HHS Public Access

Author manuscript

Best Pract Res Clin Gastroenterol. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Best Pract Res Clin Gastroenterol. 2015 October ; 29(5): 721–729. doi:10.1016/j.bpg.2015.06.008.

Environmental and infectious factors in eosinophilic esophagitis

Elizabeth T. Jensen, MPH, PhD[1,2] and **Evan S. Dellon, MD MPH**[1,3,*]

Elizabeth T. Jensen: elizabeth_jensen@med.unc.edu

[1]Center for Esophageal Diseases and Swallowing, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

[2]Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

[3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC

Abstract

Identifying possible environmental or infectious etiologic factors for eosinophilic esophagitis (EoE) may offer insight into opportunities for disease prevention and treatment. We reviewed the current literature to assess environmental and infectious factors evaluated in EoE. Few studies have been conducted, however a consistent inverse association between EoE and *H. pylori* has been described. Several studies suggest a weak association between season and EoE diagnosis, but the evidence is inconclusive. EoE has also been associated with early life factors, including Cesarean delivery and antibiotic use. Larger studies are needed to evaluate these associations more thoroughly. Several papers have speculated the potential for anti-secretory agents to contribute to EoE. This has not been formerly evaluated. In summary, there is significant opportunity in the future to advance our understanding of possible environmental etiologic factors for EoE.

Keywords

eosinophilic esophagitis; etiology; environment; infection; epidemiology; risk factors

Introduction

Much of the literature on eosinophilic esophagitis (EoE) focuses on either clinical aspects of the disease, i.e. diagnosis, treatment, and natural history, or the underlying molecular

[*]corresponding author: Evan S. Dellon MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508, edellon@med.unc.edu.

Author contact information:

Elizabeth T. Jensen MPH, PhD, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 316-4797, Fax: (919) 843-2508

Conflict of interest

No relevant conflicts

pathways for disease development and progression. Additionally, several studies have examined the descriptive epidemiology of EoE (i.e. estimating disease incidence, prevalence and demographic features of affected patients).(1–12) Although these studies have greatly enhanced our understanding of this increasingly common disease,(13, 14) our understanding of etiologic risk factors for disease remains elusive. Studies of genetics have identified several susceptibility loci for disease development,(15–18) and these are described elsewhere in this issue, but recent family studies suggest that relatively little of the disease can be explained by heritability alone.(19) This, together with the rapidly increasing incidence of disease that is not entirely explained by increased diagnostic awareness or volume of upper endoscopy procedures,(9, 12, 20) suggests that environmental factors not only contribute, but likely play a large role in EoE etiology. Understanding which environmental factors contribute to disease development is not simply an academic exercise. Identifying etiologic risk factors for disease offers the opportunity to improve our understanding of disease pathogenesis, thus helping us to identify opportunities for prevention, as well as treatment targets that may interrupt disease course.

In this review, we discuss the literature published to date on environmental and infectious etiologic factors in development of EoE. We focus on the several areas of research that have been explored thus far, including seasonal and geographical differences, possible infectious origins of disease, perinatal and early childhood factors that may contribute, and pharmacologic risk factors, specifically use of anti-secretory agents. In each of these areas of research we discuss the existing evidence in support of these factors contributing to disease development and, where applicable, identify opportunities for future research. While food triggers, may be considered an environmental cause of EoE, a detailed review of the role of allergy and food antigens is beyond the scope of this paper, and this topic is addressed elsewhere in this issue.

Seasonal differences

The question of possible seasonal differences in diagnosis of EoE has been evaluated in several studies. Identifying seasonal differences in the distribution of disease diagnosis would provide support to the literature suggesting that aeroallergens are associated with disease pathogenesis,(21–24) and the subject of aeroallergens is explored in detail elsewhere in this issue. Generally, most of the studies conducted on season and EoE are suggestive of a modest association, typically with an increase in diagnosis in the Summer or Fall months.(12, 25–32) Most of these studies, however, have been conducted at single center sites and were unable to account for possible climate differences (Table 1).

Although seasonal differences in aeroallergens are the most obvious explanation for any association between season and EoE, there are other factors that vary by season, including differences in dietary patterns due to availability of fresh produce and differences in air quality in different seasons. Diet related triggers for EoE have been explored extensively, as these form the basis for food-related therapeutic approaches to treatment for EoE. Air quality factors have not been directly studied in EoE, but have been associated with development of other atopic diseases.(33–35)

Geographic differences

A difference in the geographical distribution of disease has been documented for other gastrointestinal diseases although only a few studies have evaluated this in EoE. Any differences observed could provide clues into possible environmental contributors to disease etiology. A single-center, case control study (n=508 cases, n=508 GI controls, and n=508 allergy controls) conducted in the Greater Philadelphia area observed that patients diagnosed with EoE were more likely to reside in suburban areas when compared to allergy clinic identified controls (adjusted OR: 2.08; 95% CI: 1.22, 3.54).(36) However, no association was found when comparing EoE patients to GI clinic obtained controls (adjusted OR: 0.82; 95% CI: 0.46, 1.45).(36) A case-control study (n=14,381 cases and n=89,754 controls), using a large pathology database with cases from throughout the U.S. identified an association between EoE and population density, with increasingly rural areas exhibiting increasingly higher odds of diagnosis (adjusted OR: 1.41; 95% CI: 1.14, 1.76 for the least populous zip code residences).(37) The association was robust to using a variety of case definitions with increased specificity for EoE. While increased odds of EoE in rural areas is somewhat counter to what has been found in other allergic diseases, a similar finding was noted in a survey study of gastroenterologists and allergists.(38) Another study, from the large national pathology database noted above, observed that the prevalence of EoE varied by climate zone, with cold climate zones exhibiting the greatest odds of disease as compared to temperate climates (adjusted OR: 1.39; 95% CI: 1.34, 1.47).(39)

The implications of this variation in geographical distribution are that there may be environmental factors associated with population density or climate that are contributing to disease etiology, although direct study of these factors is needed. For lower population density areas, there may be agricultural exposures, different foliage patterns, or differences in particulate matter size or species that contribute. These hypotheses are speculative, but these studies provide support for additional investigation.

Infectious origins

Helicobacter pylori

While most studies examining risk factors for EoE have looked for environmental factors that are increasing in association with the increase in EoE, it is also possible to look for something that has been decreasing in the environment. *Helicobacter pylori* is one such potential factor. Since it's identification as a major cause of peptic ulcer disease and gastric cancer, *H. pylori* has been eradicated when found, leading to decreasing rates of colonization and infection throughout the U.S.(40, 41) Additionally, this decrease in *H. pylori* has been associated with the increase of other atopic conditions, including asthma, allergic rhinitis, and atopic dermatitis.(42–45)

Recently, a series of studies has demonstrated that *H. pylori* is also inversely associated with EoE. This observation appears to hold in both adult and pediatric populations and in multiple settings (Table 2).(46–50) For example, in the largest of these studies (n=5,767 cases, n=56,301 controls) which used a national pathology database from biopsies obtained in 41 states throughout the U.S., the odds of EoE among patients with conformed *H. pylori*

infection was 0.79 (95% CI: 0.70, 0.88). While the underlying reason for this inverse association is not known, and causality has yet to be determined in an experimental model, it is possible that lack of *H. pylori* either has a direct effect (Th2 vs Th2 polarization), or that it is a marker for the hygiene hypothesis.(46) The underlying premise for this hypothesis is that the lack of exposure to childhood infections and improved sanitation has caused a lack of immune tolerance.(42, 51, 52) However, whether this applies to EoE has yet to be examined directly. Alternatively, *H. pylori* has also been inversely associated with gastroesophageal reflux disease (53). Given the association between EoE and reflux, it may be that the decrease in *H. pylori* is driven by the inverse association shared between GERD and *H. pylori*. This hypothesis also requires additional future investigation.

Herpes Simplex Virus and other potential infectious etiologies

Case reports of herpes simplex virus (HSV) esophagitis and subsequent development of EoE suggest that there may be a potential link between these two conditions. In a case series from Melbourne, Australia, three children (ages 9–16) presented with herpetic esophagitis.(54) While none had evidence of EoE at the time HSV positive biopsies were obtained from the esophagus, all three developed esophageal eosinophil infiltration consistent with EoE (all had > 30 eos/hpf) within the following 1–2 months. All three patients had history of atopy, suggesting there may have been an underlying predisposition toward EoE. In a similar case report, a 17 year old adolescent with concomitant atopy presented with signs of both herpes esophagitis and EoE at the initial endoscopy.(55) Subsequent biopsy showed increased eosinophils (34 eos/hpf) and the presence of HSV I. Follow-up at 2 and 3 months indicated resolution of HSV but persistent EoE. Despite these isolated cases, as well as ones that report HSV as complicating topical steroid therapy in EoE,(56) additional research is needed to assess the extent to which these conditions co-exist, the temporality in the association between the conditions, and whether herpes simplex esophagitis is a causal agent in susceptible individuals.(57, 58)

Other infections that have been examined in relation to EoE are *mycoplasma pneumonia* and IgE sensitization from tick-borne, galactose-alpha-1,3-galactose (alpha gal). For *m. pneumonia*, 10 of 12 children were IgG positive with serologic testing for *m. pneumonia*. (59) However, further study is needed to establish the seroprevalence of IgG for *m. pneumonia* in controls before any association with EoE can be inferred.

In a case-control study (n=50 cases, n=50 controls), sera biobanked from adult EoE cases and controls undergoing upper endoscopy were evaluated for IgE sensitization for alpha gal. This study found a high rate of sensitization in both cases and controls being seen for upper endoscopy, but no difference between cases and controls in the absolute IgE count or proportion with sensitization (defined as > 0.35 kU_A/L).(60) Therefore, it does not appear that the recent discovery of a tick-induced food allergy is a risk factor for EoE.

Early life factors

To date, few studies have explored early life factors associated with the development of EoE, but based on parallels with other atopic conditions, understanding this critical time period is an important future direction for EoE research. For example, allergic and other

immune-mediated diseases have been hypothesized to be associated with changes in gut microbiota in early life potentially resulting from changes in diet, antibiotic exposure, Cesarean deliveries, infant feeding practices and breast milk exposure, and reduced exposure to microbial disease (the hygiene hypothesis).(46, 61–65) Preliminary data suggest that similar risk factors could be important in EoE. In a case-control study of 31 children with EoE, there was an association between certain early life factors and development of EoE in children.(66) These factors included cesarean delivery, preterm delivery, and antibiotic use in infancy, although only antibiotic use in the first year of life reached statistical significance (OR 6.1, 95% CI: 1.7, 20.8). Another small case control study (25 EoE cases) recently reported similar results, with both cesarean delivery and antibiotic use in the first year of life associated with EoE (OR 3.2 (95% CI 1.2, 8.6) and 3.6 (95% CI 1.3, 10.1) respectively).(67) These studies, although suggestive of the potential for early life factors contributing to disease pathogenesis, were based on data collected from questionnaires and may be subject to recall bias, or, for antibiotic use, subject to confounding by indication. Moreover, there are no studies in EoE that show that an alteration of the microbiome is directly responsive for disease onset. Therefore, additional larger and mechanistic studies are warranted to explore these associations further.

Anti-secretory agents

Because proton pump inhibitors (PPIs) are one of the most commonly used medications (68), were introduced more than 30 years ago around the time of the first cases reports of EoE,(69) and have had markedly increasing use infants in recent years, (70, 71) it is intriguing to speculate whether there is an association between PPIs and EoE. In 2009, Merwat and Spechler commented on the potential for anti-secretory agents to cause EoE. (72) They posited that H2 receptor antagonists and PPIs alter the permeability of the mucosa in the upper gastrointestinal tract and could allow increased uptake of allergens, subsequently leading to recruitment of eosinophils. While this has never been shown in EoE, this hypothesis is informed by studies showing that patients with reflux esophagitis and Barrett’s esophagus taking anti-secretory agents have increased mucosal permeability to sucrose,(73) similar to the increased mucosal permeability seen in animal models following use of an anti-secretory agent.(74) Increased gut permeability, in genetically susceptible individuals, may compromise oral tolerance and lead to development of food allergies. In animal models and human studies, antacid medications have inhibited digestion of dietary proteins and resulted in development of IgE antibodies in response to the dietary protein. (75–77). PPIs have also been associated with hypersensitivity reactions to medications in hospitalized patients.(78) Observational studies have suggested that use of an anti-secretory agent in pregnancy can increase risk of atopic illness in the offspring,(79–81) but the mechanism is unknown. One possibility that has been raised is that maternal use of these agents could interfere with normal digestion of dietary proteins, possibly resulting in preservation of antigens that could be transferred to and induce a Th2 response in the fetus. (82–84)

Because the possible association between anti-secretory agents and EoE has not been formally assessed, this theory remains controversial and there is an active debate in the literature. For example, in one report, there was no evidence of either an absolute increase in

EoE or a dose-response among PPI users after 400 patients undergoing outpatient upper endoscopy were assessed.(85) In contrast, three cases of EoE have been reported following PPI use after an initial diagnosis of either reflux esophagitis or infectious esophagitis.(25, 86) Finally, at least one study has suggested that PPIs can decrease the permeability of the esophageal mucosa in GERD patients.(87) As with many of the potential risk factors of EoE, additional work is needed to clarify the importance of these associations.

Research agenda

- Environmental changes are likely key in the development of EoE, but few studies have been conducted on possible non-food environmental factors that may contribute to the pathogenesis of EoE.
- Recent data have suggested that EoE is associated with seasonality, climate zone, and geographic factors such as population density. However, additional work is needed to determine the specific triggers associated with these factors.
- An inverse association between *H. pylori* and EoE has been demonstrated in a number of studies. Whether this relation is causal, and what mechanisms might underlie this, however, have yet to be investigated.
- Early life factors may contribute to disease development, potentially through immune dysregulation. Two small studies suggest are suggestive of an association with cesarean delivery and antibiotic use in early life, however larger studies are needed.
- Speculation that anti-secretory agents may be associated with EoE is intriguing but controversial, and warrants further investigation. However, confounding by indication and recall bias, as well as the availability of these medications over the counter, will be issues in such studies.

Summary

Identifying etiologic risk factors for EoE offers the opportunity to improve our understanding of disease pathogenesis, thus helping us to identify opportunities for prevention, as well as treatment strategies that may interrupt disease course. Heritability explains relatively little of disease development and thus, environmental factors are important. However, few studies have been conducted on possible environmental factors that may contribute to the pathogenesis of EoE. The studies conducted to date suggest that geography (rural location; cold or arid climate zones), absence of *H. pylori* infection, and early life factors (antibiotic use during infancy; Cesarean delivery), which might alter gut microbiota, are associated with disease development. With few exceptions, most studies conducted have been relatively small, and have not been confirmed by mechanistic investigations. Therefore, the association between environment and EoE is an underdeveloped but important area of research in the field.

Acknowledgments

None

Role of the funding source

This work was supported, in part, by NIH Awards K23 DK090073 (ESD) and U54AI117804 (CEGIR), which is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Disease Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS.

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Table 1

Association between season and eosinophilic esophagitis

Study setting	Study population	Case definition	Case sample size (n)	Study design	Association
Single center study (St. John Hospital and Medical Center, Michigan, U.S.), 2001–2006	Pediatric	≥ 20 eos/hpf	44	Retrospective chart review	No significant difference in season of symptom onset or diagnoses
Single center (University of Iowa, Iowa, U.S.); 2003–2013	Adolescent and adult	≥ 20 eos/hpf	193	Retrospective review of administrative billing data	No significant difference in diagnoses by month or season
Single center study (James Whitcomb Riley Hospital for Children, Indiana, U.S.); 1998–2004	Pediatric	≥ 15 eos/hpf	234	Retrospective chart review	Increased diagnoses in Spring, Summer, and Fall as compared to Winter
Single center (Mayo Clinic, Minnesota, U.S.); 2000–2008	Adult	≥ 20 eos/hpf	372	Retrospective review of patients in EoE registry	Increased diagnoses in December/January and May/June
Single center (Mayo Clinic, Florida, U.S.); 2007–2008	Adult	>20 eos/hpf	41	Retrospective review of pathology reports	Increased diagnoses in Spring and Summer as compared to Fall and Winter
Single center (University of North Carolina School of Medicine, North Carolina U.S.); 2000–2007	Pediatric and adult	≥ 15 eos/hpf	151	Retrospective case-control study from chart and endoscopic report review	Different distribution in season of diagnoses compared to GERD controls and increased diagnoses in Summer and Fall
Multisite (Medical University of Wroclaw, 10 regional centers, Poland); 2004–2009	Pediatric	≥ 15 eos/hpf	84	Retrospective review of pathology reports	Increased diagnoses in Spring and decreased diagnoses in Winter
Single center study (Marshall Health, Tri-state area, U.S.); 2003–2010	Pediatric	≥ 15 eos/hpf	95	Retrospective review of endoscopic reports	No significant difference in diagnoses by season
Single center study (NÄL Medical Centre, Sweden); 2004–2009	Pediatric and adults	≥ 15 eos/hpf	24	Retrospective chart review	Increased incidence of bolus impaction in EoE patients in Fall

Best Pract Res Clin Gastroenterol. Author manuscript; available in PMC 2016 October 01.

Table 2

Association between *Helicobacter pylori* and eosinophilic esophagitis

Study setting	Study population	Case definition	Case sample size (n)	Study design	Association
National, U.S.-based study; 2008–2010	Pediatric and adult	≥ 15 eos/hpf as primary definition for EoE, *H Pylori* identified from gastric specimens	5,767	Cross-sectional, case control study of pathology data	Inverse association
Single center study (Shimane Institute of Health Science, Japan); 2010–2011	Adult	≥ 15 eos/hpf for EoE, *H pylori* established from serology testing	18	Matched, case control study	Inverse association
Single center study (Marshall Health, U.S.); 2007–2012	Pediatric	≥ 15 eos/hpf as primary definition for EoE, *H Pylori* identified from gastric specimens	62	Retrospective chart review	Inverse association
Von armin et al*	Adults	Histologically proven EoE (count unspecified), *H pylori* established from serology testing	58	Matched, case control study (abstract)	Inverse association
Multisite, Kalixanda study (Northern Sweden); 1998**	Adults	Presence of any esophageal eosinophils, *H Pylori* identified from gastric specimens	48	Cross sectional, prevalence study	Inverse association

* Obtained from an abstract, no further details provided

** Year authors report subjects were randomly selected from the general population