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Pediatric Eosinophilic Esophagitis Endotypes: Are we closer to predicting treatment response?

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Abstract

Eosinophilic esophagitis (EoE) is a chronic, food antigen-driven gastrointestinal disease that is characterized by esophageal eosinophilia. Currently, there are no Food and Drug Administration (FDA)-approved treatments for EoE, but the two most commonly prescribed therapies include topical corticosteroids and food elimination diets. Clinical trials have revealed a significant proportion of cases that are resistant to topical corticosteroids, and although we define EoE as a food-antigen driven disease, not all patients with EoE respond to elimination diets or even elemental diets. The varied response to treatments highlights the heterogeneity of EoE and the need for new treatment strategies. Despite the clinical differences in treatment response, predicting the outcome remains difficult since factors including age, histologic severity at diagnosis, atopic history, and anthropometrics are not predictive of treatment response. In our practice at an academic pediatric referral center, we observe distinct clinical EoE phenotypes, including cases with atopy, connective tissue disorders, or responsiveness to a proton pump inhibitor. Similar to the work in progress with asthma, stratification of patients with EoE by clinical phenotypes and/or molecular endotypes will likely assist with therapy selection and prediction of natural history. Molecular analysis with gene expression panels also show promise in helping us classify patients based on molecular endotypes. In addition to the clinical and molecular classifications, more accurate histological diagnostic criteria for EoE may help us tease out small differences between patient cohorts. Despite the leaps in knowledge over the past decade regarding EoE pathogenesis, it remains a challenge to predict the response to treatment. Future studies focused on molecular, genetic, and immunologic analysis of larger patient cohorts are needed to assist in identifying EoE phenotypes and endotypes as we attempt to improve patient outcomes in pediatric EoE.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic, food antigen–driven gastrointestinal disease that is characterized by esophageal eosinophilia [1]. Typically, the disease manifests itself differently in pediatric versus adult patients. In the adult and adolescent populations, the symptoms include food impaction and dysphagia along with symptoms of gastroesophageal reflux (heartburn) [2]. In children, the symptoms are more general, including food refusal/selective eating, vomiting, chronic abdominal pain, failure to thrive, and pain with eating [2]. The incidence of EoE is rising, affecting about 0.5–1 in 1,000 children in the United States [3]. There is a male predominance of 3 to 1, and two-thirds of children ultimately diagnosed with EoE have a history of atopic disease or allergic predisposition, including asthma, eczema, food allergies, or allergic rhinitis [2]. There is a strong genetic component as evidenced by a large sibling risk ratio [4]. Early genetic studies have identified susceptibility loci in genes that are expressed in epithelial cells that regulate immune responses [5].

EoE remains a clinical and pathologic diagnosis with endoscopic findings indicating esophageal eosinophilia (≥15 intraepithelial eosinophils/high-power microscopic field [HPF]) despite treatment with a high-dose proton pump inhibitor (PPI) [6]. Along with esophageal eosinophilia, histologic changes can include increased mast cell numbers, epithelial basal cell hyperplasia and increased papillary height, dilated intercellular spaces, and superficial eosinophilic microabscesses [7]. The most common and severe short-term complication is food impaction [8, 9]. If the disease is left untreated, the chronic inflammation can lead to esophageal fibrostenosis and dysmotility [2].

The proposed immunologic mechanism of EoE is characterized by an immune response that is primarily regulated by type 2 T-helper cells (Th2) against an allergen, either food or aeroallergen [1, 10] (Figure 1). EoE is primarily a non-immunoglobulin E (IgE) mediated allergic response, which is supported by the knowledge that IgE-mediated food allergy testing is not effective in identifying causative food antigens and anti-IgE therapy has not been an effective treatment for EoE [11]. Esophageal epithelial cells are activated in response to injury or exposure to an allergen and secrete thymic stromal lymphopoietin (TSLP) [12]. TSLP is a cytokine that stimulates dendritic cells and other immune cells in the subepithelial layer, leading to increased cytokine expression, including interleukin-5 (IL-5), IL-13, and IL-15. These cytokines are associated with eosinophil trafficking and recruitment [1]. In particular, IL-13 and IL-15 stimulate secretion of chemokine (C-C motif) ligand 26 [CCL26 (eotaxin-3)], which is a strong eosinophil chemotactic agent [4]. IL-13 also leads to decreased epithelial barrier function by decreasing the gene expression of structural proteins including filaggrin [13]. Eosinophils and mast cells themselves also produce the cytokine transforming growth factor beta 1 (TGF-β1), which can trigger the fibrotic cascade [1]. Overall, the development of EoE is a multifactorial process with multiple pathways leading to a common disease state.

Treatment options for EoE are limited, and long-term outcomes of the disease are still being defined. Therapeutic guidelines are difficult to establish because of the heterogeneous nature of the disease. In addition, EoE clinical symptoms do not correlate with histologic findings [14]. The two main treatments include topical steroids or dietary interventions, both of

which are difficult to maintain long term. Up till the time of writing this manuscript, the Food and Drug Administration (FDA) has not approved any treatment for EoE. The American College of Gastroenterology (ACG) recommends the topical corticosteroids fluticasone or budesonide as the first line of therapy [15]. The updated consensus for EoE in children and adults published in 2011, sponsored by the American Gastrointestinal Association and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), recommends topical corticosteroids with close monitoring or dietary therapy in pediatric patients, taking into consideration the patient and family's lifestyle and resources [2]. If a dietary therapy is pursued, a registered dietician is recommended to ensure adequate intake of vitamins and minerals, calories, and micronutrients.

Classification of EoE by phenotypes, which are defined as clinically observed differences in a trait of the disease, such as treatment response, is of utmost interest for clinicians as we attempt to improve patient outcomes in pediatric EoE. Atkins et. al recently published an article reviewing EoE phenotypes in an effort to help us better understand clinical features that will help drive more directed therapeutic interventions [16]. Given that EoE is considered an atopic-disease, the authors paralleled EoE phenotypes with previously described asthma phenotypes. They acknowledge that there are many unanswered questions but suggest starting with using symptoms at presentation to help define severity and treatment selection. The ultimate goal is to further classify patients with EoE into endotypes, subgroups defined by a pathophysiologic mechanism of disease rather than observed traits, as it may be that specific endotypes present with clusters of clinical phenotypes.

EoE Phenotypes by Treatment Response

As EoE is an antigen-driven disease with two-thirds of the patients showing atopy, it is reasonable to compare EoE to other allergic, immune-mediated diseases. In asthma, for example, identifying clinical phenotypes based on response to treatment has been beneficial in personalizing therapeutic approaches and predicting disease severity. It is reasonable to use this paradigm to similarly attempt to develop EoE phenotypes as these clinical phenotypes could assist with therapy selection and prediction of natural history.

Topical Corticosteroids

Swallowed, aerosolized, or nebulized corticosteroids are first-line therapies for EoE [15]. The two most commonly used corticosteroids are swallowed fluticasone propionate (FP) and oral budesonide solution. Overall, topical corticosteroids typically have response rates of greater than 50% of cases for EoE; consistently, however, there is a group of unresponsive cases, which can be as high as 65% [5, 17–19]. In studies to date, no patient characteristics have been identified that would predict clinical response to topical corticosteroids. We highlight here a few historical studies that demonstrate this variability in response rate (Table 1).

A small retrospective study published in 2004 studied the effect of FP for EoE and the difference between patients with and without food allergy [19]. They stratified the 20 patients by skin prick test (SPT) results to food antigens. The food SPT-positive group was

also more likely to be aeroallergen SPT positive and to have a history of allergic disease. The food SPT-negative group had reduced histologic changes, including less eosinophil infiltration and reduced basal layer hyperplasia. While all 10 patients within the food SPT-negative population responded to FP therapy, the FP response rates for the food SPT-positive patients were notably lower, with 20% having a partial response and 20% with no response. The 4 patients that showed no improvement had significant allergic rhinitis and/or asthma in addition to their identifiable food sensitization. Overall, it was concluded that patients with the allergic variant EoE are resistant to FP treatment and have increased symptoms, peripheral eosinophilia, and serum IgE levels. The investigators hypothesized that the patients with EoE and allergy have persistent exposure to food antigens that were not tested by the SPT or to an unknown aeroallergen, thereby inciting persistent EoE disease.

In 2006, the association between atopy and decreased response to FP therapy was corroborated in the first published double-blind, placebo-controlled trial studying FP in pediatric EoE [20]. The investigators found 50% (10/20) of FP-treated patients had complete EoE remission, defined as peak eosinophil count/HPF ≤ 1 in both proximal and distal esophagus, compared to 9% (1/11) of placebo-treated patients showing complete EoE remission ($p = 0.047$). Non-allergic patients had a more significant reduction in eosinophil levels from pre-treatment to post-treatment in both the proximal and distal esophagus compared to allergic patients. In addition, overall, non-allergic patients had lower post-treatment esophageal eosinophil levels than allergic patients in the proximal esophagus ($p = 0.004$). FP-responders were also more likely to be younger ($p = 0.0003$), shorter ($p = 0.002$), and lighter in weight ($p = 0.02$) compared to FP non-responders.

In 2014, a larger, randomized, multisite, double-blinded study of EoE found that a high percentage of cases responded to 3 months of high dose FP (65%) whereas no cases responded to placebo [5]. However, there was still a large group of unresponsive cases (35%). A complete remission (CR) was defined as ≤ 1 eosinophil/HPF in the proximal and distal esophagus and partial remission (PR) as ≤ 14 eosinophils/HPF. After dose reduction in the cases with CR in the FP group, 73% remained in CR, 20% evidenced PR, and 7% had active disease, suggesting that there was a dose response in some patients. Extending the FP therapy in FP-resistant cases did not induce remission, suggesting an FP-resistant phenotype. The investigators did not find any differences in patients with FP-resistant and FP-responsive EoE when stratified by compliance, age, sex, atopic status, and anthropomorphic features.

A randomized, placebo-controlled trial in children with EoE published in 2015 investigated different doses of oral budesonide suspension (OBS) [17]. The study population included 71 patients, with ages ranging from 2 to 18 years. The primary end point was a compound response to therapy, including both histologic and clinical response. It is worth noting that this study was performed prior to the current guidelines recommending a PPI trial prior to diagnosis. Therefore, the study investigators used more stringent criteria for diagnosis, excluding patients with exclusively distal esophageal eosinophilia, who they felt might have had damage caused by acid reflux rather than eosinophilic esophagitis; thus, this study potentially may have selected for a more severe patient population. Patients receiving medium-dose OBS (52.6%, $p = 0.0092$) and high-dose OBS (47.1%, $p = 0.0174$) showed higher compound response rates than those receiving low-dose OBS (11.8%) and placebo

(5.6%). The significant compound response noted in medium-dose and high-dose OBS was primarily attributed to the histologic response. High-dose OBS had a 94.1% histologic response rate compared to 52.6% with medium-dose OBS, 23.5% with low-dose OBS, and 5.6% with placebo. All 4 groups had large symptom response rates, including the placebo group. There was no stratification of differential EoE histologic response to OBS by age, gender, histologic severity on the first endoscopy, or the use of additional medications [17]. These data support that histologic response does not always correlate with clinical symptom reduction.

In addition to resolution of esophageal eosinophilia as a measure of response to therapy, there are additional histologic changes with EoE treatment, such as remodeling of the lamina propria (LP). In 2010, changes in LP remodeling with OBS treatment was studied [18]. In a retrospective review of 16 pediatric patients with EoE, nine responded to OBS with residual eosinophil counts of < 7 eosinophils/HPF and reduced LP remodeling. Patients with EoE responsive to OBS treatment were similar in age, budesonide duration, atopic status, and disease duration prior to starting budesonide compared to patients who did not respond to OBS.

In summary, topical corticosteroids have a wide range of response rates, with up to 65% of cases responding with complete remission in pediatric studies. Despite the clinical differences in treatment response, predicting the outcome remains difficult. Age, sex, atopic status, and anthropomorphic features have not correlated with clinical treatment response. There is some evidence that EoE in atopic patients is more resistant to topical corticosteroids. This association is surprising, as most patients with respiratory atopic disorders respond to inhaled topical steroids.

Dietary Management and Food Elimination Diet

In 1995, Kelly, et al. was the first to describe resolution of inflammation in EoE with an amino acid-based formula in pediatric patients [21]. Since that time, elemental formulas and food elimination diets have been studied and used as treatments for managing EoE. In 2006, a pediatric retrospective study investigating a specific six-food elimination diet (SFED), eliminating cow's milk, egg, soy, wheat, nuts and seafood, was published and showed good response rates, with the esophageal eosinophilia of 26 of the 35 pediatric patients (74%) reducing significantly with the diet [22]. Milk was the most common trigger (74%), followed by wheat (26%), egg (17%) and 72% of the pediatric patients who had a single food trigger identified. A retrospective study published in 2012 by Henderson, et al., showed even higher response rates to SFED, with 81% of 26 pediatric patients achieving remission (i.e. < 15 eosinophils/HPF) [23].

One of the first large, prospective studies of the SFED for EoE was published by a Spanish group in 2013 and showed that the SFED induced and maintained long-term remission of EoE in adult patients [24]. The study diet was more exclusive than the typical six foods (wheat, milk, egg, soy, tree nuts/peanuts, fish/shellfish) and also excluded rice, corn, legumes, all nuts, as well as goat's milk and sheep's milk-derived products. This more stringent diet may account for the higher response rate compared to other studies using the standard SFED. Overall, the EoE of 49 of the 67 adult patients (73%) responded to the

elimination diet with a decrease in esophageal eosinophilia from pre-SFED levels ($p < 0.001$). Between the 18 patients with SFED-unresponsive and the 49 patients with SFED-responsive EoE, no differences were found regarding type or duration of symptoms, endoscopic findings, personal or family atopic background, or allergy testing results. A single food, 2 food, and 3 or more food triggers was found in 15, 13 and 14 of the 49 patients, respectively. The most frequent food trigger was cow's milk (62%) followed by wheat (29%), eggs (26%), and legumes (24%). The investigators also analyzed IgE serum levels and SPTs in relation to the patients' response to the SFED and reintroduction challenges. They found that on the basis of the food triggers empirically identified by food reintroduction, the sensitivity and specificity of both IgE levels and SPTs for identifying trigger foods were low. These data are consistent with current management guidelines that warn against using these tests to guide narrower food elimination diets [25].

A meta-analysis published in 2014 examined all dietary therapies for EoE. The elemental diet, which eliminates all food and provides sustenance via amino acid-based formulas (followed in most cases by a long process of food trials to attempt to add foods which do not trigger EoE in an individual patient), was effective in 90.8% of children, whereas allergy testing-directed food elimination (SPT, atopy patch testing) was effective in 45.5% [26]. The SFED showed a 72.1% positive response in a mixed population of pediatric and adult patients, which is promising given that the SFED is more palatable and should have improved compliance relative to an elemental diet. When comparing studies, it is important to note the different definitions of SFED. The Spanish study cited above used a more exclusive diet, potentially over estimating positive results. The fourth most common trigger in the Spanish study is legumes, which is a larger category of food that encompasses beans, peas, peanuts as well as soy. Many of the studies published in the United States indicate the majority of EoE is triggered by cow's milk, wheat, egg and soy (rather than legumes) [23, 27]. As a result of these findings, a four-food elimination diet has been investigated and may have improved adherence and long-term success, as well as reduced the number of endoscopies needed to complete the food trial process. A recent study of 78 children with EoE showed promising results for a four-food elimination diet, excluding milk, wheat, eggs, and soy [28]. After an 8-week trial, 50/78 patients (64%) showed histologic remission.

Although we define EoE as a food antigen-mediated disease, not all patients have EoE respond to elimination diets or even elemental diets, highlighting the presence of two clinical phenotypes—1) food antigen-dependent disease (elimination diet-responsive EoE) and 2) non-food antigen-dependent disease (elimination diet-unresponsive EoE). To date, there are no identified clinical tests or disease parameters that would predict response to dietary therapy.

Biologics

Given the reports for EoE being exacerbated by aeroallergens [29–32] there has been an interest in anti-IgE therapy as a potential approach to management. Loizou et al. published an open-label, single-arm, unblinded pilot study of omalizumab (anti-IgE) in EoE in 2015 [11]. The investigators administered omalizumab for 12 weeks in 15 patients with EoE in an effort to examine the effects of anti-IgE therapy on esophageal eosinophil levels. Inclusion

criteria were strict and selected the refractory and atopic cases of EoE. Five out of 15 (33%) patients had full disease remission with omalizumab treatment. The patients who did not have histologic improvement also did not have clinical improvement. The study investigators found no correlation between changes in symptom scores and blood absolute eosinophil counts. In conclusion, this study was small and at a single center, which makes it difficult to generalize. Overall, the success rate was low, even in a population that selected for severely atopic individuals. A slightly larger, double-blinded, placebo-control trial of adults with EoE published in 2014 found no difference in esophageal eosinophil counts with omalizumab therapy [33]. Sixteen patients treated with omalizumab every 2 to 4 weeks for 16 weeks and 14 patients treated with placebo had no statistical difference in esophageal eosinophil counts post therapy. In general, anti-IgE therapy has not been shown to be an effective treatment for EoE.

In addition to anti-IgE therapies, specific cytokines such as IL-5, which is a main mediator for blood and tissue eosinophilia, are targets for new therapeutic strategies for EoE. Monoclonal antibodies against IL-5, including reslizumab and mepolizumab, which have been approved for use in eosinophilic asthma, have also been investigated for use across the eosinophilic disease spectrum, including EoE. Reslizumab reduced esophageal eosinophilia in up to 67% of patients in a randomized control trial. However, all groups, including the placebo group, had similar improvement in symptom scores, indicating that symptom improvement was unrelated to esophageal eosinophil count [34]. Mepolizumab has also been investigated in EoE with only modest results. One of the first studies, published in 2006, found improvement in clinical symptoms, reduction in peripheral eosinophilia, and decline in esophageal eosinophilia on histology [35]. However, this study included only 4 adult patients, all of whom had longstanding history of uncontrolled disease with multiple failed prior therapies. These preliminary results suggested that mepolizumab could reverse disease even in patients with severe phenotypes and longstanding disease. In the last 10 years, more studies have been published that show more equivocal results in small sample sizes. A group in Switzerland published a randomized, double-blind controlled trial in 2010 with 11 adult patients. They found a statistically significant reduction in the number of esophageal eosinophils with mepolizumab therapy compared to the placebo group after 4 weeks of treatment, but no further reduction thereafter [36]. None of the patients had a reduction in esophageal eosinophils to less than 10 to 15 eosinophils per HPF. Therefore, despite having a reduced number of esophageal eosinophils, none of the patients reached disease remission (less than 15 eosinophils/HPF).

A larger, international, multicenter, double-blind, randomized pediatric study published in 2011 studied three treatment doses (0.55mg/kg, 2.5mg/kg and 10mg/kg) of mepolizumab in 59 children [37]. Three infusions were administered over a 12-week period, and a follow up esophageal gastro-duodenoscopy with biopsies was performed at weeks 12 and 24. At week 12, 8.8% of patients had a peak esophageal intraepithelial eosinophil count < 5/HPF, and the response did not differ based on treatment group. At week 24, only 3.7% had peak esophageal intraepithelial eosinophil count < 5. The significant decreases in peak and mean eosinophil counts were more striking. The peak esophageal intraepithelial eosinophil count decreased significantly from baseline to week 12 (122.5 to 40.2, $p = 0.0001$). This decrease was most impressive in the 2.5mg/kg treatment group. At week 24, the peak eosinophil

count increased but remained significantly lower than baseline ($p = 0.002$). The mean eosinophil count also decreased significantly from baseline to week 12 ($p = 0.0001$), and was most significant in the 10mg/kg treatment group. Although this study showed only a small percentage of patients had complete remission (<5 eos/HPF) with mepolizumab therapy, the significant decrease in intraepithelial esophageal eosinophil counts supports the theory that IL-5 plays a role in esophageal eosinophil accumulation in children with EoE. Given the low complete response rate, multiple pathogenic pathways likely contribute to the disease.

In general, trials of biologic therapies have not shown unequivocal success to date. It is possible that this is due to a multi-factorial mechanism leading to the development of disease. Thus, blockade of a single mediator (cytokine or IgE) may not halt the disease process from occurring through alternative routes. In addition, the lack of response may be due to the inability to accurately select patients for treatment. For example, in previous work in asthma the initial studies using mepolizumab were underwhelming [38]. However, when studies were performed in “eosinophilic asthma,” the response improved [39]. Similarly and as suggested by the omalizumab trial cited above, there may be subgroups of patients who respond to particular biologics, but biomarkers that identify treatment responsive subtypes are needed.

One hypothesis for the varying treatment response rates is that the resolution of esophageal eosinophilia is an insufficient primary endpoint. We know that peak eosinophil count is only one histologic change that occurs with EoE. From previous studies, there is correlation between resolution of eosinophilia and other histologic characteristics, such as lamina propria remodeling [18]. Pathologists are investigating a more extensive histologic scoring system that outperforms peak eosinophil count in the esophagus, which includes a total of eight histologic features [40]. In addition to eosinophil count and lamina propria fibrosis, the new system includes basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, and dyskeratotic epithelial cells. An improved histologic scoring system that includes additional features may more accurately diagnose EoE, monitor disease activity and response to therapy, and classify EoE phenotypes. In addition, less invasive biomarkers are needed in order to improve endotyping and improve our ability to follow disease activity over time.

The studies presented in this review demonstrate that patients with EoE have a wide range of responses to therapy. While some patients respond to steroids only, some respond to only elimination diets, and even others are difficult to control despite a combination of therapies. Currently, we have no biomarkers that can predict the response to treatment, and therefore, we continue to have difficulty guiding therapy effectively and efficiently.

EoE Endotypes via Molecular Analysis

To gain insight into EoE pathogenesis, Rothenberg and colleagues have analyzed gene expression in the esophagus of patients with active EoE, inactive EoE, and normal controls [4, 41]. An EoE transcriptome has been described that is consistent across age, sex, and inheritance patterns [41, 42]. The EoE transcriptome is independent of atopic status, which

suggests that despite different phenotypic presentations, there may be a common disease pathway [41]. In 2010, genome-wide association studies found a susceptibility locus at 5q22, which includes the genes for thymic stromal lymphopoietin (TSLP) [43, 44]. Overexpression of the TSLP protein in esophageal tissue from patients with EoE was noted [43]. However, given the strong association between TSLP and allergy [45, 46], it is not clear whether the genetic association is specific to EoE [47]. Genetic studies have found other susceptibility markers, including single-nucleotide polymorphisms in the gene that encodes CCL26 (Eotaxin-3), a potent chemoattractant for eosinophils [44]. CCL26 is highly expressed in the esophagus of patients with EoE compared to the general population [4]. Additional studies have linked mutations within the epidermal barrier gene filaggrin and the promoter region of *TGFB1* with EoE [13, 18].

In 2013, investigators at Cincinnati Children's described the use of the EoE Diagnostic Panel (EDP), which is a representative 94 gene EoE array, to monitor the FP intervention efficiency [48]. This panel has been shown to distinguish patients with EoE in remission from patients with exposure to swallowed glucocorticoids with high sensitivity and specificity [48]. The authors also published an EoE scoring algorithm based on 77 dysregulated core genes that reflects EoE disease status and severity. In 2014, Butz et al investigated the efficacy of FP, as discussed in the treatment section above, and used this EoE scoring algorithm to determine differences between patients with EoE responding to FP and non-responders [5]. In this study, the patients with EoE in histologic complete remission (< 1 eosinophil/HPF in the proximal and distal esophagus) had EDP scores that were normalized compared to those of patients treated with placebo and patients with EoE in partial remission (< 14 eosinophils/HPF). However, despite the histologic response in patients with EoE in complete remission, the gene expression profile did not completely return to normal, suggesting persistence of molecular abnormalities in these patients and potentially a reason for the clinically observed frequency of disease relapse. The patients with EoE in partial remission or EoE unresponsive to treatment had a different, more normalized EDP score than the placebo group, demonstrating that some of the gene expression changes are due to steroid exposure alone, not necessarily to improved eosinophilia. By examining the pre-treatment biopsy samples of the patients with FP-responsive and FP-unresponsive EoE, they found 15 genes on the EDP that had a higher tendency to predict subsequent response to FP. Although the sample size was small, their findings suggest that a specific molecular signature may help identify patients that will be responsive to a specific treatment.

In 2010, investigators at Rady Children's Hospital in San Diego studied molecular and genetic changes in patients with EoE treated with budesonide [18]. The 9 patients with oral budesonide suspension-responsive EoE (56%) had decreased vascular activation, as measured by VCAM-1, and decreased mediators for fibrosis, including TGF- β 1. Patients with oral budesonide suspension-responsive EoE were also more likely to have a CC genotype at the 569 position of the *TGFB1* promoter. Asthma studies have shown that patients with the *TGFB1* promoter TT genotype have higher serum TGF- β 1 levels and more severe asthma [49]. The TT genotype increases *TGFB1* promoter activity, which may lead to increased fibrosis. In this study, all the patients with the CC genotype of the *TGFB1*

promoter had oral budesonide suspension-responsive EoE, suggesting a potential that it may serve as a prognostic indicator for response to therapy.

Another gene implicated in EoE is *CAPN14*, which is a member of the calpain family [50]. This family of 16 genes is a group of intracellular, calcium-activated, regulatory proteases. Dysregulation of the calpain family has been implicated in a number of disease, including limb girdle muscular dystrophy type 2 [51], as well diabetes [52], asthma [53], Alzheimer's [54], and myocardial infarctions [55]. A study published in 2016 showed that mRNA levels for *CAPN14* are higher in patients with EoE compared to normal controls [50]. Over-expression of *CAPN14* results in impaired barrier function based on decreased transepithelial resistance and increased flux through the epithelial layer, as well as decreased expression of desmoglein-1. Interestingly, the authors also showed that silencing *CAPN14* increases IL-13 induced epithelial layer disruption, similar to what is seen in EoE. Therefore, they concluded that *CAPN14* may not only be involved in disease pathogenesis but also may play a role in repair from IL-13 mediated epithelial layer disruption. Although it is not known if a gain or loss of CAPN14 activity leads to EoE risk, there is data that supports CAPN14 as a regulatory protein in EoE. In conclusion, future genetic studies may discover additional genotypes that will help explain differing corticosteroid and dietary response rates for EoE.

EoE Clinical Phenotypes

PPI-responsive EoE

To fulfill the diagnostic criteria for EoE and distinguish it from GERD, the 2011 guidelines necessitate that a patient fail treatment with a PPI [6]. Up to 50% of children will have complete resolution of esophageal eosinophilia when treated with a PPI [56, 57]. However, we continue to lack the ability to predict treatment response. Over the past few years, the requirement of failing a PPI trial for the diagnosis of EoE has been challenged [58]. There is growing evidence to support an ambiguous and complex relationship between GERD, PPI-responsive esophageal eosinophilia (PPI-REE), and EoE. We know from pH monitoring studies that adult patients with EoE have increased acid sensitivity even in the absence of pathologic GERD [59]. Therefore, GERD in a patient with EoE may be intrinsically related. It is not clear why acid suppression with a PPI would resolve esophageal eosinophilia as EoE is defined as an immune/antigen-driven response, unless we consider the inherent anti-inflammatory effects PPIs may have. More specifically, the PPI may exert its anti-inflammatory effects through secondary inhibition of CCL26 (i.e., eotaxin-3) [60, 61]. Given the relationship between PPI and CCL26 in addition to the difficulty differentiating EoE from GERD, CCL26 has been studied as a potential biomarker to help distinguish patients with EoE, PPI-REE, and GERD [62]. A retrospective study of 68 adult patients found a significantly lower CCL26 staining score in patients with GERD compared to patients with EoE ($P = 0.002$). The PPI may also be helpful in relation to antigen-driven EoE, as it may improve healing of a disrupted epithelial cell barrier and subsequently prevent further immune activation [63]. A recent study found that PPI-REE and EoE have overlapping phenotypic, genetic, and mechanistic features [58]. Additionally, the EoE transcriptome in a mixed pediatric and adult population of patients with PPI-REE and EoE is remarkably

similar, and there is complete reversibility of the inflammatory transcriptome after PPI treatment alone in PPI-REE [64]. Furthermore, two small case series have shown that pediatric and adult patients who initially respond to PPI therapy will also respond to diet and/or topical corticosteroids [65]. Collectively, the evidence suggests that PPI-REE may exist in the continuum of the same disease process, and PPI-Responsive EoE may be a clinical phenotype of EoE. The 2017 European guidelines suggest that patients that initially have resolved esophageal eosinophilia with PPI, PPI-REE, now be classified as PPI-responsive EoE [66]. Consensus in North America on this topic was not clear at the time of publication, creating ambiguity in usage of the term “PPI-REE”, but this may drive the development of a new consensus document in the near future.

Atopic EoE

EoE is an antigen-driven gastrointestinal disease, and two-thirds of pediatric patients have a history of atopic disease or allergic predisposition including asthma, eczema, food allergies, or allergic rhinitis [2]. A recent meta-analysis published in 2017 investigating the association between atopic manifestations and EoE found a higher chance for pediatric and adult patients with EoE to present with atopic diseases, including bronchial asthma, allergic rhinitis, and eczema, compared to the control population [67]. However, a proportion of patients with EoE remain without a history of atopy [67, 68], and a causal link between atopic disease and the development of EoE has not been identified. It is likely that atopic manifestations and EoE occur via parallel but separate pathways. As described in more detail in the treatment section above, the lack of predictive success of SPTs/IgE food allergy testing and the suggestion that atopic patients might have a lower steroid response rate suggests an atopic EoE phenotype. It is unclear whether atopy is a modifier of disease activity, though EoE is likely the result of dysregulation in multiple immunologic pathways. It is yet to be determined whether patients with the atopic EoE phenotype have a different natural history of EoE.

Fibrostenotic

Untreated EoE can lead to esophageal stenosis and stricture formation in some patients. The risk factors for developing a fibrostenotic phenotype, other than symptom duration without treatment, are not well understood. A retrospective, single-site study published in 2014 described the clinical features of adult and pediatric patients with a fibrostenotic phenotype compared to those patients with an inflammatory phenotype [69]. The study investigators found that 134 out of 374 (36%) of patients had an inflammatory phenotype, 161 (43%) a mixed phenotype, and 79 (21%) a fibrostenotic phenotype, and significant clinical differences existed between the groups. The patients with the inflammatory phenotype were younger, more likely to have dysphagia, suffer from food impaction, and require esophageal dilation. The mean symptom length prior to diagnosis was shorter for the inflammatory phenotype. It is unclear whether this difference was due to earlier diagnosis and treatment, by which the progression to fibrostenotic disease was halted, or whether this subgroup of patients has another factor inherently different about their disease presentation. Regardless, a multivariate analysis showed an increased risk of fibrosis over time; with every 10-year increase in age, the odds of developing the fibrostenotic phenotype more than doubles. This has been corroborated in other studies demonstrating the positive correlation between

duration of delay in diagnosis with the prevalence of strictures [70]. It is interesting that, in the 2014 retrospective study, the maximum eosinophil count on esophageal biopsy did not significantly differ between the fibrostenotic and inflammatory phenotypes, suggesting that inflammation remains, even in the fibrostenotic group. This is clinically relevant as we currently measure success and failure of treatment on trends in tissue eosinophil count, which therefore may not be accurate in predicting which patients ultimately will have fibrostenotic disease. A more accurate histologic classification system may be helpful in classifying a fibrostenotic phenotype. Overall, improving time to diagnosis may prevent secondary complications of fibrosis related to EoE natural history. The recognition of a fibrostenotic phenotype also has clinical implications, as these patients may need more aggressive therapy as primary treatment.

EoE gender-specific phenotype

Although about 75% of patients with EoE are male [68, 71], very few studies have investigated the role of gender in the pathogenesis and clinical presentation of EoE. One retrospective study in adults published in 2015 found that females are more likely to complain of inflammatory symptoms including chest pain and heartburn [72]. Males are more likely to complain of dysphagia or have a history of food impaction. Assuming that dysphagia and food impaction are related to fibrostenosis, it may be that males are more likely than females to progress to severe disease states. However, this study did not find any endoscopic difference between genders. With this in mind, it may be that a proportion of females remain undiagnosed due to the atypical symptom presentation. The authors offer a few hypotheses for this gender difference in clinical presentation. The esophagus itself is known to vary by gender [73]. For example, the length of the esophagus is determined by height, and thus is shorter, on average, in females. We also know that the resting pressures of the upper and lower esophageal sphincters are higher in females [73]. Interestingly, male predominance is noted in other disorders of the esophagus, unrelated to EoE, for example esophageal cancer has an 8 to 1 male predominance [74]. It is still not clear whether these differences in esophageal structure are related to the differences in clinical presentation. Currently, research is underway to investigate the effects of hormone levels on eosinophil function and other pathways in EoE. We are hopeful that we will soon identify hormonal differences between the genders that can account for the differing clinical phenotypes.

EoE–Connective Tissue Disease

In 2013 a group at Cincinnati Children's Hospital Medical Center noted a high prevalence of EoE in patients with connective tissue disorders (CTDs), such as Ehlers Danlos Syndrome (EDS) [75]. They found that there was an 8-fold increased risk of EoE in pediatric patients with CTDs compared to the general pediatric population. The connection between CTDs and EoE is likely via TGF- β 1, which has been implicated in causing fibrosis and tissue remodeling in EoE [18]. Variants of the TGF- β 1 binding proteins cause CTDs including Marfan syndrome (MFS) and Loeys-Dietz syndrome [75, 76]. EDS has not been directly linked to TGF- β 1 levels, but proteins that regulate TGF- β 1 and its interactions with COL5A, the mutated collagen protein in EDS, have been reported [77]. Notably, the EoE transcriptome largely overlapped between pediatric patients with EoE-CTD and those with non-syndromic EoE [75]. The study also found significant differences in the expression of 4

specific genes in pediatric patients with EoE-CTD [75]. Overall, the pediatric patients with EoE-CTD had a lower BMI and increased risk of extra-esophageal eosinophilic gastrointestinal disease (EGID) [75]. The authors also suggested that losartan (a angiotensin receptor blocker which has long been used clinically in hypertension) has been shown to decrease TGF- β levels and reverse MFS tissue remodeling in mice models, which might also have therapeutic utility in the EoE-CTD population [75].

Conclusion

In summary, despite large advances in the understanding of EoE pathogenesis in the past 10 years, we have more to learn as we strive to improve diagnostic modalities, discover more effective and patient-targeted therapeutic strategies, and develop more accurate disease monitoring systems. From a treatment standpoint, two options remain--1) topical corticosteroids or 2) dietary elimination therapies, both of which are used as first-line therapies based on patient and/or parent preference, without the ability to predict outcome. We are hopeful that the growing number of genetic, molecular expression, and immunologic analyses, in conjunction with increased differentiation of clinical phenotypes and biomarker supported endotypes will help us explain differing therapeutic responses, predict clinical response, guide individual therapies, and improve patient outcomes.

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Abbreviations

ACG	American College of Gastroenterology
EoE	Eosinophilic esophagitis
EDP	EoE Diagnostic Panel
FP	Fluticasone propionate
FDA	Food and Drug Administration
HPF	High-power microscopic field
Ig	Immunoglobulin
IL	Interleukin
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition
OBS	Oral budesonide suspension

PPI	Proton pump inhibitor
PPI-REE	Proton pump inhibitor responsive esophageal eosinophilia
SFED	Six-food elimination diet
SPT	Skin prick test
Th2	T-helper cell
TSLP	Thymic stroma lymphopoietin
TGF-β	Transforming growth factor beta

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Figure 1. Schematic of the pathogenesis of eosinophilic esophagitis

Stimulation of the esophageal epithelium by an allergen results in release of TSLP and subsequently activation of Th2 cells, which secrete interleukin (IL)-5, IL-13 and IL-4. The cytokines lead to downstream effects including expression of CCL26 (eotaxin-3) and down-regulation of barrier proteins, including filaggrin and desmoglein. CCL26 (eotaxin-3) is a strong eosinophil chemotactic agent. Together, eosinophils and mast cells increase expression of TGF β 1, which starts the fibrotic cascade leading to esophageal remodeling

Table 1

Summary of studies investigating topical corticosteroids included in our review

Study	Population	Methods/Design	Results
Noel, R.J., et al. [19]	20 patients; ages 1–13	<ul style="list-style-type: none"> FP BID between two endoscopies SPTs done on all patients 	10 SPT (+) <ul style="list-style-type: none"> 90% sensitive to at least one aeroallergen 70% history of allergic disease 2 PR, 2 NR, and 6 CR 10 SPT (–) <ul style="list-style-type: none"> 40% sensitive to an aeroallergen 20% history of allergic disease 100% CR Reduced eosinophil infiltration, reduced basal layer hyperplasia on histology
Konikoff, M.R., et al. [20]	36 patients ages 3–18	<ul style="list-style-type: none"> Randomized to FP BID for 3 months (21) or placebo (15) CR = 1 eosinophil/HPF proximal and distal esophagus 	FP Treated 10/20 CR (50%); Placebo 1/11 CR (9%) p = 0.047 Non-allergic patients compared to allergic patients: <ul style="list-style-type: none"> More significant reduction in eosinophil counts in proximal (p = 0.03) and distal esophagus (p = 0.04) Lower post-treatment esophageal eosinophil levels in proximal esophagus (p = 0.004)
Butz, B.K., et al. [5]	42 patients; ages 3–30	<ul style="list-style-type: none"> Randomized to daily 1760 mcg FP or placebo for 3 months (28 FP, 14 placebo) If CR after 3 months → dose reduction If PR or NR after 3 months → continued current FP therapy or, if originally in the placebo group, started FP 	After 3 Months <ul style="list-style-type: none"> 65% of FP-treated patients with CR <ul style="list-style-type: none"> 73% remained in CR with dose reduction 20% went to PR with dose reduction Zero placebo-treated patients with CR Extending the FP therapy in FP-resistant EoE did not induce remission
Gupta, S.K., J.M. Vitanza, and M.H. Collins [17]	71 patients; ages 2–18	<ul style="list-style-type: none"> Primary endpoint: compound response <ol style="list-style-type: none"> peak eosinophil count <6 eosinophils/HPF at all levels of the esophagus >50% reduction in EoE symptoms Randomized to a 12-week trial of placebo, or low-, medium-, or high-dose OBS 	Compound Response Rates <ul style="list-style-type: none"> 52.6% with medium dose (p = 0.0092) 47.1% with high dose (p = 0.0174) 11.8% with low dose 5.6% with placebo Histologic Response Rates <ul style="list-style-type: none"> 94.1% with high dose 52.6% with medium dose 23.5% with low dose 5.6% with placebo
Aceves, S.S., et al. [18]	16 patients; ages 1–17	3 months of OBS CR = 7 eosinophils/HPF PR = < 20 eosinophils/HPF	After 3 Months <ul style="list-style-type: none"> 9 patients (56%) with CR

Study	Population	Methods/Design	Results
			<ul style="list-style-type: none">Responsive cases had reduced LP remodeling

BID, two times a day (*bis in die*); EoE, eosinophilic esophagitis; FP, fluticasone propionate; HPF, high-power microscopic field; SPT, skin prick test; CR, complete remission; PR, partial remission; NR, no response; OBS, oral budesonide solution; LP, lamina propria

Table 2

Summary table of stratification strategies for eosinophilic esophagitis

Stratification Strategy	Phenotypes/Endotypes	Summary
Treatment Response	Topical Corticoid Steroids: Responsive vs. Non-responsive	Up to 65% of cases respond to topical corticosteroids with complete remission. Age, sex, atopic status, and anthropomorphic features do not correlate with clinical treatment response. A small amount of evidence suggests that EoE in atopic patients is more resistant to topical corticosteroids [5, 17–20].
	Dietary Therapy: Responsive vs Non- responsive	There are varying response rates based on the restrictiveness of the diet: SFED ~72% [22, 23]; 4-food-elimination ~64% [28]; Elemental diet ~90% [21, 26]; SPT based diet ~45% [26] .
	Biologics	Response rates are variable in a limited number of small studies [33–37].
Clinical Phenotype	PPI-responsive	PPI-Responsive EoE may be a clinical phenotype of EoE [66].
	Atopic	SPTs/IgE food allergy testing-guided elimination diets lack predictive success [26]. Atopic patients might have a lower steroid response rate, but more data is needed [19].
	Fibrostenotic	A fibro stenotic phenotype may be seen in some patients that is independent of length of the disease course [69, 70].
	EoE-Gender specific	Symptomatic and histologic gender differences are observed. There is a large male to female predominance (3:1). Males present with more dysphagia and food impaction and may have more fibrostenotic disease. Females present with atypical symptoms (i.e. chest pain, heartburn) [72]. Research that explores the role of hormones on EoE is underway.
	EoE-Connective tissue disease	There is an 8-fold increased risk of EoE in pediatric patients with CTDs compared to the general pediatric population [75].
Molecular Endotype	TSLP	There is overexpression of TSLP in esophageal tissue from patients with EoE, and genetic studies have found a susceptibility locus at 5q22 that includes the genes for TSLP [43, 44, 47].
	CCL26	SNPs in the gene that encodes CCL26 (Eotaxin-3) may be susceptibility markers as CCL26 is highly expressed in esophageal tissue of patients with EoE compared to the general population [4, 44] .
	<i>TGFβ1</i>	OVB-responsive patients are more likely to have <i>CC</i> genotype at the 569 position of the <i>TGFβ1</i> promoter. The <i>TT</i> genotype increases <i>TGFβ1</i> promoter activity, which may lead to increased fibrosis [49].
	CAPN14	CAPN14 may be a regulatory protein in EoE [50].

SFED: six food elimination diet; SPT: skin prick test; CTD: connective tissue disease; TSLP: thymic stromal lymphopoietin; SNPs: single nucleotide polymorphisms; CCL26: Chemokine (C-C motif) ligand 26 (Eotaxin-3); *TGFβ1*: Transforming growth factor beta; OVB: oral viscous budesonide; CAPN14: Calpain-1