Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982-1999

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Background: Eosinophilic esophagitis (EE) is now a commonly encountered disorder that was rarely diagnosed a decade ago.
Objective: We aimed to determine the epidemiologic and histologic features of retrospective pediatric esophageal eosinophilia before the first case of EE at our institution was recognized.
Methods: Esophageal biopsy specimens obtained between 1982 and 1999 with reflux esophagitis were re-examined and reorganized into 2 groups based on peak esophageal eosinophil number (<15 eosinophils per high-powered field [hpf] and ≥15 eosinophils/hpf). The epidemiology and histology of the entire cohort and a population-based cohort were evaluated.
Results: Eight hundred seven biopsy specimens from 666 patients were re-examined; 198 patients had 15 eosinophils/hpf or greater. Among a population-based cohort of patients with 15 eosinophils/hpf or greater, there was a modest increase in incidence ($P < .001$; incidence rate ratio, 1.18; 95% CI, 1.09-1.28). After correcting for a 40-fold increase in the number of endoscopies during this time period, the proportion of biopsy specimens with 15 eosinophils/hpf or greater did not change (0.08 in 1982 vs 0.08 in 1996 [peak]; $P = .9$; incidence rate ratio, 1.02; 95% CI, 0.73-1.44). Patients who had as few as 5 eosinophils/hpf were more likely to have persistent esophageal eosinophilia on repeat esophagogastroduodenoscopy, evidence of basal layer hyperplasia, and lamina propria fibrosis compared with patients with less than 5 eosinophils/hpf ($P < .001$).
Conclusions: Esophageal eosinophilia at levels consistent with EE was present among 30% of patients given diagnoses of reflux esophagitis, and the incidence of esophageal eosinophilia did not change over time. Patients with 5 eosinophils/hpf or greater had evidence of other histologic abnormalities and were likely to have persistent esophageal eosinophilia. (J Allergy Clin Immunol 2010;126:112-9.)

Key words: *Eosinophilic esophagitis, incidence, diagnosis, chronic esophagitis, eosinophil, esophagitis, epidemiology, retrospective*

Eosinophilic esophagitis (EE) has garnered great interest as a newly appreciated disorder with a clinical presentation that can mimic gastroesophageal reflux disease (GERD).[1-4] In an effort to standardize the diagnostic approach to EE, consensus guidelines were published in 2007 that define EE as a clinicohistopathologic disorder requiring the presence of 15 eosinophils/high-powered field (hpf) or greater on esophageal biopsy and the exclusion of GERD based on a trial of high-dose proton pump inhibitor (PPI) therapy or a negative pH probe.[5,6] However, the clinical and histopathologic distinctions between EE and GERD are based on a paucity of data and remain controversial.[7,8] In particular, studies evaluating the number of esophageal eosinophils per hpf that distinguish EE from GERD are limited, and the minimum number of eosinophils used to define EE has varied widely in the medical literature.[9-11] Further investigation is needed to identify the esophageal eosinophil count at which pathological features and disease morbidity begin to emerge.

In addition to the uncertainty surrounding the diagnostic criteria, the reason for the sudden increase in EE cases is also unclear. In 2004, we reported that the first case series of recognized EE at our institution was in 1999, that the subsequent incidence of EE was approximately 1:10,000 children, and that this incidence remained constant between 2000 and 2004.[12] Subsequent epidemiologic studies have attempted to address whether the sudden burst of new patients with EE reflects a true increase in the number of new cases or increasing disease recognition.[13-15] The data from these studies are conflicting. These studies were not performed among population-based cohorts and do not account for dramatic changes in the practice of pediatric esophagogastroduodenoscopy (EGD) over the past 2 decades.[15,16] Finally, there have been no pediatric studies to evaluate fluctuations in eosinophil counts over time among patients with esophageal eosinophilia who were not treated with currently accepted therapies for EE.

We aimed to determine whether there was a significant cohort of pediatric patients who were previously given diagnoses of esophagitis before the late 1990s who had currently accepted histopathologic features of EE on histologic re-evaluation. Additionally, we aimed to determine the eosinophil count at which other pathologic abnormalities begin to arise.

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Supported by the Campaign Urging Research for Eosinophilic Disease (CURED), the Food Allergy Project, National Institute of Allergy and Infectious Diseases grant T32 AI060515 (C. W. D.), PHS grant P30 DK078392, the Buckeye Foundation, and the International Group of Eosinophilic Researchers (TIGER).

Disclosure of potential conflict of interest: M. H. Collins has subcontract relationships with GlaxoSmithKline, Ception Therapeutics, and Meritage Pharma. J. P. Abonia has received research support from the National Institutes of Health and Ception Therapeutics. M. E. Rothenberg is a speaker and consultant for Merck and a consultant for Centocor, Ception Therapeutics, Nycomed, and Array Biopharma; has received research support from the National Institutes of Health, the Food Allergy & Anaphylaxis Network, and the Dana Foundation; and is on the medical advisory board of the American Partnership for Eosinophilic Disorders and the executive council of the International Eosinophil Society. The rest of the authors have declared that they have no conflicts of interest.

Received for publication December 8, 2009; revised April 30, 2010; accepted for publication May 14, 2010.

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0091-6749/$36.00

doi:10.1016/j.jaci.2010.05.027

Abbreviations used
CCHMC: Cincinnati Children's Hospital Medical Center
EE: Eosinophilic esophagitis
EGD: Esophagogastroduodenoscopy
GERD: Gastroesophageal reflux disease
hpf: High-power field
IRR: Incidence rate ratio
OR: Odds ratio
PPI: Proton pump inhibitor
ROC: Receiver operating characteristic

We also aimed to assess whether esophageal eosinophilia (≥15 eosinophils/hpf) was a persistent histologic finding. Finally, we aimed to determine the epidemiology of esophageal eosinophilia from 1982 to 1999 using a population-based pediatric cohort.

METHODS

Study setting

This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (CCHMC).

Data sources

The CCHMC histopathology database includes all specimens obtained at our institution from 1971 through the present day. To identify esophageal biopsy specimens that might contain eosinophils, we searched the database using the terms "reflux esophagitis," "chronic esophagitis," or "eosinophilic esophagitis." Once this cohort was identified, a subsample query was performed to investigate for Barrett esophagus by using the terms "Barrett's," "metaplasia," "goblet," "columnar," "dysplasia," and "cancer."

The onset of our study period was defined by the first year in which a substantial number of esophageal biopsy specimens with a diagnosis of "chronic esophagitis" or "reflux esophagitis" were present (1982). The end of our study period was designated as the year in which the first diagnosis of EE at our institution was made (1999). The total number of esophageal biopsy specimens obtained during this study period was also identified.

Patient population. Patients' demographics and indications for initial endoscopy were obtained from chart review. There were 32 (6.8%) missing indications for endoscopy among patients with less than 15 eosinophils/hpf. A patient's race was determined by self-report. Patients were assigned to one of 2 groups based on histopathologic re-evaluation (≥15 eosinophils in at least 1 hpf on any biopsy specimen and <15 eosinophils/hpf). As trends began to emerge in our analysis, the data were also analyzed by using a lower eosinophil threshold count (≥5 eosinophils/hpf and <5 eosinophils/hpf).

Histopathologic analysis. Slides of all biopsy specimens identified by our search criteria were reviewed by a single blinded reviewer (C. W. D.). A second blinded reviewer (M. H. C.) also generated peak eosinophil counts for all biopsy specimens with 15 eosinophils/hpf or greater early in the study. All slides for which the peak counts generated by the 2 reviewers differed by more than 10% were rereviewed simultaneously by both reviewers, and the discrepancies were resolved. Subsequently, second reviews were obtained at the request of the primary reviewer.

The peak eosinophil count was determined for each biopsy specimen and was defined as the greatest number of intraepithelial eosinophils visualized at 400× magnification (area, 0.23 mm^2). If more than 1 level was biopsied, then all levels were reviewed, and the highest count was reported. The majority of biopsy specimens were obtained from the distal esophagus, and the number of biopsy specimens taken at each level was not reported at our institution during the study period. Each specimen was also assessed for other histologic abnormalities. The percentage of biopsy specimens with evidence of basal layer hyperplasia, lamina propria fibrosis, microabscesses, and surface layering was calculated. Only the incident biopsy specimen was used for these calculations to avoid including a patient more than once. Biopsy specimens were excluded from analysis if the amount of tissue present was less than 1 hpf. Biopsy specimens were also excluded if the hematoxylin and eosin staining was too faint to allow for accurate identification of epithelial cells, basal cells, or eosinophils. Eosinophil surface layering was defined as 4 contiguous eosinophils along the luminal surface of the epithelium, and an eosinophil microabscess was defined as an intraepithelial space occupying collection of 10 or more eosinophils. Basal layer hyperplasia was defined as expansion of the basal layer to 25% or greater of the total epithelial thickness in a well-oriented section.[17] Lamina propria fibrosis was defined as an increase in the deposition of thickened collagen fibers. The lamina propria was present in biopsy specimens in approximately 38% (75/198) of patients with 15 eosinophils/hpf or greater, 20% (93/468) of patients with less than 15 eosinophils/hpf, and a similar proportion of specimens evaluated at lower threshold counts (34% at ≥5 eosinophils/hpf and 19% at <5 eosinophils/hpf). A receiver operating characteristic (ROC) curve comparing peak esophageal eosinophil counts with the occurrence of basal layer hyperplasia and also for the occurrence of either hyperplasia or lamina propria fibrosis was used to identify the optimal cutoff value.

Assessment of disease chronicity and natural history. All patients who had 2 or more EGDs with biopsy specimens were assigned to one of 2 groups (≥15 eosinophils/hpf and <15 eosinophils/hpf) based on the peak intraepithelial eosinophil count observed on their

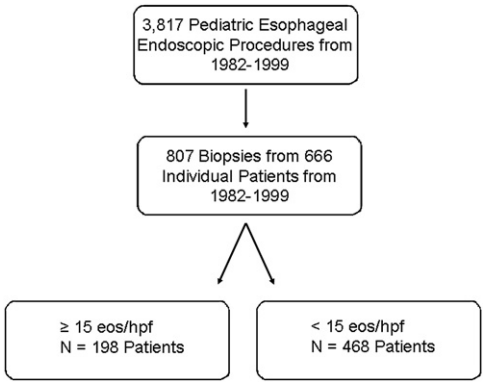

FIG 1. Initial study cohort identification. Between 1982 and 1999, a total of 3,817 esophageal biopsy specimens were obtained, and 666 patients met study criteria. On re-evaluation, 198 of these patients had 15 eosinophils/hpf or greater on esophageal biopsy. *eos*, Eosinophils.

TABLE I. Indications for initial endoscopy

	≥15 eos/hpf (n = 198)	<15 eos/hpf (n = 436)
Abdominal pain (%)	17.68	20.41
Reflux (%)	14.14	10.78
Esophagitis (%)	14.65	16.74
Vomiting (%)	12.63	8.26
Dysphagia (%)	12.12*	2.52
Esophageal stricture or foreign body (%)	2.00	1.15
Other (%)	26.78	40.14*

The 5 most common indications (abdominal pain, reflux, esophagitis, vomiting, and dysphagia) for endoscopy for patients with 15 eosinophils/hpf or greater and for patients with less than 15 eosinophils/hpf are shown. The rates of esophageal strictures and the percentage of patients with other indications for endoscopy (eg, gastrointestinal bleeding, inflammatory bowel disease, and airway abnormalities) are also shown.
eos, Eosinophils.
*$P < .001$.