have been proven to be effective with improved clinical symptoms and pathology [85,94,95] and the regimen chosen should be based on the individual patient [96]. Treatment with food avoidance is highly successful, with rates close to 100% with elemental diets (amino acid formulas) and up to 80% for elimination diet. However, amino acid formulas are unpalatable and lead to low quality of life. Elimination diet on the basis of allergy testing or empirical elimination may be sustainable in the long-term albeit with some difficulties, and many patients refuse to continue them. For additional details of dietary management, please see recent review [97].

### Esophageal dilation

Esophageal fibrosis and esophageal strictures are known complications of EoE. Endoscopic stricture dilation is sometimes necessary for short-term symptomatic relief but should be considered as a treatment option only if patients have failed dietary and medical therapy [1,2].

### Other biological treatment

Other treatments that have been investigated include anti-IL-5 [62,63] and chemoattractant homologous receptor expressed on Th2 cells (CRTH2) antagonist (Table 3). Both strategies have shown limited or no efficacy in controlling the disease, suggesting that a broader inhibition of Th2 inflammation may be needed due to the redundancy of its mediators.

### Antiinterleukin-5

IL-5 is the major survival factor for eosinophils and is indispensable for the differentiation, recruitment, and activation of the eosinophils [98]. Therefore, humanized monoclonal antibodies against IL-5 Mepolizumab (SB240563) and Reslizumab (Sch55700) have been used in clinical trials for EoE treatment [62,63]. Both antibodies in pediatrics and adult trials have failed to show symptomatic improvement beyond the placebo effect. However, both Reslizumab and Mepolizumab had a good safety profile and significantly decreased eosinophils numbers in the esophageal biopsies in adults and children with EoE, even if only few patients achieved normal biopsies. These data confirm that eosinophils are likely only one of the players in EoE inflammation and the importance of other cells and mediators in the pathogenesis of EoE that can be a target for immunological therapy.

Other biological treatment such as anti-TNFα (Infliximab) [99], anti-IgE (omalizumab) [100] have been tried in small groups of patients without showing any efficacy.

A recent study has been published on the efficacy of anti-CRTH in treatment of EoE and showed promising albeit small results. OC000459 is a potent, selective, and orally bioavailable CRTH2 antagonist, which blocks prostaglandin 2-mediated chemotaxis and activation of CRTH2-expressing cells. In a small group of patients with severe EoE dependent or resistant to corticosteroids anti-CRTH2 had a modest, but significant, antibeneficial clinical effect [101].

Anti-IL-13 antibodies have also been tried in asthma and more recently in the treatment of EoE [102–107]. Given the importance of Th2 inflammation and IL-13 in particular in EoE pathogenesis [102–105] Rothenberg *et al.* [108] tried anti-IL-13 (QAX576) in a double-blind placebo-controlled clinical trial for EoE treatment. The treated group had a significant reduction of esophageal eosinophilia and other markers of Th2 inflammation and epithelial dysfunction compared with those treated with placebo. However, even if there was a trend for improved symptoms, particularly dysphagia, this did not reach statistical significance. QAX576 was well tolerated. Therefore, the authors concluded that QAX576 significantly improved intraepithelial esophageal eosinophil counts and dysregulated esophageal disease-related transcripts in adults with EoE but the clinical significance of such treatment remains to be established.

## Antithymic stromal lymphopoietin

The recent identification of TSLP and its receptor as key components in the EoE pathogenesis suggests that blockage of the TSLP–TSLPR activation could provide an attractive approach to treating the cause of EoE [109]. This has been confirmed in animal studies wherein blockage of Noti *et al.* [52] recently described a novel mouse model of EoE in which the development of EoE-like features was dependent upon TSLP. In such a model TSLP-blocking antibodies ameliorated the EoE-like disease including the development of food impaction, when administered after the onset of disease. This is not surprising as anti-TSLP antibodies have been shown to be beneficial in various murine models of atopy [110–114].

A humanized anti-TSLP monoclonal antibody (AMG 157) that specifically binds human TSLP and prevents its interaction with TSLPR has been tested in adult asthmatic patients in a double-blind, placebo-controlled study. In the group receiving the antibody there were: attenuated allergen-induced bronchoconstriction in both early and late asthmatic responses; reduced markers of systemic and airway inflammation. Although this was only a proof-of-concept study [115▪], which did not determine whether anti-TSLP therapeutics will have clinical impact, these findings confirm that TSLP has a key role in allergic asthma. TSLP antibodies have not been tested in EoE yet.

## Food immunotherapy

We and others have reported that in both adults and children, milk is the most common trigger of EoE [116–119], initiating inflammation in a genetically susceptible individual via a disrupted epithelial barrier [27,83]. Epicutaneous immunotherapy (EPIT) has recently been

proposed as a way to bypass the dysfunctional and TSLP-producing esophageal epithelium, and induce lasting food tolerance in EoE [120]. In murine models of EoE, EPIT induces a persistent resolution of esophageal eosinophilia [121]. In humans, EPIT has been shown to be a well tolerated method to desensitize IgE food allergic patients [122]. EPIT, therefore, could be a promising strategy to cure food allergy and the consequent development of EoE in children with EoE due to food allergy.

## CONCLUSION

In summary, to date, there is no valid primary prevention strategy nor pharmacological cure for EoE. Long-term immunotherapeutic approaches to EoE are clearly needed. Recent advances in our understanding of genetics and pathophyisology of EoE will hopefully lead to such new treatments in a not distant future.

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## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

1. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007; 133:1342–1363. [PubMed: 17919504]
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011; 128:3–20. e26. [PubMed: 21477849]
3. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol. 2009; 7:1055–1061. [PubMed: 19577011]
4. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004; 351:940–941. [PubMed: 15329438]
5. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? J Allergy Clin Immunol. 2005; 115:418–419. [PubMed: 15696105]
6. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. J Allergy Clin Immunol. 2011; 128:1349–1350. e1345. [PubMed: 22019091]
7. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. Arch Dis Child. 2006; 91:1000–1004. [PubMed: 16877474]

8. van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. Neurogastroenterol Motil. 2013; 25:47–52.e5. [PubMed: 22963642]
9. Merves J, Muir A, Modayur Chandramouleeswaran P, et al. Eosinophilic esophagitis. Ann Allergy Asthma Immunol. 2014; 112:397–403. [PubMed: 24566295] Recent review of EoE pathogenesis.
10. Gonsalves N. Eosinophilic esophagitis: history, nomenclature, and diagnostic guidelines. Gastrointest Endosc Clin N Am. 2008; 18:1–9. vii. [PubMed: 18061097]
11. Lipka S, Boyce HW, Kumar A, Richter JE. The changing faces of eosinophilic esophagitis: the impact of consensus guidelines at the University of South Florida. Dig Dis Sci. 2015; 60:1572–1578. [PubMed: 25618310]
12. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr. 2014; 58:107–118. [PubMed: 24378521]
13. Sperry SL, Shaheen NJ, Dellon ES. Toward uniformity in the diagnosis of eosinophilic esophagitis (EoE): the effect of guidelines on variability of diagnostic criteria for EoE. Am J Gastroenterol. 2011; 106:824–832. quiz 833. [PubMed: 21304500]
14. Dellon ES. Epidemiology of eosinophilic esophagitis. Gastroenterol Clin North Am. 2014; 43:201–218. [PubMed: 24813510] Comprehensive review of EoE epidemiology.
15. Franciosi JP, Tam V, Liacouras CA, Spergel JM. A case-control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2009; 7:415–419. [PubMed: 19118642]
16. Ronkainen J, Talley NJ, Aro P, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. Gut. 2007; 56:615–620. [PubMed: 17135307]
17. Levin M, Motala C. Eosinophilic oesophagitis in Cape Town, South Africa (abstract). Clin Translational Allergy. 2011; 1(Suppl 1):26.
18. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of Eosinophilic Esophagitis in the United States. Clin Gastroenterol Hepatol. 2014; 12:589–596.e1. [PubMed: 24035773]
19. Sugnanam KK, Collins JT, Smith PK, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. Allergy. 2007; 62:1257–1260. [PubMed: 17711545]
20. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. J Allergy Clin Immunol. 2007; 119:731–738. [PubMed: 17258309]
21. Guajardo JR, Plotnick LM, Fende JM, et al. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. J Pediatr. 2002; 141:576–581. [PubMed: 12378201]
22. Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr. 2011; 52:300–306. [PubMed: 21057327]
23. Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. Immunol Allergy Clin North Am. 2009; 29:85–97. x. [PubMed: 19141344]
24. Blanchard C, Rothenberg ME. Basic pathogenesis of eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008; 18:133–143. [PubMed: 18061107]
25. Malerba G, Lauciello MC, Scherpbier T, et al. Linkage analysis of chromosome 12 markers in Italian families with atopic asthmatic children. Am J Respir Crit Care Med. 2000; 162:1587–1590. [PubMed: 11029380]
26. Spergel JM. New genetic links in eosinophilic esophagitis. Genome Med. 2010; 2:60. [PubMed: 20822553]
27. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nat Genet. 2010; 42:289–291. [PubMed: 20208534]
28. Sleiman PM, Wang ML, Cianferoni A, et al. GWAS identifies four novel eosinophilic esophagitis loci. Nat Commun. 2014; 5:5593. [PubMed: 25407941] First GWAS study to indicate association between EMSY and EoE and one of the two independent studies that have shown the implication of CAPN14 in EoE pathogenesis.
29. Blanchard C, Wang N, Rothenberg ME. Eosinophilic esophagitis: pathogenesis, genetics, and therapy. J Allergy Clin Immunol. 2006; 118:1054–1059. [PubMed: 17088129]

30. March ME, Sleiman PM, Hakonarson H. The genetics of asthma and allergic disorders. Discov Med. 2011; 11:35–45. [PubMed: 21276409]

31. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006; 116:536–547. [PubMed: 16453027]

32. Gupta SK, Fitzgerald JF, Kondratyuk T, HogenEsch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2006; 42:22–26. [PubMed: 16385249]

33. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. J Allergy Clin Immunol. 2001; 108:954–961. [PubMed: 11742273]

34. Straumann A, Kristl J, Conus S, et al. Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. Inflamm Bowel Dis. 2005; 11:720–726. [PubMed: 16043986]

35. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. J Allergy Clin Immunol. 2007; 120:1292–1300. [PubMed: 18073124]

36. Blanchard C, Mishra A, Saito-Akei H, et al. Inhibition of human interleukin-13- induced respiratory and oesophageal inflammation by antihuman-interleukin-13 antibody (CAT-354). Clin Exp Allergy. 2005; 35:1096–1103. [PubMed: 16120093]

37. Blanchard C, Stucke EM, Burwinkel K, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. J Immunol. 2010; 184:4033–4041. [PubMed: 20208004]

38. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. J Immunol. 2002; 168:2464–2469. [PubMed: 11859139]

39. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. Gastroenterology. 2003; 125:1419–1427. [PubMed: 14598258]

40. Schmid-Grendelmeier P, Altznauer F, Fischer B, et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. J Immunol. 2002; 169:1021–1027. [PubMed: 12097410]

41. Aceves S, Hirano I, Furuta GT, Collins MH. Eosinophilic gastrointestinal diseases: clinically diverse and histopathologically confounding. Semin Immunopathol. 2012; 34:715–731. [PubMed: 22842863]

42. Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. Immunol Allergy Clin North Am. 2009; 29:197–211. xiii–xiv. [PubMed: 19141355]

43. Aceves SS, Broide DH. Airway fibrosis and angiogenesis due to eosinophil trafficking in chronic asthma. Curr Mol Med. 2008; 8:350–358. [PubMed: 18691061]

44. Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. Nat Genet. 2014; 46:895–900. [PubMed: 25017104] One of the two independent studies that have shown the implication of CAPN14 in EoE pathogenesis.

45. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. J Allergy Clin Immunol. 2010; 126:160–165. e163. [PubMed: 20620568]

46. Jyonouchi S, Smith CL, Saretta F, et al. Invariant natural killer T cells in children with eosinophilic esophagitis. Clin Exp Allergy. 2014; 44:58–68. [PubMed: 24118614]

47. Lim DM, Narasimhan S, Michaylira CZ, Wang ML. TLR3-mediated NF-{kappa}B signaling in human esophageal epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2009; 297:G1172–G1180. [PubMed: 19779021]

48. Wang YH, Angkasekwinai P, Lu N, et al. IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. J Exp Med. 2007; 204:1837–1847. [PubMed: 17635955]

49. Oboki K, Ohno T, Kajiwara N, et al. IL-33 is a crucial amplifier of innate rather than acquired immunity. Proc Natl Acad Sci U S A. 2010; 107:18581–18586. [PubMed: 20937871]

50. Togbe D, Fauconnier L, Madouri F, et al. Thymic Stromal Lymphopoietin Enhances Th2/Th22 and Reduces IL-17A in Protease-Allergen-Induced Airways Inflammation. ISRN Allergy. 2013:971036. [PubMed: 23738146]
51. Gregory LG, Jones CP, Walker SA, et al. IL-25 drives remodelling in allergic airways disease induced by house dust mite. Thorax. 2013; 68:82–90. [PubMed: 23093652]
52. Noti M, Wojno ED, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. Nat Med. 2013; 19:1005–1013. [PubMed: 23872715]
53. Siracusa MC, Saenz SA, Hill DA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature. 2011; 477:229–233. [PubMed: 21841801]
54. Lin J, Zhao GQ, Wang Q, et al. Regulation of interleukin 33/ST2 signaling of human corneal epithelium in allergic diseases. Int J Ophthalmol. 2013; 6:23–29. [PubMed: 23550226]
55. Halim TY, Krauss RH, Sun AC, Takei F. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. Immunity. 2012; 36:451–463. [PubMed: 22425247]
56. Simon D, Aeberhard C, Erdemoglu Y, Simon HU. Th17 cells and tissue remodeling in atopic and contact dermatitis. Allergy. 2014; 69:125–131. [PubMed: 24372156]
57. Tanaka J, Watanabe N, Kido M, et al. Human TSLP and TLR3 ligands promote differentiation of Th17 cells with a central memory phenotype under Th2-polarizing conditions. Clin Exp Allergy. 2009; 39:89–100. [PubMed: 19055649]
58. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol. 2002; 3:673–680. [PubMed: 12055625]
59. Siracusa MC, Saenz SA, Wojno ED, et al. Thymic stromal lymphopoietin-mediated extramedullary hematopoiesis promotes allergic inflammation. Immunity. 2013; 39:1158–1170. [PubMed: 24332033]
60. Noti M, Kim BS, Siracusa MC, et al. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. J Allergy Clin Immunol. 2014; 133:1390–1399. 1399 e1391–1399 e1396. [PubMed: 24560412]
61. Siracusa MC, Kim BS, Spergel JM, Artis D. Basophils and allergic inflammation. J Allergy Clin Immunol. 2013; 132:789–801. quiz 788. [PubMed: 24075190]
62. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2012; 129:456–463. 463 e451–463 e453. [PubMed: 22206777]
63. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterol. 2011; 141:1593–1604.
64. Ramasamy A, Curjuric I, Coin LJ, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. J Allergy Clin Immunol. 2011; 128:996–1005. [PubMed: 22036096]
65. Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 2011; 43:246–252. [PubMed: 21297633]
66. Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet. 2008; 40:955–962. [PubMed: 18587394]
67. Esparza-Gordillo J, Weidinger S, Folster-Holst R, et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. Nat Genet. 2009; 41:596–601. [PubMed: 19349984]
68. Hirota T, Takahashi A, Kubo M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet. 2012; 44:1222–1226. [PubMed: 23042114]
69. Ferreira MA, Matheson MC, Duffy DL, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet. 2011; 378:1006–1014. [PubMed: 21907864]
70. Bonnelykke K, Matheson MC, Pers TH, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. Nat Genet. 2013; 45:902–906. [PubMed: 23817571]

71. Ezell SA, Polytarchou C, Hatziapostolou M, et al. The protein kinase Akt1 regulates the interferon response through phosphorylation of the transcriptional repressor EMSY. Proc Natl Acad Sci U S A. 2012; 109:E613–E621. [PubMed: 22315412]
72. Mitchell C, Provost K, Niu N, et al. IFN-gamma acts on the airway epithelium to inhibit local and systemic pathology in allergic airway disease. J Immunol. 2011; 187:3815–3820. [PubMed: 21873527]
73. Cohn L, Homer RJ, Niu N, Bottomly K. T helper 1 cells and interferon gamma regulate allergic airway inflammation and mucus production. J Exp Med. 1999; 190:1309–1318. [PubMed: 10544202]
74. Meephansan J, Tsuda H, Komine M, et al. Regulation of IL-33 expression by IFN-gamma and tumor necrosis factor-alpha in normal human epidermal keratinocytes. J Invest Dermatol. 2012; 132:2593–2600. [PubMed: 22673732]
75. Hsu CY, Henry J, Raymond AA, et al. Deimination of human filaggrin-2 promotes its proteolysis by calpain 1. J Biol Chem. 2011; 286:23222–23233. [PubMed: 21531719]
76. Nassar D, Letavernier E, Baud L, et al. Calpain activity is essential in skin wound healing and contributes to scar formation. PLoS One. 2012; 7:e37084. [PubMed: 22615899]
77. Chun J, Prince A. TLR2-induced calpain cleavage of epithelial junctional proteins facilitates leukocyte transmigration. Cell Host Microbe. 2009; 5:47–58. [PubMed: 19154987]
78. Aich J, Mabalirajan U, Ahmad T, et al. Loss-of-function of inositol polyphosphate- 4-phosphatase reversibly increases the severity of allergic airway inflammation. Nat Commun. 2012; 3:877. [PubMed: 22673904]
79. Consortium GT. The Genotype-Tissue Expression (GTEx) project. Nat Genet. 2013; 45:580–585. [PubMed: 23715323]
80. Uhlen M, Oksvold P, Fagerberg L, et al. Towards a knowledge-based human protein atlas. Nat Biotechnol. 2010; 28:1248–1250. [PubMed: 21139605]
81. Ueta M, Sotozono C, Kinoshita S. Expression of interleukin-4 receptor alpha in human corneal epithelial cells. Jpn J Ophthalmol. 2011; 55:405–410. [PubMed: 21617960]
82. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. Gastroenterol. 2013; 145:1289–1299.
83. Sherrill JD, Kc K, Wu D, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. Mucosal Immunol. 2014; 7:718–729. [PubMed: 24220297]
84. Yen EH, Hornick JL, Dehlink E, et al. Comparative analysis of FcepsilonRI expression patterns in patients with eosinophilic and reflux esophagitis. J Pediatr Gastroenterol Nutr. 2010; 51:584–592. [PubMed: 20808250]
85. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005; 3:1198–1206. [PubMed: 16361045]
86. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterol. 2006; 131:1381–1391.
87. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008; 6:165–173. [PubMed: 18237866]
88. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterol. 2010; 139:418–429.
89. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterol. 2010; 139:1526–1537. 1537 e1521.
90. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol. 2007; 102:2271–2279. quiz 2280. [PubMed: 17581266]
91. Dohil R, Aceves SS, Dohil MA. Oral viscous budesonide therapy in children with epidermolysis bullosa and proximal esophageal strictures. J Pediatr Gastroenterol Nutr. 2011; 52:776–777. [PubMed: 21593650]

92. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010; 139:418–429. [PubMed: 20457157]

93. Lucendo AJ, Arias A, De Rezende LC, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. J Allergy Clin Immunol. 2011; 128:1037–1046. [PubMed: 21880354]

94. Rothenberg ME, Aceves S, Bonis PA, et al. Working with the US Food and Drug Administration: progress and timelines in understanding and treating patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2012; 130:617–619. [PubMed: 22935588]

95. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006; 4:1097–1102. [PubMed: 16860614]

96. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013; 108:679–692. quiz 693. [PubMed: 23567357]

97. Greenhawt MJ, Aceves S, Spergel JM, Rothenberg ME. The management of eosinophilic esophagitis. J Allergy Clin Immunol. 2013; 1:332–340.

98. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999; 160:1001–1008. [PubMed: 10471631]

99. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. J Allergy Clin Immunol. 2008; 122:425–427. [PubMed: 18678345]

100. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. Eur J Pediatr. 2011; 170:1471–1474. [PubMed: 21809010]

101. Straumann A, Hoesli S, Bussmann C, et al. Antieosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. Allergy. 2013; 68:375–385. [PubMed: 23379537]

102. Scheerens H, Arron JR, Zheng Y, et al. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. Clin Exp Allergy. 2014; 44:38–46. [PubMed: 24131304]

103. Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. J Allergy Clin Immunol. 2013; 132:567–574. e512. [PubMed: 23726041]

104. Ultsch M, Bevers J, Nakamura G, et al. Structural basis of signaling blockade by anti-IL-13 antibody Lebrikizumab. J Mol Biol. 2013; 425:1330–1339. [PubMed: 23357170]

105. Song CH, Lee JK. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011; 365:2433. author reply 2433–2434. [PubMed: 22187994]

106. Hua F, Ribbing J, Reinisch W, et al. A pharmacokinetic comparison of Anrukinzumab, an anti IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. Br J Clin Pharmacol. 2015; 80:101–109. [PubMed: 25614144]

107. Reinisch W, Panes J, Khurana S, et al. Anrukinzumab, an antiinterleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. Gut. 2015; 64:894–900. [PubMed: 25567115]

108. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2015; 135:500–507. [PubMed: 25226850]

109. Cianferoni A, Spergel J. The importance of TSLP in allergic disease and its role as a potential therapeutic target. Expert Rev Clin Immunol. 2014; 10:1463–1474. [PubMed: 25340427]

110. Al-Shami A, Spolski R, Kelly J, et al. A role for TSLP in the development of inflammation in an asthma model. J Exp Med. 2005; 202:829–839. [PubMed: 16172260]

111. Li YL, Li HJ, Ji F, et al. Thymic stromal lymphopoietin promotes lung inflammation through activation of dendritic cells. J Asthma. 2010; 47:117–123. [PubMed: 20170316]

112. Shi L, Leu SW, Xu F, et al. Local blockade of TSLP receptor alleviated allergic disease by regulating airway dendritic cells. Clin Immunol. 2008; 129:202–210. [PubMed: 18757241]

113. Zhang F, Huang G, Hu B, et al. A soluble thymic stromal lymphopoietin (TSLP) antagonist, TSLPR-immunoglobulin, reduces the severity of allergic disease by regulating pulmonary dendritic cells. Clin Exp Immunol. 2011; 164:256–264. [PubMed: 21352203]

114. Zhou B, Comeau MR, De Smedt T, et al. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. Nat Immunol. 2005; 6:1047–1053. [PubMed: 16142237]

115. Gauvreau GM, O'Byrne PM, Boulet LP, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014; 370:2102–2110. [PubMed: 24846652] First study on anti-TSLP that show safety and efficacy in an atopic disease.

116. Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. Gastroenterol Clin North Am. 2007; 36:75–91. vi. [PubMed: 17472876]

117. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2012; 129:1570–1578. [PubMed: 22541246]

118. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol. 2013; 131:797–804. [PubMed: 23375693]

119. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012; 130:461–467. e465. [PubMed: 22743304]

120. Dupont C, Kalach N, Soulaines P, et al. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010; 125:1165–1167. [PubMed: 20451043]

121. Mondoulet L, Dioszeghy V, Larcher T, et al. Epicutaneous immunotherapy (EPIT) blocks the allergic esophago-gastro-enteropathy induced by sustained oral exposure to peanuts in sensitized mice. PLoS One. 2012; 7:e31967. [PubMed: 22363776]

122. Dioszeghy V, Mondoulet L, Dhelft V, et al. The regulatory T cells induction by epicutaneous immunotherapy is sustained and mediates long-term protection from eosinophilic disorders in peanut-sensitized mice. Clin Exp Allergy. 2014; 44:867–881. [PubMed: 24666588]

## KEY POINTS

- Eosinophilic Esophagitis (EoE) is a clinical-pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilia limited the esophagus, in absence of gastroesophageal acid reflux.
- Epidemiological studies have shown that EoE is an atopic diseases that most likely due to an interaction between environmental and genetic predisposition factors.
- Specific genetic association have been found between EoE and epithelial-related genes such as thymic stromal lymphopoietin (TSLP), CAPN14, Eotaxin 3, and other genes involved in T helper type 2 (Th2) inflammation such as TGF-β and EMSY. Recent advances in research have shown that TSLP may play a pivotal role in driving Th2 inflammation typical of EoE.
- EoE management: EoE is known to be a food antigen-driven, chronic allergic disease. There are two main clinically accepted clinical treatment strategies for EoE: dietary elimination and corticosteroid treatment.
- With the increase in our understanding of EoE pathogenesis, it is logical to anticipate that in the future there will be more specific treatment options for this rapidly increasing disease. In particular, TSLP appears to be a very promising Epicutaneous immunotherapy that may become a viable treatment if there will be studies to prove that this an effective strategy to induce food tolerance in EoE.

**Table 1**

Incidence of other atopic diseases in eosinophilic esophagitis

| | Number of patients with EoE | Atopy | Asthma | Allergic rhinitis | Atopic dermatitis | IgE specific for foods | Anaphylaxis to foods |
|---|---|---|---|---|---|---|---|
| General population | NA | 30% | 8.5% | 25% | 10% | 10% | 0.2% |
| Spergel *et al.,* Philadelphia | 620 | NA | 50% | 61% | 21% | 50 | 10% |
| Assa'ad *et al.,* Cincinnati | 89 | 79% | 39% | 30% | 19% | 75% | NA |
| Sugnanam *et al.,* Australia | 45 | NA | 66% | 93% | 55% | NA | 24% |
| Guajardo *et al.,* World registry | 39 | 80% | 38% | 64% | 26% | 62% | 23% |

EoE, eosinophilic esophagitis; NA, not available.

**Table 2**

Eosinophilic esophagitis genetic risk description of single nucleotide polymorphysims found in eosinophilic esophagitis genome-wide association studies

| Variant (effect allele) | chr: pos hg19 | Gene | Location | Function | Effect allele frequency | EoE OR | *P* EoE GWAS | SE EoE GWAS |
|---|---|---|---|---|---|---|---|---|
| rs1438673 (T) | chr5: 110467499 | TSLP | Intergenic | TSLP eSNP/ ENCODE transcription factor binding site | 0.496 | 0.626 | $2.74 \times 10^{-12}$ | 0.063 |
| rs55646091 (A) | chr11: 76299431 | c11orf30 | Intergenic | ENCODE transcription factor binding site | 0.044 | 2.219 | $5.38 \times 0^{-10}$ | 0.157 |
| rs74732520 (G) | chr2: 31396392 | CAPN14 | 3’ UTR | Transcribed and high LD with three variants (rs77997242, rs113412973, rs78464756) in ENCODE transcription factor binding sites | 0.067 | 1.782 | $1.69 \times 10^{-8}$ | 0.131 |

EoE, eosinophilic esophagitis; CAPN14, Calpain 14; ENCODE, encyclopedia of DNA elements; GWAS, genome-wide association studies; LD, linkage disequilibrium; SNP, single nucleotide polymorphysim; TSLP, thymic stromal lymphopoietin.

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## Table 3

Eosinophilic esophagitis therapy

| | Description | Use |
|---|---|---|
| Elemental diet | Diet is based on elemental formula | Currently used for short-term treatment of EoE to<br>**1** induce rapid resolution of EoE in almost all patients (adult and children)<br>**2** to establish food allergy |
| Six food elimination diet (SFED) | Most allergenic foods (milk, soy, egg, wheat, treenuts, peanuts, fish, shellfish) are eliminated | Effective in about 70% of adult an pediatric patients |
| Targeted diet with allergy tests | Food eliminated based on skin tests and milk (often only 1–2 foods are eliminated) | Effective in 80% of children, limited studies in adults |
| Proton pump inhibitors (PPI) | 1 mg/kg (20–40mg max dose) 1–2 times a day | Given to everybody 8 weeks prior to diagnostic EGD<br>May work as a stand alone therapy in PPI responsive EoE |
| Oral steroids | 1 mg/kg twice a day for 10–15 days | Very effective short-term treatment used for emergency therapy of food impaction or debilitating symptoms (failure to thrive, protracted vomiting) |
| Swallowed steroids | Fluticasone 110–220 mcg two puffs twice a day, Budesonide 0.5–2mg a day | Effective 50–70% of patients |
| Anti-IL5 | Reslizumab Mepolizumab | Significantly reduce eosinophilic infiltration in the esophagus, no effects on symptoms |
| Anti-IgE | omalizumab | Not effective |
| Anti-tumor necrosis factor (TNF)α | Infliximab | Not effective |
| Anti-CRTH2 | OC000459 | Partially effective |
| Anti-IL-13 | QAX576 | Partially effective |
| Anti-TSLP | AMG 157 | Future for EoE effective on asthma |
| Food allergy immunotherapy | EPIT | Future for EoE effective for IgE-mediated food allergy (peanut) |

EGD, esophageal gastroduodenal endoscopy; EoE, eosinophilic esophagitis; EPIT, epicutaneous immunotherapy; TSLP, thymic stromal lymphopoietin.