

# 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  $\geq 15$  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).<sup>1-4</sup> 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.<sup>5,6</sup> However, the clinical and histopathologic distinctions between EE and GERD are based on a paucity of data and remain controversial.<sup>7,8</sup> 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.<sup>9-11</sup> 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.<sup>12</sup> 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.<sup>13-15</sup> 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.<sup>15,16</sup> 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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#### 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 ( $\geq 15$  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 ( $\geq 15$  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 ( $\geq 5$  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 reviewed 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 $\times$  magnification (area, 0.23 mm<sup>2</sup>). 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

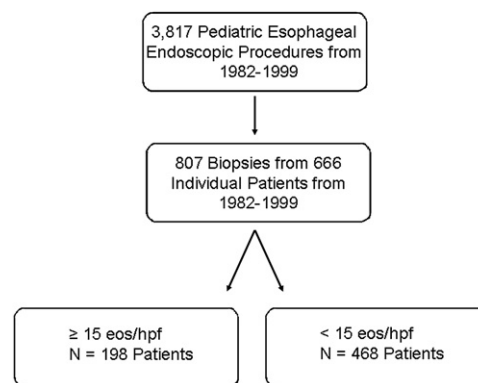


**FIG 1.** Initial study cohort identification. Between 1982 and 1999, a total of 3,817 esophageal biopsy specimens were obtained, and 666 patients met study criteria. On re-evaluation, 198 of these patients had 15 eosinophils/hpf or greater on esophageal biopsy. *eos*, Eosinophils.

**TABLE I.** Indications for initial endoscopy

|                                          | $\geq 15$ 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.

\* $P < .001$ .

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.<sup>17</sup> 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  $\geq 5$  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 ( $\geq 15$  eosinophils/hpf and  $< 15$  eosinophils/hpf) based on the peak intraepithelial eosinophil count observed on their

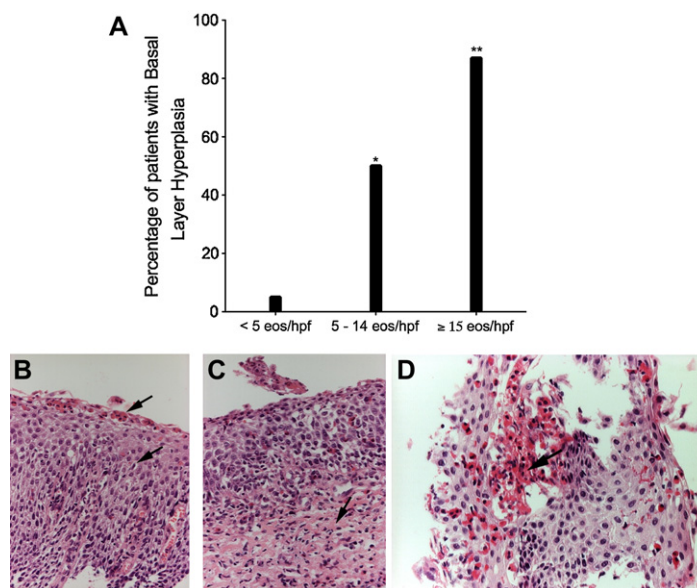


**FIG 2.** Histologic re-evaluation. **A**, Patients with 5 to 14 eosinophils/hpf and 15 eosinophils/hpf or greater were more likely to have basal layer hyperplasia than patients with less than 5 eosinophils/hpf (\* $P < .001$ ) and less than 15 eosinophils/hpf (\*\* $P < .001$ ), respectively. Examples of basal layer hyperplasia (lower arrow) and surface layering (upper arrow) (**B**), lamina propria fibrosis (arrow, **C**), and microabscesses (arrow, **D**) are shown. *eos*, Eosinophils.

initial study specimen. The percentage of patients in each group who demonstrated 15 eosinophils/hpf or greater and either complete (0 eosinophils/hpf) or partial (<15 eosinophils/hpf) histologic resolution/remission of esophageal eosinophilia on subsequent biopsy specimens was determined. As trends in the data began to emerge at peak eosinophil counts of 5 or greater, data were also compared at a lower threshold ( $\geq 5$  eosinophils/hpf and <5 eosinophils/hpf). Among subjects with multiple study specimens, assessments of disease chronicity included scatter plots comparing the peak eosinophil counts on incident EGD and subsequent EGD and the odds of repeat EGD at defined eosinophil counts ranging from 5 to 40 eosinophils/hpf.

## Epidemiology

We conducted our study at CCHMC, which is the sole pediatric gastroenterology and pathology provider for Hamilton County, Ohio, and the greater Cincinnati area. Census data from Hamilton County were obtained for our entire study period. Subjects 0 to 19 years of age with 15 eosinophils/hpf or greater on their initial study biopsy specimen who resided in Hamilton County within a given year were compared with Hamilton County population estimates for subjects 0 to 19 years of age, as defined by US Census data. Subsequently, pediatric population-based incidence rate ratios (IRRs) for patients with 15 eosinophils/hpf or greater and 5 eosinophils/hpf or greater residing in Hamilton County, Ohio, were calculated.

## Statistical analysis

Data were analyzed with JMP version 7.0 (SAS Institute, Inc, Cary, NC), SPSS version 16.0 (SPSS, Inc, Chicago, Ill), and STATA version 10.0 (StataCorp, College Station, Tex) software. Data are reported as raw numbers, proportions, and population-based incidence rates. Descriptive statistics for basic subject demographics and histopathologic findings are reported as means  $\pm$  SDs and medians (interquartile ranges) depending on the variable distributions. ANOVA or the Kruskal-Wallis test was used depending on the distribution of the data to compare groups for continuous variables. Categorical data were compared with  $\chi^2$  tests. All tests were considered significant at a  $P$  value of less than .05, and 95% CIs were calculated.

ROC curves were developed for each of the following diagnostic variables: basilar hyperplasia present (yes/no) and fibrosis present (yes/no). The optimal

**TABLE II.** Demographic and histologic features of the study population

|                                 | <5 eos/hpf | 5-14 eos/hpf     | $\geq 15$ eos/hpf |
|---------------------------------|------------|------------------|-------------------|
| No. of patients                 | 388        | 80               | 198               |
| Mean age (y)                    | 8.9        | 8.9              | 8.1               |
| Male sex (%)                    | 60         | 71               | 72†               |
| Median eos count (eos/hpf)      | 0          | 10*              | 35†               |
| Basal cell hyperplasia (%)      | 5          | 50*              | 86†               |
| Lamina propria fibrosis (%)     | 27         | 70*              | 85†               |
| Barrett esophagus (OR [95% CI]) | NA         | 1.16 (0.37-3.64) | 0.89 (0.25-3.11)  |

*eos*, Eosinophils.

\* $P < .001$  compared with less than 5 eosinophils/hpf.

† $P < .001$  compared with less than 15 eosinophils/hpf.

‡ $P < .05$  compared with less than 15 eosinophils/hpf.

eosinophil cutoff value for each variable was determined by the minimum Euclidean distance approach. The sensitivity, specificity, and area under the ROC curve are reported for the eosinophil cutoff point of 15 (currently accepted value) and the newly identified cutoff point.

## RESULTS

### Patient population

A search of the CCHMC pathology database yielded 3,817 esophageal biopsy specimens obtained between 1982 and 1999. Eight hundred sixty-eight biopsy specimens contained the terms "chronic esophagitis," "reflux esophagitis," or "eosinophilic esophagitis" within the pathologic diagnosis. Of those 868 biopsy specimens, 807 specimens from 666 patients were sufficient for analysis. The remaining 61 (7.0%) biopsy specimens were either inadequately stained or did not contain enough tissue to be analyzed adequately. Among our cohort of 666 patients, there were 430 (64.6%) male subjects. The average age was  $8.7 \pm 5.9$

years. There were 535 (80.5%) white subjects, 50 (7.5%) African American subjects, 1 (0.15%) Asian subject, and 80 (12.6%) subjects of unknown race (not available). Subjects' ethnicity data were not available. Histologic evaluation of these biopsy specimens demonstrated that 198 (30%) of the 666 patients had evidence of 15 eosinophils/hpf or greater (Fig 1). Seventy-two percent of patients with 15 eosinophils/hpf or greater were male compared with just 62% of patients with less than 15 eosinophils/hpf ( $P < .05$ ; odds ratio [OR], 1.56; 95% CI, 1.08-2.24). The mean age for patients with 15 eosinophils/hpf or greater was 8.1 years compared with 8.9 years for patients with less than 15 eosinophils/hpf ( $P = .38$ ). The percentage of white subjects was 81% and 76% among patients with 15 eosinophils/hpf or greater and less than 15 eosinophils/hpf, respectively ( $P = .47$ ). Approximately 12% (24/198) of patients with 15 eosinophils/hpf or greater had a chief complaint of dysphagia at the time of endoscopy compared with just 2.5% (11/436) of patients with less than 15 eosinophils/hpf ( $P < .0001$ ). The chief complaint of reflux, vomiting, esophagitis, or abdominal pain was present in similar rates in both groups (Table I). The indication for the second biopsy was also obtained and suggested that 87% of patients were actively symptomatic on repeat biopsy. A subsample of medical records were reviewed for additional clinical and endoscopic data (eg, history of atopic disease and esophageal rings); however, these data were not consistently documented.

### Histopathologic analysis

We evaluated all 807 biopsy specimens for evidence of other histologic abnormalities. The median eosinophil number for the entire study population was 1 eosinophil/hpf, and the median eosinophil number for patients with 15 eosinophils/hpf or greater was 35 eosinophils/hpf. Peak eosinophil counts ranged from 15 eosinophils/hpf to 187 eosinophils/hpf in patients with 15 eosinophils/hpf or greater. Interestingly, the median eosinophil number among patients with 15 eosinophils/hpf or greater was inversely associated with the patient's age ( $P < .02$ ). Among patients with greater than 15 eosinophils/hpf, the median peak eosinophil number was 50 eosinophils/hpf for children 3 years of age and younger ( $n = 61$ ), 35 eosinophils/hpf for children 4 to 12 years of age ( $n = 88$ ), and 30 eosinophils/hpf for children 13 to 18 years of age ( $n = 49$ ).

Basal cell hyperplasia was much more common among biopsy specimens with 15 eosinophils/hpf or greater (86%,  $n = 170/198$ ) than those with less than 15 eosinophils/hpf (13%,  $n = 61/468$ ;  $P < .001$ ; OR, 38.09; 95% CI, 23.55-61.60; Fig 2, A). Among 75 biopsy specimens in which the lamina propria was present and there was a peak count of 15 eosinophils/hpf or greater, 85% had evidence of lamina propria fibrosis. Only 36% (34/93) of biopsy specimens with less than 15 eosinophils/hpf had lamina propria fibrosis ( $P < .001$ ; OR, 10.40; 95% CI, 4.86-22.22).

Histologic findings of surface layering and eosinophilic microabscesses were exclusively present among biopsy specimens with 15 eosinophils/hpf or greater. The median eosinophil count among biopsy specimens with microabscesses was 85 eosinophils/hpf, and the median eosinophil count among biopsy specimens with evidence of surface layering was 65 eosinophils/hpf. The histologic data are summarized in Table II. Among our cohort of 807 biopsy specimens, 11 patients from our study demonstrated histopathologic changes consistent with Barrett esophagus: 6 patients with less than 5 eosinophils/hpf, 2 patients with

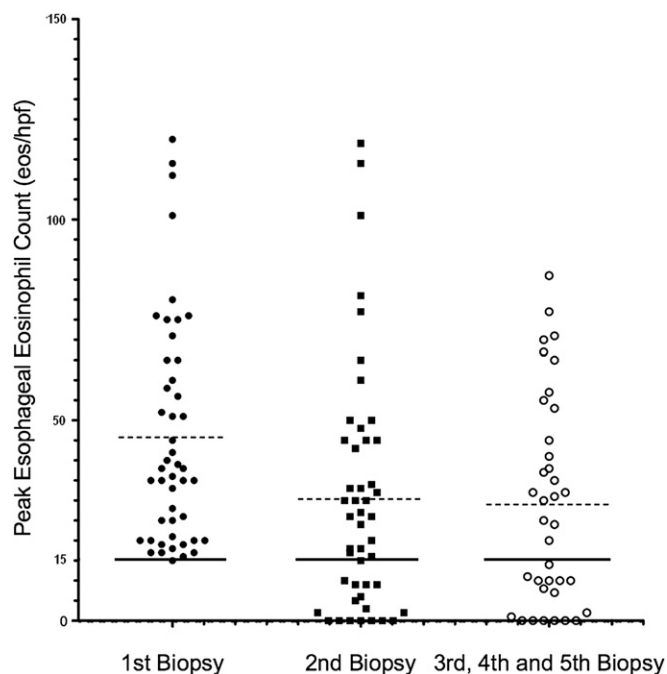


**FIG 3.** Chronicity of initial esophageal eosinophilia ( $\geq 15$  eosinophils/hpf). Among the 47 patients with 15 eosinophils/hpf or greater and at least 2 esophageal biopsy specimens, the peak eosinophil count for each specimen is shown. The solid line represents 15 eosinophils/hpf, and the dashed line represents the median eosinophil count for each group.

5 to 14 eosinophils/hpf, and 3 patients with 15 eosinophils/hpf or greater. Compared with patients with less than 5 eosinophils/hpf, patients with 15 eosinophils/hpf or greater (OR, 0.89; 95% CI, 0.25-3.11;  $P > .05$ ) and those with 5 to 14 eosinophils/hpf (OR, 1.16; 95% CI, 0.37-3.64;  $P > .05$ ) were not more likely to have histologic findings of Barrett esophagus. The data are included in Table II.

### ROC curves

ROC curves identified an optimal cutoff point of 6 eosinophils/hpf based on the presence or absence of basal cell hyperplasia. This cutoff point resulted in a sensitivity of 89% and a specificity of 87% with an area under the ROC curve of 0.92. In contrast, the sensitivity and specificity values based on basal cell hyperplasia were 72% and 94% for the currently accepted cutoff point of 15 eosinophils/hpf. Cutoff points were also investigated based on the presence or absence of either lamina propria fibrosis or basal cell hyperplasia (optimal cutoff point, 4 eosinophils/hpf; area under ROC curve, 0.925).

### Assessment of histopathologic disease chronicity and natural history

For subjects who had 15 eosinophils/hpf or greater on initial biopsy specimens and at least 1 subsequent esophageal biopsy specimen ( $n = 47$ ), the peak eosinophil count at each biopsy is shown in a scatter plot (Fig 3). Among patients with 15 eosinophils/hpf or greater on initial biopsy specimens, 66% had 15 eosinophils/hpf or greater on the subsequent biopsy specimen, and 75% had evidence of esophageal eosinophilia when all subsequent endoscopies were evaluated. A smaller fraction of patients

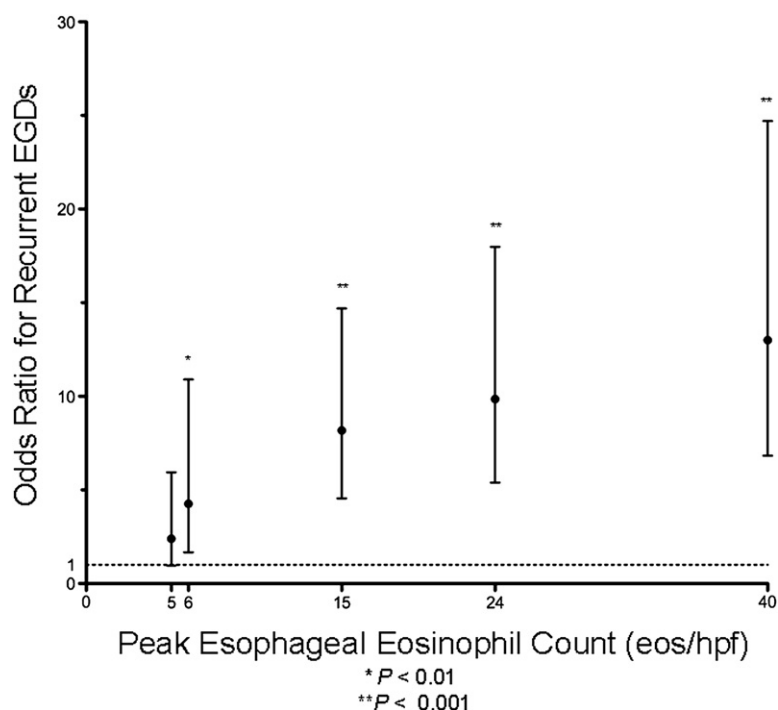


**FIG 4.** The odds of repeat EGD as a function of initial peak eosinophil count. The OR and 95% CI of repeat EGDs with biopsy as a function of the initial eosinophil count is shown. An OR of 1 is represented by the dotted line. \* $P < .01$ , \*\* $P < .001$ .

(25%,  $n = 13/49$ ) with less than 15 eosinophils/hpf on the initial biopsy had 15 eosinophils/hpf or greater on their second biopsy specimens ( $P < .001$ ; OR, 6.54; 95% CI, 2.70-15.81).

Only 13% of patients with 15 eosinophils/hpf or greater demonstrated evidence of histologic resolution/remission (0 eosinophils/hpf) over time ( $P < .0001$ ; OR, 7.72; 95% CI, 2.77-21.50). In contrast, 55% patients with less than 15 eosinophils/hpf on incident biopsy specimens had histologic resolution/remission on a subsequent biopsy specimen.

We noted that the majority of patients with 5 eosinophils/hpf or greater in the initial EGD with biopsy were more likely to have persistent esophageal eosinophilia on repeat EGD with biopsy when compared with those with less than 5 eosinophils/hpf on initial EGD with biopsy (83.6% vs 34.3%;  $P < .0001$ ; OR, 7.78; 95% CI, 3.69-25.86). Conversely, patients with less than 5 eosinophils/hpf on incident EGD with biopsy were far more likely have a peak count of 0 eosinophils/hpf on subsequent biopsy specimens than patients with initial eosinophilia ( $\geq 5$  eosinophils/hpf; 54% vs 20%;  $P < .001$ ; OR, 4.85; 95% CI, 1.94-12.13).

The odds of requiring repeat endoscopy increased as peak eosinophil counts increased (Fig 4). Patients with greater than 5 eosinophils/hpf were significantly more likely to undergo repeat endoscopy ( $P < .01$ ; OR, 4.26; 95% CI, 1.67-10.90) compared with patients without esophageal eosinophilia (0-1 eosinophils/hpf). Overall, there was a correlation between peak esophageal eosinophil counts on initial EGD and the number of endoscopies ( $r^2 = 0.32$ ;  $P < .001$ ).

## Epidemiology

The number of incident biopsy specimens with 15 eosinophils/hpf or greater ranged from 0 to 27 cases per year, with the number

of incident cases steadily increasing over time ( $P < .001$ ; (Fig 5, A). In parallel with this change, the number of esophageal biopsy specimens obtained during each year of our study period increased substantially from 12 esophageal biopsy specimens in 1982 to 471 biopsy specimens in 1999, a 40-fold increase ( $P < .001$ ; Fig 5, B). Among all biopsy specimens that met our study criteria, the proportion of specimens with 15 eosinophils/hpf or greater was 0.20 in 1982 and did not increase from 1982 to 1999 ( $P = .7$ ; IRR, 1.04; 95% CI, 0.87-1.23; Table III). The rate of biopsy specimens with 15 eosinophils/hpf or greater per total number of esophageal biopsy specimens at our institution was 0.08 in 1982 compared with 0.05 in 1999 and did not increase from 1982 to 1999 ( $P = .9$ ; IRR, 1.02; 95% CI, 0.73-1.44; Table III). When subjects were restricted to a population-based cohort, the incidence rate was 0 per 100,000 children in 1982 versus 4.9 per 100,000 children in 1996 (peak;  $P < .001$ ; IRR, 1.18; 95% CI, 1.09-1.28; Table IV). The number of esophageal biopsy specimens with 5 eosinophils/hpf or greater among patients in Hamilton County increased steadily throughout the study ( $P < .001$ ). Of note, the proportion of biopsy specimens with 5 eosinophils/hpf or greater remained the same ( $P = .9$ ; IRR, 1.01; 95% CI, 0.76-1.35).

## DISCUSSION

Herein we report that a substantial number ( $n = 198$ ) of patients (30%) previously given diagnoses of reflux esophagitis between 1982 and 1999 had histologic evidence of EE. These 198 patients were predominantly male and distinguished from patients with chronic esophagitis by a chief complaint of dysphagia. The incidence of new cases of esophageal eosinophilia dramatically increased during the study interval, but when corrected for the large increase in the number of EGDs performed, there was a

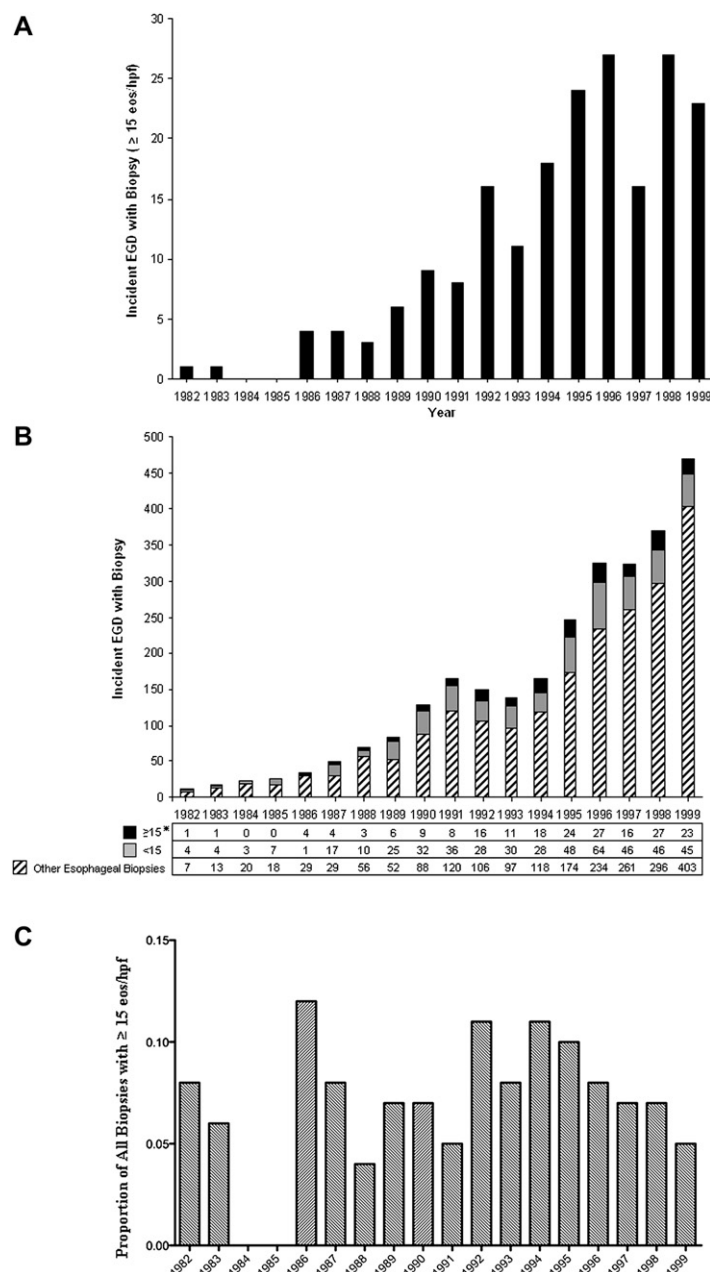


**FIG 5.** Incidence of esophageal eosinophilia over time. The number of incident biopsy specimens with 15 eosinophils/hpf or greater occurring each year is shown (**A**). The number of incident biopsy specimens with 15 eosinophils/hpf or greater and less than 15 eosinophils/hpf and all other esophageal biopsy specimens is displayed. Those with 15 eosinophils/hpf or greater had an increased number of incident biopsy specimens over time ( $*P < .001$ ). (**B**). The proportion of biopsy specimens with 15 eosinophils/hpf or greater per year is shown (**C**).

stable proportion of esophageal eosinophilia per EGD. Furthermore, we have identified that threshold counts of eosinophils associated with disease persistence emerge at 5 eosinophils/hpf or greater and that the presence of other histologic abnormalities begins to arise at a threshold of 6 eosinophils/hpf. Taken together, our data strongly suggest that EE is not a new disease but instead is a new classification of a persistent esophageal disorder.

Of the retrospective studies currently published, our cohort of 198 patients represents the largest group of pediatric patients with unrecognized histologic esophageal eosinophilia. We find the

similarities between our cohort of patients with esophageal eosinophilia and cohorts of patients with EE to be striking. Our retrospective cohort of patients with 15 eosinophils/hpf or greater includes a predominance of male and white subjects, a mean age of 8.7 years at endoscopic presentation, and dysphagia as a common indication for endoscopy.<sup>18,19</sup> The identification of histologic features of EE in nearly 30% of patients previously given diagnoses of reflux esophagitis suggests that EE might have been underdiagnosed in the 1980s and 1990s. We report a novel inverse correlation between peak eosinophil counts and age at histologic presentation

**TABLE III.** Proportion of biopsy specimens with 15 eosinophils/hpf or greater over time

|                                      | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 |
|--------------------------------------|------|------|------|------|------|------|------|------|------|
| ≥15 eos/hpf, study biopsy specimens* | 0.20 | 0.20 | 0.00 | 0.00 | 0.80 | 0.19 | 0.23 | 0.19 | 0.22 |
| ≥15 eos/hpf, all biopsy specimens†   | 0.08 | 0.06 | 0.00 | 0.00 | 0.12 | 0.08 | 0.04 | 0.07 | 0.07 |
|                                      | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 |
| ≥15 eos/hpf, study biopsy specimens* | 0.18 | 0.36 | 0.27 | 0.39 | 0.33 | 0.30 | 0.26 | 0.37 | 0.34 |
| ≥15 eos/hpf, all biopsy specimens†   | 0.05 | 0.11 | 0.08 | 0.11 | 0.10 | 0.08 | 0.05 | 0.07 | 0.05 |

\* $P = .7$  (IRR, 1.04; 95% CI, 0.87-1.23), incidence of biopsy specimens with 15 eosinophils/hpf or greater per total number of study biopsy specimens.

† $P = .9$  (IRR, 1.02; 95% CI, 0.73-1.44), incidence of biopsy specimens with 15 eosinophils/hpf or greater per total number of esophageal biopsy specimens.

**TABLE IV.** Incidence of biopsy specimens with 15 eosinophils/hpf or greater in Hamilton County

|                 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 |
|-----------------|------|------|------|------|------|------|------|------|------|
| ≥15 eos/hpf (n) | 0    | 1    | 0    | 0    | 1    | 2    | 0    | 3    | 4    |
| Incidence rate* | 0.00 | 0.38 | 0.00 | 0.00 | 0.39 | 0.78 | 0.00 | 1.19 | 1.61 |
|                 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 |
| ≥15 eos/hpf (n) | 4    | 6    | 5    | 12   | 11   | 12   | 8    | 11   | 5    |
| Incidence rate* | 1.61 | 2.42 | 2.02 | 4.86 | 4.49 | 4.93 | 3.29 | 4.56 | 2.09 |

eos, Eosinophils.

\* $P < .001$  (IRR, 1.18; 95% CI, 1.09-1.28), incidence of biopsy specimens with 15 eosinophils/hpf or greater per 100,000 children.

in children; this is consistent with findings by Straumman et al,<sup>20</sup> who demonstrated decreasing esophageal eosinophil counts with age in adult patients with EE who were treated only with esophageal dilation.

Although the incidence of patients with 15 eosinophils/hpf or greater increased during our study, increasing disease recognition and reclassification are likely responsible, at least in large part. Notably, the proportion of biopsy specimens with 15 eosinophils/hpf or greater was stable, despite a 40-fold increase in the number of biopsy specimens obtained. These data suggest that the “epidemic” of EE might be the result of increased recognition of EE rather than a genuine increase in disease incidence. Yet, a small increase in the true incidence of EE might still be occurring in conjunction with recognition and ascertainment biases.

It is interesting that patients with 15 eosinophils/hpf or greater were more likely to undergo multiple endoscopic procedures and had greater evidence of persistent disease on repeat biopsy specimens compared with patients who presented with less than 15 eosinophils/hpf. These data suggest that patients with 15 eosinophils/hpf or greater had more persistent and severe symptomatology. Given our lack of clinical data, we cannot rule out that increased surveillance of patients with esophageal eosinophilia did not contribute to this finding. It is noteworthy that 13% of patients with 15 eosinophils/hpf or greater experienced complete histologic resolution/remission. This finding is supported by 2 prior studies that have demonstrated histologic resolution/remission of esophageal eosinophilia in a subgroup of patients with EE.<sup>18,21</sup>

We were struck by our finding that 25% of patients with less than 15 eosinophils/hpf on initial biopsy went on to have peak eosinophil counts of 15 eosinophils/hpf or greater. Peak eosinophil counts of 15 eosinophils/hpf or greater are currently used to define EE and have been associated with basal cell hyperplasia and esophageal fibrosis.<sup>22</sup> Interestingly, the proportion of patients with basal layer hyperplasia and fibrosis were also increased among patients with 5 eosinophils/hpf or greater on initial EGD with biopsy. Patients who had greater than 5 eosinophils/hpf were also likely to

undergo multiple endoscopic procedures and had evidence of persistent esophageal eosinophilia on repeat biopsy. Our findings are supported by clinical data published by Ruchelli et al,<sup>22</sup> who reported that patients with a mean eosinophil count of greater than 7 eosinophils/hpf were less likely to respond to PPI therapy, and Orenstein et al,<sup>23</sup> who identified classic clinical features in a series of 30 children while defining EE at counts as low as 5 eosinophils/hpf. These data suggest that the histologic features associated with the clinicopathologic diagnosis of EE begin to emerge with relatively low numbers of eosinophils in the epithelium.

By only examining esophageal eosinophilia without clinical data and addressing the contribution of acid-induced esophagitis, our results have limitations. Without definitive proof that our patients did not respond to acid blockade, we cannot definitively attribute our findings to EE. However, it remains notable that patients with 5 eosinophils/hpf or greater had persistent esophageal eosinophilia, basal layer hyperplasia, and lamina propria fibrosis and required multiple endoscopic procedures, suggesting that disease persistence and severity emerge at low thresholds.

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**Clinical implications: Esophageal eosinophilia is a common histologic finding that was underrecognized during the 1980s and 1990s. The identification of esophageal eosinophilia, even at low thresholds (approximately 5 eosinophils/hpf), raises concern for persistent disease.**

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