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Eosinophilic Oesophagitis phenotypes: Ready for primetime?

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Abstract

Eosinophilic Oesophagitis (EoE) is one of the most common causes of reflux like symptoms and feeding problems in children and food impaction and dysphagia in adults with a prevalence of 1:2500. Therapeutic options include diet, use of swallowed corticosteroids or dilation. In the last several years, recent clinical and translational research have identified some common and distinctive features, for example, the varying response to diet and medications. As EoE shares some characteristics with both asthma and inflammatory bowel disease, the advances in these fields suggests that various phenotypes may also exist in patients with EoE. Here we provide a rationale for EoE phenotypes and provide some suggestions for potential phenotypes based on histology, molecular signature, response to therapy or dietary therapy.

Keywords

Eosinophilic Esophagitis; Phenotypes; Symptom; Treatment

Over the last 3 decades, an increasing awareness of eosinophilic esophagitis (EoE) has led to worldwide recognition as the newest inflammatory disease of the esophagus. EoE is one of the most common causes of reflux like symptoms and feeding problems in children and food impaction and dysphagia in adults. It is estimated to have a prevalence of 4 in 10,000 with a 3 to 1 predominance in males.

Clinical assessment of EoE has undergone a remarkable metamorphosis. Initial case series described an uncommon group of children and adults who presented with abdominal pain, reflux and dysphagia, unusual endoscopic findings with esophageal white exudates and rings and a dense esophageal eosinophilia. Initial and subsequent diagnostic guidelines, that were based on clinical experience and research findings defined EoE as a clinicopathological disease with symptoms referable to esophageal dysfunction observed in the face of esophageal eosinophilia. Other causes of these findings need to be ruled out prior to making the diagnosis. During the past decade, a new era of investigation developed EoE specific symptom metrics, endoscopic scoring systems, functional parameters, histological scores and molecular probes that now permit a full assessment of the patient and inflammatory state.

With this in mind, future advances in the field will be directed at understanding key clinical and molecular features that will drive therapeutic interventions. As clinical experiences and technological advances progress, EoE phenotypes have begun to emerge. In this realm, it is clear that not all patients present in a stereotypical fashion, respond to treatments the same manner or progress along the same clinical course. For instance, depending on their age, children may present with isolated commonplace reflux-like symptoms, vague abdominal pain, confounding feeding difficulties or frank dysphagia. In contrast, thus far, adults typically present with stereotypical features of solid food dysphagia and food impactions and may or may not have esophageal strictures; however, increasing reports highlight the fact that some adults have chronic reflux symptoms. While most patients have a number of atopic diatheses, some do not. EoE patients respond to either topical steroids or diet restriction. Finally, the response of patients with esophageal eosinophilia to proton pump inhibitors, or lack thereof, raises another group to consider. In this light, the natural history of EoE becomes of utmost importance, but because diagnostic guidelines are only a decade old, this information is lacking.

To develop EoE phenotypes, it is important to look at phenotypes in other related disease. EoE is a classic atopic disease. Since most patients with EoE are atopic, examining whether phenotypes identified in other atopic diseases are similar to phenotypes in EoE is reasonable. But, it is important first to review the atopic features of EoE. Histologically, EoE is characterized by a chronic inflammatory infiltrate, which includes eosinophils, mast cells, basophils and Th2-cells. Similar to other atopic diseases, EoE is triggered by food allergens and environmental allergens/irritants, culminating in esophageal fibrosis or tissue remodeling.(1, 2) Like the skin in patients with atopic dermatitis, the esophageal epithelial barrier function is altered in those with EoE. Indeed, both gene expression profiling(3) and immunolocalization studies(4) have demonstrated a down-regulation in the expression of the cell adhesion protein desmoglein-1 in the esophageal epithelium in actively inflamed EoE, which partially normalizes after clinical treatment.

Regarding asthma, the identification of specific markers has allowed for the use of personalized therapy. For example, an elevated peripheral eosinophil count is an indicator of response to anti-IL-5. (5) Similarly, sensitization to aeroallergen and an elevated IgE level identifies those likely to respond to anti-IgE. The use of anti-IgE has been shown to lead to a reduction of hospitalization in both severe asthma and children with inner city asthma with

fall exacerbations.(6) For food allergy, the use of component testing has suggested which patients might be at risk for anaphylaxis to food.(7) It is possible to envision the use of phenotypes as an aid in personalizing the selection of a therapeutic option and giving us guidance in predicting the natural history of a patient with EoE.

Understanding atopy in EoE is important for development of treatment paradigms and phenotypes, as models of phenotypes in asthma have been examined for an extended period of time. EoE is similar to other atopic disease with regard to treatment options: avoidance of the triggers (pollen and food) or controlling inflammation with topical steroids. For the dietary treatment of EoE, the total elimination of foods utilizing elemental diets has shown the greatest efficacy with resolution of symptoms and normalization of biopsies in greater than 95% of pediatric and adult patients(8–10). Because of the poor palatability of elemental formulas, elimination diets based on allergy testing (skin prick tests and atopy patch tests) (11, 12) or removal of the most common food allergens(13) have been tried(8) with success rates ranging from 50–80%. This diversity in response to therapy indicates the presence of clinical phenotypes and the need to identify and classify them.

Eosinophilic esophagitis can also be treated pharmacologically. Swallowed topical steroids can be used to coat the esophageal lining mimicking treatment for asthma or atopic dermatitis. The use of oral viscous budesonide has shown improvement in symptoms and biopsy results in up to 80% in a prospective study(14). Similar efficacy has been seen with other topical steroids with fluticasone having been the most studied(15–18) demonstrating a nearly 80% respond rate at high doses of 1760 mcg daily(19). The differing response to therapy with patients responding to different doses (19) indicates clinical phenotypes in EoE.

It is clear that EoE shares features with other atopic diseases based on pathogenesis, epidemiology and therapeutics. Therefore, it makes sense to devise phenotypes based on other atopic diseases, such as asthma. Furthermore, the rationale and the need for phenotypes in EoE is multi-fold and necessary. A recent review by Mudde found justifications for EoE phenotypes in murine models.(20) Phenotypes can help with designing therapeutic options for patients. The decision to use novel therapies such as biologics in the treatment of diseases such as asthma and inflammatory bowel diseases is often dictated by the clinical severity of the illness. It would be easy to imagine a similar scenario in patients with complicated EoE who may benefit from biologic agents currently under study (21–23). Phenotypes have already proven useful in other atopic diseases. For example, in asthma, intermittent treatment versus daily treatment had no difference in overall symptoms and lung function(24). However, for patients with severe asthma, who are at risk for hospitalization and death, daily therapy with inhaled corticosteroids, long-acting beta2-agonists along with omalizumab reduces hospitalization(25). Finally, the identification of various phenotypes could also help predict natural history and suggest appropriate maintenance therapy.

Phenotypes in other diseases

Asthma Phenotypes in Childhood

Recognition that asthma is a heterogeneous entity has led to numerous attempts over the past few decades to accurately identify and define distinct asthma phenotypes in childhood. Interest in this endeavor has been driven primarily by the notion that stratification of patients into clinically relevant phenotypes would aid not only in predicting the natural history, progression and/or severity of disease, but also in identifying those interventions or therapies most likely to provide significant benefit for a specific phenotype. Conversely, avoiding the use of therapies unlikely to work in certain phenotypes would prevent unnecessary costs and potential associated side effects. Initial efforts relied on expert opinion based upon clinical experiences and observations in early cohort studies.(26) For example, in 1995, Martinez et al(27) reported the findings of their prospective study of a birth cohort of 1246 infants in Tucson, Arizona designed to investigate factors affecting wheezing before 3 years of age and their relation to wheezing at 6 years. At 6 years of age a little more than half the cohort (51.5%) had never wheezed. Among the remaining 49.5% who had wheezed by 6 years of age they identified distinct early wheezing phenotypes including 20% of the cohort who were “transient wheezers” that wheezed at least once during the first 3 years of life, but were not wheezing by 6 years. Fifteen percent were “late onset wheezers” who did not wheeze in the first 3 years, but were wheezing by 6 years and another 14% were “persistent wheezers” who wheezed before 3 years and were still wheezing at 6 years. In comparison to the other children “transient wheezers” exhibited diminished lung function in infancy and at 6 years. They were more likely to have a history of maternal smoking, but less likely to be atopic as evidenced by elevated serum IgE levels or skin test reactivity, or have a maternal history of asthma. In contrast “persistent wheezers” were more likely than those who never wheezed to have normal lung function at a year but diminished lung function at 6 years, have a maternal history of asthma and be atopic as evidenced by an elevated serum IgE level. Thus, three wheezing phenotypes during the first 6 years of life were identified including early transient wheezing in the first 3 years of life, non-atopic wheezing in the preschool years and atopy associated wheezing or asthma.

Over the decades, since the initial report by Martinez et. al., numerous studies have attempted to improve and further personalize asthma care by better characterizing and defining discrete asthma phenotypes in childhood.(28–31) These studies have examined cohorts of different ages, demographic characteristics and degrees of asthma severity using cluster analyses. Rather than relying solely on expert opinion or clinical experiences, statistical clustering techniques have been increasingly used to provide more objective classification by deriving phenotypes from collected data based on a predefined protocol. Such an approach is exemplified in a novel study by Garden, et al (32) who defined asthma phenotypes based on data acquired at ages 1.5 – 11.5 years from a birth cohort of 370 participants having a first-degree relative with asthma. The data analyzed included respiratory symptoms, spirometry, airway hyper-responsiveness, exhaled nitric oxide concentrations, medication use, healthcare utilization and atopy. The latent transition analysis model chosen allowed a different class structure during early childhood (1.5 – 5 years) and mid-childhood (8 – 11.5 years), but was constrained to have the same class

structure within these two periods. Using this analysis model subjects were classified into 4 asthma phenotypes in early childhood (1.5–5 years) including 1) non-atopic, few symptoms, 2) atopic, few symptoms, 3) non-atopic, asthma and rhinitis symptoms and 4) atopic, asthma and rhinitis symptoms. In addition subjects were classified into 4 asthma phenotypes in mid-childhood (8–11.5 years) including 1) non-atopic, no respiratory disease, 2) atopic, no respiratory disease, 3) non-atopic, asthma symptoms and 4) atopic asthma. The analysis model chosen allowed for determining the transition probabilities of a child moving from one phenotype at a given age to another phenotype at a different age. Longitudinal analysis of the data revealed that the transitioning between phenotypes commonly observed in early childhood was less common later in childhood. In addition, the findings quantitatively supported the recognized notion that asthma in children is a heterogeneous entity and some children with wheeze and respiratory symptoms in early life become asymptomatic while others progress to asthma. Concepts regarding the stability and transition of asthma phenotypes in childhood were further explored in an accompanying editorial by Spycher, et al.(33)

The definition of asthma phenotypes continues to evolve, extending beyond the examination of clinical characteristics alone to incorporate new information regarding Th2 biomarkers, genomics, response to targeted therapies, the role of environmental exposures and the use of statistical clustering approaches. Like asthma, EoE is clearly a heterogeneous entity. In addition, given that numerous patients with EoE have asthma and that EoE is similar to asthma in regard to pathogenesis, atopic and non-atopic phenotypes, epidemiology and treatment options, incorporating lessons learned from asthma phenotypes to research EoE phenotypes should accelerate progress, resulting in a better understanding of this disease and improving treatment.

Phenotypes in IBD

To date, no other gastrointestinal diseases have been distinctly associated in the same fashion as atopic diseases have been with EoE. Gastroesophageal reflux probably approximates closest as symptoms of GERD can be similar and the inflammatory infiltrate shares an eosinophilic character. Celiac disease is chronic and triggered by a food antigen, gluten, but the histology and long-term outcomes with respect to untreated disease are dissimilar to EoE.

Inflammatory bowel diseases, may be a useful comparator to EoE in natural history and response to various therapies. IBD may be patchy, diffuse or manifest changing areas of involvement. The inflammatory process may include eosinophils, and the chronic inflammatory process may progress to stricturing disease with ineffective motility. With respect to extent of disease, patients with ulcerative colitis may have pan-colitis, left sided disease or limited rectosigmoid / perianal involvement. This topographic variability can affect therapeutic decisions. The natural history of patients with Crohn disease has also delineated a number of clinical phenotypes such as ileal, ileo-colonic or colonic disease, as well as stricturing, penetrating, or inflammatory only disease. Similarly, some EoE patients develop partially obstructing strictures, whereas others do not. Treatment responsiveness has identified subtypes including dietary responsive, steroid responsive, or biologic responsive

IBD. For instance, both UC and Crohn disease extraintestinal manifestations such as arthritis, or primary sclerosing cholangitis may also differentiate the diseases into subtypes, thus affecting the expected response to medications. An emerging body of data suggests that patients with esophageal eosinophilia may have co-morbid connective tissue diseases or other forms of immune dysregulation. Also, similar to EoE, some patients respond to dietary therapy or corticosteroids while others may rarely need immunomodulators or biologic agents. With respect to IBD, this recognition of clinical phenotypes lead to evolving paradigms to care, such as the step-down vs. step up approach. In addition, personalized approaches such as measuring TPMT enzyme activity, or monitoring of trough levels of biologics, promote safer and more effective use of medical therapies. Thus, future studies and clinical observations of patients with EoE will likely lead to improving care through the identification and characterization of novel phenotypes related to symptoms and mucosal features and individualized approaches to therapies just as it has in IBD.(34)

Proposed Phenotypes in EoE

Based on previous phenotyping done in asthma, EoE phenotypes could be identified in several ways (Table 1). One method would mirror NHLBI asthma guidelines(35) that utilize symptoms at baseline to determine what medications/diet might be need to control symptoms. A patient with intermittent symptoms in asthma needs only prn medication; might the same be true for EoE? A patient with daily symptoms or frequent flares of asthma is at risk for severe outcome (loss of lung function and hospitalization) and needs combination therapy or biologics; will EoE follow the same paradigm? For example, using a frequency of symptoms approach, intermittent EoE would encompass symptoms that occur sporadically but significantly alter daily life such as food impaction, whereas constant EoE would be defined by the presence of daily symptoms that interfere with daily activities. Another approach could be based on acuity of symptoms. Symptoms that required visits to the emergency room for emergent endoscopies for food impaction would be given more weight, similar to asthma exacerbations that require hospital or emergency room visits.

Since the symptoms of EoE often change over time, this could be helpful in tracking an individual's clinical course. For example, in a patient under 6 years of age, the frequency or severity of abdominal pain and vomiting could be the key symptoms to determine severity of EoE. In contrast, in adolescents, symptoms of dysphagia and food impaction may be given more weight. These could be assessed with one of the recent validated symptom scores such as pediatric PEES (36, 37) (Pediatric Eosinophilic Esophagitis Symptom Severity) or adult EESAI (Eosinophilic Esophagitis Severity Activity Index) (38). Phenotypic severity could also be subtyped based on quality of life. (39, 40) Validated tools have been developed to assess QOL in EoE adults and children. Interestingly, they demonstrate moderate correlation with endoscopy and histology indicating the need for multiple ways to measure disease severity.(41) In asthma, another key feature in determining severity is the frequency of asthma flares requiring oral steroids or hospitalization. An equivalent approach in EoE could be used to assess the frequency of symptoms such as abdominal pain or food impaction requiring emergency room visits. A patient with severe EoE could be having these symptoms monthly, while a mild EoE patient would experience these symptoms only once a year or less.

Instead of frequency of symptoms, an alternative method is based on age of onset and type of clinical presentation as not all EoE patients present in the same fashion or have the same clinical features. Potential differences include: age of presentation (toddler, child, adolescent or adult), symptoms unrelated to esophageal anatomy (reflux, abdominal/chest pain), or symptoms related to abnormal esophageal anatomy (dysphagia, evidence of esophageal fibrosis or stricture). Alternatively, examining atopic features could delineate phenotypes as approximately 80% of EoE patients have features of atopy (42, 43). Some have multiple atopic features with severe asthma, atopic dermatitis and multiple IgE-mediated food allergies, while others are only mildly atopic. These features might be a way to define different EoE phenotypes. It could be similar to asthma where 1/3 of children with earlier onset and viral respiratory illness induced wheezing outgrow it and children with older onset wheezing do not(27). Also, the presence of other atopic features in asthma indicates less likelihood of outgrowing asthma(44). Will EoE follow the same phenotype with co-morbid features of asthma, atopic dermatitis or food allergy making it less likely to outgrow EoE?

As seen in asthma, more objective measures of EoE would be welcomed. For asthma, spirometry with measurement of FEV1 (forced expiratory volume at 1 second) is used as a marker of disease severity. A potential marker for severe EoE could be histologic evidence of >100 eos/hpf (eosinophils per high per field) in an esophageal biopsy, while the mild EoE would have 15–30 eos/hpf. Other important measures to examine in EoE include the function and appearance of the esophagus. Radiographic assessment of the esophageal lumen could assess for strictures providing insights into groups of patient with fibrosis. Examination of esophageal function could be done by looking at esophageal compliance using newer modalities, such as the Endolumenal Functional Lumen Imaging Probe(Endoflip)(45). Endoflip could also be used to measure esophageal dimensions and function and provide objective measures like spirometry does for asthma.

Additional potential objective markers include newer combined EoE histologic scoring systems (46) and visual inspection of the esophageal mucosal surface using a standardized score like EREFs(exudate rings edema furrows).(47) Severe EoE would have multiple classic features seen in endoscopy with furrows, strictures and edema which would give an EREFS score of 5, while mild EoE would have fewer features with a score of 1–2. Of course, these assessments must be correlated with symptoms and response to therapy. Finally, biological markers could be assessed based on various tissue markers, such as the Eosinophilic Diagnostic Panel, which has demonstrated some correlation with histology scores(48). Recent work by Fiebiger et al using mRNA expression in qRT-PCR clustered EoE into 4 different groups(49–51) ((1) Th2-type inflammatory profile with high expression of TSLP and leukotriene C4 synthase: (2), elevated IL-23, (3) iNKT phenotype(52) and (4) mast cell phenotype). These phenotypes have been also seen in mouse models (reviewed in Mudde(20)). These phenotypes might help identify patients suitable for specific treatments; i.e. a high TSLP phenotype might respond to anti-TSLP antibody treatment that is currently in clinical trials for asthma and atopic dermatitis. Also, these phenotypes may be a marker for early onset disease as Fiebiger et al found that the iNKT phenotype occurred in children < 6 years of age.(50)

Genetic analysis might identify additional phenotypes. We have recently found that patients with the TSLP risk allele have more identified food triggers causing EoE compared to patients without the TSLP risk allele(53). It is possible other genetic risk factors (CAPN14, EMSY, Eotaxin-3) might identify additional clinical phenotypes.

Instead of using symptoms to identify disease severity, responses to therapy have been used to separate mild to severe phenotypes like the NHLBI asthma guidelines. Corresponding therapies in EoE would be based on treatment responses to diet and swallowed topical corticosteroid therapy. For example, a mild EoE patient would respond to the elimination of only one food, while severe EoE patients would need to eliminate 6 or more foods. For swallowed steroid dosing, mild EoE patients would have a normal endoscopy while on low dose therapy, while severe EoE patients would require high dose therapy twice a day to control their symptoms and histology. The rationale behind this phenotyping is based on current responses to therapy that have been observed. In our population at The Children's Hospital of Philadelphia, 40% of our cohort were allergic to one food, 20% to 2 foods, and approximately 30% were allergic to more than 3 foods.(54) Kagalwalla found a higher rate of single causative foods; one food in 55% of children is the group of patient that responded to six food elimination diet.(13) This differential response to diet indicates a mild to severe phenotype. For response to topical steroids, in initial studies, approximately 80% of patients responded to swallowed aerosolized budesonide(14, 55) while 50% responded to fluticasone(18). Higher doses of fluticasone (1760 mcg) had a better response rate of 65%, however, only 50% responded when the dose was reduced to 880 mcg a day of fluticasone. (19) These results suggest a dose response curve with possibly an increased severity of disease in patients requiring a higher dose of medication. The delineation of phenotypes will help to define the natural history of disease, as mild EoE might not progress to the development of fibrosis, whereas the patient with severe EoE will need high dose medications to prevent fibrosis. Currently, there is no ideal way to predict which patients need which therapy; however, it is easy to foresee that symptoms on presentation or genetic phenotype (see above for TSLP) might predict response to a specific therapy.

The natural history of EoE could also be used to generate phenotypes. Currently the literature suggests that patients do not outgrow the disease(8); however, we have discovered a small subgroup of patients that have outgrown their disease and can eat all foods normally without medication.(56) Nevertheless, although it is common for some adults to develop fibrosis and strictures(57), it is not clear whether all adults would eventually develop a fibrostenotic lesion. In addition, we have seen a small portion of children develop early fibrosis suggesting a rapid onset fibrotic phenotype. The risk of associated with the fibrotic phenotype will be an important piece of information and teach us how aggressive treatment needs to be (i.e. whether reducing the eosinophil count to 0 in esophageal biopsies is necessary).

Other clinical features, including feeding difficulties and failure to thrive, could be used to differentiate clinical phenotypes. The last category of phenotypes consists of EoE patients with other associated diseases such as collagen-vascular syndrome(58), primary immune deficiency(59), celiac disease(60), esophageal atresia(61, 62) or even a family history of EoE or fibrostenotic EoE.(63) To determine whether these subtypes represent true EoE or

other disease, additional analysis is needed. But, they have features of EoE and respond similarly to diet and medications.

One final method would be based on computer learning and latent analysis (31, 32) like was done for asthma cohorts. Latent cluster analysis uses unbiased examination of clinical features to find common patterns to group patients in to phenotypes. This approach has been useful in multiple other diseases ranging from asthma to amyotrophic lateral sclerosis. (31, 32, 64) However, the development of additional EoE databases is needed for this type of analysis. Future analysis of the current NIH cohort (CEGIR) funded by the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and funded through collaboration between NIAID, NIDDK, and NCATS could provide a valuable resource for this.

There are multiple ways to begin to define EoE phenotypes: age of presentation, presence of atopy, current symptoms, histology, endoscopy, anatomy, treatment and dose needed to control symptoms and normalize histology. But, it is unclear what is mild or severe? A simple mild patient might just have intermittent symptoms that resolve on baked milk elimination or once daily low dose corticosteroids. A severe patient might have daily symptoms, and a weekly food impaction that only resolves on an elemental diet. But, there is a large range of patients in between. Is a patient mild labeled as mild if they have daily symptoms that resolve on a single food elimination? Or is that patient who has monthly symptoms that resolve only when 8 foods are eliminated labeled as severe? Do we use phenotypes similar to those of asthma by defining severity based on the most severe criteria? Also, can severity change over time? Does a patient presenting with severe symptoms always stay severe or can that patient change to become mild over time?

Although we do not have answers to many of these questions, beginning to address them is a key step to personalizing treatment and advancing our understanding of EoE. A logical place to start is to use symptoms at presentation to begin to define severity and possible treatment options.

It is clear that EoE shares many features with related heterogeneous diseases such as asthma. The use of phenotypes has helped with the development of therapies and informing patients and their families about the natural history of asthma. EoE phenotypes can be developed using different models: one purely based on symptom frequency and severity (with the matching therapies). Phenotypes can also be based on simple objective markers such as eosinophils per high power field. Alternatively, phenotypes could be based on clinical features ranging from age of disease onset to atopic phenotypes. Future assessment of severity will be more complex and multivariate using objective parameters such as compliance measured by Endoflip, molecular signature measured in biopsies and validated symptoms scores (PEESS or EESAI) or combinations of these. Through the use of these phenotypes, we will gain a better understanding of the disease and define the optimal therapies for each phenotype.

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Abbreviation

EoE	eosinophilic esophagitis
TSLP	Thymic stromal lymphopoietin
PEESS	Pediatric eosinophilic esophagitis symptom severity
EESAI	Eosinophilic Esophagitis severity activity index
eos/hpf	eosinophils per high per field
FEV1	forced expiratory volume at 1 second

References

1. Robinson DS, Hamid Q, Jacobson M, Ying S, Kay AB, Durham SR. Evidence for Th2-type T helper cell control of allergic disease in vivo. Springer seminars in immunopathology. 1993; 15:17–27. [PubMed: 8103244]
2. Bieber T. Atopic dermatitis. N Engl J Med. 2008; 358:1483–94. [PubMed: 18385500]
3. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006; 116:536–47. [PubMed: 16453027]
4. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. Eur J Pediatr. 2011; 170:1471–4. [PubMed: 21809010]
5. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371:1198–207. [PubMed: 25199059]
6. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011; 364:1005–15. [PubMed: 21410369]
7. van Veen LN, Heron M, Batstra M, van Haard PM, de Groot H. The diagnostic value of component-resolved diagnostics in peanut allergy in children attending a Regional Paediatric Allergology Clinic. BMC Pediatr. 2016; 16:74. [PubMed: 27255511]
8. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005; 3:1198–206. [PubMed: 16361045]
9. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr. 2009; 48:30–6. [PubMed: 19172120]
10. Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. Gastroenterol Clin North Am. 2007; 36:75–91. vi. [PubMed: 17472876]
11. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2002; 109:363–8. [PubMed: 11842310]
12. Spergel JM, Brown-Whitehorn T. The use of patch testing in the diagnosis of food allergy. Curr Allergy Asthma Rep. 2005; 5:86–90. [PubMed: 15659270]
13. Kagallwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006; 4:1097–102. [PubMed: 16860614]

14. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol*. 2007; 102:2271–9. quiz 80. [PubMed: 17581266]
15. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2012; 10:742–49 e1. [PubMed: 22475741]
16. Abu-Sultaneh SM, Durst P, Maynard V, Elitsur Y. Fluticasone and food allergen elimination reverse sub-epithelial fibrosis in children with eosinophilic esophagitis. *Dig Dis Sci*. 2011; 56:97–102. [PubMed: 20458625]
17. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol*. 2008; 6:165–73. [PubMed: 18237866]
18. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006; 131:1381–91. [PubMed: 17101314]
19. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology*. 2014; 147:324–33 e5. [PubMed: 24768678]
20. Mudde AC, Lexmond WS, Blumberg RS, Nurko S, Fiebiger E. Eosinophilic esophagitis: published evidences for disease subtypes, indications for patient subpopulations, and how to translate patient observations to murine experimental models. *World Allergy Organ J*. 2016; 9:23. [PubMed: 27458501]
21. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012; 129:456–63. 63 e1–3. [PubMed: 22206777]
22. Stein ML, Villanueva JM, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy reduces eosinophil activation ex vivo and increases IL-5 and IL-5 receptor levels. *The Journal of allergy and clinical immunology*. 2008; 121:1473–83. 83 e1–4. [PubMed: 18410960]
23. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut*. 2010; 59:21–30. [PubMed: 19828470]
24. Rodrigo GJ, Castro-Rodriguez JA. Daily vs. intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: a systematic review with meta-analysis. *Respir Med*. 2013; 107:1133–40. [PubMed: 23769720]
25. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *The Journal of allergy and clinical immunology*. 2003; 111:87–90. [PubMed: 12532101]
26. Spycher B, Silverman M, Kuehni C. Phenotypes of childhood asthma: are they real? *Allergy*. 2010; 40:1130–41.
27. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995; 332:133–8. [PubMed: 7800004]
28. Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *The Journal of allergy and clinical immunology*. 2011; 127:382–89. e1–13. [PubMed: 21195471]
29. Howrylak JA, Fuhlbrigge AL, Strunk RC, et al. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *The Journal of allergy and clinical immunology*. 2014; 133:1289–300. 300 e1–12. [PubMed: 24892144]
30. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J*. 2012; 40:55–60. [PubMed: 22267763]

31. Schatz M, Hsu JW, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *The Journal of allergy and clinical immunology*. 2014; 133:1549–56. [PubMed: 24315502]
32. Garden FL, Simpson JM, Mellis CM, Marks GB, Investigators C. Change in the manifestations of asthma and asthma-related traits in childhood: a latent transition analysis. *Eur Respir J*. 2016; 47:499–509. [PubMed: 26493805]
33. Spycher BD, Kuehni CE. Asthma phenotypes in childhood: conceptual thoughts on stability and transition. *Eur Respir J*. 2016; 47:362–5. [PubMed: 26828043]
34. Mazor Y, Maza I, Kaufman E, et al. Prediction of disease complication occurrence in Crohn's disease using phenotype and genotype parameters at diagnosis. *J Crohns Colitis*. 2011; 5:592–7. [PubMed: 22115380]
35. NHLBI issues updated guidelines for the diagnosis and management of asthma. *Am Fam Physician*. 1997; 56:621–3. [PubMed: 9262536]
36. Franciosi JP, Hommel KA, DeBrosse CW, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. *BMC Gastroenterol*. 2011; 11:126. [PubMed: 22099448]
37. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *The Journal of allergy and clinical immunology*. 2015; 135:1519–28 e8. [PubMed: 26051952]
38. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014; 147:1255–66 e21. [PubMed: 25160980]
39. Franciosi JP, Hommel KA, Bendo CB, et al. PedsQL eosinophilic esophagitis module: feasibility, reliability, and validity. *J Pediatr Gastroenterol Nutr*. 2013; 57:57–66. [PubMed: 23478422]
40. Varni JW, Kay MT, Limbers CA, Franciosi JP, Pohl JF. PedsQL Gastrointestinal Symptoms Module Item Development: Qualitative Methods. *Journal of pediatric gastroenterology and nutrition*. 2011
41. Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms Have Modest Accuracy in Detecting Endoscopic and Histologic Remission in Adults With Eosinophilic Esophagitis. *Gastroenterology*. 2016; 150:581–90 e4. [PubMed: 26584601]
42. Guajardo J, Plotnick L, Fende J, Collins M, Putnam P, Rothenberg M. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr*. 2002; 141:576–81. [PubMed: 12378201]
43. Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. *Immunol Allergy Clin North Am*. 2009; 29:85–97. [PubMed: 19141344]
44. Guilbert TW, Morgan WJ, Zeiger RS, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *The Journal of allergy and clinical immunology*. 2004; 114:1282–7. [PubMed: 15577824]
45. Lin Z, Kahrilas PJ, Xiao Y, et al. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. *Therap Adv Gastroenterol*. 2013; 6:97–107.
46. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus*. 2016
47. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013; 62:489–95. [PubMed: 22619364]
48. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterol*. 2013; 145:1289–99.
49. Lexmond WS, Pardo M, Rooney K, et al. Elevated levels of leukotriene C4 synthase mRNA distinguish a subpopulation of eosinophilic oesophagitis patients. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology*. 2013; 43:902–13. [PubMed: 23889244]

50. Lexmond WS, Neves JF, Nurko S, et al. Involvement of the iNKT cell pathway is associated with early-onset eosinophilic esophagitis and response to allergen avoidance therapy. *Am J Gastroenterol*. 2014; 109:646–57. [PubMed: 24513807]
51. Lexmond WS, Hu L, Pardo M, et al. Accuracy of digital mRNA profiling of oesophageal biopsies as a novel diagnostic approach to eosinophilic oesophagitis. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology*. 2015; 45:1317–27. [PubMed: 25728460]
52. Jyonouchi S, Smith CL, Saretta F, et al. Invariant natural killer T cells in children with eosinophilic esophagitis. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology*. 2014; 44:58–68. [PubMed: 24118614]
53. Fahey L, Cianferoni A, Sleiman P, Spergel J. TSLP Risk Alleles are Increased in Pediatric Patients With Eosinophilic Esophagitis and atopy. *Gastroenterology*. 2016; 150:S672–73.
54. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012; 130:461–67 e5. [PubMed: 22743304]
55. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral Viscous Budesonide Is Effective in Children With Eosinophilic Esophagitis in a Randomized, Placebo-controlled Trial. *Gastroenterology*. 2010
56. Ruffner, MA., Brown-Whitehorn, TF., Cianferoni, A., et al. Outgrowing eosinophilic esophagitis: it is possible. *American Academy of Allergy Asthma and Immunology Annual Meeting*; Atlanta, GA. 2017.
57. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointestinal endoscopy*. 2014; 79:577–85 e4. [PubMed: 24275329]
58. Abonia JP, Wen T, Stucke EM, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *The Journal of allergy and clinical immunology*. 2013; 132:378–86. [PubMed: 23608731]
59. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med*. 2009; 361:2046–55. [PubMed: 19776401]
60. Thompson JS, Lebwohl B, Reilly NR, Talley NJ, Bhagat G, Green PH. Increased incidence of eosinophilic esophagitis in children and adults with celiac disease. *J Clin Gastroenterol*. 2012; 46:e6–e11. [PubMed: 21778897]
61. Dhaliwal J, Tobias V, Sugo E, et al. Eosinophilic esophagitis in children with esophageal atresia. *Dis Esophagus*. 2014; 27:340–7. [PubMed: 23947919]
62. Batres LA, Liacouras C, Schnaufer L, Mascarenhas MR. Eosinophilic esophagitis associated with anastomotic strictures after esophageal atresia repair. *J Pediatr Gastroenterol Nutr*. 2002; 35:224–6. [PubMed: 12187303]
63. Collins MH, Blanchard C, Abonia JP, et al. Clinical, Pathologic, and Molecular Characterization of Familial Eosinophilic Esophagitis Compared With Sporadic Cases. *Clin Gastroenterol Hepatol*. 2008
64. Ganesalingam J, Stahl D, Wijesekera L, et al. Latent cluster analysis of ALS phenotypes identifies prognostically differing groups. *PLoS One*. 2009; 4:e7107. [PubMed: 19771164]

Table 1

Possible Eosinophilic Oesophagitis Clinical Phenotypes

Clinical Category	Criteria for each category	Method to assess
Age of Presentation	Infancy Childhood Adult	History
Atopic Status	No evidence of asthma, allergic rhinitis, atopic dermatitis or IgE-mediated Food Allergy; 1–2 Atopic Conditions 3–4 Atopic Conditions	Immunoassay, skin prick test, history
Natural History of Disease	Fibrostenotic; Food impaction; Resolution	History Endoscopic Histologic Radiologic Endoflip
Pollen Associated Disease	Yes No	History and endoscopy
Foods eliminated to establish remission	1 Food 2–4 foods >4 foods	History, endoscopy
Responsiveness (clinical and histological) to topical steroids	Traditional dose; High dose CS; Non-responsive to CS	Normalization of histology and symptoms
Molecular Phenotype	TH2 (high TSLP, LTC4); IL23; iNKT (early onset); Mast Cell (high tryptase)	Molecular Signature
Stricture Formation	None; Early Onset; Late Onset	History, radiographic or endoscopic
Familial History of EoE	Yes/No(63)	History, genetic screens
Associated with Immune Deficiency	Frequent infection, known primary immune deficiency (e.g., Dock8)(59)	Genetic Analysis
Associated with Collagen Vascular Defects	Marfan-like syndrome(58)	Genetic Analysis
Associated with Esophageal Atresia	Esophageal Atresia(61, 62)	Genetic Analysis, History
Severe Atopic Phenotype: Immune Dysregulation	Associated with severe asthma, atopic dermatitis, multiple IgE mediated food allergies, high peripheral eosinophilia	History