Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2017 November ; 65(5): 520–525. doi:10.1097/MPG.0000000000001553.

Using serum IgE antibodies to predict esophageal eosinophilia in children

Elizabeth A. Erwin, MD^{1,3,*}, Dale A. Rhoda, MSPH², Margaret Redmond, MD³, Jean B. Ly, MD⁴, John M. Russo, MD⁵, Ivor D. Hill, MD⁵, and Thomas A.E. Platts-Mills, MD, PhD⁶

¹Center for Innovation in Pediatric Practice, Nationwide Children's Hospital, Columbus, OH

²Biostat Global Consulting, Worthington, OH

³Division of Allergy and Immunology, Nationwide Children's Hospital and The Ohio State University Wexner Medical Center, Columbus, OH

⁴Division of Allergy and Immunology, All Children's Hospital, Sarasota, FL

⁵Division of Gastroenterology, Hepatology and Nutrition, Nationwide Children's Hospital, Columbus, OH

⁶Division of Allergy and Immunology, University of Virginia, Charlottesville, VA

Abstract

Objectives—Symptoms of eosinophilic esophagitis (EoE) are variable and can be nonspecific. Food-specific serum IgE antibodies are frequently found in EoE patients and are obtained using a widely available blood test. Our objective was to evaluate the ability of food-specific IgE antibodies to predict the presence of esophageal eosinophilia.

Methods—We reviewed 144 medical records for pediatric patients having esophageal biopsy and serum analysis for IgE antibodies to food (exploratory group). We performed logistic regression using gender and number of positive food-specific IgE tests to develop a model that predicts 15 eosinophils/high power field (hpf) in the esophagus. We tested the model using 142 additional patients (validation group).

Results—The probability of having 15 eosinophils/hpf in the esophagus was higher in males and increased with the number of positive food-specific IgE tests from 12% (95% confidence interval [CI] 4.8-26) in females with 0 foods positive to 86% (95% CI 71-94) for males with 4 or 5 foods positive. The statistical model using gender and number of positive IgE tests to predict patients having 15 eosinophils/hpf showed acceptable discriminative ability (area under the receiver operating characteristic [ROC] curve 0.80). The performance metrics for the model to predict 15 eosinophils/hpf in the validation group were similar (area under the ROC curve 0.75).

Conclusions—Requiring only a blood test and a simple algorithm, analysis for IgE antibodies to food may expedite an esophagogastroduodenoscopy and decrease delays in the diagnosis and

treatment of patients with nonspecific gastrointestinal symptoms who have increased eosinophils in the esophagus.

Keywords

esophagus; eosinophils; IgE antibodies; pediatrics

Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized disease process with recently reported prevalence estimates ranging from 0.05-0.1% in the general population (1). In a 2011 expert consensus document, EoE was defined as a “chronic, immune/antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation” (2). In that updated consensus document with expert recommendations, esophagogastroduodenoscopy (EGD) with esophageal biopsy showing at least 15 eosinophils per high power field (hpf) was reaffirmed as the gold standard for diagnosis (2,3). Although symptoms have been described in many different cohorts, the clinical picture is heterogeneous and includes failure to thrive, food aversion, regurgitation or vomiting, dysphagia, and food impaction (4-7). In some patients, cough that fails to respond to medical treatment is the predominant presenting symptom (8). Furthermore recent studies have suggested that the risk of esophageal stricture increases with the duration of untreated eosinophilic inflammation (9,10). Given the variation in presenting symptoms and the increased morbidity associated with delayed treatment, a specific screening test to predict the presence of eosinophils and expedite an esophageal biopsy would be useful.

Food antigens seem to be the primary cause of EoE in combination with recently recognized genetic predisposition and environmental factors (11,12). Cow's milk is a common causal food, and wheat, egg, and soy are also frequent offending foods (13-15). Low levels of IgE antibodies to milk and other foods are a remarkably common finding in patients with EoE and are often found even when skin prick tests are negative (16-18). In spite of having IgE antibodies, most EoE patients do not experience typical symptoms of an IgE mediated reaction (i.e. hives or angioedema). High levels of IgG4 antibodies to food have also been reported (19). The role of IgE and IgG4 antibodies in EoE is not yet clear. We have recently observed that patients with very low or undetectable IgE antibodies to milk can respond to treatment with cow's milk elimination diet (20). Taken with evidence that EoE does not respond to treatment with anti-IgE, our previous results suggest that IgE antibodies are a marker of an inflammatory response to food but not the cause of the disease process (18,19).

Serological methods to measure IgE antibodies are analytically sensitive, easily performed, widely available, and are not subject to interobserver variation (21). Traditionally IgE levels have been used with a patient's history to obtain information about clinical relevance at baseline and monitored over time to make decisions about possible food reintroduction (22). The objective of the current study was to evaluate the feasibility of using the presence of low levels of IgE to multiple foods in patients who have gastrointestinal symptoms as a biomarker to predict having 15 eosinophils/hpf in the esophagus.

Methods

Medical records were reviewed for pediatric patients having both serum analysis for IgE antibodies to food by ImmunoCAP and EGD with esophageal biopsy for any reason at Nationwide Children's Hospital (Columbus, Ohio) between April and September of 2015 (n=144). These patients were designated the “exploratory” subset. Clinical data collected by chart review included demographics, symptoms, peripheral blood eosinophil counts, esophageal biopsy results, and levels of IgE antibodies to five foods that are most commonly implicated as causative for EoE (i.e. milk, egg, wheat, soy, and peanut). As a “validation” sample, the same data were collected from medical records of pediatric patients having EGD with esophageal biopsy between January and June of 2009 and between January and June of 2012 (n=174). All charts were reviewed by three medically trained professionals (EE, MR, JL). This study was approved by the Institutional Review Board at Nationwide Children's Hospital.

A logistic regression model (Model One) was estimated on the exploratory dataset. The outcome of interest was a binary indicator of whether the patient showed ≥ 15 eosinophils/hpf on the current, or any prior, esophageal biopsy. Given that EoE is generally thought to be chronic, a prior esophageal biopsy with ≥ 15 eosinophils/hpf was considered an indicator of previous diagnosis of esophageal eosinophilia. We excluded patients with inflammatory bowel disease from the analysis. Those with proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) were not excluded because they typically have similar clinical, endoscopic, and genetic features when compared with EoE patients (23). Explanatory variables in the model included the binary variable gender and a categorical variable for having detectable IgE antibodies ≥ 0.10 IU/ml (i.e. a positive test by ImmunoCAP analysis) to the foods milk, egg, wheat, soy, or peanut. Only unique patients who were tested for all five foods were included (n=119). The presence of IgE antibodies to food was coded using three different levels: i) 0 foods positive, ii) 1-3 foods positive, and iii) 4 or 5 foods positive. (See supplementary materials for details relating to IgE testing and additional potential variables that were considered for the model.)

The model performance metrics, including area under the receiver operating characteristic (ROC) curve (c-statistic), sensitivity, specificity, positive likelihood ratio (LR), and negative LR, were estimated. Likelihood ratios were calculated to estimate the usefulness of the model for predicting the probability of disease independent of its prevalence. We assessed the prediction and discrimination characteristics of Model One using the validation dataset. After validation, we re-estimated the model on the combined data (exploratory and validation datasets) to provide readers with a table that shows the predicted probability of finding ≥ 15 eosinophils/hpf for male and female patients based on the number of positive IgE tests. Statistical analyses were performed using Stata 14 (StataCorp, College Station, Texas).

As we studied the model, it seemed that it would be especially useful to be able to predict esophageal eosinophilia in patients who have non-specific symptoms. In order to focus on this group, we excluded patients who reported food impactions and dysphagia and developed a model (Model Two) using the variables gender and number of positive IgE tests as

explained previously (Table S1). We calculated the model performance metrics as a measure of the utility of serum IgE results in this group.

(See supplementary materials for Model Three- Examining a lower threshold for eosinophil counts)

Results

Exploratory and validation patient subsets

The prevalence of esophageal eosinophilia in patients having EGD was significantly higher in the exploratory subset from 2015 as compared with the historical, validation subset from 2009 and 2012 (Table 1A). As expected, detectable IgE antibodies (i.e. >0.10 IU/ml) to food were common among patients with eosinophils infiltrating the esophagus. The proportion of patients with ≥ 15 eosinophils/hpf who also had a low level of IgE antibodies to at least one food was 85% in both datasets as compared with 44% (exploratory group) and 46% (validation group) in patients with <15 eosinophils/hpf ($p<0.001$ for each group). In the “exploratory” dataset, milk was the most common food sensitization (78%) for patients with esophageal eosinophilia followed in frequency by wheat (69%), egg (64%), peanut (54%), and soy (53%) (Table 1B). These proportions were similar among the patients with ≥ 15 eosinophils/hpf in the validation group. Detectable IgE antibodies were significantly more common in patients with >15 eosinophils/hpf vs patients with <15 eosinophils/hpf for nearly every food tested (Table 1B).

Exploratory Model

Patients who were tested for IgE antibodies to all five foods (i.e. milk, egg, wheat, soy, and peanut) ($n=119$) were included in the “exploratory” dataset used to develop the model to predict the outcome of ≥ 15 eosinophils/hpf on esophageal biopsy. The probability of having ≥ 15 eosinophils/hpf on esophageal biopsy increased with the number of foods with positive IgE results. The predicted probability of having ≥ 15 eosinophils/hpf ranged from 12% [95% confidence interval (CI) 4.8-26] for females without detectable IgE antibodies to food to 86% (95% CI 71-94) for males with four or five positive foods. Of note, the probability of having ≥ 15 eosinophils/hpf was higher for males compared with females at each level of having IgE to foods. Given the gender differences, we analyzed females separately in relation to age and symptoms to determine whether additional variables improved the model. We did find a significant interaction between female gender and vomiting ($p=0.05$) suggesting that vomiting has one effect on the model for boys and a different effect for girls. However, including the interaction did not improve the model, so we continued by fitting the model without the interaction.

When we measured the performance of the model (Model One) on the exploratory dataset, it was able to correctly predict esophageal biopsy results 75% of the time. Sensitivity and specificity of the model were 78% and 72% respectively (Table 2). The positive LR was 2.75 (95% CI 1.80-4.21) and the negative LR was 0.31 (95% CI 0.19-0.51). The area under the ROC curve (c-statistic) was 80% (Fig 1A). A non-significant Hosmer-Lemeshow goodness-of-fit p-value of 0.5 suggests that the model fits the data.

Validation testing

We tested Model One using patients in the validation group who had IgE antibody results for all five foods (n=142). To classify model performance, patients with probability $\geq 50\%$ were considered to be predicted to have ≥ 15 eosinophils/hpf. The performance metrics were similar when the model was applied to the observations from 2009 and 2012. In this separate group of patients, the sensitivity was 76% and specificity 69% (Table 2). The positive LR was 2.44 (95% CI 1.74-3.43) and the negative LR was 0.35 (95% CI 0.21-0.60). The area under the ROC curve was 75% (Fig 1B). The proportion correctly classified was in the acceptable range of discrimination ability at 71 (24).

Cases that were incorrectly classified by Model One

Overall 25% of patients were incorrectly classified by using Model One. When the model was applied to the combined exploratory and validation datasets (n=261), 30 patients were *not* predicted to have increased esophageal eosinophils but had a biopsy with ≥ 15 eosinophils/hpf. This group of patients was classified as having a false negative test. The proportion of male (n=13) and female (n=17) patients was similar, and the mean ($\pm$ standard deviation) esophageal eosinophil count was 42 (± 3.5). However, 12/30 were females with 1-3 positive IgE tests. A second distinct subgroup of patients (18/30) had no detectable IgE antibodies to the foods milk, egg, wheat, soy, and peanut.

In contrast, 51 patients were classified as having a false positive test. Using the predictive model, these patients were more likely than not to have increased eosinophils in the esophagus, but their biopsies yielded <15 eosinophils/hpf. The majority of these patients were male (87%). No eosinophils were noted in 33/51 (65%) and 1-14 eosinophils were reported in 18/51 (35%). A proportion (33/51) were on PPI prior to having esophageal biopsy performed, and some of these patients may have responded resulting in a biopsy with <15 eosinophils/hpf. Additionally, there was a small group of patients (n=4) avoiding foods with milk before the biopsy. We do not know whether they had a negative biopsy because of dietary “treatment”.

Model Two- Patients without food impaction or dysphagia

A proportion of our patients with esophageal eosinophilia (44/104) presented with symptoms other than food impaction and dysphagia (Table 3). When we developed a model that included only these patients, we found that the number of positive IgE tests yielded the same predictions as Model One (Table S2). Patients with nonspecific symptoms who were predicted to have a positive biopsy by Model One were also predicted to have a positive biopsy in Model Two. The performance metrics of the model were slightly lower with sensitivity 70%, specificity 66%, positive LR 2.1 (95% CI 1.4-3.1), and negative LR 0.46 (95% CI 0.24-0.87) with 67% predicted correctly.

Discussion

Similar to reports from other groups, the finding of eosinophils in the esophagus is increasing over time at our institution. A screening test to identify patients who may need esophageal biopsy would be helpful due to the heterogeneous nature of the symptoms and

the increase in esophageal strictures associated with delays in treatment of eosinophilic inflammation (9,10). Levels of IgE antibodies are a common finding in EoE patients, and we have recently proposed that they may be a marker of causal foods and have some utility in planning dietary treatment (18,20). The current study suggests a new role for serum analysis for IgE antibodies. In patients with symptoms for which an EGD is a consideration, serum IgE antibodies to food may be used as a noninvasive biomarker to calculate the probability of having 15 eosinophils/hpf on biopsy with moderate sensitivity and specificity and satisfactory positive and negative LR. Incorporating the results of such a model in the evaluation of patients could be helpful in the diagnosis of the complex disease processes that involve esophageal eosinophilia.

Our model to predict the presence of 15 or more eosinophils/hpf in the esophagus (labeled Model One) is simple. With the variables gender and serum IgE levels to milk, egg, wheat, soy, and peanut, the probability of a patient having esophageal eosinophilia can be determined by consulting a table (Fig 2). A patient with predicted probability 50% would be classified as more likely than not to have EoE. Our model can be described as moderately predictive based on its statistical performance characteristics (24-26). However, the clinical value of a predictive test depends on how it will be used (i.e. diagnosis or screening) and the patient population for which it is intended. We propose that measurement of serum IgE levels be considered in patients who present for gastrointestinal evaluation in order to obtain information about eosinophils in the esophagus prior to performing a biopsy and to minimize delays in diagnosis and treatment of esophageal eosinophilia.

We are not proposing that this predictive score would apply to the general population. We are suggesting that it could be useful for patients who have gastrointestinal symptoms. Patients presenting for gastrointestinal evaluation might be classified as moderate risk or high risk for esophageal eosinophilia depending on the nature of their symptoms. Patients with classic EoE symptoms of dysphagia or food impaction would be considered high risk. Those with nonspecific symptoms such as abdominal pain, failure to thrive, or severe gastroesophageal reflux would be considered to have “moderate risk”. It is for this group with “moderate risk” that the serologic test may be most valuable. We have identified such patients whose diagnosis has been delayed for several years. A patient with nonspecific symptoms who had a positive predictive test would be twice as likely to have esophageal eosinophilia compared with someone who did not have a positive test. A predictive model also raises the question of whether other populations who are at increased risk compared with the general population should be screened. This group would include siblings or family members of patients with EoE in whom an increased prevalence ranging from 2% to 10% has been reported (10,27). Patients with connective tissue disorders including Marfan Syndrome, Loeys-Dietz Syndrome, and Ehlers-Danlos Syndrome, who also have an increased risk of EoE, would also be potential candidates for the screening test prior to performing EGD (28,29).

Celiac disease, another gastrointestinal condition requiring EGD for diagnosis, provides a model for using a serologic assay for preliminary information. In most patients with celiac disease, IgA autoantibodies to tissue transglutaminase (tTG) can be detected (30,31). These results are used with pathology findings to increase the detection rate and/or minimize the

delay in diagnosis of celiac disease (32). Although the demonstration of villous atrophy in duodenal biopsy is considered the gold standard, biopsy results are graded histologically based on the Marsh criteria. The clinical significance of early changes may not be clear without serological results (32). For a patient with non-specific symptoms or risk factors that are associated with celiac disease, serologic testing can also be helpful (33,34). Comparison of groups of patients diagnosed with celiac disease before and after the use of serologic testing has revealed a “new” subgroup of patients who are less symptomatic based on nutritional status, growth measures, and tissue abnormalities noted on pathologic examination (33,34).

A variety of methods are available for serum IgE testing. Biochip technologies such as Immune Solid-phase Allergen Chip (ISAC) assays that measure IgE antibodies to a single protein have become increasingly available and utilized. It is important to note that these technologies cannot be used to detect IgE antibodies to food or to plan dietary treatment in patients with EoE (35,36). This is likely due to high levels of IgG4 antibodies to food in EoE patients. As such, component resolved diagnostic testing by ISAC would not be interchangeable with measurement of IgE antibodies to allergenic extracts (or components) using ImmunoCAP analysis for the purposes of predicting esophageal eosinophilia.

Our study has several limitations. Over the last decade, a major point of confusion in interpretation of eosinophilic inflammation in the esophagus has been the existence of a subgroup of patients who respond to proton pump inhibitor (PPI). Because of concerns about multiple endoscopies, some pediatric experts started treating patients who had suspicious symptoms with PPI before performing the first EGD, and this practice even seemed to be endorsed in pediatric guidelines (37). This affects our study in two ways. First, we were unable to specifically define patients with PPI-REE in order to analyze them separately. Second in keeping with this practice, some of our patients may have had a negative esophageal biopsy after treatment with PPI, but a predicted probability 50%. These patients would be classified as false positives, and they would lower the specificity of the model. Due to similar clinical, endoscopic and genetic features as well as recent case series suggesting that individual patients can be responsive to both PPI and other dietary and medical treatments for EoE; it has been proposed that PPI simply be considered as a treatment option for esophageal eosinophilia (20,38). It is not yet clear, how this proposal will be incorporated into clinical practice. As a next step, our model will need to be tested in additional patients. Our results suggest that the predictive model may be even more helpful if patients have an EGD before starting a PPI. Another obvious challenge for this model is that there is a known subgroup of patients with EoE who are not atopic. As such, there were no detectable IgE antibodies for 16/104 (15%) of the patients with increased esophageal eosinophils in this study. In contrast in a separate group of EoE patients, we have recently measured high levels of IgG4 antibodies to milk proteins in 97% of those tested (39). Further testing of a model that includes IgE and IgG4 antibodies to predict esophageal eosinophilia would be the next step.

In conclusion, screening tests are useful tools for predicting disease outcomes in groups of patients. This is especially true when symptoms can be nonspecific and a timely diagnosis is important in order to prevent future complications. In our study, the finding of an objective

blood test and the resulting ease of use of the predictive model make analysis for IgE antibodies to food a practical and useful tool to be considered in the evaluation of patients with nonspecific gastrointestinal symptoms who may have eosinophils in the esophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: National Institutes of Health grants K23-AI-059317, AI-20565

References

1. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol*. 2014; 12:589–96. [PubMed: 24035773]
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3–20. [PubMed: 21477849]
3. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007; 133:1342–63. [PubMed: 17919504]
4. Orenstein SR, Shalaby TM, DiLorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol*. 2000; 95:1422–30. [PubMed: 10894574]
5. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol*. 2007; 119:731–8. [PubMed: 17258309]
6. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr*. 2009; 48:30–6. [PubMed: 19172120]
7. Dellon ES, Gonsalves N, Hirano I, et al. ACG Clinical Guideline: Evidence-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. *Am J Gastroenterol*. 2013; 108:679–92. [PubMed: 23567357]
8. Hill CA, Ramakrishna J, Fracchia S, et al. Prevalence of eosinophilic esophagitis in children with refractory aerodigestive symptoms. *JAMA Otolaryngol Head Neck Surg*. 2013; 139:903–6. [PubMed: 24051745]
9. Schoepfer A, Safroneeva E, Bussmann C, et al. Duration of untreated inflammation represents the main risk factor for stricture development in eosinophilic esophagitis. *Gastroenterology*. 2013; 144(suppl 1):S485. Su 1832.
10. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*. 2014; 79:577–85. [PubMed: 24275329]
11. Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet*. 2014; 46:895–900. [PubMed: 25017104]
12. Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2014; 134:1094–92.
13. Kagalwalla AF, Shah A, Li B, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr*. 2011; 53:145–9. [PubMed: 21788754]
14. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults: food reintroduction identifies causative factors. *Gastroenterology*. 2012; 142:1451–9. [PubMed: 22391333]

15. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012; 130:461–7. [PubMed: 22743304]
16. Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2008; 6:531–5. [PubMed: 18304887]
17. Erwin EA, James HR, Gutekunst HM, et al. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2010; 104:496–502. [PubMed: 20568382]
18. Erwin EA, Tripathi A, Ogbu PU, et al. IgE antibody detection and component analysis in patients with eosinophilic esophagitis. *J Allergy Clin Immunol Pract*. 2015; 3:896–904. [PubMed: 26099818]
19. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014; 147:602–9. [PubMed: 24907494]
20. Erwin EA, Kruszewski PG, Russo JM, et al. IgE antibodies and response to cow's milk elimination diet in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2016 In press.
21. Hamilton RG, Oppenheimer J. Serological IgE analyses in the diagnostic algorithm for allergic disease. *J Allergy Clin Immunol Pract*. 2015; 3:833–40. [PubMed: 26553612]
22. Peters RL, Gurrin LC, Dharmage SC, et al. The natural history of IgE-mediated food allergy: can skin prick tests and serum-specific IgE predict the resolution of food allergy? *Int J Environ Res Public Health*. 2013; 10:5039–61. [PubMed: 24132133]
23. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut*. 2016; 65:524–31. [PubMed: 26685124]
24. Hosmer DW, Taber S, Lemeshow S. The importance of assessing the fit of logistic regression models: a case study. *Am J Public Health*. 1991; 81:1630–5. [PubMed: 1746660]
25. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) Plots: A fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993; 39:561–77. [PubMed: 8472349]
26. El Khouli RH, Macura KJ, Barker PB, et al. The relationship of temporal resolution to diagnostic performance for dynamic contrast enhanced (DCE) MRI of the breast. *J Magn Reson Imaging*. 2009; 30:999–1004. [PubMed: 19856413]
27. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med*. 2004; 351:940–1. [PubMed: 15329438]
28. Abonia JP, Wen T, Stucke EM, et al. *J Allergy Clin Immunol*. 2013; 132:387–86. [PubMed: 23810152]
29. Frischmeyer-Guerrero PA, Guerrero AL, Oswald G, et al. TGF β receptor mutations impose a strong predisposition for human allergic disease. *Sci Transl Med*. 2013; 195:195ra94.
30. Dieterich W, Eberhardt L, Schopper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. *Gastroenterology*. 1998; 115:1317–21. [PubMed: 9834256]
31. Chan AW, Butzner JD, McKenna R, et al. Tissue transglutaminase enzyme-linked immunosorbent assay as a screening test for celiac disease in pediatric patients. *Pediatrics*. 2001; 107:E8. [PubMed: 11134472]
32. Hill ID, Dirks MH, Liptak GS, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005; 40:1–19. [PubMed: 15625418]
33. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. *Pediatrics*. 2009; 124:1572–8. [PubMed: 19948628]
34. Garnier-Lengline H, Brousse N, Candon S, et al. Have serological tests changed the face of childhood coeliac disease? A retrospective cohort study *BMJ Open*. 2012; 11:1–6.
35. van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, et al. *J Allergy Clin Immunol*. 2015; 136:1095–7.e3. [PubMed: 25935104]
36. van Rhijn BD, van Ree R, Versteeg SA, et al. Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. *Allergy*. 2013; 68:1475–81. [PubMed: 24351068]

37. Papadopoulou A, Koletzko S, Heuschkel R, et al. ESPGHAN Eosinophilic Esophagitis Working Group and the Gastroenterology Committee. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr.* 2014; 58:107–18. [PubMed: 24378521]
38. Molina-Infante J, Bredenoord A, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: An entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut.* 2016; 65:524–31. [PubMed: 26685124]
39. Schuyler AJ, Kruszewski PG, Russo JM, Tripathi A, Workman LJ, Platts-Mills TA, Erwin EA. Serum IgG4 antibodies in pediatric subjects with eosinophilic esophagitis treated with cow's milk elimination diet or swallowed fluticasone: medium to high levels of specific IgG4 to cow's milk components despite low to negative IgE antibodies. *J Allergy Clin Immunol.* 2016 abstr.

Abbreviations

EoE	eosinophilic esophagitis
hpf	high power field
EGD	esophagogastroduodenoscopy
PPI-REE	proton pump inhibitor-responsive esophageal eosinophilia
ROC	receiver operating characteristic
PPV	positive predictive value
NPV	negative predictive value
tTG	tissue transglutaminase
ISAC	Immune solid-phase Allergen Chip
EDP	EoE Diagnostic Panel
PPI	proton pump inhibitor

Specific author contributions

	Erwin	Rhoda	Redmond	Ly	Russo	Hill	Platts-Mills
Study design	X						X
Collection of data	X		X	X	X		
Interpretation of data	X	X				X	X
Drafting manuscript	X	X	X	X	X	X	X
Approval of final version	X	X	X	X	X	X	X
Accept responsibility	X	X	X	X	X	X	X

Summary Box

1. What is known?

- Symptoms of eosinophilic esophagitis (EoE) in children can be nonspecific.
- Most children with EoE have food-specific IgE antibodies.

2. What is new?

- The probability of having esophageal eosinophilia is increased in patients who have IgE antibodies to multiple foods.
- Analysis for IgE antibodies to food in patients with nonspecific gastrointestinal symptoms may decrease delays in diagnosis and treatment of esophageal eosinophilia.

Fig 1.

Receiver operating characteristic (ROC) curves illustrate the performance of the model for predicting an esophageal biopsy that shows 15 eosinophils/hpf as estimated using the exploratory group (A) and evaluated using the validation dataset (B).

Predicted Probability of having ≥ 15 eosinophils/hpf					
IgE antibodies ≥ 0.10 IU/ml	0 foods 1-3 foods 4-5 foods	Male		Female	
		22% (14-34)		10% (5-17)	
		52% (41-63)*		29% (19-42)	
		77% (65-86)		56% (40-71)	

* Shaded boxes indicate that patients are more likely than not to have esophageal eosinophilia.

Fig 2.

An index card version of the model estimated on the combined exploratory and validation datasets, showing the predicted probability for having ≥ 15 eosinophils/hpf based on grouping patients by gender and the number of positive food specific IgE tests. Values given in parentheses are 95% confidence intervals. A predicted probability greater than 50% suggests that the patient is more likely than not to have esophageal eosinophilia.

Table 1A

Prevalence of esophageal eosinophils among patients included in two separate datasets.

Esophageal eosinophils	Exploratory Set (n=119)	Validation Set (n=142)	p value*
15 eos/hpf [‡] (esophageal eosinophilia)	59	45	32%
5-14 eos/hpf	6	9	6%
1-4 eos/hpf	8	12	9%
0	46	76	53%
			p=0.004
			p=0.8
			p=0.7
			p=0.02

* p value based on the chi square test comparing exploratory and validation groups.

[‡] eos/hpf=eosinophils/high power field

Table 1B

Results of analysis of IgE antibodies to food among patients with 15 eosinophils/high power field (eos/hpf) compared with patients with <15 eosinophils/hpf in two datasets.

	Exploratory Set			Validation Set						
	15 eos/hpf (n=59)	<15 eos/hpf (n=60)	p value *	15 eos/hpf (n=45)	<15 eos/hpf (n=97)	p value				
IgE antibody levels [†] , n										
0 foods	9	15%	35	58%	p<0.001	7	15%	49	51%	p<0.001
1-3 foods	20	34%	17	28%	p=0.5	21	47%	36	37%	p=0.3
4 or 5 foods	30	51%	8	13%	p<0.001	17	38%	12	12%	p<0.001
IgE antibodies detected, n										
Milk	46	78%	21	35%	p<0.001	31	69%	34	35%	p<0.001
Egg	38	64%	18	30%	p<0.001	24	53%	23	24%	p<0.001
Wheat	41	69%	16	27%	p<0.001	30	67%	32	33%	p<0.001
Soy	31	53%	10	17%	p<0.001	15	33%	21	22%	p=0.1
Peanut	32	54%	10	17%	p<0.001	21	47%	20	21%	p=0.001

* p value based on using the chi square test to compare patients with 15 eosinophils/hpf and those with <15 eosinophils/hpf.

[†] Number of foods for which IgE antibodies >0.10 IU/ml were detected.

Table 2

Model performance when fit to the exploratory data and evaluated using the validation and combined datasets.

	Exploratory (n=119)	Validation (n=142)	Combined (n=261)
Sensitivity	78 %	76 %	77 %
Specificity	72 %	69 %	70 %
Positive likelihood ratio	2.75	2.44	2.57
Negative likelihood ratio	0.31	0.35	0.33
Area under ROC curve	80 %	75 %	77 %
Percent correct	75 %	71 %	73 %

Table 3

Symptoms in patients with 15 eosinophils/high power field (eos/hpf) compared with patients with <15 eosinophils/hpf in two datasets.

	Exploratory Set			Validation Set						
	15 eos/hpf (n=59)	<15 eos/hpf (n=60)	p value *	15 eos/hpf (n=45)	<15 eos/hpf (n=97)	p value				
Symptoms										
“High risk” for EoE										
Food stuck	10	17%	7	12%	p=0.4	14	31%	8	8%	p=<0.001
Dysphagia	18	31%	10	17%	p=0.08	18	40%	15	15%	p=0.001
“Moderate risk” for EoE										
Vomiting	26	44%	15	25%	p=0.03	15	33%	37	38%	p=0.6
Epigastric pain	3	5%	4	7%	p=0.7	8	18%	22	49%	p=0.5
Periumbilical pain	10	17%	25	42%	p=0.003	13	29%	44	45%	p=0.06
Diarrhea	2	3%	9	15%	p=0.05	1	2%	13	13%	p=0.04
Gastroesophageal reflux	10	17%	13	22%	p=0.5	nd		nd		
Failure to thrive	7	12%	3	5%	p=0.2	nd		nd		
Cough	5	8%	6	10%	p=0.9	nd		nd		

Abbreviations: nd is not determined

* p value based on using the chi square test to compare patients with 15 eosinophils/hpf and those with <15 eosinophils/hpf.