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The 2010–2015 Prevalence of Eosinophilic Esophagitis in the United States: A Population-based Study

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Abstract

Background & Aims—Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder with increasing prevalence. However, epidemiologic data has mostly been acquired from small studies. We sought to describe the epidemiology of EoE in the United States, utilizing a large database.

Methods—We queried a commercial database (Explorys Inc, Cleveland, OH), an aggregate of electronic health record data from 26 major integrated US healthcare systems from 1999 to July 2015. We identified an aggregated patient cohort of eligible patients with EoE and a history of proton pump inhibitor use between July 2010 to July 2015, based on Systematized Nomenclature Of Medicine – Clinical Terms (SNOMED-CT). We calculated the prevalence of EoE among different patient groups.

Results—Of the 30,301,440 individuals in the database, we identified 7,840 patients with EoE with an overall prevalence of 25.9/100,000 persons. Prevalence was higher in males than females (Odds Ratio [OR] 2.00; 95% CI=1.92–2.10, p<0.0001), Caucasians vs. African-Americans and Asians (OR 2.00; 95% CI: 1.86–2.14, p<0.0001) and adults (18–65yrs) vs. elderly (>65yrs) and children (<18yrs) (OR 1.63; 95% CI: 1.54–1.71, p<0.0001). Compared with controls (individuals in database without EoE), individuals with EoE were more likely to have other gastrointestinal diagnoses such as dysphagia and at least one allergic condition.

Conclusions—In this large study, we found that the estimated prevalence of EoE in the US is 25.9/100,000, which is at the lower end of prevalence rates reported in US and other industrial countries. We confirmed that EoE has a strong association with allergic and gastrointestinal diagnoses.

Keywords

eosinophilic esophagitis; epidemiology; prevalence

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Background and Aims

Eosinophilic esophagitis (EoE) is a disease that is clinically defined by symptoms related to esophageal dysfunction and pathologically defined by >15 eosinophils/high power field in one or more biopsy specimens of the esophagus in the absence of other causes of esophageal eosinophilia [1]. First described in 1978 [2], EoE has become increasingly common in both adults and children with recent studies showing increasing incidence and prevalence [3–6]. Numerous studies in the United States and other industrial countries have reported prevalence rates of EoE in the adult and pediatric population, which have ranged from 2.3 to 400 cases per 100,000 in various time frames between 1976 to 2014 [4–17]. However, most of these studies were niche studies, specific to some locations, and have many limitations, including small sample sizes and referral bias.

Although there have been three recent epidemiological studies in EoE [7,16,17] utilizing large databases, we added previous proton-pump inhibitor (PPI) exposure to the case definition of EoE to exclude cases of PPI-responsive esophageal eosinophilia (PPI-REE) [1,18], to make our estimate of prevalence more precise. We sought to describe the epidemiology of EoE in the United States (US), and identify associated disorders by using a population-based database. The aims of the study were to identify cases of EoE, identify other disorders associated with EoE, assess differences in comorbidities between adults and children with EoE, estimate overall prevalence of EoE in US and among different age-based, race-based and gender-based subgroups. These data will help better define the epidemiology of EoE.

Methods

Database

We performed a retrospective analysis of a large population-based, commercial database (Explorys Inc, Cleveland, OH). This database contains an aggregate of Electronic Health Record (EHR) data from 26 major integrated healthcare systems spread over 50 states in the US from 1999 to 2015. Explorys contains de-identified patient data from participating institutions and uses a health data gateway (HDG) server behind the firewall of each participating healthcare organization that collects de-identified data from various health information systems—EHR using billing inquiries. Data are then standardized and normalized by Explorys. As such diagnoses, findings, and procedures are mapped into the Systematized Nomenclature Of Medicine – Clinical Terms (SNOMED–CT) hierarchy while prescription drug orders are mapped into SNOMED (to represent the pharmacological class) and RxNorm (to represent the drug itself). Each participating healthcare institution has access to Explorys online (password protected), which provides for browsing of the data from all participating healthcare institutions. Explorys data are automatically updated at least once every 24 hours [19]. Explorys is a Health Insurance Portability and Accountability Act (HIPAA) compliant platform and thus Institutional Review Board (IRB) is not required.

Patient selection

Using the Explorys search tool, we identified an aggregated patient cohort of eligible patients with EoE. EoE patients were defined as those having a SNOMED-CT diagnosis of "eosinophilic oesophagitis" with an RxNorm prescription of "proton-pump inhibitor", at any point between July 2010 to July 2015. PPI use was included in the definition to ensure that cases of PPI-REE are excluded and only true cases of EoE are captured [1,18] since there is no separate SNOMED-CT diagnostic code for PPI-REE. SNOMED-CT diagnosis for GERD was not used as exclusion criteria since consensus criteria for EoE provide for overlap between EoE and GERD [18].

Associated medical conditions of interest

We identified multiple medical conditions and medications associated with EoE, as demonstrated by prior studies [1,5,6,7,8,12]. Data on these conditions, which included GI and allergic disorders, was extracted by using SNOMED-CT diagnostic terms for these disorders. The associated GI disorders that were studied included GERD, heartburn, dysphagia, esophageal stricture, chest pain, foreign body in esophagus, nausea and vomiting, esophageal web, failure to thrive, esophageal perforation, Barrett's esophagus, eosinophilic gastritis and eosinophilic colitis. The associated allergic disorders that were studied included any allergic condition, drug allergy, rhinitis, asthma, sinusitis, dermatitis, food allergy, eczema and urticaria. The associated medications that were studied included antihistamines, histamine receptor 2 (H2) antagonists and topical form steroids and data on these was extracted by using SNOMED terms for pharmacologic class.

Statistical Analysis

For patients with EoE, demographics, associated diseases and medications were characterized by descriptive statistics. Bivariate analysis was done to assess the differences in associated medical conditions in patients with EoE and patients without EoE by using the Pearson Chi-square test. Bivariate analysis was also carried out to assess the differences in associated medical features of children with EoE (aged under 18 yrs) and adults with EoE (aged 18 yrs and above) by using the Pearson Chi-square test.

For calculation of overall period prevalence, we identified all patients in the database with EoE from July 2010 to July 2015. We then divided this number by the total number of patients in the database (from July 2010 to July 2015), thus making sure that all patients in the denominator (population at risk) had an equal opportunity of being diagnosed with EoE if they had the disease. Similarly, age-based, gender-based and race-based prevalence rates were calculated. The confidence intervals for prevalence rates were calculated using the Wald method for calculation of confidence intervals for single proportions [20].

The Odds Ratio (OR), its standard error and 95% confidence interval were calculated according to Altman, 1991 using the MedCalc Statistical Software [21] using a case-control design.

It should be mentioned that as a measure to protect the identities of patients, Explorys rounds cell counts to the nearest 10, and treats all cell counts <10 as equivalent to zero.

Results

A total of 30,301,440 individuals in the database from July 2010 to July 2015 made up the source population. Of these, 7,840 had at least 1 SNOMED-CT diagnosis of EoE and an RxNorm prescription of PPI and represented the EoE case group. 5,660 individuals, from July 2010 to July 2015, had at least 1 SNOMED-CT diagnosis of EoE but did not have an RxNorm prescription of PPI and thus were excluded from analysis. This was done to ensure that cases of PPI-responsive esophageal eosinophilia (PPI-REE) are excluded and only true cases of EoE are captured [1,18].

In the EoE case group, the majority were male (61.9%), Caucasian (89.3%), and aged 18 to 65 years (74.5%) (Table 1). The overall period prevalence was 25.9 (95% CI: 25.3–26.5) per 100,000 persons. The prevalence in male patients was twice as high as prevalence in female patients (35.8 vs 17.8/100,000), (OR=2.00, 95% CI: 1.92–2.10, p<0.0001). The prevalence of EoE was highest in Caucasians (compared to Asians and African Americans) at 36.7/100,000 (OR=2.00, 95% CI: 1.86–2.14, p<0.0001), followed by Asians (compared to Caucasians and African Americans) at 28.2/100,000 (OR=0.85, 95% CI: 0.77–0.93, p=0.0008) and African Americans (compared to Caucasians and Asians) at 13.9/100,000 (OR=0.39, 95% CI: 0.35 to 0.42, p<0.0001) (Table 2).

The prevalence was highest in the adult population (between 18 to 65 yrs of age) at 30.0/100,000 (OR=1.63, 95% CI: 1.54–1.71, p<0.0001) compared to children and elderly, followed by children (<18 yrs) at 25.1/100,000, (OR=0.97, 95% CI: 0.91–1.03, p=0.2580) compared to adults and elderly, and elderly (>65 yrs) at 12.8/100,000 (OR=0.44, 95% CI: 0.40–0.48, p<0.0001) compared to children and adults (Table 2).

Association of EoE with other medical disorders

Among GI symptoms and associated disorders (Table 3), individuals with EoE, were more likely than controls to have GERD, heartburn, dysphagia, esophageal strictures, chest pain, foreign body in esophagus, nausea and vomiting, esophageal webs, failure to thrive, esophageal perforation, Barrett's esophagus, eosinophilic gastritis and eosinophilic colitis. Among allergic disorders (Table 3), individuals with EoE, were also more likely than controls to have at least one allergic condition, drug allergy, rhinitis, asthma, sinusitis, dermatitis, food allergy, eczema and urticaria.

When children (under 18 yrs of age) were compared with adults (aged 18 yrs and older) (Table 4), among the GI disorders, they were less likely to have GERD, heartburn, dysphagia, esophageal strictures, chest pain, foreign body in esophagus, esophageal webs, esophageal perforation and Barrett's esophagus. However, children were more likely to have eosinophilic gastritis, eosinophilic colitis, and failure to thrive. There was no significant difference in the prevalence of nausea and vomiting.

When children (under 18 yrs of age) were compared with adults (aged 18 yrs and older) (Table 4), among allergic disorders, they were less likely to have drug allergy and sinusitis, however they were more likely to have at least one allergic condition, food allergy, rhinitis, asthma, dermatitis, eczema and urticaria.

Overall, 70.7% received antihistamines, 25.8% received H2 antagonists and 16.6% received topical form steroids.

Discussion

Over the last few years, EoE has become a significant cause of GI morbidity in children and adults with studies showing increasing incidence and prevalence [3–6]. However, most of the epidemiological studies that have provided prevalence estimates on EoE have been small in size. The objective of our study was to estimate the prevalence of EoE in the US using a large database. We used SNOMED-CT diagnosis to identify cases of EoE from the Explorys database. This methodology has been used in the past by Dellon et al [7] to estimate the prevalence of EoE using ICD-9 codes through a large health plan claims database. While, ICD-9 and SNOMED-CT are both medical terminology systems for recording medical diagnoses and concepts, SNOMED-CT has many more concepts to be coded per clinical document than ICD-9 [22] which makes it more accurate in terms of enlisting pertinent clinical information.

We estimated the prevalence of EoE to be 25.9/100,000 in the US. The overall prevalence estimate in our study does fall in the same order of magnitude of prevalence rates reported in other studies in the past, thereby lending empiric validity to our study. The Explorys methodology has been used in the past by Maradey-Romero C et al [17] to determine the prevalence of EoE in the elderly population. However, they studied a source population of 10 million individuals over a period of 3 years from January 2011 to January 2014. Our study included a much larger source population of 30 million individuals over a period of 5 years from July 2010 to July 2015. While Maradey-Romero C et al estimated the prevalence of EoE in the US to be 50.6/100,000, almost twice as much as our estimate, this difference can be attributed to the differences in the case definition of EoE as well as the size of source population. While we defined individuals with EoE as those having a SNOMED-CT diagnosis of EoE with an RxNorm prescription of PPI to exclude cases of PPI-REE [1,18], they defined EoE individuals as those having a SNOMED-CT diagnosis of EoE. Given that there is no separate SNOMED-CT code for PPI-REE, the addition of PPI use to the case definition might make our estimate more precise. With regards to the size of source population, when we defined individuals with EoE as those having a SNOMED-CT diagnosis of EoE, the overall prevalence was 44.6/100,000 individuals, lower than the prevalence reported by Maradey-Romero C et al. The inclusion of two more years in our study led to a disproportional increase in the total sample population compared to the number of EoE cases, suggesting that the incidence of EoE might have decreased.

We performed sensitivity analysis of the case definition of EoE. When individuals with EoE were defined as those having a SNOMED-CT diagnosis of EoE, the overall prevalence increased from 25.9 to 44.6/100,000 individuals. Rybnicek et al [23] found the ICD-9 530.13 code for EoE (equivalent of the SNOMED-CT code for EoE) to be 37% sensitive and 99% specific for diagnosis for EoE. Given that we included history of PPI use in our case definition, we might have underestimated the prevalence of EoE by increasing specificity.

Smaller studies in the past have estimated the prevalence rates of EoE among the pediatric population between 2.3–89/100,000 [4,7,8,9,11,13]. In our study, we estimated the prevalence in children (under 18 yrs of age) to be 25.1/100,000. In the adult population (18–65 yrs of age), we estimated the prevalence of EoE at 30/100,000, while previous studies in literature have reported prevalence rates ranging from 9.5–56.7/100,000 [6,7,8,12,15,16,17]. Multiple factors likely contribute to the variation in prevalence rates among studies, some of which include methods of data collection, data analyses, case definition of EoE and regional variation of EoE. Given that in our study we had large numbers of both the EoE cases and total number of individuals in the database, our estimate of prevalence might be more precise. However, a direct comparison with previous studies for prevalence estimates would not be possible because of the difference in the time period over which prevalence was estimated (ranging from point prevalence to period prevalence over more than a decade).

We also found that EoE has a male predominance, it is more common in adults (18 to 65 yrs of age) and also is found predominantly in the Caucasian population. These features of EoE have been reported in the literature [1,24]. Previous studies have reported familial clustering of EoE, thereby pointing towards a genetic predisposition [4]. Subsequently, multiple studies [25,26,27] have proposed genetic markers for EoE, however, none of the genetic markers identified yet has been shown to be conserved across males and/or Caucasians to justify higher prevalence in these groups.

Recent studies have shown that prevalence of EoE is higher in Northeastern and urban areas [14] and in cold and arid zones [28], lending credibility to regional and seasonal variation of EoE. However, while we did not look at region-wise burden of EoE, it is safe to assume that regional differences in gender and race distribution cannot alone account for male and Caucasian predominance of disease. Furthermore, health institutions affiliated with Explorys cover all 50 states and span the East, Midwest, South, Central and West divisions of the US [19], thus providing a broad regional and climatic distribution of source population. Further genetic, environmental and behavioral studies are needed to understand the higher prevalence in males and Caucasians.

Furthermore, we found that EoE is strongly associated with high rates of GI and allergic disorders. Given the large sample size, all the differences that were statistically significant may not be clinically meaningful. However, these associations have been described in the past by other studies [1,5,6,7,8,12,24,29]. These co-morbid disorders can serve as surrogate markers of presence of EoE and should trigger evaluation for disease. However, data is lacking on association of co-morbid GI and allergic disorders with endoscopic or histologic severity of the disease. The high prevalence of allergic disorders in EoE patients in our study has been demonstrated in previous studies [12], however, per consensus guidelines [1], individuals with EoE should be referred for evaluation by an allergist and thus there is an inherent bias in patients with EoE having high rates of allergic co-morbidities.

Co-existent eosinophilic gastritis and eosinophilic colitis were found in 1.3% and 0.4% of individuals with EoE respectively. Compared to EoE, they are rare diseases [30] and their exclusion from the case definition would not have had a significant impact upon the overall prevalence of disease in adults and children.

We further compared the differences in frequencies of allergic and GI disorders between adults and children. We found that while GI disorders were more commonly associated with adults with EoE, allergic disorders were more commonly associated with children with EoE. The predominance of allergic disorders in children with EoE could be due to underlying environmental factors such as Western lifestyle, higher levels of personal hygiene leading to decreased exposure to infection in early life, high body weight in early childhood and changes in gut microflora, lending support to the “hygiene hypothesis” [31,32]. Conversely, it would be interesting to speculate that the relatively low frequency of allergic disorders in adults with EoE could point towards a higher contribution of genetic factors [25–27] in the pathogenesis of EoE in the adult population.

Looking at the medications prescribed for patients with EoE, a significant proportion received antihistamines, presumably for co-existent allergic disorders. One-sixth received topical form steroids. Per the American College of Gastroenterology (ACG) guidelines, the initial treatment of EoE is 8 weeks of topical steroids (swallowed rather than inhaled) [18]. The likely reasoning for the low proportion of EoE patients on steroids would be that the SNOMED-CT diagnosis of EoE does not distinguish between incident and prevalent cases and that topical form steroids are prescribed for initial treatment in incident cases but not for prevalent cases especially if they are asymptomatic.

This study has a few limitations that should be acknowledged. First, with regards to the estimate on EoE prevalence, we might have underestimated the true prevalence since not all individuals with EoE are brought to medical notice. Moreover patients who used over the counter (OTC) PPIs and were diagnosed with EoE might have been missed by our algorithm, thus leading to underestimation of prevalence. We could also have underestimated the true prevalence of EoE since the SNOMED-CT diagnostic code for EoE was not validated clinically so individuals might have been misclassified, validation of the SNOMED-CT diagnostic code for EoE was not possible since the patient information in the database is de-identified. On the other hand, we could have overestimated the overall prevalence since our source population included 89% of Caucasians and EoE has increased prevalence in this race group.

However, this is countered by the fact that our study found EoE to have male, Caucasian and adult (18–65 yrs.) predominance with high rates of GI and allergic concomitant diagnoses which is expected for EoE patients [1,24]. Furthermore, the case definition of EoE included history of PPI use to exclude cases of esophageal eosinophilia secondary to GERD and PPI-REE, thus ensuring that only true cases of EoE are captured as per the updated consensus recommendations for EoE [1,18].

Besides misclassification, another limitation of this study is the inability to capture information that is unavailable in the Explorys database. This includes information about socioeconomic status, geographic data on patient population, endoscopic abnormalities, histology reports, and specific indications for medications prescribed.

Moreover, although Explorys uses a master–patient identifier to match the same patient across different healthcare institutions and combine the data [33], a few patients may have

received care in multiple institutions within Explorys healthcare partners and thus could have been counted multiple times. However, this is countered by the fact that Explorys uses a robust patient matching algorithm [33] and thus the effect of this error might be minimal and might affect the EoE and control group equally.

Finally, due to the de-identified nature of information, we were unable to look at specific dates due to which our analysis was based on the prevalence of EoE throughout the 5-year study period. Thus, our study did not distinguish between patients with EoE responsive to treatment and EoE refractory to treatment.

Conversely, this study has its strengths as well. This is a large database that has demonstrated to be precise in the past with incidence estimates of other disorders [33]. This database has provided one of the largest sample of EoE cases yet to be reported in literature.

In summary, the analysis of one of the largest samples of EoE cases so far, from the large commercial database Explorys, estimates the prevalence of EoE in US to be 25.9/100,000 persons. This estimate is at the lower end of estimates reported by smaller studies in literature. However, for a recently diagnosed entity that was first reported in 1978 [2], this estimate signifies a high burden of disease. Further studies are needed to delineate reasons for the evolving epidemiology of EoE.

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Table 1

Demographic Characteristics of EoE Cases

Total number of EoE cases, n	7840
Male, n (%)	4850 (61.9)
Age group	
Children (<18 yrs. of age), n (%)	1250 (15.9)
Adults (18 to 65 yrs. of age), n (%)	5840 (74.5)
Elderly (>65 yrs. of age), n (%)	750 (9.6)
Race	
Caucasian, n (%)	7000 (89.3)
African American, n (%)	480 (6.1)
Asian, n (%)	440 (5.6)

Table 2

Prevalence of EoE in the Explorys Database between July 2010 to July 2015:

Group	Source Population	EoE cases, n (%)	Prevalence (per 100,000)
Overall	30,301,440	7840 (100)	25.9 [95% CI: 25.3–26.5]
Male	13,536,470	4850 (61.9)	35.8 [95% CI: 34.8–36.8]
Female	16,764,970	2990 (38.1)	17.8 [95% CI: 17.2–18.4]
Children (<18yrs.)	4,967,040	1250 (15.9)	25.1 [95% CI: 23.8–26.4]
Adults (18–65yrs.)	19,437,830	5840 (74.5)	30.0 [95% CI: 29.2–30.8]
Elderly (>65yrs.)	5,850,430	750 (9.6)	12.8 [95% CI: 11.9–13.7]
Caucasian	19,065,180	7000 (89.3)	36.7 [95% CI: 35.9–37.5]
African American	3,447,610	480 (6.1)	13.9 [95% CI: 12.7–15.1]
Asian	1,561,330	440 (5.6)	28.2 [95% CI: 25.6–30.8]

Table 3

Clinical Features of EoE Cases vs Controls (individuals without EoE):

Diagnoses	EoE Cases, n (%)	Controls, n (%)
GI Diagnoses[1]		
GERD	5120 (65.3)	7,420,150 (10.2)
Heartburn	600 (7.6)	224,260 (0.7)
Dysphagia	6180 (78.8)	673,390 (2.2)
Esophageal stricture	1960 (25)	103,470 (0.3)
Chest pain	2110 (26.9)	3,293,360 (10.7)
Foreign body in esophagus	920 (11.7)	28,230 (0.1)
Nausea and vomiting	1510 (19.3)	1,216,320 (3.9)
Esophageal web	420 (5.4)	19,930 (0.06)
FTT (Failure to thrive)	270 (3.4)	144,600 (0.5)
Esophageal perforation	60 (0.8)	2300 (0.007)
Barrett's esophagus	380 (4.8)	107,010 (0.3)
Eosinophilic gastritis	100 (1.3)	480 (0.002)
Eosinophilic colitis	30 (0.4)	540 (0.002)
Allergic Diagnoses[2]		
Allergic condition	5260 (67.1)	7,802,410 (25.3)
Drug allergy	3130 (39.9)	5,802,650 (18.9)
Rhinitis	2750 (35.1)	2,214,140 (7.2)
Asthma	2290 (29.2)	2,383,590 (7.8)
Sinusitis	2270 (29.0)	2,538,420 (8.3)
Dermatitis	2060 (26.3)	2,482,670 (8.0)
Food allergy	1590 (20.3)	646,170 (2.1)
Eczema	1490 (19.0)	1,624,530 (5.3)
Urticaria	380 (4.8)	353,600 (1.1)
Medications		
Antihistamines	5500 (70.2)	
H2RB	2020 (25.8)	
Topical form corticosteroids	1300 (16.6)	

[1] p-values (by Pearson Chi-square test) for all GI Diagnoses were <0.0001.

[2] p-values (by Pearson Chi-square test) for Allergies Diagnoses were <0.0001.

Table 4

Clinical Features of Adults with EoE (aged 18 yrs and above) and Children with EoE (aged under 18 yrs):

Diagnoses	Adults, n (%)	Children, n (%)
GI Diagnoses[3]		
GERD	4340 (65.9)	780 (62.4)
Heartburn	550 (8.3)	50 (4.0)
Dysphagia	3810 (57.8)	370 (29.6)
Esophageal stricture	1910 (29.0)	50 (4.0)
Chest pain	2000 (30.4)	110 (8.8)
Foreign body in esophagus	860 (13.0)	60 (4.8)
Nausea and vomiting	970 (14.7)	200 (16.0)
Esophageal web	410 (6.2)	20 (1.6)
FTT (Failure to thrive)	50 (0.8)	210 (16.8)
Esophageal perforation[4]	50 (0.8)	0 (0.0)
Barrett's esophagus[5]	380 (5.8)	0 (0.0)
Eosinophilic gastritis	70 (1.1)	30 (2.4)
Eosinophilic colitis	20 (0.3)	10 (0.8)
Allergic Diagnoses[6]		
Allergic condition	4320 (65.6)	940 (75.2)
Drug allergy	2780 (42.2)	350 (28.0)
Food allergy	980 (14.9)	610 (48.8)
Rhinitis	2230 (33.8)	520 (41.6)
Asthma	1750 (26.6)	530 (42.4)
Sinusitis	1960 (29.7)	310 (24.8)
Dermatitis	1530 (23.2)	530 (42.4)
Eczema	1080 (16.4)	420 (33.6)
Urticaria	280 (4.2)	100 (8.0)
Medications		
Antihistamines	4530 (68.7)	970 (77.6)
H2RB	1650 (25.0)	380 (30.4)
Topical form corticosteroids	1030 (15.6)	270 (21.6)

[3] p-values (by Pearson Chi-square test) for all GI Diagnoses were <0.0001 except for GERD (p=0.019), nausea and vomiting (p=0.24) and eosinophilic colitis (p=0.009).

[4] Esophageal perforation and

[5] Barrett's esophagus: These associated diagnoses had positive events in adults and zero events in children and thus tests of statistical significance were not applied to these.

[6] p-values (by Pearson Chi-square test) for all Allergies Diagnoses were <0.0001 except for sinusitis (p=0.0004).