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Eosinophilic Esophagitis: An Important Co-Morbid Condition of Asthma?

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Abstract

Eosinophilic esophagitis and asthma are frequently found as co-morbid conditions in children and adults along with other manifestations of atopic diathesis. These two conditions have similar T helper 2 responses driven pathophysiology and share common management strategies such as using systemic corticosteroids and targeted anti-cytokine biologic therapies. Review of the literature finds that asthma is often a comorbid condition in eosinophilic esophagitis in both children and adults; however, the EoE-asthma relationship remains poorly characterized mechanistically and clinically. EoE and asthma commonly share several co-morbid conditions such as allergic rhinitis and gastroesophageal reflux disease; therefore, addressing these co-morbid conditions has the potential to improve and/or maintain control in both diseases. Similar to asthma, patients with EoE frequently demonstrate elevations in serum markers of atopy, including serum IgE levels, peripheral eosinophil counts, and T helper 2-related cytokines. Gastroesophageal reflux disease is thought to affect asthma through microaspirations, airway hyperresponsiveness and increased vagal tone. The understanding of the relationship between gastroesophageal reflux and EoE is still evolving but seems to be bidirectional and interactive. In terms of treatment, similar classes of medications have been used in both EoE and asthma. In both children and adults, EoE remission can be achieved by food trigger avoidance and use of corticosteroids and biologic therapies. Asthma control is mostly achieved through inhaled corticosteroids and long but biologic therapies are increasingly used in severe subsets of the disease. Significant clinical and mechanistic work needs to be accomplished to better understand the relationship between asthma, EoE and their interaction with other allergic diseases. Understanding whether shared mechanisms exist can lead to the development of new diagnostic and therapeutic strategies. The following review examines the existing literature regarding prevalence, common co-morbidities, potential therapeutic approach and identifies gaps in knowledge and future directions.

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Keywords

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Introduction

Asthma is one of the leading causes of morbidity worldwide. While a vast majority of adults and children are controlled with inhaled corticosteroids (ICS), a minority of patients have severe and/or difficult-to-control asthma. Importantly, regardless of severity and control, U.S. and international asthma guidelines recommend regular assessment and treatment of co-morbid conditions such as allergic rhinitis, gastroesophageal reflux disease (GERD) and sinusitis.[1,2] Eosinophilic esophagitis (EoE), a relatively new clinico-pathologic disorder, is often associated with allergic diseases such as asthma, allergic rhinitis and atopic dermatitis (AD). Both asthma and EoE are often characterized immunologically by T helper 2 (TH2) responses and allergic sensitizations.[1,3] Further, EoE and GERD overlap frequently. GERD is thought to affect asthma through microaspiration, airway hyperresponsiveness and increased vagal tone.[4] It is plausible that similar mechanisms exist for EoE to affect asthma given the pulmonary-esophageal relationship in airway disease and similarities between GERD and EoE. Therefore, it may be reasonable for healthcare professionals to infer that EoE is an important co-morbid condition in asthma. However, as reviewed below, sparse evidence exists characterizing an EoE-asthma relationship.

Comorbid Prevalence of Asthma and EoE

Most of the knowledge about the co-existence of EoE and asthma comes from the EoE literature and is primarily focused on the prevalence of asthma seen in patients with EoE. Importantly, in most of these studies, asthma is generally diagnosed by patient- or parental-reported history alone. Retrospective studies conducted throughout the world have demonstrated that 12–68% of adults with a diagnosis of EoE have a history of asthma[5–11], while studies of U.S. databases have found children and adults diagnosed with EoE have concomitant asthma 23–37.5% of the time.[12–14] In studies focused on children with EoE, the prevalence of asthma has been estimated between 32–84%.[15–20] A recent systematic review of 21 studies including 53,592 adult and pediatric EoE patients and 54,759 controls found that asthma was significantly more common among EoE patients compared to control subjects (OR 3.06; 95% CI 2.01–4.66)[21]

Mechanisms Common to Asthma and EoE

Atopy

Very few mechanistic studies specifically examine both disorders when found concomitantly in patients. However, general observations regarding common underlying mechanisms of both diseases are of interest. EoE is an inflammatory condition of the esophagus driven in large part by TH2 immunopathology.[22] Similar to many children and adults with asthma, patients with EoE frequently demonstrate elevations in serum markers of atopy, including

serum IgE levels, peripheral eosinophil counts, and TH2-related cytokines (IL-4, IL-5, IL-13).[23,24] Other biomarkers of atopy linked to the pathogenesis of EoE and asthma include eotaxin, epidermal growth factor (EGF) and thymic stromal lymphopoeitin (TSLP).[25–27,22].

Clinical Observations of Asthma and EoE

There are few observational studies or clinical trials examining allergic disease and asthma characteristics or outcomes in patients with asthma and EoE. In a study by Rajan and colleagues,[28] subjects with both EoE and asthma had significantly higher baseline esophageal eosinophil counts than nonasthmatic subjects and higher eosinophilic esophageal inflammation despite topical corticosteroid (CS) therapy. Other studies have found that patients with EoE and asthma were more likely to be polysensitized to food allergens and environmental allergens and have higher IgE levels.[29,7] Krupp and colleagues[15] found that a subgroup of children with EoE and asthma not on asthma controller therapy had higher mean fibroblast growth factor - 2 (FGF-2) than children with EoE but without asthma (110 pg/ml vs. 65 pg/ml; $p = 0.04$). Airway hyperreactivity (AHR) occurred in 33% of children with EoE and 11% of healthy controls ($P=0.04$).[15] Overall, 69.7% of EoE subjects had either asthma or AHR.[15] The authors suggested that many EoE patients may have subclinical asthma based on the AHR findings although this conclusion needs further work in larger studies.[15] Finally, a recent retrospective analysis of a large database of 156 patients with asthma and EoE and 276 controls found that patients with EoE and asthma were more likely to have an allergic asthma phenotype.[30] This study observed EoE and asthma patients had significant associations with AR, food allergies and peripheral eosinophilia.[30] Moreover, the use of inhaled corticosteroids (ICS) for asthma had a protective effect against having EoE.[30] Although not specifically measured, the authors speculated that incidental swallowing of the inhaled corticosteroid did not lead to EoE improvement but rather represented clinical evidence that control of airway disease may be a potential approach to prevent EoE.[30] This is of particular relevance since multiple murine studies have found that lung exposures to various antigens can induce EoE symptoms and esophageal histology similar to human EoE, and there is evidence of seasonal worsening of EoE from environmental allergies in children.[22,31]

EoE and Asthma Relationship with Gastroesophageal Reflux Disease

GERD may impact both asthma and EoE. A systematic review of patients with asthma found evidence of reflux either by symptoms or by an abnormal 24-hour esophageal pH test approximately 50–60% of the time.[32] Moreover, respiratory symptoms such as cough and breathlessness, wheeze and chest discomfort are increased in GERD.[33] Three large randomized clinical trials have found that treatment of symptomatic GERD can improve asthma although the results were mixed depending on outcome studied.[34–36] However, treatment of clinically silent GERD has not been found to improve asthma outcomes in 3 studies.[35,37,38] Nonetheless, asthma guidelines recommend to consider GERD an important co-morbid condition in asthma that, if present, should be treated appropriately.[1,2]

It has been suggested that EoE and GERD are different entities and may co-exist in an unrelated manner or each may exacerbate the other.[39] Gastroesophageal reflux disease may contribute to the pathogenesis of EoE by disrupting esophageal mucosal integrity, promoting trans-epithelial allergen exposure and subsequent TH2 immune responses.[40] EoE patients have been shown to have hypersensitivity to acid within the esophagus with lower thresholds for onset of symptoms and pain.[41] Acid hypersensitivity might also explain symptom improvement or remission on proton pump inhibitor (PPI) therapy despite persistent esophageal inflammation in pediatric and adult EoE patients.[42–44] EoE may also provoke architectural and functional changes in the esophagus that can induce GERD.[42,40] Recent evidence has shown that subjects with clinical and histological features of EoE may respond to PPI treatment (a clinical entity termed PPI-responsive esophageal eosinophilia (PPI-REE).[45] One possible explanation of this phenomenon is an anti-inflammatory effect of PPIs via decreased eotaxin-3 expression in the esophagus demonstrated in two studies [46,45], Finally, in PPI-REE patients, PPI therapy restores esophageal mucosal integrity, decreases Th2 inflammation and reverses the abnormal EoE gene expression signature similar to the effects of topical steroid treatment in EoE.[45] Ultimately, the proposed mechanisms of PPI-induced effects in EoE need to be replicated in larger studies.

Potential Therapies Common to Asthma and EoE

Food Trigger Avoidance

In both children and adults, EoE remission can be achieved by removing disease-inciting foods.[39] Choice of food elimination can be driven by allergy testing or by empirically removing high-risk allergenic foods. Unfortunately, food allergy testing-based elimination diets achieves biopsy-proven remission in EoE only about one-third of the time in adults with rates slightly higher in pediatrics.[39,47] Approximately three-quarters of adult and pediatric EoE patients will achieve histologic remission with use of empiric elimination diets such as the 6-food elimination diet (milk, eggs, soy, wheat, peanuts/tree nuts and fish/shellfish).[39,47] Elemental diets are associated with remission rates for EoE over 90%.[39,47] Importantly, while food allergy is often seen as a comorbid condition in asthma, there is no evidence that food allergy causes the chronic inflammation seen in asthma; therefore, food allergy testing or elimination diets are not indicated in the management of asthma.[48,2,1]

Corticosteroids

Asthma and EoE are diseases of chronic inflammation that respond to corticosteroids. The efficacy of inhaled corticosteroids (ICS) and oral corticosteroids (OCS) in pediatric and adult asthma has been comprehensively validated. Use of ICS decreases both impairment (e.g., symptoms, rescue inhaler use, etc) and future risk (e.g., exacerbations).[2,1] Further, while effective, use of OCS in asthma is generally reserved for exacerbations or severe disease.[2,1] The use of swallowed CS (SCS) and OCS in EoE has been less extensively evaluated. Treatment validation has been difficult to due variability in trial design and outcomes studied.[39] An interesting overlap between EoE and asthma occurs as the only method currently to deliver SCS to the esophagus uses asthma medications. Both oral

viscous budesonide and fluticasone administered by MDI have been found to induce and maintain remission in EoE in both children and adults.[49,50,39] Other than small case series with ciclesonide, no other asthma inhalers have been demonstrated to be effective. [51,52] Moreover, other swallowed steroid delivery mechanisms, such as enteric coated budesonide (Entocort), used in inflammatory bowel disease, have not been found to be effective. Oral CS have been found to be efficacious in achieving and maintaining remission in EoE but are not recommended due to systemic effects.[53,39]

Swallowed CS likely have less systemic side effects compared to ICS due to extensive first pass hepatic metabolism; however, this has not definitively been established. Moreover, as previously discussed, children and adults with EoE often have other allergic co-morbidities such as allergic rhinitis and atopic dermatitis. Importantly, these diseases are all generally treated by corticosteroids delivered by various routes; thus, additive side effects remain a possibility. The safety of ICS use in pediatric asthma has been extensively investigated. Other than increased risk of a modest decline in growth (average ~1.1cm), the overall side effect profile of the use of ICS in preschool- and school-aged children with asthma is low. [54,55] A recent meta-analysis in EoE observed topical CS were not associated with significant adverse events - other than a risk for developing asymptomatic esophageal candidiasis.[56,39] However, the short- and long-term adverse effects of using corticosteroids administered by different routes for co-morbid allergic disease in individual patients remains poorly characterized.

Biologic Therapies

Since asthma and EoE may have similar molecular pathophysiology, the possibility of using targeted therapies aimed at phenotypes/molecular endotypes in EoE, similar to standard of care in asthma, has become an area of research. There is extensive evidence that anti-IL5 and anti-IgE therapies are effective in the treatment of moderate to severe allergic asthma with particular efficacy shown in reducing frequency of exacerbations.[57–63] However, these therapies have largely been ineffective when studied in patients with EoE alone. For example, the efficacy of mepolizumab and reslizumab, anti-IL5 monoclonal Abs, has been assessed in studies involving both children and adults with active EoE.[64–66] Most studies did not find symptomatic improvement.[64,65] Interestingly, a significant decrease of esophageal eosinophilic infiltration was seen without histologic remission.[64,65] Despite some observational studies reporting clinical benefit from omalizumab,[67,68] a recent trial in adult EoE patients demonstrated no relevant effects on esophageal symptoms or eosinophilia compared to placebo.[69] Other agents currently being studied in both EoE and asthma include dupilumab, an anti-IL4α receptor Ab which blocks the activity of both IL4 and IL13 and which has shown some promise in both EoE and asthma. In a phase 2 trial in adults with EoE, dupilumab was found to improve dysphagia and both endoscopic and histologic scores. [70] In adults with moderate to severe asthma, 2 studies have found that dupilumab decreases exacerbations and improves lung function. [71,72] After an initial phase 2 study found that high periostin moderate-to-severe asthmatics had significant improvement in lung function with use of an anti-IL13 monoclonal Ab, [73] lebrikizumab, subsequent studies with larger populations did not replicate these results. [74] However, in EoE, anti-IL13 approaches have shown some promise. In one study in adult EoE patients, a

60% reduction of mean eosinophil count and downregulated gene expression of EoE-relevant esophageal transcripts was observed with an anti-IL13 monoclonal Ab; however, there was no significant symptomatic improvement.[75] An anti-IL13 receptor Ab, RPC4046, binding both alpha subunits of the IL13 receptor, has shown initial safety, tolerability and promise in both asthma and EoE [76] Finally, benralizumab, an anti-IL5 receptor Ab which strongly induces antibody dependent cytotoxicity of eosinophils, has been found to reduce symptoms, improve exacerbations and lung function in adult asthma and likely will be of research interest in EoE. [77,78]. For a summary of current and future research in EoE and asthma involving biologics please see Table I and II. Further, for a more extensive review on biological therapies in EoE, please see chapter titled Monoclonal Antibodies for Treatment of Eosinophilic Esophagitis.

While the overall data regarding biologics in EoE has been disappointing, these agents have not been evaluated specifically in patients who have EoE and asthma. It has been clearly been shown in asthma that targeting certain phenotypes, for example, eosinophilic asthma with mepolizumab, has been shown to be most effective when utilizing biologics. Thus, further studies in EoE with asthma as a comorbid condition are needed; moreover, studies should be conducted using more recent standardized/validated assessments of EoE symptomatology and quality of life.[39]

Systemic Immunosuppression

Studies examining the efficacy of immunomodulator therapy such as cyclosporine A, methotrexate or azathioprine have not found clear evidence to support their general use in the treatment of asthma. [79] Moreover, the recent American Thoracic Society/European Respiratory Society guidelines on severe asthma recommend that immunomodulators should not be used in children with severe asthma due to low quality of available evidence, the high risk of side effects and availability of more effective immunobiologic therapies [80]. Evidence for the use of systemic immunosuppression in EoE is limited to one case series with azathioprine and 6-mercaptopurine.[81] In 3 adults patients with EoE, immunomodulation with these agents had a corticosteroid-sparing effect and induced and maintained remission. At this time, more study is needed for use of these drugs in EoE although they could be considered in severe oral corticosteroid-dependent recalcitrant disease not responding to elemental therapy.[39,81]

Future Work

As evidenced above in EoE epidemiologic studies, asthma is often observed as a co-morbid condition. However, clearly based on the above review of the literature, the exact nature of the relationship between the two diseases remains poorly characterized. This is likely in large part due to the relative rarity of EoE in the general population. Additionally, EoE was only just recently recognized in the 1990s as a clinico-pathologic disorder resulting in research that is in its infancy. Moving forward, Table III highlights important questions to address through analysis of existing databases of well-characterized asthma and EoE patients and prospective clinical trials.

Studying the effects of treatment modification on EoE and asthma is challenging as both diseases are often intermittent and evolve over years. If a significant relationship between EoE and asthma were observed, prospective studies involving patients with both EoE and asthma would take years at considerable expense. This is in large part due to the lack of noninvasive methods to assess control in EoE. While clinical history and objective measurements such as spirometry and fractional exhaled nitric oxide are useful in monitoring severity and control in asthma, currently the only method to monitor disease control in EoE is endoscopy. Importantly, symptoms have not been found to reflect histology in EoE; however, this may be due to the fact that prospectively validated symptom measures have not been developed similar to the Asthma Control Test and Asthma Control Questionnaire in asthma. Without noninvasive measures, clinicians must rely on repeated endoscopy to monitor disease activity, which can be a significant barrier due to cost, risks from repeated sedation and procedures, and quality of life. Further, lack of noninvasive measures impacts the ability to conduct research. Nonetheless, In spite of these difficulties, increasing our knowledge of how these two diseases potentiate each other and effective therapies that target both diseases will be increasingly important moving forward given the rising rates of allergic disease globally.

Conclusions

Significant clinical and mechanistic work needs to be accomplished to better understand the relationship between asthma, EoE and their interaction with other allergic diseases. Hypothesis generating examinations of existing well-characterized asthma and EoE databases should be the initial priority. This will lead to meaningful prospective clinical and mechanistic trials and long-term to the development of new diagnostic and therapeutic strategies that could impact both EoE and asthma.

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Abbreviations:

Ab	antibody
CS	corticosteroid

EoE	eosinophilic esophagitis
EGF	epidermal growth factor
FGF-2	fibroblast growth factor 2
TSLP	thymic stromal lymphopoietin
GERD	gastroesophageal reflux disease
ICS	inhaled corticosteroid
PPI	proton pump inhibitor
PPI-REE	proton pump inhibitor - responsive esophageal eosinophilia
SCS	swallowed corticosteroid
TH_2	T helper 2

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Table I.

FDA approved medications with potential utility in EoE and Asthma

Medication	Mechanism	Approved Indication	Ages Approved	Route of Administration	EoE Efficacy	Asthma Efficacy
Mepolizumab	Humanized anti-IL5 antibody	Eosinophilic Asthma	12 and older	IV infusion	In published data, generally would improve histology without improvement in symptoms [64,66]	Reduced exacerbations [60,61]
Resilizumab	Humanized anti-IL5 antibody	Eosinophilic Asthma	18 and older	SC injection	In published data, improved histology without improvement in symptoms [65]	Reduced symptoms and exacerbations, improved FEV1 [62,63]
Benralizumab	Humanized antibody blocking IL5α Receptor-has cytotoxic effect on eosinophils	Eosinophilic Asthma	12 and older	SC injection	No published data	Reduced symptoms and exacerbations, improved FEV1 [77,78]
Dupilumab	Humanized antibody blocking IL4α receptor-blocks activity of both IL4 and IL13	Severe Atopic Dermatitis	18 and older	SC injection	Phase 2 Trial showed improvement in dysphagia, endoscopic score, and histology [70]	Improved FEV1 and reduced exacerbations [71,72]
Omalizumab	Humanized anti-IgE antibody	Moderate to Severe Asthma, Chronic Idiopathic Urticaria	6 and older	IV infusion	Unlikely to be of benefit [67–69]	Reduces exacerbations, corticosteroids need and improved QOL. No effect on lung function [57–59]

Table II.

Potential therapies that are undergoing testing

Medication	Mechanism	Age Studied	Route of Administration	EoE Data	Asthma Data
RPC4046	Humanized antibody blocking IL13 receptor	18 and older	IV loading dose, then SC injections	Phase 1 study completed demonstrating adequate safety, tolerability, pharmacokinetics, and pharmacodynamics [76]	Phase 1 study completed demonstrating adequate safety, tolerability, pharmacokinetics, and pharmacodynamics [76]
QAX576	Humanized anti-IL13 antibody	18–50	IV infusion	Significant improvement in histology, trend towards improved symptoms[75]	No benefit seen in larger studies involving anti-IL13 [74] but phase 2 study involving QAX576 found reduced symptoms [82]

Table III.

Important questions to address regarding the relationship between and EoE.

1	Does control of EoE affect asthma control and severity in a meaningful way? Conversely, does treatment of asthma improve EoE outcomes?
2	Is the relationship only significant in severe asthma or severe EoE?
3	Does ICS affect or even protect EoE? Similarly, does SCS affect asthma?
4	Is there an additive risk of adverse events when using both ICS and SCS in children and adults? Is the effect on younger children more pronounced?
5	Is biologic therapy more effective in phenotypes of subjects with both EoE and asthma than when studied in each disease alone?
6	Does treatment for GERD symptoms with a PPI improve outcomes in subjects with both EoE and asthma?
7	Would multi-disciplinary clinics that include allergy, pulmonology, otolaryngology and gastroenterology expertise improve outcomes in patients with both EoE and asthma?