

Eosinophilic Esophagitis: A Comprehensive Review

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Abstract Eosinophilic esophagitis (EoE) is an emerging chronic atopic clinical-pathologic disease with an estimated prevalence of 1/1000 similar to the one of Crohn's diseases. Usually, EoE is firstly suspected due to symptoms that are caused by esophageal dysfunction and/or fibrosis. EoE diagnosis is confirmed if the esophageal biopsy shows at least 15 eosinophils per high power field (eos/hpf) as a peak value in one or more of at least four specimens obtained randomly from the esophagus. 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 non-IgE-mediated reaction to food and/or environmental allergens. Recently published genetic studies showed also that EoE is associated with single nucleotide polymorphism (SNP) on genes which are important in atopic inflammation such as thymic stromal lymphopoietin (TSLP) located close to the Th2 cytokine cluster (IL-4, IL-5, IL-13) on chromosome 5q22. 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. EoE is treated like many other atopic diseases with a combination of topical steroids and/or food antigen avoidance.

Keywords Eosinophilic esophagitis · Genome-wide association study · Th2 inflammation

Abbreviations

APC	Antigen-presenting cells
CHOP	The Children's Hospital of Philadelphia
DC	Dendritic cells
CAG	Center for Applied Genomics
CRTH2	Chemoattractant receptor expressed on Th2 cells
DSG-1	Desmoglein-1
EGD	Esophago-gastroduodenal endoscopy
EoE	Eosinophilic esophagitis
eos	Eosinophils
GERD	Gastro-esophageal reflux
hpf	High power field
IBD	Inflammatory bowel disease
IL	Interleukin
iNKT	Invariant-natural killer cells
LC	Langerhans cells
PG2	Prostaglandin D2
PPI	Proton pump inhibitors
R	Receptor
SNP	A small nuclear polymorphism
TNF α	Tumor necrosis factor alpha
TGF β	Transforming growth factor beta
Th2	T helper type 2
TSLP	Thymic stromal lymphopoietin

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Introduction

Eosinophilic esophagitis (EoE) is an emerging chronic atopic clinical-pathologic disease. EoE is defined by eosinophil infiltration limited to the esophageal epithelium and, if left untreated, it results in esophageal fibrosis and dysfunction [1, 2]. The first clinical case of EoE was reported in 1968; however, since 2000, EoE has become exponentially more prevalent in western countries, with a yearly incidence now considered to be similar to that of Crohn's disease [3–8]. For example, from 1994 to 2011 at the Children's Hospital of Philadelphia (CHOP), there has been a 70-fold increment in EoE incidence [9, data not published].

Usually EoE is firstly suspected due to symptoms that are caused by esophageal dysfunction and/or fibrosis. Typical children present with signs of esophageal dysfunction. Often these symptoms mimic the gastro-esophageal reflux (GERD) but do not respond to maximized anti-reflux medication (i.e., proton pump inhibitors [PPI]). Symptoms due to ongoing fibrosis, such as dysphagia and food impaction, are the most common presenting symptoms in teenagers and adults [1, 9–11] (Table 1).

Once EoE is suspected based on symptoms, patients undergo a diagnostic esophago-gastroduodenal endoscopy (EGD) after completing an optimal anti-GERD therapy with PPI (20–40 mg, once or twice daily in adults, and 1 mg/kg in children once or twice daily for 8 to 12 weeks) (Table 2). EoE diagnosis is confirmed if the esophageal biopsy shows at least 15 eosinophils per high power field (eos/hpf) as a peak value in one or more of at least four specimens obtained randomly from the esophagus [2].

Most of the patients affected by EoE have other atopic diseases such as allergic rhinitis, asthma, IgE-mediated food allergies, and/or atopic dermatitis. Given the localized eosinophilia, the co-presence of other atopic diseases, it does not surprise if the local inflammation is a T helper type 2 (Th2) flogosis, which most likely is driven by a mixed IgE and non-IgE-mediated reaction to food and/or environmental allergens [12–22]. Recently published genetic studies showed also that EoE is associated with single nucleotide polymorphism (SNP) on genes which are important in atopic inflammation such as thymic stromal lymphopoietin (TSLP) located close to the Th2 cytokine cluster (IL-4, IL-5, IL-13) on chromosome 5q22.

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 [2, 9]. EoE is treated like many other atopic diseases with a combination of topical steroids and/or food antigen avoidance (Table 2 and Fig. 1). Such treatment options are not disease specific, greatly impact the quality of life of patients and their families, and are associated with important side effects. There are currently widespread efforts in the immunology, allergy, and gastroenterology communities to better understand the EoE pathogenesis in order to design treatment strategies that can specifically target this new disease.

Epidemiology

EoE has been reported in children and adults from all continents including isolated cases in South Africa [23]. The highest incidence is reported in the western world where EGD is more readily available to make a definite diagnosis and where it has an estimated prevalence of 56.7/100,000 [24]. In children, EoE has prevalence of 50.5/10,000, similar to pediatric inflammatory bowel disease (IBD) [24]. These numbers are likely to underestimate the real incidence and prevalence of EoE as ICD-9 codes were only introduced in 2009. Interestingly, EoE affects significantly more males than females with a male-to-female ratio of 3:1 in both children and adults [2, 24]. The prevalence of the disease appears to increase with age and peaks at around 35–39 years of age [2, 24]. Suburban Caucasian children are disproportionately affected compared to the typical population affected by allergies or chronic gastrointestinal diseases [25]. Family history especially in male members is very frequent with a sibling risk of 80, meaning that having a sibling with the disease increases 80 times the risk of developing a similar disease in other siblings [4]. Altogether, the epidemiological data suggest a strong genetic component in EoE development.

Diagnosis

The first step to suspect EoE is to elicit possible symptoms typical of EoE through a careful history and screening question in atopic patients. In younger patients, the disease typically presents as manifestation of gastro-esophageal dysfunction, most likely because fibrosis has not developed yet (Table 1). Failure to thrive, feeding difficulties (i.e., gagging, arrest in advancing solid food introduction, food refusal), and persistent GERD symptoms not responsive to PPI treatment are common presenting symptoms in infants and toddlers. Persistent GERD symptoms, abdominal pain, and frequent vomiting are more common in older children. On the other

Table 1 More common symptoms of EoE by age

<5 years of age	6–14 years of age	>15 years
Failure to thrive	Vomiting	Dysphagia
Feeding difficulties	Abdominal pain	Food impaction
Gagging on solid foods	Dysphagia	Strictures

Table 2 Medical treatment of EoE

	<10 years of age	>10 years of age	Maximum dose
Omeprazole (PRILOSEC)	1 mg/kg twice a day	1 mg/kg twice a day	40 mg twice a day
Lansoprazole (PREVACID)	1 mg/kg twice a day	1 mg/kg twice a day	60 mg daily
Esomeprazole (NEXIUM)	1 mg/kg once daily	1 mg/kg once daily	40 mg daily
Fluticasone	220 µg twice a day	440 µg twice a day	
Budesonide	1 mg once a day	2 mg once a day	
Oral steroids	1 mg/kg twice a day	1 mg/kg twice a day	30 mg twice a day

hand, older children, teenagers, and adults have more frequent signs of esophageal fibrosis such as dysphagia and food impaction [4, 9, 26] (Table 1). Even if symptoms tend to vary in different age groups, any of the characteristic symptoms can present at any age. The difficulties in swallowing are a sign of fibrosis and range from subtle changes in eating habits (meat avoidance) to signs of progressive solid food dysphagia (excessive chewing and drinking with meals) to frequent episodes of food impaction. In a large population study based on ICD-9 coding, 55.8 % of EoE patients reported dysphagia and 12.5 % had a history of food impaction [24]. This underscores the importance of obtaining a thorough and targeted history in both established EoE patients as well as all new patients presenting with food allergy, atopy, and GERD-like symptoms.

The primary care physician and the allergist should specifically ask for sign of dysphagia especially in older patients, who often have developed spontaneously a coping mechanism for the disease (i.e., drinking a lot of fluids during meals, being unable to eat unless a drink is available, chew the food for a long time, cut the food in small pieces). As often EoE is familial, patients and their parents may not be aware that the way they eat is not a universal eating behavior. If the history is very important in screening for EoE to determine who may need an EGD evaluation, it is far less useful to determine the EoE triggers. The patient needs to be asked specifically if any

food seems to trigger the EoE, if there is any self-limitation in the ingestion of any food, or if there is any seasonal variation of EoE; however, usually the patient cannot cite any offending food. This is not surprising as the reactions to the trigger foods are delayed and patients have often symptoms to foods that are more difficult to chew (i.e., meat, celery, raw carrots) and not to those which cause the inflammation (i.e., milk) [9, 26].

Because of the high rate of allergic rhinitis, asthma, IgE-mediated food allergy, and/or eczema in EoE patients, a complete evaluation by a well-informed allergist for food allergy and other atopic diatheses is recommended [1].

Once EoE is suspected, its presence needs to be confirmed by EGD. Current consensus diagnostic guidelines for EoE recommend a minimum threshold of 15 eos/hpf on at least one esophageal biopsy specimen, with eosinophilia limited to the esophagus [2]. Several biopsies (four or more) of both the proximal and distal esophagus should be obtained during diagnostic and follow-up endoscopic procedures, as the disease is often patchy [2, 27].

EGD macroscopically can show furrowing, white mucosal plaques, esophageal trachealization, esophageal narrowing, stricture, and mucosal tearing (Fig. 2). Often, however, the macroscopic appearance of the esophagus endoscopically is normal, hence specimens should be obtained not only from macroscopically abnormal esophagus but also from normal ones. Microscopically, in addition to esophageal eosinophilia, the biopsies can show superficial layering, eosinophilic microabscess, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, and lamina propria fibrosis [2, 27] (Fig. 3).

Before performing a diagnostic or a surveillance EGD, all patients should be treated with high-dose PPI therapy (i.e., 20–40 mg BID in adults and 1 mg/kg twice per day in children) for 8–12 weeks, as eosinophilia in the esophagus can be due to GERD or to other types of PPI-responsive esophageal eosinophilia (PPI-REE) [2, 28] (Table 2). Diagnosis and follow-up of EoE currently rely upon repeated EGD because there are no available symptom tools, biomarkers, or pathognomonic elements that can replace clinicopathologic diagnosis monitoring [2].

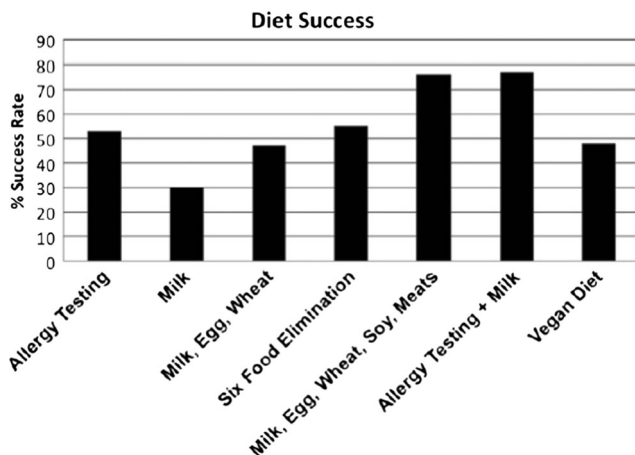
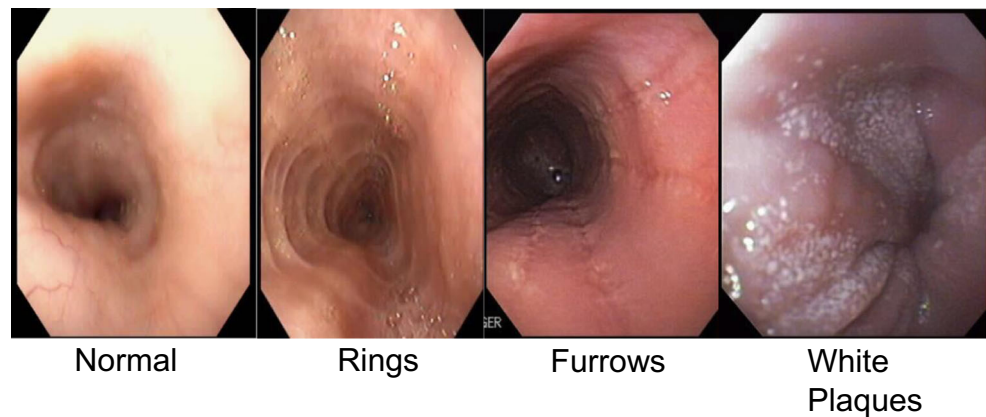
**Fig. 1** Success rate of various diets

Fig. 2 Endoscopic typical macroscopic appearances

Pathogenesis

Despite being a relatively newly described disease, in the last several years, there has been a rapid advancement in the understanding of EoE pathogenesis [9, 12]. Most researchers now agree that in EoE, the eosinophilic inflammation is due to a Th2 inflammation driven by TSLP secreted by esophageal epithelial cells [29, 30] and is under the influence of genetic predisposition [13, 29, 30] (Fig. 4 and Table 3).

Several human and mice studies have shown that EoE inflammation has all the typical characteristic of a Th2 atopic inflammation. Esophageal biopsies and blood samples of patients with active EoE have increased levels of Th2 prototypical cytokines and chemokines such as interleukin (IL)-5, IL-4, IL-13, IL-15, TSLP, and eotaxin-3 secreted by the typical cells involved in allergic inflammation: T cells, mast cells, basophils, invariant natural killer T cells (iNKTs), and esophageal epithelial cells [15, 16, 31, 32].

Th2 cytokines are responsible for the inflammation observed in EoE, as they induce an increased Th2 response from T cells, basophils, iNKTs, and mast cells; they enhance survival and activation of eosinophils and are responsible for the

fibrotic changes. In a mouse model of EoE, mice that have been genetically modified so they do not express Th2 cytokines, in particular IL-13 or transcriptional factors that determine Th2 switching such as Stat6 or Stat1, are less likely to develop disease [18, 21, 33]. IL-4 increases Th2-lymphocyte survival and eotaxin-3 secretion from epithelial cells, which in turn significantly promotes eosinophilic migration; in addition, it induces fibroblast to secrete periostin, collagen, and β -actin, therefore promoting local fibrosis [34, 35]. IL-5 is the major cytokine responsible for the differentiation, recruitment, and survival of eosinophils [36]. It promotes eosinophil activation and their trafficking into the lungs and esophagus [20, 36]. IL-5 knock-out mice are resistant to the development of EoE, whereas IL-5 transgenic mice that overexpress IL-5 have elevated levels of eosinophils in the esophagus [21, 37–39]. Moreover, patients with EoE have been shown to have high esophageal tissue levels of IL-5 and its receptor (R) IL-5-R [31, 32].

The Th2 cytokines appear to exert redundant functions, as they have many similar 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

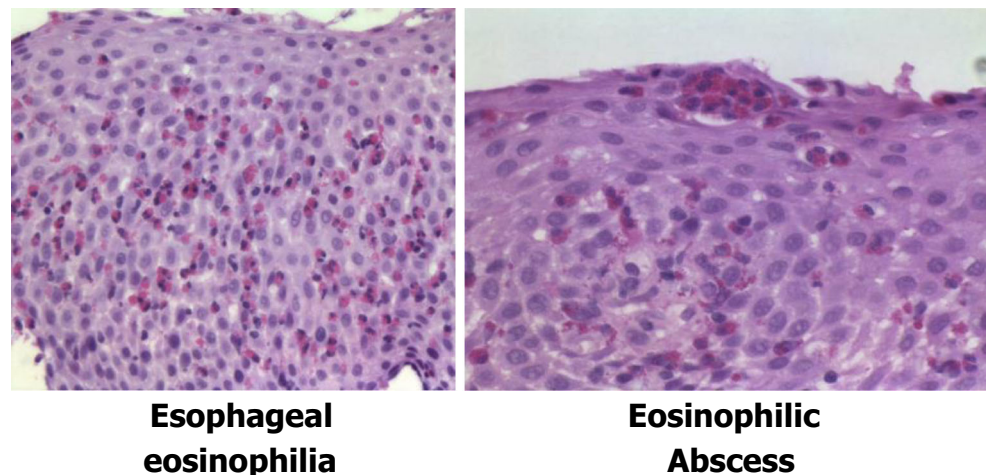
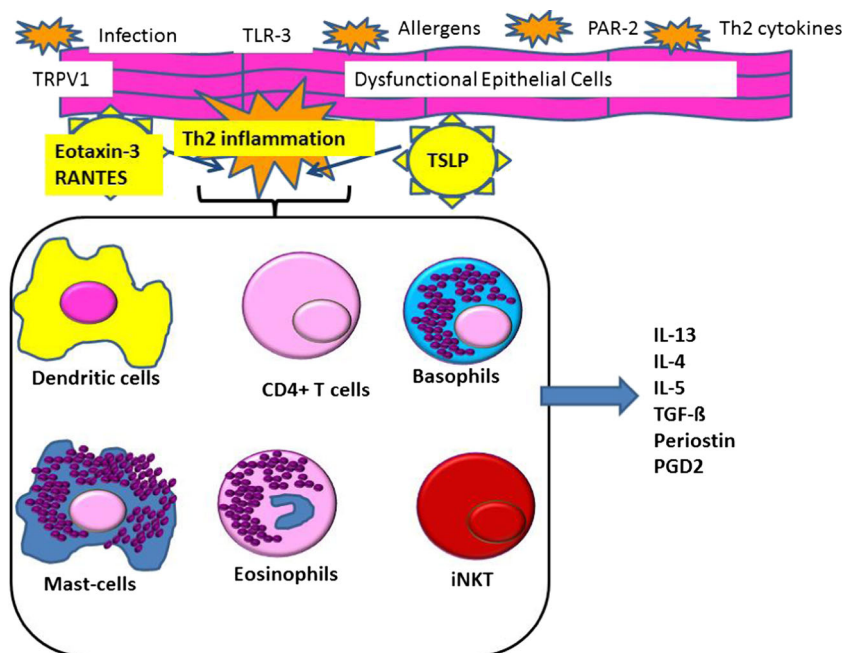
Fig. 3 EoE biopsies: typical histology

Fig. 4 Th2 Inflammation in EoE

administration in patients with EoE has resulted in the partial reduction of esophageal inflammation and minimal symptomatic relief [40, 41].

Another key cytokine in EoE pathogenesis is thymic stromal lymphopoietin (TSLP) that is most likely responsible for the overall Th2 inflammation observed in EoE. TSLP is a cytokine primarily secreted by epithelial cells at barrier surfaces such as skin, gut, and lung in response to danger signals, infectious agents, atopic cytokines (IL-4, IL-13, TNF α), and environmental allergens. It is similar to IL-7, and it binds to TSLP-R. TSLP was firstly cloned in 1994. Since then, there has been accumulating evidence that TSLP is very important for the maturation of antigen-presenting cells (APCs) and other hematopoietic cells, and it is a master regulator of Th2-type allergic inflammation. TSLP gene is located on chromosome 5q22.1. SNPs on TSLP gene, which are associated with its dysregulated expression, have been linked to atopic diseases such as eczema, asthma, allergic rhinitis, and EoE [42, 43]. In particular, TSLP is increased in the esophageal biopsies of EoE subjects compared to non-EoE subjects [29, 44–47]. TSLP drives Th2 inflammation by promoting Th2 cytokine

secretion from inflammatory cells such as basophils, T cell, iNKTs, mast cells, or, indirectly, by inducing maturation and activation of dendritic cells (DC) involved in migration and differentiation of naïve CD4+ T cells into Th2 cells [43] (i.e., T cells that express CCL26, IL-4, IL-5, and IL-13). In addition, in EoE, TSLP is responsible for the development of a unique basophil subpopulation which secretes pro-Th2 cytokines (IL-4, IL-6, CCL3, CCL4, and CCL12) independently from IgE stimulation [46]. Noti et al. further confirmed the pivotal role of TSLP and basophils in EoE development, independently from IgE stimulation. Indeed, in a novel mouse model of EoE, TSLP and basophil but not IgE were essential for the progression of EoE-like features [48].

Another epithelial factor, eotaxin-3/CCL-26, plays a major role in EoE pathogenesis. Eotaxin-3 (CCL-26) is a chemokine that is a potent eosinophil and mast cell chemoattractant, by activating CCR3, a chemokine receptor, found on activated eosinophils, lymphocytes, iNKTs, and mast cells. Interestingly, its gene is overexpressed in EoE subjects, both in the esophageal biopsies and peripheral blood [13]. Importantly, a gain-of-function polymorphism in the gene that encodes eotaxin-3 is associated with an increased risk of EoE in children [13, 49]. In vitro, esophageal epithelial cells secrete eotaxin-3 in response to pro-inflammatory Th2 cytokines such as IL-4 and IL-13 and may be inhibited by steroids and PPI [19, 50]. This observation suggests that PPI therapy may play a role in reducing esophageal eosinophilia with a poorly understood mechanism most likely independent from acid suppression.

Mast cell-derived prostaglandin D2 (PGD2), a prostanoid molecule specifically produced by mast cells in allergic responses, may also be another important chemoattractant by

Table 3 Genetics of EoE

	SNP	Chromosome
TSLP SNP	rs3806932 (A/G)	5q.22.1
TSLP-R SNP	rs36133495 (A/V)	Xp22.3; Yp11.3
Eotaxin 3	rs2302009 (T/G)	7q11.23
CAPN14	rs77569859 (G/A)	2q.23
EMSY	rs55646091	11q13.5

acting on the chemoattractant receptor expressed on Th2 cells (CRTH2), which is a G-protein-coupled receptor highly expressed on all cells (i.e., Th2 lymphocytes, eosinophils, and basophils) involved in a Th2 inflammation, and has been found to be elevated on eosinophils from patients with EoE [51].

These data show that the epithelium plays a major role in EoE by promoting a local Th2 inflammation. However, as for atopic dermatitis, EoE patients appear to have a dysfunctional epithelial barrier that favors antigen penetration and consequent sensitization. Indeed, EoE patients with active disease have a downregulation in the expression of the cell adhesion protein desmoglein-1 (DSG-1) in the esophageal epithelium, which tends to normalize after medical treatment [52–54].

Finally, we and others have demonstrated that human esophageal epithelial cells express Toll-like receptors [55, 56] and produce pro-inflammatory cytokines in response to both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [55]. We have also demonstrated that esophageal epithelial cells can secrete the chemokine RANTES (CCL5) [57] which may play a role in the migration and activation of IL-13 producing iNKT cells in EoE. Finally, others have shown that esophageal epithelial cells may be non-professional antigen-presenting cells because they can internalize and process chicken egg ovalbumin and present it to T cells that become activated [58]. This is an alternative hypothesis to the more commonly accepted notion that professional APCs take up an antigen perhaps via contact through a dysfunctional esophageal epithelial barrier, initiate immune responses in EoE, and promote the polarization of Th2-type T cells. Against such hypothesis, there are two facts. First, Langerhans cells (LC) are present in the esophageal epithelium, but their density is not greater in EoE compared to non-EoE populations [54]. Secondly, clinical observations that patients receiving enteral nutrition via post-pyloric feeding tubes can develop EoE suggest that direct contact between food antigens and the esophageal epithelium is not a requirement for disease pathogenesis.

Eosinophils are pathognomonic of EoE inflammation in the absence of GERD, but they are not essential for EoE pathogenesis and are most likely a consequence of the local Th2 inflammation. Indeed, clinical trials with anti-IL-5 have shown that patients can be still symptomatic even when the treatment depletes eosinophils from the esophagus of EoE patients [59, 60]. T cell, mast cell, iNKTs, and basophils have been reported to be active in EoE pathogenesis [15, 46, 61–64].

As in other atopic diseases such as asthma, the major long-term consequence in chronic inflammation in EoE is esophageal remodeling which can lead to the development of irreversible strictures. Interestingly, the incidence of esophageal food bolus impaction has increased dramatically in the last 5–10 years [65], and in adult patients, EoE is the most common cause of EGD for food impaction [66].

Fibrosis is defined as excess deposition of components of the extracellular matrix (ECM), leading to organ dysfunction. It is poorly understood how fibrosis develops in vivo, and much of our understanding of fibrosis pathogenesis derives from in vitro assays and models of fibrosis in other organ systems. Aceves and colleagues [67] have demonstrated basal membrane thickening and increased vascular activation in untreated patients who have EoE, associated with elevated TGF- β and VCAM-1 expression. Moreover, fibrosis is characterized by activated myofibroblast, a unique cell type which exhibits properties of both smooth muscle cells and fibroblasts. It is hypothesized that the myofibroblasts contract and place tension on the extracellular matrix resulting in the activation and differentiation of neighboring cells. Once contracted, the myofibroblasts secrete extracellular matrix components, including type 1 collagen, to stabilize its new, contracted position [68]. Interestingly, it appears that at least in vitro esophageal epithelial cells can undergo transdifferentiation to a myofibroblast phenotype in a process known as epithelial to mesenchymal transition (EMT), by which epithelial cells lose epithelial markers (e.g., E-cadherin) and gain markers and properties typical of myofibroblasts (i.e., contractile properties and expression of α -smooth muscle actin) [35, 69]. In such in vitro models, profibrotic cytokines including TGF β , TNF α , and IL1 β are major drivers of EMT [35, 69]. However, whether EMT occurs in vivo remains to be proven. TGF β has also been localized to the esophageal lamina propria in patients with EoE [70], and its presence is associated with nuclear p-SMAD translocation in EoE patient biopsies, but not in non-EoE controls [71]. Hence, TGF β could be very important for fibrosis development because it is the prototypical cytokine which stimulates myofibroblast differentiation and it is released by local cells including fibroblasts, epithelial cells, and infiltrating inflammatory cells. Moreover, TGF β targets members of the SMAD family of transcription factors that are important for the expressions of genes responsible for the fibroblast phenotype including α -smooth muscle actin (α -SMA) and collagen.

Genetics

Genome-wide association studies have found SNPs in TSLP and TSLP-R that correlate with TSLP levels and diseases prevalence [13, 30, 46], suggesting that the Th2 inflammation could be driven locally by TSLP secreted by esophageal epithelial cells [13, 29, 30, 46] (Table 3).

Similar to other atopic diseases, EoE is linked to a growing list of genetic risk factors. In collaboration with Center for Applied Genomics (CAG) at CHOP and Cincinnati Children's Hospital, we recently found an association between a SNP (rs3806932) in the gene encoding TSLP and risk for EoE [29]. rs3806932 involves the nucleotides A/G, and it is

present in the promoter region of TSLP gene. The protective minor allele (G) is present in a higher percentage of control subjects (45.8 %) compared to EoE subjects (31.2 %). Individuals homozygous for the TSLP risk allele (AA) have increased TSLP expression and basophil infiltration in the esophageal epithelium compared to those carrying heterozygous (AG) risk allele and homozygous (GG) protective minor alleles [29, 44, 47]. In addition, Sherrill et al. also identified a significant association between a SNP rs36133495 (Ala to Val) on Xp22.3 and Yp11.3 in the TSLP-R gene region and male sex in EoE [30]. The SNP Val/Val was indeed significantly more expressed in EoE patients, as it was present in 27 % in male patients with EoE vs. 15 % in male ($P=.039$).

A third identified risk factor linked to EoE is a SNP in eotaxin-3 [13] (Table 3). Patients with EoE are more often compared to healthy unrelated controls, the genotype GG in the SNP rs2302009, T/G located in Eotaxin 3 gene (13 vs. 3.2 % $P=0.001$). The GG genotype, however, was not predominant in atopic EoE patients, and it was therefore speculated that the association of this SNP with EoE was not dependent on atopic status. Most recently, a SNP (rs77569859 G/A) located in proximity to the calpain 14 (CAPN14) gene on chromosome 2p23 has been associated with increased risk of developing EoE. CAPN14 is specifically expressed in the esophagus and is upregulated in patients with active disease and after exposure of epithelial cells to IL-13 [72, Sleiman et al., submitted].

Epigenetics

Epigenetics are the heritable phenotypic modifications that influence gene expression without changes to the DNA sequence. Epigenetic changes can be due to environmental stimuli, hence their role is very important in complex multifactorial diseases such as EoE, where the pathogenesis is due to an interaction between genes and environmental influences.

Epigenetic reversible changes, in general, can occur in chromosomal DNA (e.g., methylation of CpG residues) or via covalent posttranslational modification of specific histone amino acids (e.g., methylation or acetylation) [73]. H3K4 trimethylation (H3K4me3) is specific for the active transcriptional state of multiple genes, whereas H3K27 trimethylation (H3K27me3) is specific for repression of promoters and enhancers [74–76]. Such histone changes can indeed modify the accessibility to the transcriptional machinery of gene promoters located proximally or distally to the modified histone [73]. In EoE, there have been several studies suggesting that regulation of CCL26 involves epigenetic changes. Lim et al. [77] demonstrated that Eotaxin 3 (CCL26) promoter is activated by IL-13 acetylation of Histone 3 (H3), which leads to further accessibility of the promoter to three coactivators, activating transcription factor 2 (ATF2), the histone

acetyltransferase cyclic adenosine monophosphate (cAMP)–responsive element (CRE)–binding protein (CBP), and STAT6. Furthermore, PPIs have been reported to decrease the levels of H3K4 and therefore reducing STAT6 binding to the CCL26 promoter, and consequently eotaxin-3 expression [78].

CCL26 promoter is also regulated by DNA methylation of its two CpG (cytosine-guanine) dinucleotide motifs. Patients with active EoE have been reported to have hypomethylation of those CpG sites, which correlated with increased STAT6 and CBP binding to the CCL26 promoter [79]. These data suggest that the above described epigenetic changes may happen in coordination with DNA demethylation being followed by histone acetylation at the CCL26 promoter in response to IL-13 to induce CCL26 transcription [79].

Other epigenetic regulatory molecules, such as micro-RNA (miRNA), have been shown to play a role in EoE pathogenesis and in particular in contributing to the Th2 inflammation. miRNA are single-stranded RNA molecules which are very conserved during the evolution and can regulate inflammation by silencing target genes [80]. Indeed, miRNAs are short, non-coding RNAs that tightly regulate posttranscriptionally the expression of target genes, by suppression or inducing mRNA degradation. In active EoE, miRNA implicated in the downregulation of the Th1 response such as miR-21, mi-146a, and mi146b are upregulated, and those associated with Th2 response, such as miR-375, are downregulated. These data suggest that miRNA profile in EoE patients could promote their Th2 inflammation [80].

Triggers of EoE

In most patients, foods have been identified as the trigger of EoE Th2 inflammation with non-IgE-mediated mechanism [9, 81–83] (Fig. 1). In a cohort of 315 patients from CHOP, the most common food allergens that are involved in EoE based on biopsy confirmation are milk, followed by wheat, egg, beef, soy, and chicken [10]. Similarly, the foods that caused EoE symptoms (primarily vomiting and abdominal pain) were milk, egg, soy, and wheat. These data are very similar to that of Kagalawa and colleagues found in their food reintroduction from the six-food elimination diet (SFED) [84].

Very limited evidence and clinical experience suggest that aeroallergens may play a causative role in the development of EoE in humans [85]. Indeed, sensitization to inhalant allergens increases with age, particularly after 4 years, while the sensitization to food allergens decreases with age [86]. Hence, there could be a stronger role for aeroallergens in adults and for food allergens in children, although no study has addressed such issue and the literature on the role of aeroallergen in EoE remains limited.

Allergens most likely induce EoE with an IgE-independent mechanism. Indeed, mice that do not express IgE can develop EoE-like disease similar to wild-type mice [48]. Similarly, clinical trials have shown anti-IgE administration does not significantly reduce esophageal eosinophilia [87]. Also, oral immunotherapy for food allergen such as milk has been successfully used in clinical research trial to achieve desensitization to IgE-mediated food allergy, but 10 % of patients later develop EoE. In addition, children who outgrow IgE-mediated food allergy and reintroduce the food in the diet later can develop EoE to the same food [88].

These phenomena are highly suggestive that a non-IgE mechanism mediates food allergy in EoE [89]. So it is not surprising that testing for IgE-mediated food allergy by skin prick testing (SPT) or specific sera IgE has not proven successful in definitive identification of causative foods in EoE [90, 91]. Indeed, Kelly and colleagues [81] demonstrated that the introduction of skin test-negative foods into the diet could induce clinical disease. Moreover, removal of skin test-positive foods have a low rate of success (13 % in adults and less than 30 % in pediatrics [1, 9–11, 92]). Rather, the addition of atopy patch testing (APT) which represent a T-lymphocyte-mediated allergen specific response helps to determine causative foods in EoE [91] and further suggests that EoE is a non-IgE-mediated disease.

Treatment

As in many allergic diseases, current management of EoE is based on the use of steroids to suppress the inflammation and/or food allergy avoidance (Fig. 5).

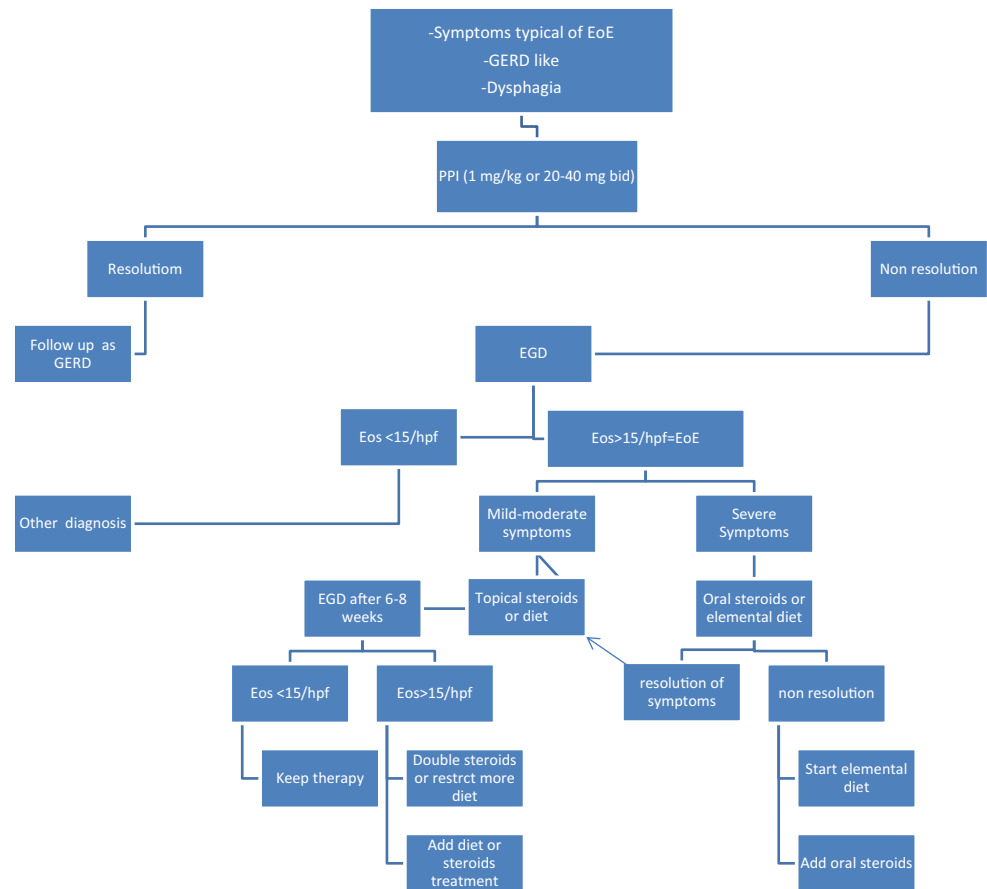
Steroids

Oral steroids (Table 2) are very effective in quickly resolving the eosinophilic esophageal inflammation; however, they have well-known side effects when used for long periods of time, and once suspended, the inflammation comes back unchanged [93]. Liacouras et al. [93] reported the effect of treatment with oral methylprednisolone (1.5 mg/kg/day to a max of 40 mg) daily for 4 weeks in 38 patients with EoE. Twenty-nine of the 38 patients had GERD symptoms and 27 of those became asymptomatic when placed on oral steroids, whereas the remaining two patients showed an improvement during the third and fourth weeks of therapy. Ten patients had dysphagia, and all of them became clinically asymptomatic after 4 weeks of oral steroids. Upon discontinuing therapy, clinical symptoms recurred or worsened in the majority of patients within 6 months. After oral steroids, the esophageal biopsies showed a marked decrease in the eosinophil infiltration after 4 weeks of treatment (i.e., from 33.5 ± 9.5 eos/hpf pre-

treatment to 0.9 ± 0.6 eos/hpf). However, after 6 months of oral steroid discontinuation, eosinophils return to pre-treatment levels (i.e., 28.7 ± 5.8 eos/hpf). Because EoE is most likely a chronic disease, oral steroids are not indicated in daily management of the disease and should be reserved only for emergency cases, such as severe dysphagia, hospitalization, and weight loss [2]. Oral steroids should be suspended for 6–8 weeks prior to a diagnostic or follow-up EGD.

Swallowed inhaled corticosteroids (Table 2) such as swallowed fluticasone or budesonide have low bioavailability, less potential for systemic side effects, and are considered *topical*. They are very effective, even if not at the same extent of the oral ones, and induce EoE remission in up to 90 % of patients depending on the different studies. Aerosolized fluticasone propionate is administered from a metered dose inhaler ($110 \mu\text{g} \times 2$ puffs twice daily for children <8 years of age and $220 \mu\text{g} \times 2$ puffs twice daily for children >8 years of age) without a spacer [94–97]. Budesonide is delivered as slurry, which is made by mixing each 1 mg Pulmicort RespuleTM (liquid budesonide intended for nebulized administration) [98, 99] with 10 g (ten packets) of sucralose (SplendaTM) or a teaspoon of apple sauce or honey to create a volume of approximately 8 mL [98, 99]. The dose of swallowed budesonide in children under the age of 10 years is typically 1 and 2 mg/day in those who are older than 10 years. After administration of topical steroids, no food or drink is allowed for 30 min. Aerosolized corticosteroids may be difficult for young children to ingest, as they are often bitter to taste and require twice daily administration.

In a prospective randomized trial [100] in children with EoE younger than 18 years, a 4-week therapy either with oral prednisone (32 patients) (1 mg/kg/dose twice a day; maximum 30 mg twice a day) or swallowed fluticasone by metered dose inhaler (36 patients) ($110 \mu\text{g}$ per puff for ages 1–10 years and $220 \mu\text{g}$ per puff for ages 11 years or older, 2 puffs 4 times/day) was compared. The drugs were weaned off over the next 8 weeks. Histologically, both treatments led to a significant reduction in eosinophilic infiltration in 93 % of the patients, but the reduction was significantly greater in the group receiving oral steroids. Clinically, 100 % of patients on prednisone and 96 % of those on fluticasone were symptom free after 4 weeks of therapy. Symptoms returned at pre-treatment levels in 45 % of patients 12 weeks after discontinuation of treatment with no significant difference between the two groups. Forty percent of patients receiving oral steroids had systemic adverse effects, whereas 15 % of the fluticasone arm had only local adverse reaction (esophageal *Candida* overgrowth). Other studies have reported an efficacy ranging from 50 to 90 % for fluticasone therapy [94–97]. Konikoff et al. [94] in a randomized, double-blind, placebo-controlled trial (fluticasone at $220 \mu\text{g}$ 2 puffs twice a day ($880 \mu\text{g}$ daily) for 3 weeks) showed that 50 % percent of pediatric patients with active EoE achieved histological remission compared with

Fig. 5 Algorithm of EoE treatment management

9 % of patients receiving placebo ($P=0.047$). Fluticasone induced a reduction in esophageal eosinophils from 84.6 ± 19.7 to 19.6 ± 12.9 eos/hpf in the distal esophagus. Improvement of symptoms was also significantly more likely in patients treated with fluticasone than in those treated with placebo (67 vs. 27 %, respectively). On the contrary, another study in adult patients showed that fluticasone was able to induce improvement in histological eosinophilia but not in the clinical symptoms [101].

Budesonide slurry appears to be effective in children. In a study with 20 children with EoE treated with oral viscous budesonide, it was observed that there was a significant decrease in esophageal eosinophilic infiltration (87 eos/hpf (range 30–170) pre-treatment to 7 eos/hpf (range 0–50, $P<0.0001$) post-treatment). Resolution of the esophageal eosinophilia was observed in 80 % of patients (responders); the other were other partial responders (5 %) and no responders (15 %). Similarly, the mean symptom score fell from 4.4 to 0.8 ($P<0.0001$). No significant adverse events were reported. Morning cortisol levels were within normal limits [98]. Further randomized placebo controlled study showed similar efficacy in children [99] and adults [102].

Even if the two types of topical steroids are both used in clinical practice, a study that compared the effectiveness of

nebulized versus viscous topical corticosteroid in EoE showed that viscous budesonide leads to a significantly higher esophageal exposure to the steroid and to a consequent lower eosinophil infiltration in the esophageal biopsies [103]. Moreover, topical budesonide but not fluticasone is able to reverse esophageal fibrosis [70, 104]. While topical steroids are effective for treatment, clinical and histological features of EoE return upon discontinuation [90].

Topical steroids have been shown to be safe in limited studies that have analyzed their effect in the short term. The only major side effect has been oral and/or esophageal candidiasis in up to 10 % of patients. It has been also shown that fluticasone 220 µg twice a day may induce a mild inhibition of morning cortisol level at 98 [2, unpublished data]. However, there are no studies on the side effects of long-term use of topical steroid as no study longer than 1 year has been conducted on bone health and children growth. From experience for topical steroid use in asthma, it is known that moderate or high dose of topical steroids like the one used to treat EoE is associated with significant reduction in growth in children [105, 106]. Moreover, there are many unanswered questions on the chronic use of topical steroids. In particular, there is no consensus of dosage, formulation, frequency, and how to obtain remission using minimal steroid dosage. Hence,

investigation needs to be performed regarding the most effective topical steroid dose required for initial disease treatment and maintenance therapy for both children and adults. In addition, further research needs to be performed with regard to steroid resistance, the effect of corticosteroids on esophageal fibrosis, the need to treat to histological normalcy, quality-of-life issues, growth, and consequences of prolonged use (e.g., adrenal suppression) [2].

Diet

Foods have been shown to be the cause of EoE through the use of targeted elimination diets, six-food elimination diet (SFED), or elemental formulas [9, 81, 82, 92, 107] (Fig. 1). Diet treatment compared to swallowed steroid has the advantage to achieve the remission of the disease with similar success rate without using drugs. Especially in pediatrics, where side effects of steroids are typically more severe, drug administration is often problematic for children refusal, and diet is an attractive therapeutic option. Even more interesting is the fact that the few children, who have been reported to truly outgrow the disease, were all treated with diet [9]. Dietary elimination should be considered therefore in all children diagnosed with EoE and in motivated adults, in particular women at risk of osteoporosis. Current diet approach can be (1) a strictly elemental diet, (2) specific antigen avoidance based on allergy testing, and (3) empiric food elimination based on the most common food antigens, commonly known as SFED, in which patients avoid milk, egg, soy, wheat, peanut/nuts, and seafood [90]. All three methods have been proven to be effective with improved clinical symptoms and pathology [82, 91, 93], and the regimen chosen should be based on the individual patient [28].

Elemental diet is the most effective diet treatment with histological and clinical resolution in greater than 95 % of pediatric and adult patients [9, 83, 93]. Kelly and colleagues were the first to report the utility of elemental diet in ten children who had persistent GERD and esophageal eosinophilia refractory to pharmacotherapy and/or Nissan fundoplication. Following a 6-week trial of elemental formula, all patients showed significant decrease in esophageal eosinophils and clinical symptoms, with eight of them demonstrating complete resolution [81]. However, elemental diets are very difficult to establish; they often require nasogastric or gastric tube feeding to achieve caloric goal, have poor palatability, and are difficult to sustain long term [2, 93].

Hence, elimination diets based on removal of the most common food allergens [82] (SFED) or of the foods positive to SPTs or APTs (targeted elimination diets) have been tried with similar rates of improvement [108, 109]. Kagalwalla and colleagues [82], using SFED, demonstrated improvement in 74 % of EoE patients compared with an 88 % response in

children treated with an elemental diet. More recently, in 50 adult patients, Gonsalves et al. [92] showed similar effectiveness of a SFD in adults. Symptom scores decreased in 94 % ($P<0.0001$). Based on reintroduction, the foods most frequently associated with EoE were wheat (60 % of cases) and milk (50 % of cases) [92].

Many other studies have looked at the value of SPT and APT in children and adults to identify foods that are triggering EoE (Table 4). In adults, positive SPT to food allergens are rare, whereas positive SPT to environmental allergens are more frequent [110]. In another study, SPT predicted only 13 % of foods associated with EoE [92]. In pediatric patients, more comprehensive studies have been reported [9, 108]. Approximately two thirds of children with EoE have positive skin tests to at least one food allergen, but their positive predictive value (PPV) is poor especially for key foods such as milk and wheat [9, 111] (Table 4). To increase PPV of skin testing in predicting the food that triggers EoE, APTs have been used [9, 111] (Table 4). APTs are typically used for the diagnosis of non-IgE, cell-mediated immune responses driven by T cells, such as contact dermatitis. In the evaluation of food allergy, APTs have been most extensively studied in atopic dermatitis and found that APTs are better in identifying late reactions and gastrointestinal symptoms in children with eczema [112–114]. The food to be tested is typically placed in aluminum cups (Finn Chambers on Scan pore; Alerter Laboratories, Inc., Petaluma, CA) and then applied on the patient's back in the 12-mm chambers [108]. Similar to patch testing for contact dermatitis, a 48-h occlusion time is used, and the patches are subsequently read at 24 h after removal of the Finn chamber, examining for erythema and papules (hence the reading is different than one for contact dermatitis) [115]. Any food can be assessed with patch testing, although cow's milk, hen's egg, wheat, and soy have been studied most extensively [26]. In 361 children with biopsy specimen-

Table 4 Positive and negative predictive values of APT+SPT for food allergies testing in EoE

Food	Combined SPT and APT			
	PPV	NPV	Specificity	Sensitivity
Milk ($n=211$)	81.5 %	44.9 %	77.8 %	50.2 %
Egg ($n=78$)	60.6 %	93 %	83.0 %	80.8 %
Wheat ($n=72$)	87.8 %	42 %	73.3 %	65.3 %
Soy ($n=52$)	33.3 %	92.8 %	72.3 %	71.2 %
Corn ($n=39$)	42 %	99.1 %	81.8 %	94.9 %
Beef ($n=33$)	31.2 %	96.3 %	81.5 %	72.7 %
Chicken ($n=32$)	32.9 %	98.3 %	80.1 %	87.5 %
Peanut ($n=16$)	22.4 %	99.6 %	82.8 %	93.8 %
Pork ($n=19$)	36.2 %	98.5 %	82.3 %	57.9 %
Potato ($n=21$)	17.2 %	96.9 %	89.0 %	81.0 %

diagnosed EoE and relative food allergy trigger, and who had eliminated foods based on SPT and APT, the authors found that 77 % of the patients had resolution of their biopsy specimens. The sensitivity and specificity of APT+SPT for the most common food involved in EoE are reported in Table 2 [92].

In addition, in the aforementioned study, the effectiveness of the various elimination diets was compared with targeted food antigen elimination. Definitive foods causing EoE were identified, with milk, egg, wheat, and soy as the most common foods in 319 patients. IgE-mediated reactions in patients with EoE triggered by food were seen in 15 %. The NPV for the combination of SPTs and APTs averaged 92 %, with the exception of milk at 44 %, and the PPV averaged 44 %. An empiric six-food elimination diet or removal of positive foods on allergy testing (SPTs/APTs) both had a histological success rate of 53 %. However, removal of foods identified on SPTs/APTs plus empiric elimination of milk led to resolution in 77 % of patients. In addition, targeted elimination diet based on SPT/APT required that fewer foods be removed compared to SFED. These observations suggest that both methods are acceptable options [10].

After 8 weeks of diet initiation, an EGD has to be performed to verify the efficacy of the diet. If a diet is effective, the EGD on a diet should show <10–15 eos/hpf in the esophageal biopsy. The goal of diet treatment is to maintain disease remission with the least restrictive diet; therefore, a slow reintroduction of eliminated foods is recommended. For the major allergenic foods such as milk, soy, wheat, egg, and meats, it is recommended to reintroduce one food a week and each food reintroduction should be followed by a repeat EGD about 2 months after the food introduction. Less allergenic foods can be introduced in groups to have fewer endoscopies by the patients. A food that once reintroduced triggers a reactivation of the disease (>15 eos/hpf) is considered causative and should be permanently removed from the diet [10]. For additional details of dietary management, please see recent review [116].

However, long-term elimination diets are not easy to follow. Milk and wheat proteins generally are the most difficult allergens to remove because they are present in the diets of the majority of children. In our clinical experience and from unpublished data, their removal may also result in the greatest nutritional impact, may reduce significantly the quality of life of patients and their family, and may pose a significant health risk of malnutrition and calcium, iron, vitamin D, vitamin E, and zinc deficiencies [117]. Therefore, a nutrition assessment by a registered dietitian experienced in food allergy is advisable for all EoE patients treated with any kind of elimination diets [117].

Even if for the most part EoE is manageable, often it takes several months to find the right therapy either because EoE is partially resistant to steroids, hence increased dosages need to

tried, or because the patient is allergic to multiple foods and multiple types of elimination diet, and consequent biopsies need to be obtained. In general, if steroids are given at high enough dosage (oral 2 mg/kg max 30 mg BID) or elemental diet is initiated, the disease goes to remission.

Biological Treatment

Several biological treatments have been tried to make treatment more specific, effective, and with less side effects. To date, none of the biological agents tried has been successful.

Anti-IL-5 IL-5 is the major survival factor for eosinophils and is considered essential for the differentiation, recruitment, survival, and activation of the eosinophils [36]. It has also been shown in animal models that IL-5-deficient mice are resistant to the development of EoE, whereas mice that over-express IL-5 have elevated levels of eosinophils in the esophagus at baseline [21, 37–39]. Moreover, patients with EoE, by definition, have elevated numbers of esophageal eosinophils and high esophageal tissue levels of IL-5 and IL-5R [31, 32]. Therefore, the first biological agent tried in treatment of EoE aimed to neutralize IL-5. Two humanized monoclonal antibodies against IL-5, Mepolizumab (SB240563) and Reslizumab (Sch55700), have been tried to target eosinophilic inflammation in EoE. They have a slightly different mechanism of action. Mepolizumab blocks binding of human IL-5 to the α -chain of the IL-5 receptor complex expressed on the surface of eosinophils and other cells [118, 119], whereas Reslizumab binds with high affinity to human IL-5, hence neutralizes circulating IL-5 and prevents it from binding to its receptor [119]. Both antibodies in pediatrics and adult trials have failed to show symptomatic improvement beyond the placebo effect [60, 120]. However, both Reslizumab and Mepolizumab had a good safety profile and significantly decrease eosinophil numbers in the esophageal biopsies in adults and children with EoE, even if only few patients achieved normal biopsies. These data confirm the importance of other cells and mediators in the pathogenesis of EoE that can be a target for immunological therapy.

Other biological treatments such as anti-TNF α (infliximab) [121] and anti-IgE (omalizumab) [122] 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 the treatment of EoE and showed promising albeit small results. OC000459 is a potent, selective, and orally bio-available CRTH2 antagonist, which blocks PGD2-mediated chemotaxis and activation of CRTH2-expressing cells, and has been used in a small group of patients with severe EoE dependent on or resistant to corticosteroids. No serious adverse events were observed and anti-CRTH2 had a modest, but significant, anti-eosinophil and beneficial clinical effects

in adult patients with active, corticosteroid-dependent, or corticosteroid-refractory EoE [123]. The lack of large improvement in esophageal biopsies indicated that other cells or molecules need to be blocked.

Immunotherapy

Oral immunotherapy (OIT) has been successfully used for treatment of IgE-mediated food allergy in several research protocols [124]. OIT mechanism of action is not known, but it is clinically clear that it works by gradually increasing doses of allergen consumption so the body does not mount an immune response against the allergen [125, 126]. Many uncontrolled and controlled studies have shown that the majority of patients with IgE-mediated food allergy can achieve clinical tolerance to different foods, such as milk, egg, fish, fruit, peanut, and celery [127–130]. One of the increasingly reported side effects of OIT is the development of EoE [89, 131–133]. Sanchez-Garcia et al. reported three cases of EoE in 110 patients with milk allergy treated with OIT [133]. Riodolo et al. reported a case of EoE due to egg in a child who had undergone a successful desensitization to egg [89]. In our experience, EoE develops in over 10 % of the patients undergoing OIT (data not published). We speculate that OIT may be triggering EoE by repeated low-dose antigenic exposure of an allergen that is only partially tolerated.

These data also confirm that IgE-mediated food allergy and EoE have a different pathogenetic mechanism. This is supported by the fact that the mechanism underlying the immunologic reaction to foods in EoE is probably not IgE mediated but cell mediated. In conclusion, at the present time, a role of OIT in the treatment of EoE has not been established or recommended at this time.

Some evidence suggests that aeroallergens may play a causative role in the development of EoE in humans. A seasonal variation in cases of newly diagnosed EoE [85], increased numbers of eosinophils in patients with AR compared to normal controls [134], a case report, in whom full disease control was achieved only during non-pollen seasons [9], and a case report of EoE development during oral immunotherapy for environmental allergen are all indications that environmental allergens may all play a role in EoE. Two further clinical reports suggest that treatment of EoE with environmental injectable immunotherapy (ITS) leads to improvement of EoE symptoms [135, 136] and indicates that ITS to environmental allergens may need to be further studied as a treatment of EoE.

Esophageal Dilation

Esophageal fibrosis and esophageal strictures are known complications of EoE. Endoscopic stricture dilation is a common

procedure performed in adults with EoE to provide short-term symptomatic relief. However, it should be used only in emergency situations or only if patients have failed dietary and medical therapy. Indeed, it is important to remember that esophageal mucosal fragility is a known feature of EoE [90], and stricture dilation in EoE is associated with increased risk of complications including pain, bleeding, and esophageal perforation [28, 90].

Conclusions

- Eosinophilic esophagitis (EoE) is a clinical-pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilia limited to the esophagus, in absence of gastro-esophageal acid reflux (GERD).
- Recent advances in research have shown that TSLP may play a pivotal role in driving Th2 inflammation typical of EoE.
- EoE development is most likely due to an interaction between environmental and genetic predisposition factors.
- 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 of 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 very promising.
- Environmental immunotherapy in its current injectable form may become a viable treatment if there will be larger studies to prove a role of environmental allergens in EoE pathogenesis.

Funding Institutional Support from The Department of Pediatrics, The Children's Hospital of Philadelphia, and Joint Center for Gastroenterology and Nutrition of CHOP-HUP, and The CHOP Food Allergy Family Research Fund

Conflict of Interest None

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