SYSTEMATIC REVIEWS AND META-ANALYSES

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The Prevalence and Diagnostic Utility of Endoscopic Features of Eosinophilic Esophagitis: A Meta-analysis

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BACKGROUND & AIMS: Endoscopic findings such as esophageal rings, strictures, narrow-caliber esophagus, linear furrows, white plaques, and pallor or decreased vasculature might indicate the presence of eosinophilic esophagitis (EoE). We aimed to determine the prevalence and diagnostic utility of endoscopic features of EoE. **METHODS:** We conducted a systematic review and meta-analysis. PubMed, EMBASE, and gastrointestinal meeting abstracts were searched to identify studies that included more than 10 patients with EoE and reported endoscopic findings. Pooled prevalence, sensitivity, specificity, and predictive values were calculated using random- and mixed-effects models. **RESULTS:** The search yielded 100 articles and abstracts on 4678 patients with EoE and 2742 without (controls). In subjects with EoE, the overall pooled prevalence was as follows: esophageal rings, 44%; strictures, 21%; narrow-caliber esophagus, 9%; linear furrows, 48%; white plaques, 27%; and pallor/decreased vasculature, 41%. Substantial heterogeneity existed among studies. Results from endoscopy examinations were normal in 17% of patients, but this number decreased to 7% when the analysis was limited to prospective studies ($P < .05$). Overall levels of sensitivity were modest, ranging from 15% to 48%, whereas levels of specificity were greater, ranging from 90% to 95%. Positive predictive values ranged from 51% to 73% and negative predictive values ranged from 74% to 84%. **CONCLUSIONS: There is heterogeneity among studies in the reported prevalence of endoscopic findings in patients with EoE, but in prospective studies at least 1 abnormality was detected by endoscopy in 93% of patients. The operating characteristics of endoscopic findings alone are inadequate for diagnosis of EoE. Esophageal biopsy specimens should be obtained from all patients with clinical features of EoE, regardless of the endoscopic appearance of the esophagus.**

Keywords: Esophagus; Inflammation; Immune Response; Detection.

Eosinophilic esophagitis (EoE) is a clinicopathologic disease first described in 1978 that is characterized by esophageal dysfunction and marked esophageal eosinophilic infiltration.[1,2] Presenting symptoms differ among patient populations. Adults typically present with symptoms of dysphagia, food impactions, and heartburn.[3,4] Although children also can present with swallowing difficulties, they most commonly have nonspecific symptoms such as abdominal pain, vomiting, and failure to thrive.[5–7] EoE is a relatively new disease, so our understanding is limited; because patients often present with nonspecific symptoms, it can be a challenge to diagnose.[8]

Diagnostic guidelines for EoE were created by participants of the First International Gastrointestinal Eosinophil Research Symposium in 2007, and updates to these guidelines were published in the spring of 2011.[2,9] These diagnostic guidelines include features of the clinical presentation and histologic findings characteristic of the disease, but there are currently no recommendations regarding the role of endoscopic findings in the diagnosis of EoE.[2,9]

Endoscopic findings of EoE include esophageal rings, strictures, narrow-caliber esophagus, linear furrows, white plaques or exudates, and pallor or decreased vasculature.[4,10] Some studies have reported abnormal results from endoscopic examinations in as few as 33% of cases,[11–13] but other studies have reported endoscopic findings in as many as 95% of patients.[14,15] Although some studies have reported the sensitivity, specificity, and predictive values of the presence of classic endoscopic findings of EoE,[16–19] the operating characteristics of these endoscopic findings are poorly described. We aimed to determine the prevalence, operating characteristics, and diagnostic utility of individual endoscopic features of EoE by performing a systematic review and meta-analysis of the literature.

Methods

Search Strategy and Data Collection

Two authors (H.P.K., R.B.V.) independently searched the MEDLINE-indexed literature using the PubMed search engine from the National Center for Biotechnology Information (http://www.pubmed.gov). All studies with a print or electronic publication date from January 1, 1950, through June 30, 2011 were eligible for inclusion. To identify all relevant articles, the following search terms were used: *eosinophilic esophagitis, allergic esophagitis, corrugated esophagus, ringed esophagus, eosinophil AND gastrointestinal, eosin* AND esoph**. The search was repeated in the EMBASE search engine to ensure that all eligible articles were reviewed, and the bibliographies of identified articles were

Abbreviations used in this paper: EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; NPV, negative predictive values; PPV, positive predictive values.

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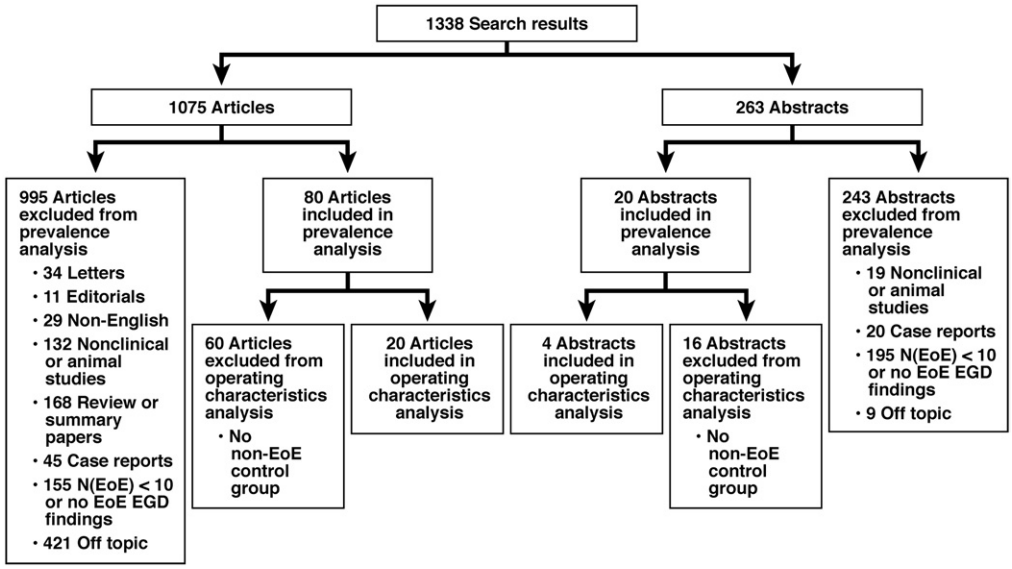

Figure 1. Flow diagram delineating the inclusion and exclusion of studies from the prevalence and operating characteristics analyses.

hand-searched. We also searched the published proceedings from the annual national meetings of the American Gastroenterological Association and the American College of Gastroenterology from 2000 to 2011.

After the search was complete, both authors reviewed each abstract to determine eligibility for inclusion. If there was any discrepancy, the full article was reviewed. Exclusion criteria comprised nonhuman studies, basic science/nonclinical studies, letters to the editor, editorials, review and summary articles, case reports, non-English studies without available translations, studies with fewer than 10 patients diagnosed with EoE, and studies that did not report upper endoscopy (esophagogastroduodenoscopy [EGD]) findings. If studies reported a composite endoscopic score, the primary investigators were contacted to request original data regarding specific findings. We included case series, cross-sectional and cohort studies, case-control studies, and clinical trials. All eligible studies were included in the prevalence analysis; however, the analysis of operating characteristics was restricted to studies that had a non-EoE control group.

Pertinent data were extracted from each study and organized into evidence tables independently by 2 authors. Data collected included year of publication, study design, study population (adults vs children, defined as age <18 y), number of patients in the study diagnosed with EoE, numbers of control participants (without EoE) if applicable, patients' sex and age, and all reported endoscopic findings. Endoscopic findings included esophageal rings (which could be termed *rings*, *felinization*, *trachealization*, or *corrugation*), strictures (defined as a focal narrowing of the esophagus), narrow-caliber esophagus (defined as a diffusely narrowed esophagus without clear focal stricture), linear furrows (longitudinal grooves or crevices parallel to the length of the esophagus, which could be termed *linear furrows*, *linear fissures*, or *tram tracks*), white plaques or exudates, pallor or decreased vasculature (defined as abnormal color, granularity, or congestion of the esophageal mucosa with loss of the normal vascular pattern), and erosive esophagitis (defined as erosions and erythema in the area of the distal esophagus and gastroesophageal junction). The number of normal endoscopies per study also was recorded. All extracted data were collected and reviewed by both authors, with discrepancies reviewed and reconciled by all of the authors.

Statistical Analysis

All study findings were compiled in tabular form, and the prevalence, sensitivity, specificity, and positive and negative predictive values were calculated for each finding by study. Overall unweighted prevalence and operating characteristics also were calculated using the raw data.

Statistical analysis was performed using Stata software (version 12.0; StataCorp LP, College Station, TX). Meta-analysis was performed to determine pooled prevalence rates and 95% confidence intervals using a random-effects model and with I^2 as the measure of heterogeneity. The I^2 statistic estimates the percentage of total variation across studies that is secondary to study heterogeneity. An I^2 statistic of 0% indicates no observed heterogeneity, and that all variation can be attributed to chance, whereas larger values indicate increasing heterogeneity. An I^2 of 25%, 50%, and 75% are considered to represent low, moderate, and high levels of heterogeneity, respectively.[20] The pooled operating characteristics (sensitivity, specificity, predictive values, and corresponding 95% confidence intervals) were determined using a mixed-effects model. To assess for sources of heterogeneity, stratified analyses were performed by age (adults vs children), study design (retrospective vs prospective), publication date (before vs after publication of guidelines), and study size ($N_{EoE} < 30$, $N_{EoE} > 30$). Stratification for publication was set at 2008 because of publication of the initial diagnostic guidelines for EoE in late 2007.

Results

Search Results

Of the 1338 publications initially identified, 80 original articles and 20 abstracts were included in the prevalence analysis, including more than 4600 patients with EoE (Figure 1). A total of 995 articles were excluded: 34 letters, 11 editorials, 29 reports that were not in the English language, 151 nonclinical or nonhuman studies, 168 review or summary articles, 65 case