Current perspectives

Environmental factors and eosinophilic esophagitis

Elizabeth T. Jensen, MPH, PhD,[a,b] and Evan S. Dellon, MD, MPH[b] *Winston-Salem and Chapel Hill, NC*

The incidence and prevalence of eosinophilic esophagitis (EoE) have markedly increased over the past 2 decades, outpacing increased detection of the disease. Although genetic susceptibility markers for EoE have begun to be elucidated, the rate at which EoE has increased in incidence suggests environmental factors predominate. Despite many advances in understanding of the pathogenesis of EoE, the cause of EoE is unknown. This article reviews the emerging data related to environmental risk factors for EoE. Many of these environmental factors are rooted in the theoretical framework of the hygiene hypothesis, specifically mediation of disease development through dysbiosis. Other hypotheses are based on associations that have been observed in studies of non-EoE allergic disease. We describe the evidence that early-life exposures, including antibiotic use, acid suppression, and cesarean delivery, can increase the risk of disease. We also describe the evidence that infectious agents, such as *Helicobacter pylori*, are inversely associated with disease. Current evidence on geographic risk factors, such as population density, climate zone, and seasonality, is reviewed. We also describe behavioral factors that have been evaluated. Limitations of the existing research are discussed, and recommendations for future areas of research, including assessment of gene-environment interaction, are presented. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: *Environment, early life, microbiome, epigenetics, gene-environment interaction*

Abbreviations used
alpha-gal: Galactose-alpha,1,3-galactose
aOR: Adjusted odds ratio
CTD: Connective tissue disorder
EoE: Eosinophilic esophagitis
HSV: Herpes simplex virus
NSAID: Nonsteroidal anti-inflammatory drug
PPI: Proton pump inhibitor

Eosinophilic esophagitis (EoE) is an immune-mediated[1-6] chronic disease associated with significant morbidity, including dysphagia, food impactions, and, in the pediatric population in particular, food intolerance and faltering growth.[7-13] Disease management can be challenging. No pharmacologic therapies have been approved for the treatment of EoE, and current treatments necessitate dietary elimination strategies, topical steroids, or elemental formula diets. Most patients with EoE have evidence of concomitant atopic illness. However, although specific foods elicit clinical and histologic manifestations of disease for many patients, EoE is not believed to be an IgE-mediated disease.[14,15]

The incidence and prevalence of EoE have increased dramatically since its initial recognition as a unique disease entity just 2 decades ago.[16-20] In the 1990s, when EoE was first described, disease incidence was estimated at just 0.4 cases/100,000/y. Current estimates of disease incidence and prevalence vary but are generally described to be approximately 10 cases/100,000/y, with a prevalence of 50 to 100 cases/100,000.[17,20-23] The economic burden of EoE is substantial. In the United States, where as many as approximately 400,000 persons are affected,[24] the estimated annual health care costs associated with EoE are $1.4 billion.[25]

Although some of this increase can be attributed to increased awareness and surveillance of the disease, incident diagnoses have outpaced the increase in upper endoscopies.[17,20,26] Candidate and genome-wide association studies have identified possible susceptibility genes associated with disease development[27-30]; however, given the rate at which disease incidence has increased, environmental factors are likely implicated in disease pathogenesis. Furthermore, a twin and family study of EoE identified a stronger concordance for EoE between dizygotic twins than in siblings, suggesting that not only do environmental factors contribute but also shared environmental factors experienced in early life might be important to disease cause.[31]

To date, the body of evidence to support the contribution of environmental factors in patients with EoE is still under development, with considerable gaps in knowledge. Much of the existing evidence has focused on early-life factors implicated in patients with other allergic diseases, infectious disease factors,

From [a]the Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Wake Forest Baptist Medical Center, Winston-Salem, and [b]the Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill.

Supported in part by U54AI117804 (CEGIR), which is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Disease Research (ORDR), National Center for Advancing Translational Sciences (NCATS), and is funded through collaboration between the National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, and NCATS. CEGIR is also supported by patient advocacy groups including the American Partnership for Eosinophilic Disorders (APFED) CURED and EFC. This work was also supported by R01DK101856 (to E.S.D.).

Disclosure of potential conflict of interest: E. S. Dellon is a consultant for Adare, Allakos, Alvio, Banner, Enumeral, GlsxoSmithKline, Celgene/Receptos, Regeneron, and Shire; receives research funding from Adare, Meritage, Miraca, Nutricia, Celgene/Receptos, Regeneron, and Shire; and has received educational grants from Banner and Holoclara. E. T. Jensen declares that she has no relevant conflicts of interest.

Received for publication January 18, 2018; revised March 30, 2018; accepted for publication April 24, 2018.

Corresponding author: Evan S. Dellon, MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd, UNC-CH, Chapel Hill, NC 27599-7080. E-mail: edellon@med.unc.edu.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2018.04.015

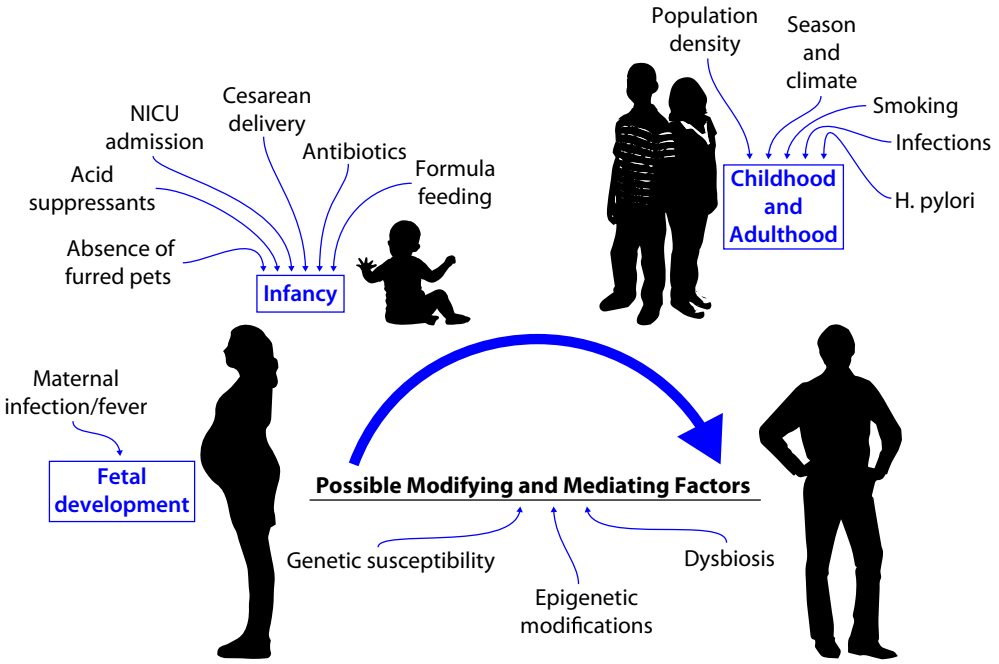

FIG 1. Candidate risk factors for development of EoE. *NICU*, Neonatal intensive care unit.

geographic factors, and behavioral factors, with limited data on the contribution of genetic and epigenetic factors in relation to these environmental factors (Fig 1). This article describes the evidence thus far and provides recommendations for future directions to address these gaps in knowledge (Table I).

ALLERGIC DISEASES, THE HYGIENE HYPOTHESIS, AND THE MICROBIOME

Given the high proportion of patients with EoE with concomitant atopic disease, it is not surprising that the focus of much of the research on environmental factors and EoE has focused on factors implicated in other atopic diseases. As with EoE, the incidence and prevalence of other atopic diseases have also been increased in recent decades. One of the prevailing theories to explain this increase, the hygiene hypothesis, asserts that an overly hygienic environment, although important in the reduction of infectious disease, might have untoward effects on the host-microbiome balance necessary for immune system development. However, this theory has been met with scrutiny and has been adapted recently with advances in our ability to characterize the human gut microbiome.[32-35] Evidence supports the role of the microbiome in establishing immune function health, but it is not necessarily an aseptic environment that is to blame but rather the absence of certain necessary commensal bacteria. Although the microbiome research field is still relatively underdeveloped (ie, technology for characterizing species continues to evolve and our capacity to analyze the complexity of the microbiota remains relatively crude),[36-42] numerous studies have identified differences in microbiota diversity and patterns of relative abundance in association with atopic disease.[43] A challenge in the literature is establishing the temporality of the association, specifically whether the differences observed are attributable to the disease process itself or whether differences in the microbiota lead to the cascade of events that elicit disease development (eg, microbiota-host interactions and alterations in barrier function that contribute to aberrant immune response and loss of antigen tolerance).[44-47]

Although much of the microbiota research initially focused on gut microbiota, the field has expanded to include assessment of the entire human microbiome. Differences in the esophageal microbiome have been described between patients with EoE, patients with gastroesophageal reflux disease, and healthy control subjects,[48] but again, it is unknown whether these differences are driven by disease or whether they preceded disease development. With treatment, the differences between patients with EoE and healthy control subjects has been suggested to diminish, although not completely.[37]

Studies evaluating the use of synbiotics to prevent atopic disease have yielded varied results,[49-51] likely because our understanding of the microbiome and microbiota interactions is relatively immature, establishing which synbiotics confer protection remains elusive.[52] For patients with EoE, a single study conducted in a murine model identified a beneficial effect of the probiotic *Lactococcus lactis* NCC 2287 on esophageal inflammation.[53] Because only a few studies of the esophageal microbiome have been conducted, this is an area where further research is needed to establish the significance, if any, of the esophageal microbiome in disease pathogenesis.

EARLY-LIFE FACTORS AND EoE

EoE can develop in infancy but is observed more frequently later in childhood and sometimes into adulthood. Thus it might not be readily apparent how factors experienced in early life could contribute to disease development later in life. However, early life is a period of unique developmental susceptibility, and immune maturation might be sensitive to early-life experiences.[54,55] Furthermore, it has been suggested that EoE might be part of the atopic march continuum, appearing later in the cascade of atopic illnesses frequently coexisting in childhood.[56]