

Early Infant Risk Factors for Pediatric Eosinophilic Esophagitis

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See “Early Life Factors and Eosinophilic Esophagitis: Building the Evidence” by Jensen and Gupta on page 549.

ABSTRACT

Objectives: Eosinophilic esophagitis (EoE) is an inflammatory, atopic disease of the esophagus without a clear etiology. Our objective was to identify exposures and conditions in early infancy associated with the development of EoE.

Methods: A case-control study was performed using the Military Health System Database. Subjects diagnosed with EoE from October 2008 to September 2015 were matched 1:2 on age and sex. Early infant risk factors from the first 6 months of life were investigated.

Results: A total of 1410 cases with EoE were matched to 2820 controls. The median (interquartile range) age at diagnosis of EoE was 4.2 years (2.1–7.2) and 68.7% were boys. Proton pump inhibitors (adjusted odds ratio [aOR], 2.73; 95% confidence interval [CI] 1.93–3.88), histamine-2 receptor antagonists (aOR, 1.64; 95% CI 1.27–2.13), and antibiotics (aOR, 1.31; 95% CI 1.10–1.56) were associated with EoE. Prematurity (aOR, 1.46; 95% CI 1.12–1.89) and early manifestations of atopic disease such as milk protein allergy (aOR, 2.37; 95% CI 1.26–4.44) and eczema (aOR, 1.97; 95% CI 1.64–2.36) were related to increased odds for EoE. Erythema toxicum in infancy was strongly associated with a diagnosis of EoE (aOR 3.52; 95% CI 1.03–12.04). Infants with feeding difficulty (aOR, 1.45; 95% CI 1.18–1.77) and gastroesophageal reflux disease (aOR, 1.79; 96% CI 1.43–2.26) were also at increased risk for EoE.

Conclusions: Acid-blocking medications and antibiotics during infancy were associated with later diagnosis of EoE. Erythema toxicum neonatorum, an eosinophilic immune phenomenon, was strongly associated with EoE. Identifying early infant risk factors for EoE may help to risk stratify the need for endoscopy.

Key Words: antibiotics, atopic disease, eosinophilic esophagitis, erythema toxicum neonatorum, infancy, proton pump inhibitor

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What Is Known

- Eosinophilic esophagitis is associated with other atopic diseases.
- Early infancy exposures can modify the risks for atopic conditions.
- Antibiotics and acid-blocking medications are frequently prescribed in infancy, and antibiotics have been linked to an increased risk for eosinophilic esophagitis in a few studies.

What Is New

- Early exposure to antibiotics and acid-blocking medications are associated with increased odds for pediatric eosinophilic esophagitis.
- Erythema toxicum neonatorum, an eosinophilic proliferation and proinflammatory response, is a risk factor strongly associated with eosinophilic esophagitis.
- Among the atopic diseases examined, milk protein allergy was the most strongly associated with eosinophilic esophagitis.

Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus that is characterized by chronic eosinophilic inflammation and fibrosis, leading to esophageal dysfunction. A child with EoE may experience feeding intolerance, dysphagia, food impaction, abdominal pain, or vomiting (1,2). This nonspecific constellation of symptoms can result in delayed diagnosis or underdiagnosis, ultimately impacting growth and development (3). The prevalence of EoE has been increasing worldwide over the last decade, although the pathogenesis is still not widely

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understood (4–6). One study in Australia estimated an increase in prevalence from 0.05 to 0.89 cases per 10,000 patients over the last decade (5). In 1 reported US cohort, there was a 70-fold increase in the prevalence of EoE from 1994 to 2011 (6). The current estimate of prevalence in children and adults in the United States is about 1 in 2000 (7,8).

EoE has often been described as an atopic phenomenon, and its rise in prevalence occurs simultaneously with the rise of asthma, eczema, and food allergies (9,10). Allergists and immunologists have carefully studied how environmental triggers for atopic diseases set off a cellular infiltration predominated by eosinophils and T cells, the latter of which are responsible for the Th2 cytokine response (10–12). A unifying mechanism for the disruption of epithelial barriers and subsequent inflammation that occurs in EoE, eczema and asthma remains under investigation. For EoE in particular, Sherrill et al (13) has suggested that the disruption of esophageal epithelium may come from a reduced expression of an intracellular adhesion protein known as desmoglein-1. Leung et al (14) examined gastric and intestinal permeability in patients with EoE compared to controls, finding no significant difference in their lactose to mannitol ratios in urine. The authors hypothesized that, rather than a more distal change in permeability, an abnormal expression of esophageal barrier proteins may play a role in local immune response (14). This disruption is important because chronic exposure to environmental antigens in the esophagus can eventually result in fibrosis and dysfunction (10,11).

When disruptions occur in the gut epithelium, there is also a delay in the natural immunologic processes for healthy bacterial colonization (15). There is an intimate connection between early changes in the gut microbiome and the development of atopic diseases (15–17). As an example of the significance of these shifts in the microbiome, multiple studies have demonstrated atopic diseases associated with early microbiome-altering events such as children born via Cesarean section (15,18,19). Jensen et al (6) also demonstrated a 6-fold increase in EoE in children exposed to antibiotics in early infancy.

There continues to be a gap in knowledge when it comes to early infant exposures and their role in the development of EoE. Some studies have looked only at risk factors in childhood rather than infancy, depend on family recall, or are unable to demonstrate clinical significance due to limited enrollment (6,20–22). The objective of this retrospective case-control study was to identify the exposures and conditions in early infancy that are associated with the development of pediatric EoE.

METHODS

A case-control study of patients in the TRICARE Management Activity's Military Health System (MHS) database was performed. TRICARE is the United States health insurance program for all uniformed service members and their beneficiaries. The MHS database is comprised of data on inpatient admissions, outpatient visits, and outpatient prescriptions from both military and civilian medical facilities. To be eligible for the study, all subjects had to have a birth record in the MHS between October 1, 2001, and September 30, 2014. They also had to be enrolled for >1 year (Figure 1). Cases of EoE were defined by querying the MHS databases for both outpatient and inpatient billing records for the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 530.13. This ICD-9-CM code for EoE was first implemented in the MHS starting October 1, 2008. Case definitions were limited for the time period of October 1, 2008, to September 30, 2015. The study population of patients with EoE included only those who had a birth/maternal record, those who had been followed in the MHS since birth, and those who were

diagnosed with EoE after 6 months of life. Using a computer generated random number, patients with EoE were then matched 1:2 to controls by sex (due to male predominance of EoE) and by date of birth. Controls were also required to have the same or longer enrollment time as their match with EoE. The institutional review board reviewed and approved this study design.

The early infant risk factors that were investigated, by definition, had to occur during the first 6 months of life. They were defined by using ICD-9-CM billing codes or American Hospital Formulary Service therapeutic class codes, as listed in Supplemental Table 1 (Supplemental Digital Content, <http://links.lww.com/MPG/B472>). Perinatal exposures evaluated included prematurity (<37 weeks gestation), Cesarean section delivery, chorioamnionitis, and prolonged rupture of membranes. The atopic and miscellaneous infancy conditions included eczema, seborrheic dermatitis, erythema toxicum neonatorum (ETN), milk protein allergy, hematochezia, asthma, esophageal reflux, feeding problems, infantile colic, and oral candidiasis. Early infancy medication exposures were examined using outpatient pharmaceutical coding records from the MHS and defined categorically as any prescription medication with a pharmacy fill data before 6 months of age. The medications of interest included all outpatient antibiotics, proton pump inhibitors, and histamine-2 receptor antagonists. Dosing or patient weight information was not available.

Statistical Analyses

Univariate and multivariable conditional logistic regression was performed to calculate both unadjusted and adjusted odds ratios (OR and adjusted odds ratio [aOR]) with a 95% confidence interval (CI). The dependent variable was EoE and the various maternal, perinatal, medication, atopic, and miscellaneous binary variables were included as independent variables. An additional model was evaluated after creating a categorical variable for acid suppressing medication exposure with 4 levels (no exposure, H2RA only, PPI only, or H2RA and PPI exposure). *P* values <0.05 were considered statistically significant. Statistical analysis was conducted using SAS software 9.3 (SAS Institute, Cary, NC).

RESULTS

There were 1,111,611 patients in the MHS cohort that met criteria based on enrollment and date of birth. Exclusions were made based on the criteria listed above, and displayed in Figure 1. The final study population included 1410 children with EoE, matched to 2820 controls. By design, patients were matched by sex and 68.7% were boys. The median age of diagnosis of EoE was 4.2 years with an interquartile range of 2.1 to 7.2 years, and range of 0.5 to 13.7 years. Table 1 presents the characteristics of children with and without EoE.

In adjusted conditional logistic regression, there was a statistically significant increased risk of developing EoE with certain medication exposures, perinatal exposures, and medical diagnoses in the first 6 months of life (Table 2). In regards to medication exposure, patients exposed to proton pump inhibitors or histamine-2 receptor antagonists were more likely to develop EoE, with an aOR of 2.73 (95% CI 1.93–3.88) and 1.64 (95% CI 1.27–2.13), respectively. There was an incremental increase in odds when exposed to H2RA, PPI, and both acid suppression medications, when compared to no acid suppression at all. The OR for H2RA compared to no acid suppression medication was 1.63 (95% CI 1.23–2.16), the OR for PPI compared to no acid suppression medication was 2.64 (95% CI 1.53–4.55), and the OR for both H2RA and PPI compared to none was 4.56 (95% CI 2.88–7.20). Antibiotic exposure also was statistically significant, but had a

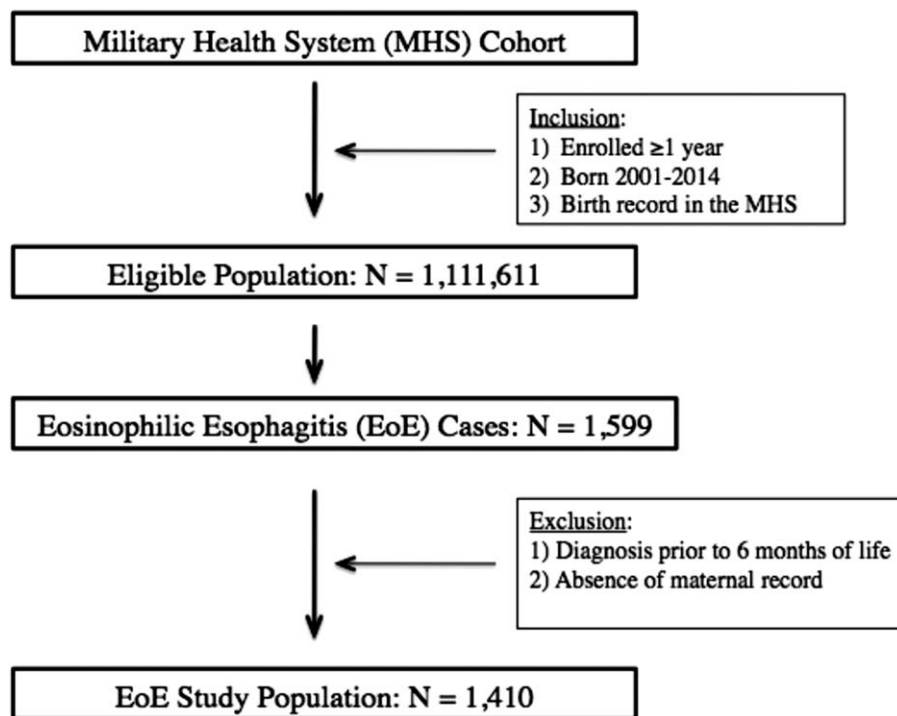


FIGURE 1. Study design for the retrospective case-control study of patients with eosinophilic esophagitis in the TRICARE Management Activity's Military Health System (MHS) database.

lower aOR than the acid suppression medications, at 1.31 (95% CI 1.10–1.56).

Some factors related to perinatal exposure also were noted to be significant predictors of EoE. The odds of developing EoE were 46% higher for premature infants than for term infants (aOR, 1.46; 95% CI 1.12–1.89). Although Cesarean section was associated with EoE in unadjusted analysis (OR, 1.27; 95% CI 1.09–1.47), we

found no significant association after adjusting for other variables (aOR, 1.14; 95% CI 0.97–1.34). Pregnancies complicated by either chorioamnionitis or prolonged rupture of membranes (likely markers for prenatal exposure to antibiotics), were not found to be associated with EoE (aOR, 1.08; 95% CI 0.84–1.39).

Within the category of early atopic disease risk factors, milk protein allergy and hematochezia had the highest risk for EoE, with

TABLE 1. Characteristics and exposures of children with eosinophilic esophagitis and matched controls

Risk Factors	EoE cases (n = 1410)	Controls (n = 2820)
Medication exposure		
Antibiotics	409 (29%)	548 (19%)
Proton pump inhibitor	184 (13%)	73 (3%)
H2R antagonist	383 (27%)	280 (10%)
Perinatal exposures		
Male	969 (69%)	1938 (69%)
Prematurity	168 (12%)	187 (7%)
Cesarean section delivery	418 (30%)	710 (25%)
Chorioamnionitis/prolonged rupture	135 (10%)	217 (8%)
Markers of atopic disease		
Eczema	386 (27%)	422 (15%)
Seborrheic dermatitis	168 (12%)	186 (7%)
Milk protein allergy	54 (4%)	17 (0.6%)
Hematochezia	61 (4%)	37 (1%)
Asthma/wheeze/bronchiolitis	215 (15%)	304 (11%)
Miscellaneous		
Esophageal reflux	504 (36%)	397 (14%)
Feeding problems	315 (22%)	345 (12%)
Fussy infant/infantile colic	124 (9%)	145 (5%)
Oral Candidiasis	48 (3%)	81 (3%)
Erythema toxicum neonatorum	11 (0.8%)	4 (0.1%)

TABLE 2. Unadjusted and adjusted conditional logistic regression results for the diagnosis of eosinophilic esophagitis

Risk Factors	Unadjusted odds ratio	Adjusted odds ratio
Medication exposure		
Antibiotics	1.73 (1.48–2.01)	1.31 (1.10–1.56)
Proton pump inhibitor	6.42 (4.72–8.73)	2.73 (1.93–3.88)
H2R antagonist	3.76 (3.12–4.53)	1.64 (1.27–2.13)
Perinatal exposures		
Prematurity	1.95 (1.56–2.44)	1.46 (1.12–1.89)
Cesarean section delivery	1.27 (1.09–1.47)	1.14 (0.97–1.34)
Chorioamnionitis/prolonged rupture	1.27 (1.02–1.60)	1.08 (0.84–1.39)
Markers of atopic disease		
Eczema	2.21 (1.88–2.60)	1.97 (1.64–2.36)
Seborrheic dermatitis	1.91 (1.54–2.39)	1.59 (1.24–2.04)
Milk protein allergy	6.35 (3.68–10.96)	2.37 (1.26–4.44)
Hematochezia	3.30 (2.19–4.96)	1.94 (1.20–3.14)
Asthma/wheeze/bronchiolitis	1.51 (1.25–1.82)	1.08 (0.87–1.36)
Miscellaneous		
Esophageal reflux	3.53 (3.01–4.15)	1.79 (1.43–2.26)
Feeding problems	2.15 (1.81–2.57)	1.45 (1.18–1.77)
Fussy infant/infantile colic	1.79 (1.40–2.31)	1.02 (0.76–1.37)
Oral candidiasis	1.19 (0.83–1.71)	0.96 (0.64–1.44)
Erythema toxicum neonatorum	5.50 (1.75–17.27)	3.52 (1.03–12.04)

an aOR of 2.37 (95% CI 1.26–4.44) and 1.94 (95% CI 1.20–3.14), respectively. Other atopic skin manifestations with aORs indicating increased risk of EoE included eczema (aOR, 1.97; 95% CI 1.64–2.36) and seborrheic dermatitis (aOR 1.59; 95% CI 1.24–2.04). Wheezing and bronchiolitis did not meet statistical significance based on the adjusted logistical regression.

The miscellaneous category of potential risk factors included multiple diagnoses related to feeding as well as some skin disorders. ETN was the most strongly associated with EoE, with an aOR of 3.52 (95% CI 1.03–12.04). Esophageal reflux had the next highest aOR at 1.79 (95% CI 1.43–2.26), while diagnoses related to feeding difficulty had an aOR of 1.45 (95% CI 1.18–1.77). The miscellaneous risk factors that did not meet statistical significance based on the adjusted logistical regression included oral candidiasis and infantile colic.

DISCUSSION

This case-control study of 1410 patients with EoE revealed a statistically significant association between EoE and certain medical conditions in infancy, as well as certain medication exposures. Data analysis demonstrated an increased risk of developing EoE after exposure to proton pump inhibitors, histamine-2 receptor antagonists, and antibiotics in the first 6 months of life. Proton pump inhibitors were associated with the highest risk for EoE. Acid-blocking medications are frequently prescribed in infancy due to esophageal reflux, subjective feeding difficulty, or, less commonly, poor growth. Infantile reflux can sometimes be a manifestation of food allergy or milk protein allergy, which is also associated with EoE. One should also consider the possibility that the prescription of these medications could be a marker for treatment of early manifestations of EoE. An interesting finding was the incremental increase in odds for EoE when an infant was exposed to H2RA alone, PPI alone, then both medications in the first 6 months of life. Although true causation cannot be inferred in this case, it may be worth considering whether early exposure to acid-blocking medication and antibiotics potentially alters the developing gut microbiome and immune development, which may relate to this increased

risk for EoE. As previously mentioned, the Jensen et al study of 127 infants with EoE also demonstrated a significant association with antibiotic use and acid suppression in infancy (22).

In regards to perinatal exposures, data analysis showed an increased risk for developing EoE in children who are born prematurely. A potential explanation for this association would be the differences in the gut microbiome and gut permeability between term and preterm infants (15,17). This association in premature infants possibly could be explained by sensitization caused by exposure to oral antigens (such as milk) prior to epithelial maturity. Various studies already have demonstrated an increased risk for asthma in premature infants, but fewer have examined a link to other atopic disease (14,23,24). Cesarean section and maternal chorioamnionitis (as markers for perinatal exposure to antibiotics) were significant in univariate logistic regression analysis but were not statistically significant in the adjusted analysis. Three studies previously reported an association between Cesarean section and EoE (6,21,22). The lack of association found in our much larger study likely can be explained by the additional conditions and variables that were included and found to be more strongly associated with EoE, yet also associated with Cesarean section.

EoE is known to be linked with atopic conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergies (25,26). Our results demonstrate that this association relates to early infancy as well. Infants who displayed early markers of atopic disease were more likely to be diagnosed with EoE later in childhood. Among atopic diseases, milk protein allergy was the most strongly associated with EoE, followed by hematochezia. Hematochezia is a common manifestation of milk protein allergy in infants, so this association likely represents a complementary surrogate marker for the identified association of EoE with a diagnosis of milk protein allergy during infancy. Eczema and seborrheic dermatitis also were associated with increased odds for EoE.

Breathing difficulties in infancy, including bronchiolitis and wheezing, did not demonstrate an association with EoE. This finding could be explained by the relative rarity of asthma in younger infants, or other likely non-atopic causes of wheezing in infancy, such as viral bronchiolitis.

A novel finding from our study is the identified association of EoE with ETN, which had an unadjusted OR of 5.5 and an aOR of 3.5 for developing EoE. ETN has been described as a common benign rash in the newborn period that resolves within the first few weeks of life (27). It is characterized by papules and pustules with erythematous halos. It is interesting that these eruptions are defined by eosinophilia, both within the pustules and on skin scrapings, and less commonly in the peripheral blood (7%–15% of cases) (27). Although the pathophysiology of ETN remains unknown, it has been proposed to be related to proinflammatory mediators, such as interleukins and nitric oxide synthases, which are thought to be generated in response to the colonization of microbes within the newborn hair follicles during the first day of life (27,28). The role of microbial colonization in the development of ETN is further supported by reports that both Cesarean section and colonization with coagulase-negative *Staphylococcus* have been associated with ETN (29). It is possible that the connection between ETN and EoE may result from a combination of both dysbiosis, whether cutaneous or intestinal, and a genetic predisposition towards eosinophilic immune dysregulation. A greater fundamental understanding of the connection between genetic predisposition, environment (such as effects on the microbiome), and the eosinophilic immune dysregulation of EoE may lead to early preventive targets.

Finally, gastroesophageal reflux disease and feeding difficulty were associated with increased odds of EoE. As discussed earlier regarding acid suppression medications, gastroesophageal reflux can be a manifestation of food allergy. Both gastroesophageal reflux and feeding difficulties can be symptoms of EoE in infants. Thus, it is possible that this association may simply represent early and undiagnosed EoE. Early food allergies can also present with reflux, which may later lead to the development of EoE in childhood.

EoE is a challenging disease to diagnose, due to the variety of nonspecific symptoms and the large age window for disease presentation. One study in older children demonstrated an average of 5 years between symptom onset and diagnosis (30). It is possible that time frame is longer in younger children who are unable to communicate their symptoms (31,32). Consequences of delayed diagnosis include poor growth and developmental delay, as well as increased risk of stricture formation and food impaction (31,32). Better understanding infant risk factors may be key to diagnosis.

In this study, we were limited by our reliance on ICD-9-CM codes for identification of risk factors and the outcome of EoE, which can lead to misclassification bias. EoE is a histological diagnosis, and this study design does not allow for a review of biopsy results or a confirmation that endoscopy was performed after a trial of PPI. Finally, the medication exposure in this study was defined by prescription fill data, rather than parent reporting, which would not account for partial or complete non-adherence to prescribed medications.

The strengths of this study come from the large demographically and ethnically diverse population. Our sample size is the largest to have assessed early infant risk factors for EoE, and the young age of our study population is unique. While the average age at diagnosis for pediatric EoE is 10 to 11 years old (7,8), our population has an average age of 4 years old. The young average age at diagnosis is likely the result of the study design, as patients had to be born between 2000 and 2014, as well as the structure of the military-dependent population. The military tends to have a larger population of young parents with younger children. Fortunately, the MHS is a universal healthcare system, known for accessibility and good follow-up, which limits access-to-care bias. This is especially important for the 0 to 6 month visits, which occur during the period of interest in our study.

In conclusion, exposure to acid-blocking medication and antibiotics is associated with an increased risk for the pediatric EoE. Providers may consider prescribing these medications more

judiciously in early infancy, or maintaining a higher level of suspicion for EoE among these patients. Among symptomatic children, early atopic conditions and/or feeding difficulty in infancy may help raise suspicion for EoE and risk stratify the need for invasive testing for conclusive diagnosis. Conceptually, identifying early risk factors for the development of EoE may lead to improved understanding of the underlying pathogenesis, as well as more targeted prevention and interventions.

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