Clinical Reviews in Allergy & Immunology (2019) 57:213–225
https://doi.org/10.1007/s12016-018-8701-4

Impact of Gastroesophageal Reflux Disease on Mucosal Immunity and Atopic Disorders

Elizabeth J. Hait[1] · Douglas R. McDonald[2]

Published online: 11 September 2018

Abstract

Atopic disorders and gastroesophageal reflux disease (GERD) are some of the most common medical conditions treated by primary care physicians and specialists alike. The observation that atopic disorders, like asthma, allergic rhinitis and sinusitis, food allergies, atopic dermatitis, contact dermatitis, and eosinophilic esophagitis are common comorbidities in patients with GERD raises the question of the nature of the relationship that may exist between GERD and atopic disorders. In this article, we review the pathophysiology of GERD, its effect on the immune system, the effect of acid-blocking medications on allergic responses, as well as several common atopic conditions that have been associated with GERD including asthma, chronic rhinosinusitis (CRS), allergic rhinitis (AR), atopic dermatitis (AD), contact dermatitis (CD), food allergies, proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE), and eosinophilic esophagitis (EoE). In each condition, the evidence of a causal link is not definitive. Although the relationship between asthma and GERD remains controversial, evidence suggests that a subset of asthma patients with documented GERD may experience improved asthma control following appropriate treatment of GERD. The relationship of GERD to allergic rhinitis and chronic sinusitis is weak; however, studies support the concept that treatment of frequent episodes of GERD can have a positive effect on rhinitis and sinusitis overall. The relationship between allergic sensitization and GERD is likely bidirectional. GERD may induce changes in the mucosal immune system that may favor the development of food allergy and allergic sensitization to aeroallergens; however, the underlying mechanisms have not been established.

Keywords Mucosa · Gastroesophageal reflux disease · Proton pump inhibitor · PPI-responsive esophageal eosinophilia Eosinophilic esophagitis · Asthma · Allergic rhinitis · Sinusitis · Inflammation · Atopic dermatitis · Contact dermatitis

Introduction

The human digestive tract is a truly remarkable structure that performs multiple, critical functions. The major function of the digestive tract is to transport, process, and absorb the nutrients required for the function and growth of the entire body. The absorptive mucosal surface of the small and large intestines of an average adult has a total surface area of approximately 200 m^2, roughly the size of a badminton court [1]. The GI system is a tubular structure lined by a continuous epithelial cell layer, which sits on basement membrane, forming a barrier to the external environment. Underneath of the epithelial layer is the lamina propria, which contains blood, lymphatic vessels, and mucosa-associated lymphoid tissues (MALTs). MALTs are unencapsulated but organized collections of B and T lymphocytes, dendritic cells, and macrophages, which are sites of adaptive immune responses. As the gastrointestinal tract absorbs nutrients from the environment, it must do so in the presence roughly 3.8×10^{13} commensal microbes within the gut without inappropriate activation of inflammatory responses [2]. These commensal microbes perform numerous beneficial functions, including degradation of nutrients that our own cells cannot digest. While maintaining tolerance to an enormous number of commensal microbes, the immune system of the GI tract must be able to appropriately detect and respond to much rarer, potentially harmful pathologic microbes. The GI tract has several strategies to prevent infection. First is the production of a thick mucus layer that prevents most organisms

✉ Douglas R. McDonald
douglas.mcdonald@childrens.harvard.edu

[1] Harvard Medical School, Division of Gastroenterology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

[2] Harvard Medical School, Division of Immunology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

from contacting the epithelial layer. Second is the production of anti-microbial peptides by epithelial cells, as well leucocytes that destroy pathogens. Thirdly, IgA produced by plasma cells within the lamina propria is transported to the lumen where it can neutralize pathogens before they can invade the epithelia.

In general, a healthy gastrointestinal mucosal system is considered to be an effective route of development of tolerance to food proteins. Damage to the mucosa of the GI tract is believed to be a risk factor for a breakdown in tolerance to food antigens. We will focus on the esophagus and upper airways, which can be affected by damage due to gastric acid and proteases resulting from gastroesophageal reflux disease (GERD). We will explore possible mechanisms through which GERD may impair mucosal function, perhaps increasing susceptibility to allergic sensitization. As will be discussed below, GERD can elicit robust inflammatory responses within the esophagus, with pathological consequences.

The esophagus is similar to other regions of the GI tract in that it is comprised of as mucosa, submucosa, and muscularis propria. The esophageal mucosa consists of non-keratinized, squamous epithelium, connective tissue of the lamina propria and the muscularis mucosa. In the stratum superficiale, squamous cells are more flattened. The presence of tight junctions and mucus secretions form a protective barrier. While varying numbers of eosinophils are found throughout the small and large intestines with the largest numbers being found in the right colon, eosinophils are absent in the esophagus of children [3]. Rare eosinophils may be observed in the esophagus of normal, healthy adults. A variety of immune cells are present in the esophagus, including T lymphocytes, regulatory T lymphocytes, B lymphocytes, plasma cells, mast cells, and dendritic cells [3]. In infectious and inflammatory conditions, the number of immune cells increases markedly, recruiting lymphocytes, neutrophils, eosinophils, mast cells, basophils, and innate lymphoid cells type 2 (ILC2). Additionally, esophageal epithelial cells, keratinocytes, and fibroblasts are capable of responding to a wide variety of inflammatory stimuli. Thus, although the healthy esophagus contains fewer immune cells in comparison to the intestines, complex inflammatory responses do occur within the esophagus. We will explore the possible relationships of the effects of GERD on mucosal immunity within the esophagus and the development of atopic disorders, including asthma, allergic rhinitis, sinusitis, atopic dermatitis, contact dermatitis, and eosinophilic esophagitis.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is one of the most common diagnoses made by both primary care physicians and gastroenterologists [4]. The prevalence of GERD is estimated to be between 20 and 30% of adults in western countries. It is defined as a gastrointestinal motility disorder that results from the reflux of stomach contents into the esophagus or oral cavity, causing symptoms or complications [5]. The typical symptoms of GERD are heartburn and regurgitation of gastric contents into the oropharynx. There is a lengthy list of extraesophageal symptoms that have been attributed to GERD (Table 1) [6]. However, the evidence supporting causation is quite variable.

Pathophysiology of GERD

Gastroesophageal reflux can be physiologic or pathologic. Physiologic reflux mostly occurs during the postprandial state, is transient, does not occur during sleep, and does not result in heartburn symptoms. Most episodes of gastroesophageal reflux are brief and do not cause symptoms, esophageal damage, or complications. Pathologic reflux is related to transient loss of pressure in the lower esophageal sphincter (LES) [7]. LES tone and activity of the crural diaphragm maintains gastroesophageal junction (GEJ) pressure. LES tone is maintained by the activity of neurotransmitters released by the vagus nerve and by stimulation of the enteric nervous system [8].

Various risk factors have been attributed to transient relaxation of the LES (Table 2), such as diet and lifestyle (smoking, alcohol), abdominal obesity, connective tissue disease (e.g., scleroderma), and esophagitis [9]. Among these risk factors, obesity accounts for 50–70% of patients with reflux symptoms, and 15% of the obese patients also have a hiatal hernia [10]. The mechanism related to development of reflux symptoms in obese patients is thought to be secondary to chronic increased intraabdominal pressure, which in turn results in an ineffective LES, delayed gastric emptying, and hiatal hernia.

GERD and Mucosal Injury

The effects of GERD on the esophageal mucosa have been the subject of a recent excellent review [4]. GERD results in the exposure of the esophagus to gastric contents including acid and proteases. Roughly 30% of patients in western countries with GERD symptoms present with erosive esophagitis. Prolonged GERD can lead to Barrett's esophagus, a precancerous lesion which can develop into adenocarcinoma of the lower esophagus [5]. The first characterization of the morphological changes induced by GERD within esophageal mucosa

Table 1 Extraesophageal symptoms attributed to GERD

1) Laryngopharyngeal reflux
2) Allergic rhinitis
3) Asthma
4) Sinusitis
5) Food Allergy
6) Otitis media
7) Dental erosions

Table 2 Risk factors for development of reflux

1) Lifestyle (smoking, alcohol consumption)
2) Diet (fatty, spicy, acidic, chocolate, caffeine)
3) Abdominal obesity
4) Connective tissue disease (e.g., scleroderma)
5) Esophagitis

included basal cell hyperplasia and papillary elongation [6]. Subsequently, dilatation of intercellular spaces was described. In 2011, standardized diagnostic criteria were developed for the histological diagnosis of GERD, including basal cell hyperplasia, papillary elongation, intraepithelial eosinophils, neutrophils, and mononuclear cells, as well as dilated intercellular spaces [7]. Following optimal acid blockade, these histological changes can regress over time [8].

Dilated intercellular spaces are observed in patients with erosive and non-erosive reflux disease. Dilated intercellular spaces are associated with impaired mucosal integrity and decreased transepithelial resistance. Dilation of intercellular spaces can be induced in animal models and human subjects following instillation of acid into the esophagus. Interestingly, in these experiments, dilation of intercellular spaces was also observed in non-exposed, proximal esophageal mucosa, suggesting that acid exposure can affect esophageal mucosa indirectly [8].

GERD is caused by damage resulting from exposure of the esophagus to gastric acid and proteases. This is followed by infiltration of inflammatory cells into the mucosa to remove cellular debris. Prolonged exposure of esophagus to gastric contents leads to deeper involvement of the mucosa. As acids and proteases penetrate deeper into the mucosa, there is degradation of junctional proteins, impaired epithelial function, and mucosal inflammation [9, 10]. Throughout this process, cytokines and chemokines are produced not only by infiltrating inflammatory cells but also by epithelial cells, keratinocytes, and fibroblasts. On endoscopy, GERD can lead to erosive esophagitis and the development of linear erosions (Fig. 1). Overtime, untreated GERD can result in the development of peptic strictures (Fig. 2).

The inflammatory response induced by GERD includes the production of a variety of cytokines (IL-1, IL-6, IL-4, IL-10), chemokines (IL-8), and platelet-activating factor (PAF) [4, 11–14]. IL-1 and IL-8 are produced by keratinocytes and their level of expression correlates with the severity of inflammation observed endoscopically and histologically [14]. Levels of IL-1 and IL-8 are reduced following acid suppressive therapy [15]. Additionally, PAF is produced by esophageal mucosa following exposure to acid and levels of PAF are increased in esophageal mucosa of patients with chronic esophagitis [16]. Production of cytokines and chemokines by mucosal cells recruits immune cells to esophageal mucosa followed by their subsequent activation, leading to further recruitment and activation of additional immune cells.

Activation of proteinase-activated receptor 2 (PAR2) has also been implicated in the mucosal inflammatory response in GERD. PAR2 is expressed on the surface of GI and respiratory epithelia and on neuronal cells [17, 18]. PAR2 is activated by serine proteases, such as trypsin and tryptase from mast cells within the GI tract [19]. Cleavage of an N-terminal sequence of PAR2 leads to activation of its intracellular domain. Activation of PAR2 leads to release of IL-8 from epithelial cells. PAR2 expression is increased in patients with erosive, as well as non-erosive, esophagitis. High levels of PAR2 expression correlate with high levels of IL-8 within the mucosa, with subsequent recruitment of inflammatory cells into the mucosa [20]. These observations support the concept that GERD is an immune-mediated process triggered initially by esophageal mucosa exposed to acid and proteases. Targeting of PAR2 has been proposed as a possible therapeutic intervention in GERD [20]. Impaired barrier function in the presence of inflammatory cytokines is hypothesized to be a mechanism whereby allergens (food, environmental) can penetrate mucosal surfaces, leading to

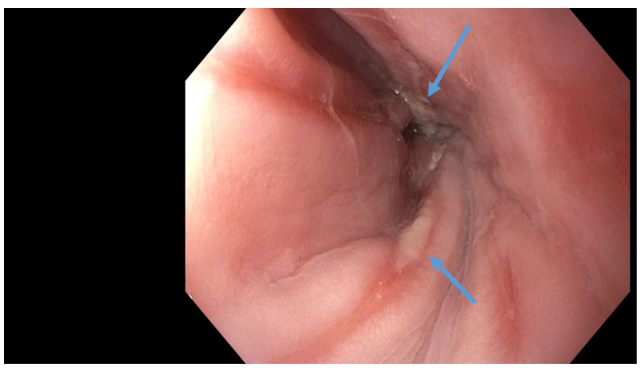

Fig. 1 Upper endoscopy in a 3-year-old with erosive esophagitis with notable linear ulcerations (blue arrows), pale mucosa (photo courtesy of Dr. Peter Ngo)

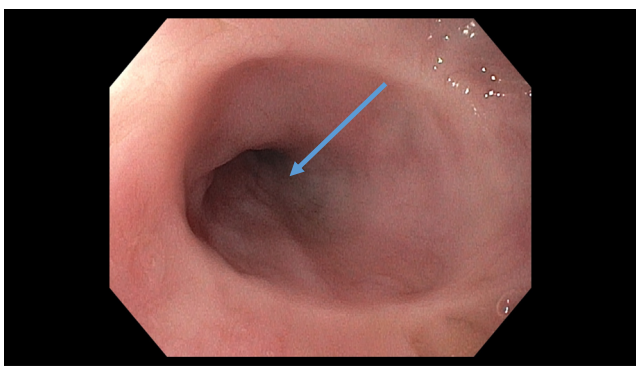

Fig. 2 **a**, **b** Upper endoscopy in a 2-year-old with a peptic stricture. Stricture indicated by blue arrow (photo courtesy of Dr. Peter Ngo)

potential allergic sensitization and subsequent development of atopic disorders (Fig. 3).

Treatment of GERD

In patients with mild and intermittent symptoms, treatment initially involves lifestyle and dietary modification and, as needed, antacids and/or sodium alginate. Lifestyle recommendations include weight loss for patients with GERD who are overweight or have had recent weight gain, and elevation of the head of the bed in individuals with nocturnal or laryngeal symptoms (e.g., cough, hoarseness, throat clearing). This can be achieved either by putting 6–8 in. blocks under the legs at the head of the bed or a wedge under the mattress. In addition, it is recommended to refrain from assuming a supine position after meals and avoidance of meals two to 3 h before bedtime. In addition, it is recommended that fatty foods, caffeine, chocolate, spicy foods, food with high fat content, and carbonated beverages be avoided. If symptoms do not improve within 2 weeks, histamine 2 receptor antagonists (H2RAs) are added. For patients with continued symptoms despite these measures, the H2RA is discontinued and once-daily proton pump inhibitor (PPI) therapy is initiated. Once symptoms are controlled, treatment should be continued for at least 8 weeks.

Effect of Proton Pump Inhibitors on Allergic Responses

Proton pump inhibitors (PPIs) are a class of medication that has been in use for over 2 decades for the treatment of gastroesophageal reflux disease (GERD). PPIs work by inhibiting H + K + ATPase, the proton pump of the gastric parietal cell. Initially, it was believed that inhibition of gastric acid secretion by PPIs was the sole mechanism by which PPIs functioned in the treatment of GERD. Subsequent studies suggested that PPIs may exert additional biologic effects on a variety of cells. Early studies demonstrated that PPIs could have anti-inflammatory effects by inhibiting reactive oxygen species production in neutrophils [21, 22]. Additionally, PPIs were shown to inhibit *H. pylori*-induced IL-8 production in a human gastric cancer cell line [23]. As discussed above, IL-8 is a potent chemotactic factor for neutrophils and plays a key role in initiation of inflammatory responses.

Further support for anti-inflammatory effects of PPIs has been obtained by the identification of a subset of patients with esophageal eosinophilia whose symptoms and eosinophilia respond to PPIs without evidence of GERD on endoscopy or 24 h esophageal pH monitoring [24]. Such patients were labeled as having a "PPI-responsive esophageal eosinophilia," possibly responding to the anti-inflammatory effects of PPIs, rather than inhibition of acid

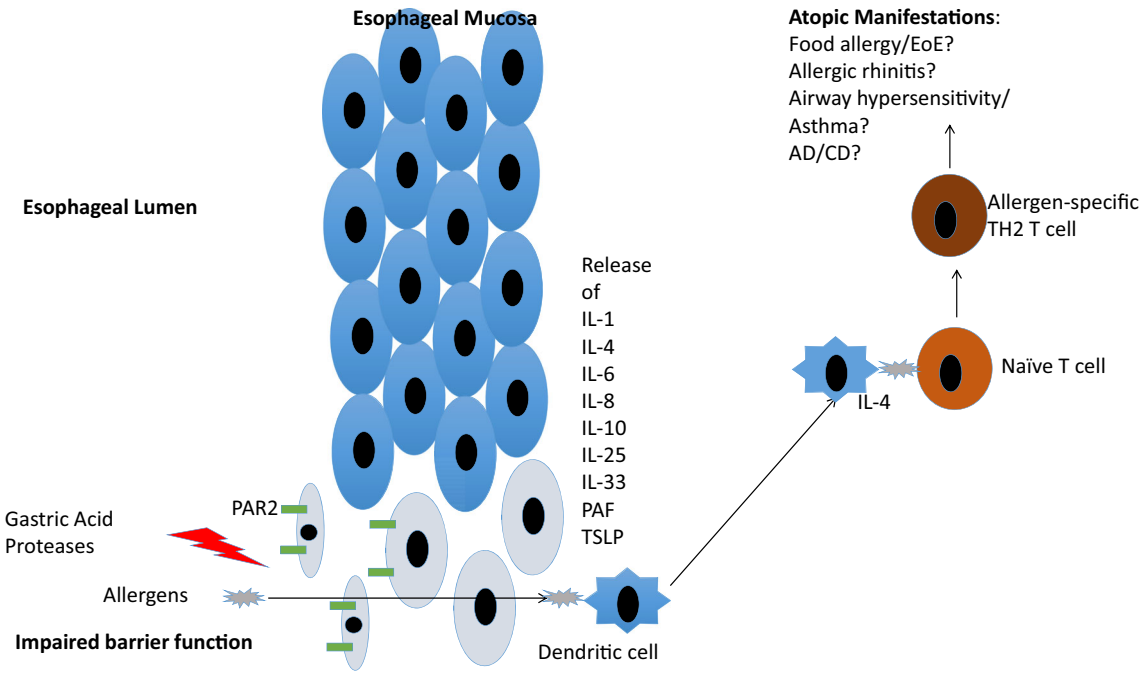

Fig. 3 Proposed mechanism of inflammation induced by gastroesophageal reflux and allergic sensitization to food or aeroallergens. Exposure of esophageal mucosa to gastric acid and proteases leads to dilation of intercellular spaces and impaired barrier function. Increased expression of PAR2 leads to increased release of IL-8, which recruits inflammatory cells, leading to release of additional inflammatory cytokines (IL-1, IL-6, IL-10, platelet-activating factor (PAF)). Inflammatory stimulate may induce expression of IL-33, IL-25, and thymic stromal lymphopoietin by keratinocytes, which are potent inducers of TH2 differentiation. Release of IL-4 by dendritic cells may promote differentiation of naïve T cells into TH2 allergen-specific T cells, potentially promoting atopic manifestations, including food allergies, eosinophilic esophagitis, allergic rhinitis, asthma, atopic dermatitis, and contact dermatitis

secretion. Eotaxin-3, a chemokine that recruits eosinophils into tissues, including the esophagus of patients with eosinophilic esophagitis, is induced by TH2 cytokines, such as IL-4 and IL-13. The PPIs omeprazole and lansoprazole were shown to inhibit eotaxin-3 expression in IL-4-stimulated esophageal squamous cell lines pretreated with high doses of omeprazole or lansoprazole in vitro [25]. The reduced Eotaxin-3 protein production was shown to be associated with reduced binding of STAT6 to its binding site on the eotaxin-3 promoter [25, 26]. Although these observations are intriguing, the biological significance of the observed in vitro effect of PPIs on Eotaxin-3 production are not clear, given the high concentrations of PPI used in these studies.

Subsequently, the effect of high dose omeprazole (40 mg twice daily) was evaluated in adults with esophageal eosinophilia [27]. Patients had a history of dysphagia or food impaction, along with > 15 eosinophils per high-power field on esophageal biopsy of the proximal or distal esophagus. Patients were treated for 8 weeks with omeprazole 40 mg bid, but no corticosteroids (topical or systemic) or dietary interventions. Study endpoints were clinical and histological remission and downregulation of esophageal expression of eotaxin-3, IL-5, and IL-13 after therapy with PPI compared to baseline expression. A total of 53 patients were studied. Of these patients, 23 (43%) had clinical and histological remission and were labeled as having PPI-responsive esophageal eosinophilia (PPI-REE). Thirty patients (57%) did not have histological remission after PPI treatment and were considered to have eosinophilic esophagitis (EoE). Fifteen of the EoE patients were treated with swallowed fluticasone propionate twice daily and of these patients, 8 (53%) had complete clinical and histological remission. Baseline expression of Eotaxin-3 and IL-13 were similar in PPI-REE and EoE patients. IL-5 expression was similar in the distal esophagus of both groups, but higher in the proximal esophagus of EoE patients. Omeprazole therapy led to significantly decreased expression of Eotaxin-3 and IL-13 in proximal and distal esophagus of PPI-REE patients. IL-5 expression was decreased in the distal, but not proximal esophagus of PPI-REE patients. However, in patients identified as having EoE, there was no significant decrease in Eotaxin-3, IL-13, or IL-5 in response to omeprazole alone. In EoE patients responsive to swallowed fluticasone propionate, there were significant decreases in Eotaxin-3 and IL-5 expression in the proximal and distal esophagus. Non-significant decreases in IL-13 expression were observed in the proximal and distal esophagus. Based upon similar baseline expression of TH2 cytokines, the authors suggest that PPI-REE and EoE likely represent a continuum of a common TH2-mediated disease [27]. Decreased expression of Eotaxin-3, IL-13, and IL-5 in PPI-REE patients treated with omeprazole is consistent with a possible anti-inflammatory effect of PPIs. However, this study did not elucidate the mechanism(s) through which PPIs may exert an anti-inflammatory effect. Additionally, this study did not assess a potential contribution of GERD to the expression of Eotaxin-3, IL-13, or IL-5, since 24-h pH monitoring was not performed on the study patients.

More recently, further support for anti-inflammatory effects of PPIs has come from transcriptome analysis in patients with GERD, PPI-REE, and EoE [28, 29]. A major advance in our understanding of the mechanisms that underlie PPI-REE and EoE versus GERD has been the identification of a panel of 94 genes that are differentially regulated in PPI-REE and EoE, but not GERD, referred to as the EoE diagnostic panel (EDP). The EDP was found to be comparable in both pediatric and adult patients with PPI-REE and EoE. Analysis of the EDP involves extraction of messenger RNA (mRNA) from esophageal biopsy samples, followed by reverse transcription of mRNA into cDNA. Changes in gene expression in patient samples compared to controls are measured by quantitative PCR. Analysis of the EDP identified a unique set of 77 genes that were dysregulated in EoE patients compared to controls. Gene expression heat maps observed in patients with non-erosive reflux disease or GERD was not significantly different from controls, indicating that GERD alone is not sufficient to induce changes in gene expression that occur in EoE. Categories of genes analyzed in the EDP included genes involved in cell adhesion, epithelial-related, inflammation, tissue remodeling, eosinophils and mast cells, chemokines, and cytokines [28]. The differential effect of EoE versus GERD on the expression of genes within the EDP demonstrates underlying molecular differences between GERD and EoE. Subsequent studies compared the transcriptomes from patients diagnosed with PPI-REE and EoE [29]. This analysis demonstrated significant molecular overlap between PPI-REE and EoE, reinforcing the understanding that PPI-REE is best considered to be on the same continuum of allergic disease as EoE. As a result, some practitioners have advocated for eliminating PPI-REE as a diagnosis in favor of PPI-responsive EoE. The investigators found that the transcriptome essentially normalized in PPI-REE patients following high-dose PPI treatment. Similarly, the transcriptome nearly normalized in EoE patients treated with topical steroids. These findings support the hypothesis that PPIs have anti-inflammatory effects, in addition to acid suppression. The precise mechanism through which PPIs exert these anti-inflammatory effects remains unclear and why PPIs are effective only in a subset of EoE patients remains to be determined. Interestingly, these investigators found that differential expression of the gene KCNJ2 (potassium inwardly-rectifying channel, subfamily J, member 2/Kir2.1) may differentiate patients with EoE versus PPI-REE pre-treatment [29]. Such observations may allow greater precision in the treatment of these patients and avoid a need for elimination diets or treatment with topical steroids and the need for multiple endoscopies.

Eosinophilic Esophagitis and GERD

Eosinophilic esophagitis (EoE) is an allergy-mediated, chronic disorder resulting in severe eosinophilic inflammation and dysfunction of the esophagus. It is a chronic disorder that affects all ages and can cause significant morbidity [30]. It is thought that EoE represents a localized delayed hypersensitivity reaction to food and/or environmental allergens. EoE is a polygenic allergic disorder with mostly non-IgE-mediated allergic reactions [31]. The incidence of IgE-mediated food allergy is higher in EoE patients. Eosinophils, T cells, and mast cells are elevated in esophageal mucosal biopsies of patients with eosinophilic gastrointestinal disorders. Clinical symptoms of EoE vary depending upon the age of presentation (see Table 3).

Eosinophilic Esophagitis Versus PPI-Responsive Esophageal Eosinophilia

The differentiation of patients with GERD versus PPI-REE or EoE is often a source of confusion. Both GERD and EoE are more common in young males [30]. Typical GERD symptoms include heartburn or regurgitation and upper endoscopy is not indicated for patients with typical GERD symptoms. However, upper endoscopy is indicated in GERD patients with alarm symptoms (dysphagia, odynophagia, GI bleeding, anemia, weight loss, vomiting) or failure to respond to high-dose PPI therapy over a 4 to 8-week course (Table 4). Visible esophagitis is observed in approximately 30% of patients with GERD. The severity and duration of symptoms do not necessarily correlate with the severity of esophagitis, however. Ulcerations observed in peptic esophagitis (GERD) tend to occur in the distal esophagus (Fig. 1). Histologic findings in GERD are nonspecific and include dilation of intercellular spaces, as well as the presence of neutrophils and eosinophils and thickening of the basal cell layer. In comparison to eosinophilic esophagitis, however, esophageal eosinophilia is usually much less pronounced in patients with GERD. Esophageal 24-h pH/impedance monitoring may be used to help confirm the diagnosis of GERD in patients with atypical symptoms.

Table 3 Clinical presentation of eosinophilic esophagitis by age

Infants and toddlers
1) Regurgitation
2) Vomiting
3) Feeding refusal
4) Failure to thrive
Older children
5) Vomiting
6) Abdominal pain
7) Retrosternal pain
8) Weight loss
Adolescents/adults
9) GERD
10) Dysphagia
11) Food impactions/esophageal strictures

Table 4 Indication for endoscopic evaluation in GERD patients

Dysphagia
Odynophagia
GI bleeding
Anemia
Weight loss
Vomiting
Failure to respond to high-dose PPI therapy

PPI-REE and EoE can present at any age and symptoms vary with age (Table 3). Older children, adolescents, and adults can present with chest pain, solid food dysphagia, and food impactions. In younger children and infants, symptoms can include reflux, vomiting, abdominal pain, feeding refusal, and failure to thrive. Such symptoms require further evaluation with upper endoscopy. Visible findings consistent with PPI-REE or EoE may include pale mucosa, linear furrows, and white exudates (Fig. 4); however, the esophagus may be normal-appearing. Biopsies should be obtained, preferably from the proximal, mid, and distal esophagus. Increased sensitivity of diagnosis is correlated with increasing numbers of biopsies, with six biopsies recommended. Findings consistent with EoE include the presence of > 15 eosinophils per high-power field, eosinophil micro-abscesses, basal zone hyperplasia, dilated intercellular spaces, papillary elongation, and lamina propria fibrosis (Fig. 5). Eosinophils tend to be present throughout the entire length of the esophagus, whereas in GERD, eosinophils are typically found only in the distal esophagus, usually in smaller numbers than observed in EoE.

It is important to emphasize that GERD and EoE are distinct diagnoses and patients may have one or both disorders at the same time. The relationship between GERD and EoE is likely complex [30]. One hypothesis is that GERD may lead to esophageal mucosal damage induced by gastric acid, leading to impaired mucosal integrity and allowing penetration of food allergens and the potential for subsequent allergic sensitization [31] (Fig. 3). Direct proof of this mechanism of allergic sensitization is lacking, however. On the other hand, impaired epithelial integrity is also a characteristic of EoE, which may lead to acid hypersensitivity and symptoms of GERD. Atopic disorders, such as atopic dermatitis, allergic rhinitis, and asthma are common comorbidities observed in patients with EoE. Thus, in patients with symptoms of esophageal

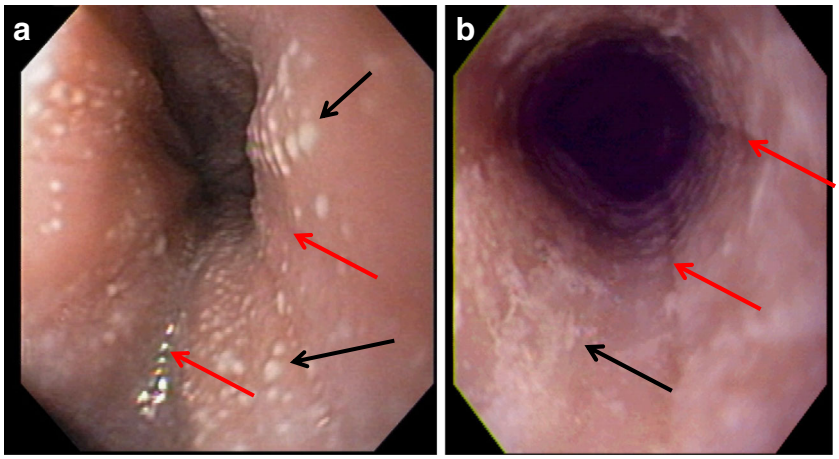

Fig. 4 **a**, **b** Eosinophilic exudate (black arrows) and linear furrows (red arrows) visualized endoscopically in a patient with eosinophilic esophagitis (photo courtesy of Dr. Peter Ngo)

dysfunction, the presence of atopic disorders increases the index of suspicion of having EoE. Consensus guidelines recommend that patients with histologic evidence of > 15 eosinophils per high-power field be treated aggressively with at least 2 months of acid blockade therapy or carefully tested with impedance monitoring before a definitive diagnosis of EoE can be made, even in highly atopic patients [31, 32]. The PPI-REE Task Force of the European Society for Eosinophilic Esophagitis recently recommended that patients suspected of having PPI-REE or EoE should first undergo an endoscopy before starting PPI therapy and then repeat an endoscopy on a PPI to conclusively distinguish between the PPI-REE and EoE [33]. However, this practice remains controversial particularly among pediatric practitioners.

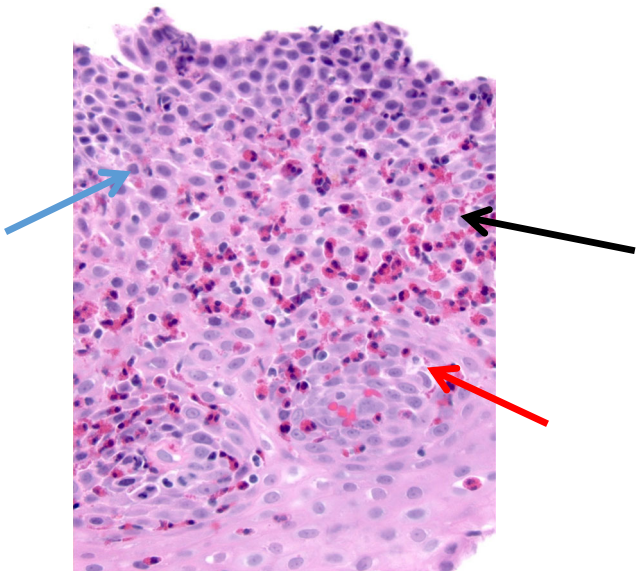

Fig. 5 Esophageal histology of a child with EoE reveals eosinophilic degranulation (black arrow) and basal layer hyperplasia (blue arrow) with dilated intracellular spaces (red arrow) (photo courtesy of Dr. Jeffrey Goldsmith)

Asthma and GERD

Asthma and GERD are both very common, but their frequent coexistence has led to the suggestion that there is a pathological link between the two diseases. GERD has been found to occur in 32% to 80% of asthmatic patients [34]. Asthma is thought to promote reflux by increasing the pressure gradient between the thorax and the abdomen.

Reflux Versus Reflex Theories

There are two proposed mechanisms by which GERD can aggravate asthma. The reflux theory suggests a direct mechanism by which micro-aspiration of gastric contents causes damage to the bronchopulmonary tree. The aspirate directly stimulates the pharynx or larynx, causing pulmonary symptoms and lung injury [35]. The lung injury caused by micro-aspiration is likely multifactorial. Mechanical obstruction of the airways occurs from small particles in the aspirate. Chemical pneumonitis or aspiration-related bacterial pneumonia can also occur. Finally, failure of physiological protective mechanisms such as intact lower and upper esophageal sphincters which usually act as a barrier to prevent refluxate from causing symptoms and tissue damage may account for at least part of asthma symptoms in GERD patients [36].

The reflex theory suggests an indirect mechanism in which distal esophageal reflux stimulates the vagal nerve which in turn leads to bronchoconstriction [37]. This theory is based on the fact that the esophagus and tracheobronchial tree share an embryonic origin. Therefore, they share the same neural innervation, explaining why stimuli in the distal esophagus could lead to respiratory symptoms via vagally mediated reflexes.

The hypothesis that GERD can trigger or exacerbate asthma is supported by several small studies that have shown a reduction in asthma symptoms and/or an improvement in pulmonary function after anti-reflux therapy [38–41]. However,

there are other studies that have investigated the effect of PPI treatment on asthma outcome with inconclusive results.

Effect of Proton Pump Inhibitors on Asthma

It has long been thought that treatment of reflux in asthma patients improves their asthma control. This belief was even reflected in the last set of guidelines from the National Institutes of Health (NIH) for the treatment of asthma [42]. These guidelines recommended that physicians consider administering an empiric trial of anti-reflux therapy to patients with poorly controlled asthma, even in the absence of GERD symptoms. However, new evidence is shifting our practice away from treating asthma patients with asymptomatic GERD with anti-reflux medications [43].

The possibility of occult gastroesophageal reflux contributing to refractory asthma led to SARCA (Study of Acid Reflux in Childhood Asthma), which studied the effect of empiric lansoprazole on the treatment of uncontrolled asthma [44]. The clinical effectiveness of PPI drugs is closely associated with plasma concentrations and variation within the CY2C19 gene. Several loss-of-function CYP2C19 single-nucleotide polymorphisms are fairly common in the population and consistently associate with higher PPI levels [45]. Lang et al. explored the effect of lansoprazole and metabolizer phenotype on asthma control by comparing longitudinal data among three groups (placebo-treated, lansoprazole-treated extensive metabolizers, and lansoprazole-treated poor metabolizers) in a 6-month asthma trial [46]. In this study, they demonstrated that poor metabolizers taking lansoprazole developed significantly worse asthma control compared with both lansoprazole-treated extensive metabolizers and placebo-treated children. At 6 months, poor metabolizers displayed significantly worsened asthma control compared with extensive metabolizers (10.16 vs. −0.13; $p = 0.02$) and placebo-treated children (10.16 vs. −0.23; p, 0.01). The authors hypothesized that increased exposure to proton pump inhibitor may worsen asthma control by altering responses to respiratory infections; however, their study was not powered adequately to demonstrate this definitively.

A recent study by Sadur et al. determined the effect of omeprazole on asthma symptoms, pulmonary function, and on the requirement of asthma medications in 40 patients with difficult to control asthma [34]. All patients underwent 24-h pH-monitoring and pulmonary function tests were performed before and after treatment. In the asthma patients with GERD, post-treatment reflux symptom score, pulmonary symptom score, and nighttime asthma symptom score improved, and there was a significant increase of FEV1. The authors concluded that PPI therapy improves nocturnal and daytime asthma symptoms in select patients with asthma and concomitant GERD.

One small study by Granéli et al. prospectively describes the clinical outcomes of 40 children at their institution who underwent computer-assisted robotic Nissen fundoplication surgery [47].

All 40 patients required anti-reflux medication before the fundoplication. This number decreased significantly to 8 (20%) after the fundoplication ($p < 0.001$). Before the fundoplication, 22 children (55%) were using asthma medication and only 12 (30%) after the fundoplication ($p = 0.04$). While these results are compelling, unfortunately they do not clarify why these children were able to reduce their asthma medication. It could have been due to the reduction in exposure to anti-reflux medications or the reduction in GERD itself. Larger studies would be required to elucidate the effect of Nissen fundoplication surgery on asthma.

In summary, the interaction between asthma and GERD is complex, and the mechanism through which PPIs may affect asthma outcomes is not clear. Treatment of GERD seems to improve asthma symptoms in selected patients, but paradoxically lung function does not uniformly improve. These disappointing results have been attributed to the wide variation in GERD treatment (H2-antagonists, PPI therapy, anti-reflux surgery). Furthermore, most studies had small sample sizes and had variable dosages and duration of therapy. In the majority of the studies, treatment periods were usually short. It is possible that a longer observation period could be necessary before control of GERD results in benefits for asthma-related symptoms. It is also thought that perhaps subgroups of asthmatics may benefit from acid blockade therapy, specifically those with nocturnal reflux proven by 24-h pH monitoring.

Chronic Rhinosinusitis and GERD

Chronic rhinosinusitis (CRS) is a common disorder characterized by inflammation of the mucosal membranes of the nose and paranasal sinuses. CRS, especially refractory disease that does not improve with medical therapy, has been associated with increased risk of GERD.

Similar to asthma and AR, it has been proposed that there is a direct cytotoxic effect of refluxate on the respiratory mucosa. However, according to The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012), there is insufficient evidence for a causal relationship between GERD and CRS [48]. Nevertheless, there is still debate over whether an association exists. Patients with GERD have a higher 20-item Sino Nasal Outcome Test (SNOT-20) score than control subjects, indicating that GERD patients have a reduced sinonasal quality of life [49].

Katle et al. recently conducted a study that showed patients with CRS had more gastroesophageal reflux as well as proximal reflux, than healthy controls [50]. The CRS patients also had significantly more bolus exposure in both the upright and

supine positions. There were significantly higher numbers of acid and non-acid reflux episodes in CRS patients than asymptomatic controls which the authors concluded suggest that GERD may be a causative or contributing factor of CRS. Supporting this hypothesis is the observation that gastric acid exposure may cause dilation of intercellular spaces in proximal, unexposed esophageal mucosa. Such a mechanism could exacerbate inflammation within the mucosa of the upper airways and sinuses. A recent report by Lin et al. followed 15,807 new diagnosed GERD patients, compared to 47,421 subjects without GERD and matched by age, sex, index year, and comorbidity as a control cohort. Subjects with GERD were found to have a 2.36-fold greater risk of developing CRS (95% confidence interval = 2.08–2.68: $p < 0.001$) [51].

The current position statement of the American Academy of Otolaryngology–Head and Neck Surgery does not support use of PPIs for pediatric CRS [52]. The recently published International Consensus Statement on Allergy and Rhinology: Rhinosinusitis [53] outlines the data surrounding CRS and GERD. It assigns grade B evidence to support the association between these entities but again states that treatment guidelines or mechanistic studies are lacking. They recommend definitive testing to accurately diagnose GERD before initiating PPI treatment in patients with non-responsive CRS.

Allergic Rhinitis and GERD

Allergic rhinitis (AR) may be defined as inflammation of the nasal mucous membranes caused by immunoglobulin E (IgE)-mediated allergic reaction to aeroallergens. It is characterized by symptoms of nasal obstruction and secretion in the absence of common cold and is associated with a significant reduction in the health-related quality of life, including impaired quality of sleep [54]. It has been suggested that frequent symptoms of GERD are associated with an increased risk of developing AR.

Hellegren et al. demonstrated in a general population sample of 3307 subjects, aged 25–75 years that symptoms of GERD occurring > 25 times per year were associated with an increased risk of developing rhinitis during a 4-year follow-up [55]. A recent retrospective study by Mahdavinia et al. evaluated the odds of developing allergic rhinitis and asthma in CRS patients with and without GERD [56]. The odds ratios (ORs) for asthma and allergic rhinitis in the CRS group with GERD compared with the CRS group without GERD were 2.89 (95% confidence interval (CI), 1.905–4.389) and 2.021 (95% CI, 1.035–3.947), respectively. The authors concluded that patients with CRS and GERD were more likely to have atopic disorders than patients with CRS alone. The mechanisms that underlie an increased susceptibility to atopic disorders in individuals with CRS and GERD remains to be elucidated; however, it is tempting to speculate that conditions that promote impaired barrier function (GERD) and inflammation (CRS) may increase the likelihood of allergic sensitization (Fig. 3).

The RHINE study, a large Northern European multicenter study where the subjects were followed for 10 years, demonstrated that nocturnal GERD was associated with the development of rhinitis and this association strengthened with the frequency of nocturnal reflux episodes [57]. However, these studies only identified non-infectious rhinitis and did not differentiate allergic rhinitis from non-allergic rhinitis. Of note, the recent International Consensus Statement on Allergic Rhinitis does not even mention GERD at all as a potential risk factor [58].

Atopic Dermatitis, Nickel Allergy, and GERD

Most commonly, the response to food antigens in the GI tract and skin is one of immunologic tolerance. Antigen presentation is mediated by $CD103^+$ dendritic cells (DCs) in the GI tract and by $CD11b^+$ DCs and Langerhans cells in the skin [59]. These DCs migrate to draining lymph nodes where they induce food antigen-specific regulatory T cells, which promote tolerance. However, in the presence of inflamed barriers, it is believed that a breakdown of tolerance to food antigens may occur, perhaps mediated by expression of IL-33, IL-25, and thymic stromal lymphopoietin by keratinocytes (Fig. 3) [59]. Impaired and/or inflamed barriers occur in atopic dermatitis (AD), contact dermatitis (CD) induced by nickel allergy, and GERD. The degree to which inflammatory skin conditions (AD, CD) may influence GI inflammation (GERD) and vice versa is presently unknown.

A potential relationship of nickel allergy to GERD has recently been investigated [60]. Delayed type hypersensitivity to nickel is a common cause of CD. Exposure to nickel can occur through contact of jewelry and clothing with skin surfaces. Nickel is also present in significant quantities in a variety of foods, including tomatoes, cocoa, peanuts, oats, beans, whole wheat, lentils, hazelnuts, walnuts, peas, and soy [61]. Thus, nickel exposure through the GI tract is also common. Interestingly, nickel sensitization was found to be more prevalent in GERD patients than controls (39.5% versus 16.4%; $p = 0.001$) determined by atopy patch testing. In spite of this observation, nickel allergy was not shown to have a demonstrable effect on GERD, as "low nickel diets" (i.e., avoidance of foods from the diet known to be high in nickel) had no effect on GERD symptoms or medication requirement (use of PPIs) [60]. Thus, although nickel allergy may be a common cause CD, evidence of an influence of nickel sensitization on GERD is lacking.

Similarly, evidence for an influence of atopic dermatitis on GERD and vice versa is lacking. Both processes represent mixed IgE/non-IgE-mediated allergic disorders. Atopic dermatitis and GERD are both common manifestations of food allergy in infants [62]. Presently, there are no published

studies that demonstrate a direct relationship between atopic dermatitis and GERD. As will be discussed below, treatment of GERD by acid blockade has been associated with an increase in food specific IgEs; however, clinical manifestations of food allergy were not demonstrated.

Food Allergy and GERD

Approximately 7–8% of children are affected by food allergies, the most common being cow's milk, egg, and peanut allergies [63]. The frequent coexistence of GERD with food allergies in children, particularly young children under the age of 5 years, has been extensively reported [62–68]. The mechanisms involved include both immunoglobulin E (IgE)- and non-IgE-mediated reactions. IgE-mediated allergic reactions can occur within seconds to minutes and range from a tingling sensation around the mouth and lips to hives and anaphylaxis. Delayed type allergic reactions that take days to weeks to appear are more often non-IgE-mediated.

Acid-Blocking Medications as Augmenting Factors in Food Allergy

Antacids, including PPI's, H2 blockers, as well as sucralfate, have all been implicated as augmenting factors for food allergy reactions. Augmenting factors are defined as factors which lower the reaction threshold or which make allergic symptoms more severe by directly influencing the immunological mechanism of type I allergy [69]. Antacids may be involved in allergic reactions by several mechanisms, both long term and short term (Table 5).

The most widely postulated mechanism by which acid-suppressing medications might accentuate allergic sensitization is their potential to impair digestion so that intact allergens reach lower parts of the gastrointestinal tract [70]. Acid-reducing medications work by either binding protons in the gastric lumen or reducing gastric acid output. Gastric acidity itself is not only required for protection against infectious agents but also initiates protein degradation by influencing food protein interactions, as well as structural properties of proteins. Low gastric acid pH is crucial for activation and liberation of gastric and pancreatic proteases. Together, these enzymes degrade proteins to small nutritionally valuable peptides, which ideally are ignored by the immune system or lead to tolerance. Studies suggest that by increasing the gastric pH, food proteins are incompletely broken down with the potential to present as antigens or even allergens.

Untersmayr et al. studied of a cohort of 152 adult patients treated for GERD with either H2-recptor blockers or PPIs who underwent allergy screening before and after a 3-month course of antacid treatment. Those patients demonstrated an increase of preexisting food-specific IgE antibodies in 10% or de novo IgE formation towards regular constituents of the daily diet in 15% of all patients [71]. Even though food-specific IgE levels decreased in some patients 5 months after discontinuation of anti-ulcer medication intake, sensitization was still confirmed by positive skin tests. However, the study did not comment on any subjects developing clinical manifestations of allergy.

Another potential mechanism for allergy induction by acid reduction medication might be its interference with epithelial barrier function. Interestingly, high levels of total and food-specific IgE were measured in the gastrointestinal mucosa of peptic ulcer patients who had enhanced mucosal permeability due to *H. pylori* infection [72]. Increased transepithelial leak has also been described in patients with Barrett's esophagus. However, it was unclear whether the increased mucosal permeability was secondary to the inflammation versus the disease. In 2008, Mullin et al. used sucrose permeability testing to demonstrate that some, but not all, healthy volunteers taking esomeprazole developed paracellular leak in the esophagus. This paracellular leakage reversed with discontinuation of the PPI [73].

Finally, gastric acid suppression has consequences to the gastrointestinal microbiome, which has been postulated as a mechanism for food allergy. PPIs increase the number of bacteria in the oral cavity and the upper gastrointestinal tract due to lack of gastric acidity [74]. Alternatively, PPIs might have an anti-microbial effect on certain microbes by inhibiting the H + K + ATPase found in bacterial and fungal cell membranes. Microbiome changes during acid blocking drug treatment and the known influence of the intestinal bacterial composition on food allergy could offer a further mechanistic explanation for the observed association between acid-suppressing medications and allergy development [75, 76] (Table 5).

Table 5 Proposed mechanisms to explain how acid suppressing medications act as augmenting factors for food allergy

1) Incomplete food protein degradation
2) Interference with epithelial barrier function
3) Influence on gastrointestinal microbiome
A) Increased numbers of oral and upper GI tract bacteria
B) Anti-microbial effect on certain microbes

Association Between Non-IgE Mediated Food Allergy and GERD in Children

The development of food allergy has also been linked to GERD itself, not only antacid treatment. Gastroesophageal reflux disease commonly occurs during the first year of life, and some forms of severe GERD have been shown to be associated with food allergy. Nielsen et al. identified an association between GERD and cow's milk hypersensitivity in 10 out of 17 patients with severe GERD using strict criteria for both GERD and food hypersensitivity

[77]. The vast majority of the food allergies in these children seem to be non-IgE mediated with negative specific IgE and skin prick testing. Diagnosis is most often made by oral challenge [78]. Iacono et al. reported that food allergy was diagnosed in 41.8% of children with pathological gastroesophageal reflux [64]. Semeniuk et al. identified cow's milk allergy in 43% of children aged 2 to 15 months with GERD [78]. Janiszewska et al. studied a large group of children aged 1 to 16 years diagnosed with GERD based on 24-h esophageal pH-metry, and in 48% of cases found IgE-dependent food allergy [79]. More recently, Yukselen et al. studied a large group of GERD patients to evaluate the prevalence of food allergy and, as reported in the previous studies, they found that 43% of children with GERD also had food allergy [77]. These studies suggest that GERD is considered a manifestation of both IgE and non-IgE-mediated food allergies.

Conclusion

In this article we reviewed several common atopic conditions that have been associated with GERD including asthma, CRS, AR, AD, CD, food allergies, PPI-responsive esophageal eosinophilia, and eosinophilic esophagitis. In each condition, the evidence of a causal link is not definitive. Although the relationship between asthma and GERD remains controversial, evidence suggests that a subset of asthma patients with documented GERD may experience improved asthma control following appropriate treatment of GERD. The relationship of GERD to allergic rhinitis and chronic sinusitis is weak; however, studies support the concept that treatment of frequent episodes of GERD can have a positive effect on rhinitis and sinusitis overall. GERD is a common manifestation of food allergy, particularly in infants and children. The relationship between food allergy (including PPI-REE and EoE) and GERD is likely bidirectional. GERD may induce changes in the mucosal immune system that favor the development of food allergy; however, the underlying mechanisms have not been established. The observation that GERD does not induce dysregulation of atopy-related genes associated with EoE (EoE transcriptome) argues that GERD alone may not be sufficient to induce allergic inflammation. Esophageal pH-monitoring and/or pH-impedance monitoring is the standard of care to correlate reflux and symptoms. With increasing evidence of risks of long term PPI use, it is important to conclusively test for GERD before assuming the refractory nature of the atopic disease can be attributed to it. Effective treatment of GERD in symptomatic patients with atopic disorders is likely to provide additional improvement in the control of the atopic disorder by virtue of the common anatomical locations where GERD and these atopic disorders occur.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest. This report is a review of the literature and no human subjects were involved.

References

1. Helander HF, Fandriks L (2014) Surface area of the digestive tract - revisited. Scand J Gastroenterol 49(6):681–689
2. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 14(8):e1002533
3. Aceves S, Hirano I, Furuta GT, Collins MH (2012) Eosinophilic gastrointestinal diseases–clinically diverse and histopathologically confounding. Semin Immunopathol 34(5):715–731
4. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, DiBonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ (2012) Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 143:1179–1187
5. N Vakil, SV van Zanten, P Kahrilas, J Dent, R Jones, the Global Consensus Group, The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol2006(101): 1900, 1920
6. Vaezi MF, Katzka D, Zerbib F (2018) Extraesophageal symptoms and diseases attributed to GERD: where is the pendulum swinging now? Clin Gastroenterol Hepatol S1542-3565(18):30145–30149
7. Boeckxstaens G, El-Serag HB et al (2014) Symptomatic reflux diease: thepresent, the past and the future. Gut 63:1185–1193
8. Roman S et al (2017) Validation of criteria for the definition of transient lower esophageal sphincter relaxation using high resolution manometry. Neurogastroenterol Motil 29:e12920
9. Koduru P, Irani M, Quigley EMM (2017) Definition, pathogenesis, and management of that cursed dyspepsia. Clin Gastroenterol Hepatol S1542-3565(17):31063–31067
10. Che F, Nguyen B, Cohen A, Nguyen NT (2013) Prevalence of hiatal hernia in the morbidly obese. Surg Obes Relat Dis 9:920–924
11. Kandulski A, Malfertheiner P (2011) Gastroesophageal reflux disease–from reflux episodes to mucosal inflammation. Nat Rev Gastroenterol Hepatol 9(1):15–22
12. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L (2008) The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol 168(3):237–249
13. Ismail-Beigi F, Horton PF, Pope CE 2nd. (1970) Histological consequences of gastroesophageal reflux in man. Gastroenterology 58(2):163–174
14. Yerian L, Fiocca R, Mastracci L, Riddell R, Vieth M, Sharma P, Franzen S, Fernstrom P, Ruth M (2011) Refinement and reproducibility of histologic criteria for the assessment of microscopic lesions in patients with gastroesophageal reflux disease: the Esohisto Project. Dig Dis Sci 56(9):2656–2665
15. Fiocca R, Mastracci L, Engstrom C, Attwood S, Ell C, Galmiche JP et al (2010) Long-term outcome of microscopic esophagitis in chronic GERD patients treated with esomeprazole or laparoscopic antireflux surgery in the LOTUS trial. Am J Gastroenterol 105(5): 1015–1023
16. Tobey NA, Carson JL, Alkiek RA, Orlando RC (1996) Dilated intercellular spaces: a morphological feature of acid reflux–damaged human esophageal epithelium. Gastroenterology 111(5): 1200–1205

17. Orlando RC (2008) Pathophysiology of gastroesophageal reflux disease. J Clin Gastroenterol 42(5):584–588
18. Isomoto H, Wang A, Mizuta Y, Akazawa Y, Ohba K, Omagari K, Miyazaki M, Murase K, Hayashi T, Inoue K, Murata I, Kohno S (2003) Elevated levels of chemokines in esophageal mucosa of patients with reflux esophagitis. Am J Gastroenterol 98(3):551–556
19. Yoshida N, Katada K, Handa O, Takagi T, Kokura S, Naito Y, Mukaida N, Soma T, Shimada Y, Yoshikawa T, Okanoue T (2007) Interleukin-8 production via protease-activated receptor 2 in human esophageal epithelial cells. Int J Mol Med 19(2):335–340
20. Rieder F, Cheng L, Harnett KM, Chak A, Cooper GS, Isenberg G, Ray M, Katz JA, Catanzaro A, O'Shea R, Post AB, Wong R, Sivak MV, McCormick T, Phillips M, West GA, Willis JE, Biancani P, Fiocchi C (2007) Gastroesophageal reflux disease-associated esophagitis induces endogenous cytokine production leading to motor abnormalities. Gastroenterology 132(1):154–165
21. Monkemuller K, Wex T, Kuester D, Fry LC, Peitz U, Beyer M et al (2009) Interleukin-1beta and interleukin-8 expression correlate with the histomorphological changes in esophageal mucosa of patients with erosive and non-erosive reflux disease. Digestion 79(3):186–195
22. Isomoto H, Saenko VA, Kanazawa Y, Nishi Y, Ohtsuru A, Inoue K, Akazawa Y, Takeshima F, Omagari K, Miyazaki M, Mizuta Y, Murata I, Yamashita S, Kohno S (2004) Enhanced expression of interleukin-8 and activation of nuclear factor kappa-B in endoscopy-negative gastroesophageal reflux disease. Am J Gastroenterol 99(4):589–597
23. Cheng L, Cao W, Behar J, Fiocchi C, Biancani P, Harnett KM (2006) Acid-induced release of platelet-activating factor by human esophageal mucosa induces inflammatory mediators in circular smooth muscle. J Pharmacol Exp Ther 319(1):117–126
24. Steinhoff M, Vergnolle N, Young SH, Tognetto M, Amadesi S, Ennes HS, Trevisani M, Hollenberg MD, Wallace JL, Caughey GH, Mitchell SE, Williams LM, Geppetti P, Mayer EA, Bunnett NW (2000) Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. Nat Med 6(2):151–158
25. Soreide K (2008) Proteinase-activated receptor 2 (PAR-2) in gastrointestinal and pancreatic pathophysiology, inflammation and neoplasia. Scand J Gastroenterol 43(8):902–909
26. Dery O, Corvera CU, Steinhoff M, Bunnett NW (1998) Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. Am J Phys 274(6 Pt 1):C1429–C1452
27. Kandulski A, Wex T, Monkemuller K, Kuester D, Fry LC, Roessner A et al (2010) Proteinase-activated receptor-2 in the pathogenesis of gastroesophageal reflux disease. Am J Gastroenterol 105(9):1934–1943
28. Wandall JH (1992) Effects of omeprazole on neutrophil chemotaxis, super oxide production, degranulation, and translocation of cytochrome b-245. Gut 33(5):617–621
29. Suzuki M, Nakamura M, Mori M, Miura S, Tsuchiya M, Ishii H (1995) Lansoprazole inhibits oxygen-derived free radical production from neutrophils activated by Helicobacter pylori. J Clin Gastroenterol 20(Suppl 2):S93–S96
30. Furuta GT, Katzka DA (2015) Eosinophilic esophagitis. N Engl J Med 373:1640–1648
31. Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, Bussmann C, Amil Dias J, Bove M, González-Cervera J, Larsson H, Miehlke S, Papadopoulou A, Rodríguez-Sánchez J, Ravelli A, Ronkainen J, Santander C, Schoepfer AM, Storr MA, Terreehorst I, Straumann A, Attwood SE (2017) Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J* 5(3):335–358
32. Liacouras CA, Furuta GT et al (2011) Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol 128:3–20 e6. 30
33. Molina-Infante J, Bredenoord AJ, Cheng E, Dellon ES, Furuta GT, Gupta SK, Hirano I, Katzka DA, Moawad FJ, Rothenberg ME, Schoepfer A, Spechler SJ, Wen T, Straumann A, Lucendo AJ, PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS) (2016) PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS). Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut 65(3):524–531
34. Sadur V, Murugesh M, Banait V, Rathi PM, Bhatia SJ, Joshi JM, Kate A (2014) Prevalence of gastro-esophageal reflux disease in patients with difficult to control asthma and effect of proton pump inhibitor therapy on asthma symptoms, reflux symptoms, pulmonary function and requirement for asthma medications. J Postgrad Med 60(3):282–287
35. Raghavendran K, Nemzek J, Napolitano LM, Knight PR (2011) Aspiration induced lung injury. Crit Care Med 39:818–826
36. Sontag SJ (2005) The spectrum of pulmonary symptoms due to gastroesophageal reflux. Thorac Surg Clin 15:353–368
37. Wright RA, Miller SA, Corsello BF (1990) Acid-induced esophagobronchial cardiac reflexes in humans. Gastroenterology 99:71–73
38. Vandenplas Y (1997) Asthma and gastroesophageal reflux. J Pediatr Gastroenterol Nutr 24:89–99
39. Harding SM, Guzzo MR, Richter JE (1999) 24-h esophageal pH testing in asthmatics: respiratory symptom correlation with esophageal acid events. Chest 115:654–659
40. Sontag SJ, Schnell TG, Miller TQ, Khandelwal S, O'Connell S, Chejfec G et al (1992) Prevalence of oesophagitis in asthmatics. Gut 33:872–876
41. Naik RD, Vaezi MF (2015) Extra-esophageal gastroesophageal reflux disease and asthma: understanding this interplay. Expert Rev Gastroenterol Hepatol 9:969–982
42. Reddy AP, Gupta MR (2014) Management of asthma: the current US and European guidelines. Adv Exp Med Biol (795):81–103
43. Solidoro P, Patrucco F, Fagoonee S, Pellicano R (2017) Asthma and gastroesophageal reflux disease: a multidisciplinary point of view. Minerva Med 108(4):350–356
44. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, Lima JJ, Mastronarde JG, Sockrider MM et al (2012) Writing Committee for the American Lung Association Asthma Clinical Research Centers Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA 307:373–381
45. Lima JJ, Lang JE, Mougey EB, Blake KB, Gong Y, Holbrook JT, Wise RA, Teague WG (2013) Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr 163:686–691
46. Lang JE, Holbrook JT, Mougey EB. Lansoprazole is associated with worsening asthma control in children with the CYP2C19 poor metabolizer phenotype. Ann Am Thorac Soc 2015 (12):878–885
47. Granéli C, Kockum CC, Arnbjornsson E, Anderberg M (2015) Outcome after computer-assisted (robotic) Nissen fundoplication in children measured as pre- and postoperative acid reducing and asthma medications use. Eur J Pediatr Surg 25(6):532–536 45
48. Fokkens WJ, Lund VJ, Mullol J, et al. (2012) EPOS 2012: European Position Paper on Rhinosinusitis and Nasal Polyps 2012. A summary for otorhinolaryngologists. Rhinology 50(1): 1–12
49. Katle EJ, Hart H, Kjaergaard T, Kvaloy JT, Steinsvag SK (2012) Nose- and sinus-related quality of life and GERD. Eur Arch Otorhinolaryngol 269(1):121–125
50. Katle EJ, Hatlebakk JG et al. (2017) Gastro-oesophageal reflux in patients with chronic rhinosinusitis investigated with multichannel impedance - pH monitoring rhinology (55):0–0
51. Lin YH, Chang TS, Yao YC, Li YC (2015) Increased risk of chronic sinusitis in adults with gastroesophageal reflux disease. Medicine (Baltimore) 94(39):e1642

52. Brietzke SE, Shi JJ, Cho S et al (2014) Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg 151(4):542–553
53. Orlandi RR, Kingdom TT, Hwang PH et al (2016) International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol 6(suppl1):S22–S209
54. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F et al. (2012) EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology (50):1–12
55. Hellgren J, Olin AC, Toren K (2014) Increased risk of rhinitis symptoms in subjects with gastroesophageal reflux. Acta Otolaryngol 134:615–619
56. Mahdavinia M, Bishehsari F, Hayat W et al (2016)Prevalence of allergic rhinitis and asthma in patients with chronic rhinosinusitis and gastroesophageal reflux disease. Ann Allergy Asthma Immunol 117(2): 158–162
57. Schiöler L, Ruth M, Jõgi R, Gislason T, Storaas T, Janson C, Forsberg B, Sigsgaard T, Torén K, Hellgren J (2015) Nocturnal GERD - a risk factor for rhinitis/rhinosinusitis: the RHINE study. Allergy 70(6):697–702
58. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, Azar A, Baroody FM, Bachert C, Canonica GW, Chacko T, Cingi C, Ciprandi G, Corey J, Cox LS, Creticos PS, Custovic A, Damask C, DeConde A, DelGaudio JM, Ebert CS, Eloy JA, Flanagan CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ, Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M, Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU, Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L, Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL, Tantilipikorn P, Tversky JR, Veling MC, Wang DY, Westman M, Wickman M, Zacharek M (2018) International consensus statement on allergy and rhinology: allergic rhinitis. Int Forum Allergy Rhinol. 8(2):108–352
59. Tordesillas L, Berin MC (2017) Immunology of food allergy. Immunity 47:32–50
60. Stanghellini V, Tosetti C (2016 Apr) Nickel sensitization in patients with gastro-esophageal reflux disease. UEGJ 4(2):184–190
61. Sharma AD (2017) Relationship between nickel allergy and diet. Indian J Dermatol Venereol Leprol 73:307–312
62. Ho MH et al (2014) Clinical spectrum of food allergies: a comprehensive review. Clin Rev Allergy Immunol 46:225–240
63. Branum AM, Lukacs SL. Food allergy among US children: trends in prevalence and hospitalizations. NCHS data brief no 10. Hyattsville, MD: National Center for Health Statistics National Health Interview Survey (NHIS)/CDC Report. 2008
64. Iacono G, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, Soresi M, Notarbartolo A (1996) Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol 97:822–827
65. Cavataio F, Carroccio A, Iacono G (2000) Milk-induced reflux in infants less than one year of age. J Pediatr Gastroenterol Nutr 30(Suppl):S36–S44
66. Kamer B, Chilarski A, Lange A, Piaseczna-Piotrowska A (2000) Gastroesophageal reflux in infants with food allergy. Med Sci Monit 6:348–352
67. Milocco C, Torre G, Ventura A (1997) Gastro-oesophageal reflux and cow's milk protein allergy. Arch Dis Child 77:183–184
68. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Carroccio A (1996) Clinical and pH-metric characteristics of gastrooesophageal reflux secondary to cow's milk protein allergy. Arch Dis Child 75:51–56
69. Niggeman B, Beyer K (2014) Factors augmenting allergic reactions. Allergy 69(12):1582–1587
70. Pali-Scholl I, Jensen-Jarolim E (2011) Anti-acid medication as a risk factor for food allergy. Allergy 66:469–447
71. Untersmayr E, Bakos N, Schöll I, Kundi M, Roth-Walter F, Szalai K, Riemer AB, Ankersmit HJ, Scheiner O, Boltz-Nitulescu G, Jensen-Jarolim E (2005) Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J 19:656–658
72. Mullin JM, Valenzano MC, Whitby M, Lurie D, Schmidt JD, Jain V et al (2008) Esomeprazole induces upper gastrointestinal tract transmucosal permeability increase. Aliment Pharmacol Ther 28: 1317–1325
73. Vesper BJ, Jawdi A, Altman KW, Haines GK 3rd, Tao L, Radosevich JA (2009) The effect of proton pump inhibitors on the human microbiota. Curr Drug Metab. (10):84–9
74. Noval Rivas M, Burton OT, Wise P, Zhang YQ, Hobson SA, Garcia Lloret M, Chehoud C, Kuczynski J, DeSantis T, Warrington J, Hyde ER, Petrosino JF, Gerber GK, Bry L, Oettgen HC, Mazmanian SK, Chatila TA (2013) A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol 131:201–212
75. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, Tjota MY, Seo GY, Cao S, Theriault BR, Antonopoulos DA, Zhou L, Chang EB, Fu YX, Nagler CR (2014) Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A 111(36):13145–13150
76. Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S, Husby S (2004) Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr 39:383–391
77. Yukselen A, Celtik C (2016) Food allergy in children with refractory gastroesophageal reflux disease. Pediatr Int 58:254–258
78. Semeniuk J, Kaczmarski M, Nowowiejska B, Białkoz I, Lebensztejn D (2000) Food allergy as a cause of gastroesophageal reflux in the youngest children. Pediatr Pol 75:793–802
79. Janiszewska T, Czerwionka-Szaflarska M (2003) IgE-dependent allergy: an intensifying factor of gastroesophageal reflux in children and adolescents. Med Wieku Rozwoj 7:211–222