

An allergic phenotype and the use of steroid inhalers predict eosinophilic oesophagitis in patients with asthma

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SUMMARY

Background

Patients with eosinophilic oesophagitis (EoE) commonly have asthma and atopy.

Aims

To determine the predictive factors of EoE in patients with asthma.

Methods

A retrospective analysis of a large database identified 156 asthma patients with EoE and 276 patients without EoE between 2000 and 2010. Clinical and laboratory characteristics were first analyzed in half of each group. Significant differences and modelling were then applied to the other half of each group in a split half analysis.

Results

Odds ratios and *P*-values found to predict the presence of EoE in asthma patients were: allergic vs. non-allergic asthma (4.07, <0.01), food allergies (45, <0.01), allergic rhinitis (2.13, =0.01) and peripheral eosinophilia (4.51, <0.01). The use of inhaled corticosteroids was negatively associated with EoE (0.41, <0.01) for asthma patients and (0.37, *P* < 0.01) for allergic type asthma patients. EoE patients were also younger (27.4 vs. 41.6 years old, *P* < 0.01). By logistic regression analysis, allergic asthma, presence of peripheral eosinophilia and use of inhaled steroids remained significant. From these parameters, a 3.5-point scoring system model for EoE in asthma was formed with an ROC = 0.787 on split analysis.

Conclusions

In descending order, peripheral eosinophilia, allergic asthma and allergic rhinitis are associated with EoE in patients with asthma. Steroid inhalers appear to have a protective effect against EoE. An accurate and simple scoring system can be used as a screening tool to predict the presence of EoE in patients with asthma and dysphagia. EoE should be viewed as part of a generalised allergic phenotype rather than isolated oesophageal disease.

Aliment Pharmacol Ther

INTRODUCTION

The interaction between pulmonary and oesophageal diseases has long been appreciated. In particular, there are studies outlining the complex pathophysiologic interactions between gastro-oesophageal reflux in patients with severe asthma. Recently, however, another oesophageal disease, eosinophilic oesophagitis has been found to be frequently associated in patients with asthma.

Primary eosinophilic oesophagitis (EoE) is an allergic disease generally defined by oesophageal symptoms, and oesophageal eosinophilic infiltration in the absence of documented gastro-oesophageal reflux disease and other oesophageal diseases associated with eosinophilic infiltration. It has been proposed that oesophageal eosinophilia develops in response to exposure of the oesophageal epithelia to specific antigens likely in the background of a genetic predisposition. The prevalence of this disease is estimated to occur in 0.23 - 4/1000 of the general population.¹ It has a classic phenotype occurring more commonly in male Caucasian children and young adults with dysphagia and a personal and family history of atopic disorders. It has characteristic endoscopic findings and responds to avoidance of specific food antigens and/or steroid therapy.² Predictive factors for EoE in patients with dysphagia have been identified and include male sex, younger age, food impaction and endoscopic findings suggestive of EoE.² While asthma, allergic rhinitis and allergic dermatitis have been associated with EoE, the predictors of EoE in patients with asthma have not been carefully evaluated.

Asthma is a common disease present in 8% of the US adult population³ and in up to 50% of EoE patients.² It would be important to determine which demographic, clinical and laboratory factors amongst asthmatics are predictive of EoE. This will facilitate screening for this disease and permit differentiation from gastro-oesophageal reflux. Moreover, as there is both animal model and clinical data to suggest that airway inflammation is a potential priming mechanism for eosinophilic oesophagitis,^{4, 5} it would be helpful to know if control of airway allergy might have therapeutic potential for eosinophilic oesophagitis. In this study, we analysed these factors in a large population of patients with asthma to determine common and predictive factors of eosinophilic oesophagitis. We also developed a predictive model based on a simple scoring system of these factors as a means of determining which patients with asthma and dysphagia are likely to have EoE.

METHODS

Retrospective analysis of a Mayo IRB-approved searchable patient database (Enterprise Data Trust Query) of all Mayo Clinic patients was used to identify patients with asthma and a diagnosis of eosinophilic oesophagitis (EoE) between January 2000 and January 2010. Patients were identified by searching the database for the keywords 'eosinophilic oesophagitis' or 'EoE' and 'asthma' documented in the past medical history, history of present illness, impression/report/plan, final diagnosis or pathology report. Exclusion criteria for the EoE and asthma group included lack of biopsy proven EoE defined by 15 eosinophils/ HPF (high power field). The same Mayo database was utilised to identify asthma patients without a diagnosis of EoE. The database was searched for subjects with the key word 'asthma' in the past medical history or diagnosis note sections and without the keywords 'eosinophilic oesophagitis' or 'EoE' present. The latter identified a total of 99 007 patients. Two controls per case were randomly selected from the asthma only group. There were 314 subjects selected with 38 patients subsequently excluded due to lack of clear documentation of asthma. This group was then divided into two equal groups. In the first group (I), a primary analysis was performed with formation of a predictive model. In the second group (II), the model was applied to validate the model score and to determine reproducibility by a split half analysis.

Data gathered by chart review for both groups included age, gender, use of inhaled corticosteroids, type of asthma (allergic vs. non-allergic), peripheral eosinophilia and diagnosis of other atopic diseases (allergic rhinitis, atopic dermatitis, eczema, urticaria and food allergies). For the EoE group, additional data gathered included pathology specimen eosinophil count, and peripheral eosinophilia at time of EoE diagnosis. Peripheral eosinophilia was defined as an absolute eosinophile count of $0.50 \times 10^{-9}/L$. Allergic asthma was defined as asthma with positive skin prick testing, specific IgE to aeroallergens or documentation of asthma exacerbations with specific allergen triggers. Non-allergic asthma was defined as documented asthma with negative tests for aeroallergens and no allergic triggers clinically. The presence of allergic rhinitis, eczema, atopic dermatitis and urticaria were defined by physician-documented diagnosis or a standardised Mayo Clinic patient/family history form. The presence of food allergy was defined as a positive history of food allergy and elevated specific IgE to food allergen or by skin prick test. Family history was by the physician or on a standardised Mayo Clinic patient/

family history form. If data were not available for the variable in question, the subject was considered not to have the disease. Oesophageal eosinophilia was defined by a peak eosinophil level of 15 or more eos/hpf on oesophageal biopsy using a 40× objective with standard field area and diameter. Oesophageal biopsy protocols changed in 2006 at our institution from obtaining four mid-oesophageal biopsies to obtaining eight biopsies, four mid-proximal and four distal oesophageal. All specimens were read by one of five specialised gastrointestinal staff pathologists familiar with the histological diagnosis of EoE.

Analysis

Data were analysed using JMP version 9.0.1 statistical software (SAS, Cary, NC, USA). The subjects were randomised into two groups (split analysis). For Group I, odds ratios and Chi-squared analysis was used for the categorical independent variables. Statistical significance was achieved for $P < 0.05$ (two-tailed). Fisher's exact test was used for three independent variables (atopic dermatitis, eczema and urticaria) due to low subject numbers. Five independent variables were identified with statistical significance in the univariate analysis which also had less than 10% missing values. These were further assessed in a single multivariate logistic regression model. To create a predictive model easy enough to use at the point of care, the coefficients from the multivariate model were rounded to an easy-to-remember number (i.e. 1, 1.5, 2). This maintained the relative value of the variables from our model while providing a score a physician could easily calculate while working with a patient. Two versions of the calculated score were created initially to ensure that the rounding accurately reflected the original multivariate score. The model was then applied to Group II to validate the model.

Finally, to assess the final EoE risk score, we used logistic regression. The outcome, EoE plus asthma vs. asthma alone, was predicted by only the EoE risk score. On the basis of this model, we calculated a receiver-operated characteristic (ROC) plot with area under the curve. From this plot, we identified cut-offs discriminating scores into high, moderate and low-risk groups.

RESULTS

Association of demographic, clinical and laboratory parameters with EoE

From the database, there were 156 patients with asthma and EoE and 276 patients with asthma but without

EoE. The mean age of the EoE and asthma group was 27.24 (1–79) years and for the asthma only group, 41.6 (1–93) years. There was a decreasing prevalence of EoE with increasing age in the EoE and asthma group (Figure 1). For example, only 12% (19/156) of subjects in the EoE and asthma group were older than 50 with 42% between the ages of 0 and 20 (66/156). One hundred and forty six of 156 (93.6%) patients with EoE had dysphagia. Thirteen of the patients with EoE had a normal endoscopic appearance with abnormal histology. The initial group was then split into two cohorts: group I (development group) and group II (validation group). The demographic comparisons of group I are summarised in Table 1. Using Chi-squared analysis in group I (78 patients with EoE and asthma and 138 control patients with asthma alone), the following factors were significantly predictive of the EoE given the presence of asthma (Table 1): allergic type asthma, personal history of food allergies or rhinitis, and peripheral eosinophilia. Male gender approached significance. On the other hand, when food allergy was strictly defined as requiring a documented positive food challenge, these values were not significant ($P = 0.66$, Odds ratio: 0.201). This may be due to the few patients with food allergy in the subjects studied (55% EoE and asthma group vs. 4% asthma only group). Similarly, differences in history of urticaria and atopic dermatitis between the EoE and asthma group and the asthma only group did not reach statistical significance although odds ratios were elevated. The use of corticosteroid inhaler was negatively associated with eosinophilic oesophagitis in patients with asthma (Odds

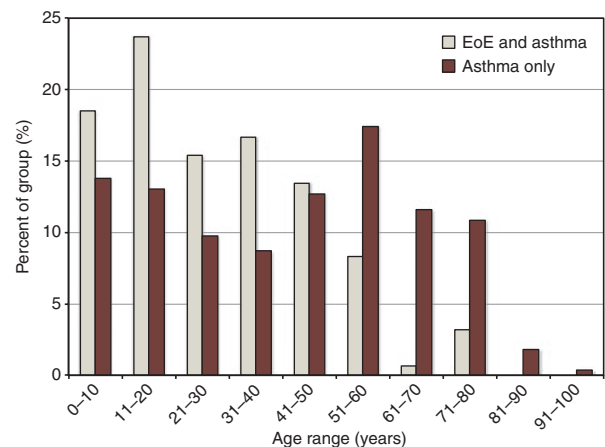


Figure 1 | Age distribution of all subjects in the study.

Predictor	Group I EoE and Asthma (N = 78) N (% of cohort)	Group I Asthma only (N = 138) N (% of cohort)	OR (95% CI), P
Male vs. Female	45 (49.07) vs. 33 (50.03)	61 (44.20) vs. 77 (55.8)	1.72 (0.98–3.02), 0.058
Allergic asthma	36 (46.15)	24 (17.39)	4.07 (2.18–7.61), <0.001
Peripheral EOS	48 (48.71)	24 (17.39)	4.51 (2.42–8.43), <0.001
Inhaled steroid use	26 (33.33)	76 (55.07)	0.41 (0.23–0.73), 0.002
Allergic rhinitis	55 (70.15)	73 (52.3)	2.13 (1.18–3.84), 0.012
Eczema	13 (16.67)	17 (12.32)	1.42 (0.65–3.11), 0.376
Atopic dermatitis	5 (6.41)	6 (4.35)	1.51 (0.45–5.11), 0.510
Urticaria	4 (5.12)	4 (2.30)	1.81 (0.44–7.45), 0.411
Food allergy	39 (50.0)	3 (2.17)	45.00 (13.19–153.51), <0.001
Family history of asthma	32 (41.02)	52 (37.68)	1.15 (0.65–2.03), 0.628
Family history of allergies	15 (19.23)	18 (12.04)	1.59 (0.75–3.36), 0.227

Table 1 | Group I (development cohort) demographic, clinical, and laboratory factor comparison between the EoE and asthma group and the asthma only group. The univariate analysis results are also listed

ratio of 0.41, $P < 0.01$). Furthermore, when patients were analysed according to allergic asthma vs. patients with allergic asthma with EoE, the use of a corticosteroid inhaler by the allergic asthma group demonstrated a lower odds ratio (OR: 0.37, $P < 0.01$).

Multivariate analysis model of variable predictive of eosinophilic oesophagitis in asthma

Multivariate logistic regression examined the influence of the independent variables (allergic asthma, peripheral eosinophilia, use of inhaled corticosteroid, presence of allergic rhinitis and male gender) upon the dependent variable (diagnosis of EoE). The multivariate regression comparing the five aforementioned variables demonstrated the following results (Table 2): allergic asthma- OR: 3.19, <0.01, peripheral eosinophilia- OR: 4.99, <0.01 use of inhaled corticosteroid- OR: 0.29, <0.01. Male gender and the presence of allergic rhinitis were not significantly different.

Table 2 | Multivariate model predicting EoE in asthma patients

Predictor	Group I/Development cohort (N = 216) OR (95% CI), P
Male	1.66 (0.87–3.17), 0.122
Allergic asthma	3.19 (1.57–6.47), 0.001
Peripheral EOS	4.99 (2.42–10.18), <0.001
Inhaled steroid use	0.29 (0.14–0.57), <0.001
Allergic rhinitis	1.46 (0.73–2.90), 0.285

Predictive model and development of an eosinophilic oesophagitis risk score in patients with asthma complaining of dysphagia

Based on the estimated coefficients of the three variables described earlier that were found to be significant, two predictive models were constructed with slight differences in assigned weights for peripheral eosinophilia (peripheral eosinophilia = 1 vs. 1.5, Table 3). Individual scores using both versions were then calculated for each subject in both groups.

Application of the model to asthma patients by split analysis

The scoring system created was applied to Group II (validation group) and a total score for each subject was calculated. Then a correlation plot comparing the probability of EoE against both versions for each subject was calculated (version 1 = 0.93 and version 2 = 0.94). Based on the slightly higher correlation when compared with version 1, version 2 was chosen.

A ROC curve (Figure 2) was created comparing the presence of EoE with the total calculated score (0–3 1/2

Table 3 | Final multivariate model predicting EoE in asthma patients. This model was then applied to Group II, the validation group

Predictor	Coefficient	Score 1	Score 2
Allergic asthma	1.2699	1	1
Peripheral EOS	1.6076	1	1.5
No inhaled steroid use	1.2849	1	1

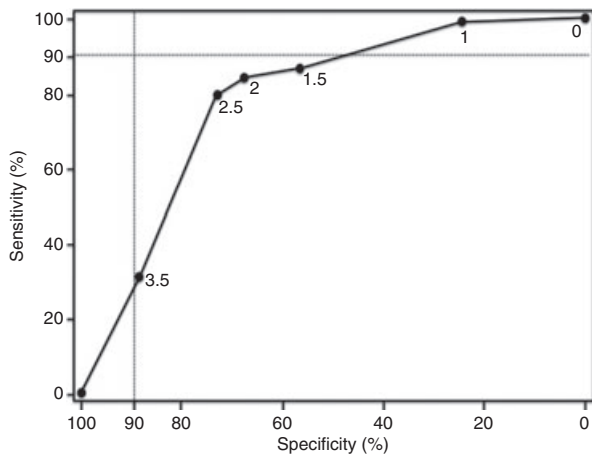


Figure 2 | ROC comparing the presence of EoE with the total calculated score. Reference lines demonstrate the 90% sensitivity and specificity cut-offs for creating the high, moderate and low-risk categories.

points) and the sensitivity, specificity and probability of detecting EoE for each scoring level were identified. Cut-offs were also established to stratify patients into low, moderate and high-risk groups. As a result, on the basis of this scoring system, patients with asthma could be classified as low (0–1 points), moderate (1.5–2.5 points) or high-risk (3.5 points) to have eosinophilic oesophagitis. When evaluating the odds ratio of the ROC curve, which compared the final EoE risk score with the patients' actual EoE status, the odds ratio was calculated at 3.24. Thus, the odds of a subject having EoE tripled for every point added to the EoE risk score. The area under the curve was calculated at 0.787.

DISCUSSION

Eosinophilic oesophagitis is becoming a common disease not only because of increased recognition but also because of a true increase in the disease itself.^{2, 6} Although, eosinophilic oesophagitis is commonly associated extra-oesophageal allergic disorders in 28–86% of adults and 42–93% of paediatric patients,^{2, 6–16} the main clue to finding eosinophilic oesophagitis is in their presentation with dysphagia that is severe enough to require endoscopic evaluation. As a result, patients with this disease are commonly identified when advanced disease in terms of stricture formation or occurrence of food impaction have already become manifest. It would be helpful if specific subset populations could be screened for eosinophilic oesophagitis before advanced disease develops by using various clinical and laboratory criteria.

In this study, examining a relatively large population of patients with combined asthma and eosinophilic oesophagitis, we were able to identify specific criteria and devise a predictive model that significantly increases the chances of finding eosinophilic oesophagitis in patients with asthma. Specifically, the presence of allergic-type asthma, peripheral eosinophilia and allergic rhinitis significantly increased the odds ratios of having eosinophilic oesophagitis. Male gender approached significance. Predominance of male gender in and finding of allergic rhinitis with EoE have been well documented.^{2, 9} On the other hand, the finding of specifically allergic type asthma and peripheral eosinophilia in EoE are novel. In our study, the presence or allergic type asthma increased the chances of having eosinophilic oesophagitis almost four fold over non-allergic asthma.

The finding of marked peripheral eosinophilia in almost 50% of patients with asthma and oesophageal eosinophilia was striking. As expected, the majority of these patients (58%) also had allergy-type asthma. Elevation of blood eosinophils is common in asthma with some correlation with activity of disease.¹⁷ This high prevalence of eosinophilia is more than one would expect in stable asthma or eosinophilic oesophagitis alone, however. In eosinophilic oesophagitis, peripheral eosinophilia is uncommon often not noted in many series of eosinophilic oesophagitis patients. Why such a relatively high prevalence of peripheral eosinophilia occurs in this combined population of eosinophilic oesophagitis and asthma patients is unclear but may serve as a valuable marker for the presence of both diseases as it does for atopic diseases in general.

One of the intriguing findings of our study was the possible protective effect of inhaled steroids on having eosinophilic oesophagitis. In the animal model of eosinophilic oesophagitis, oesophageal eosinophilia develops when the animal is first primed by an initial infection such as airway exposure to *aspergillus fumigatus*.⁴ Similarly, in adults, several types of data suggest a similar priming mechanism of the oesophagus through respiratory infection and /or allergy. Such data include the epidemiologic occurrence of airway allergies such as asthma and rhinitis on average 10 years prior to development of eosinophilic oesophagitis⁵ and a potential allergy seasonal predilection for diagnosis or flare of eosinophilic oesophagitis.^{5, 12} Our data support these hypotheses by demonstrating that inhaled steroids significantly decrease the chances of finding eosinophilic oesophagitis, particularly in patients with allergy type asthma. Although one might suggest that some of this protection is derived

from incidental swallowing of inhaled steroids, it is important to note that in our opinion this incidental swallowing is unlikely to deliver the level of steroid doses delivered directly to the oesophageal mucosa that are used to treat eosinophilic oesophagitis.¹⁸ Whether or not an approach to therapy of eosinophilic oesophagitis using pharmacologic and/or environmental control of airway allergic disease will be clinically useful would be interesting to explore.

With this data, we were able to construct a predictive model for the presence of eosinophilic oesophagitis in patients with asthma. Specifically, devising a scoring system using the criteria of allergic asthma, history of peripheral eosinophilia, no use of inhaled steroid, we were able to construct a predictive model that yielded close to 90% specificity for inclusion of disease with maximum points and an accurate negative predictive value when no criteria were met. Furthermore, we were able to apply this scoring system to a second group of asthma and asthma/EoE patients with equal accuracy.

Use of this scoring system could have many applications. For example, it will encourage those physicians who care for patients with asthma with these predictive factors to specifically ask about dysphagia and their subsequent needs for endoscopy. Whether this scoring system will be useful in all patients with asthma with or without dysphagia has yet to be determined although not all our patients with EoE had dysphagia. This scoring system when highly positive may also obviate a first step of EoE consensus guidelines, that is performing pH monitoring systematically to rule out gastro-oesophageal reflux as a cause of oesophageal eosinophilia. It is also hoped that the predictive factors discussed in this model might become applicable to other atopic diseases associated with eosinophilic oesophagitis.

This study has several limitations. First, it is a retrospective chart review study covering a 10 year period where there could be variation in the reporting and diagnosing eosinophilic oesophagitis. As a result, it is difficult to determine how reliably our data reflect the disease of asthma as a whole. The second limitation of this study is the referral bias that occurs with allergic type asthma patients being referred to an allergist and therefore much more likely to be tested for peripheral eosinophilia and allergy testing. This could skew our data towards these findings and allow our data to appear more robust than it is. There is also a referral bias in terms of which types of asthma patients obtain care at a tertiary outpatient referral centre such as the Mayo Clinic. We

therefore cannot be completely reassured that the two groups of approximately 400 patients used in this study reflect asthma patients as a whole. The EoE risk score should be studied in a nonreferral population to better assess its value for such patients. Third, we did not strictly define eosinophilic oesophagitis by standard criteria including systematic evaluation for gastro-oesophageal reflux.² On the other hand, one would not expect the young age and allergic phenotypes found to be more likely associated with reflux disease. If we were to be strict, this would be classified as oesophageal eosinophilia rather than eosinophilic oesophagitis. Lastly, is the bias of endoscopy in this study. Although some patients may have undergone endoscopy for other reasons and EoE was suspected by the endoscopic appearance of the oesophagus, it is probably the majority of the EoE patients that had oesophageal biopsies performed because of dysphagia. Therefore, our investigation primarily evaluates asthma patients with symptomatic EoE. It is important to consider, however, the likelihood of many asthma patients with subclinical EoE who have compensated for their dysphagia and do not routinely bring it to the attention of their physician. Similarly, we cannot exclude subclinical EoE in the patients with asthma who did not undergo endoscopy.

In conclusion, this study suggests that in patients with asthma and many with dysphagia, there are specific factors which individually and when used in a defined scoring system strongly suggest the presence of eosinophilic oesophagitis. These factors include presence of peripheral eosinophilia, allergy-type asthma and no use of inhaled steroids. It also adds further support to the hypothesis that EoE may represent a part of a spectrum of systemic allergic disease rather than viewing it as an isolated oesophageal phenomenon. Finally, this study further suggests that certain subsets of patients with asthma should be carefully questioned for dysphagia as it is commonly subtle in EoE patients. Whether this scoring system will be helpful in patients with asthma and other atopic diseases but without dysphagia will be important to determine.

AUTHORSHIP

Guarantor of the article: David A. Katzka.

Author contributions: Drs Katzka, Harer and Enders were involved in the conception and design of the study. Drs Katzka, Harer and Enders were involved in the generation, collection, assembly, analysis and/or interpretation of data. Dr Katzka, Harer, Enders and Lim were

involved in the drafting or revision of the manuscript. All authors have approved the final version of the article, including the authorship list.

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