

Eosinophilic Esophagitis in Adults

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Eosinophilic esophagitis (EE) is a disease characterized by eosinophilic infiltration of the esophageal mucosa, and is associated with a clinical syndrome of dysphagia and food impaction (FI) in adults. First described in 1978 [1], this syndrome is being recognized increasingly in the developed world, with multiple case series reported from the United States, Europe, and Australia during the past decade [2–9]. It is unclear if the increasing recognition of the disease is due to a truly increasing incidence or is a reflection of increased recognition by pathologists and clinicians. Endoscopic features suggestive of EE have also been described, including the presence of rings, longitudinal furrows, and mucosal fragility, although a proportion of patients may have normal-appearing mucosa. Recently, the specificity of these endoscopic findings has been questioned [10]. Diagnosis is established by the presence of eosinophilic infiltration of the esophageal mucosa; different thresholds have been used by various investigators, ranging from more than 15 eosinophils/high-power field (HPF) to more than 24 eosinophils/HPF. A recent consensus statement proposed the use of more than 15 eosinophils/HPF as the diagnostic criteria for EE in the proper clinical context [11]. The cause of EE remains unclear, with allergic (allergies to food or aeroallergens) and immunologic mechanisms being proposed [12]. Successful treatment in adults has been reported with systemic and swallowed topical steroid preparations (in case series and randomized controlled trials) [2,13] and with oral leukotriene inhibitors in small case series [14]. Endoscopic dilation alone, and in combination with medications, has also been reported as a treatment modality in patients who have EE [15,16]. The natural history and clinical course of EE in adults is thought to be characterized by recurrent symptoms [17,18] but remains poorly defined.

EPIDEMIOLOGY

Data on the epidemiology of EE in adults remain scarce, particularly in the United States. Straumann and Simon [9] reported the increasing prevalence

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of EE diagnosed in adults in Olten County, Switzerland. Olten County is a defined geographic area with a stable population of 100,000, with a single gastroenterologist and a single pathologist providing care. The investigators provided estimates from 1989 to 2004. They reported an average annual incidence of 1.48 cases/100,000 population (range, 0–6) with a marked increase in cases during the past few years of this time period. The prevalence of EE progressively increased over this time period, to 23 cases/100,000 population. The investigators considered this figure to be an underestimate, given that it represented only severely symptomatic patients.

The first truly population-based estimate of esophageal eosinophilia was provided from northern Sweden [7], where 1000 randomly selected subjects from two counties who had completed an abdominal symptom questionnaire underwent endoscopy with biopsies (taken 2 cm above, and at, the gastroesophageal junction). Biopsies were taken by three trained gastroenterologists and were interpreted by two gastrointestinal pathologists. The investigators classified patients into those with definite EE (≥ 20 eosinophils/HPF), probable EE (15–19 eosinophils/HPF), and possible EE (5–14 eosinophils/HPF). They found that 4 patients had definite EE, 7 had probable EE, and 25 had possible EE. In addition, they reported that 48 patients in all had eosinophils present in their esophageal biopsies; hence, the prevalence of EE by the current consensus definition of EE (>15 eosinophils/HPF) was 1.1%. Of the 4 patients who had definite EE in this study, 3 had symptoms of gastroesophageal reflux disease (GERD) and 1 was completely asymptomatic. Given the cross-sectional nature of this study, estimates of the incidence of EE could not be assessed.

Secular trends in the epidemiology of EE were assessed in Olmsted County, Minnesota, during the past 3 decades (1976–2006) in a retrospective study. All cases of EE diagnosed between 1976 and 2006 were identified using the resources of the Rochester Epidemiology Project. All esophageal biopsies with any evidence of eosinophilic infiltration were reviewed by a single pathologist. Patients presenting with unexplained FI needing endoscopic therapy were included as probable surrogates of EE, to maximize case identification. The clinical course of all patients was also defined using medical records and, prospectively, by using a telephone questionnaire. A total of 3456 patient charts were reviewed; 82 patients who had EE and 80 patients who had idiopathic FI were identified. The incidence of EE increased significantly during the past 3 decades (from 0.86 cases [95% CI, 0.15, 1.56]/100,000 population/year from 1976 to 1985, to 8.78 cases [95% CI, 7.19, 10.37]/100,000 population/year from 1996 to 2006). The prevalence of EE was 104.7 cases (87.5, 122.0)/100,000 population as of 1/1/2007 in Olmsted County. In this study, the prevalence and incidence of EE appear to be higher than previously reported. The incidence of EE has increased significantly during the past 3 decades, perhaps indicating the presence of an as-yet-unidentified cause of EE in the environment.

Estimates of the prevalence and incidence of EE in pediatric patients have been reported by investigators from Hamilton County, Ohio. The incidence ranged from 0.9 cases/10,000 population in 2000 to 1.28 cases/10,000

in 2003, with the prevalence in 2003 estimated to be 4.29 cases/10,000 population; these estimates were higher than estimates of Crohn's disease in the pediatric population [19]. Lower estimates of prevalence were reported in a pediatric population from western Australia by Cherian and colleagues [20] (0.89 cases/10,000). A common feature among all case series reported in the literature is the male preponderance of cases and the diagnosis of the disease in younger patients. Other factors influencing EE, such as racial predilection or socioeconomic status, have yet to be evaluated.

Natural History

The natural history of EE in adults was perhaps best described by Straumann and colleagues [16], who followed 30 adults who had EE (>24 eosinophils/HPF) with periodic dilations alone during a mean of 7.2 years. They reported that quality of life was affected in a severe manner in only 1 patient and in a minor manner in 15. Nutritional status was not compromised in any patient. Of the 30 patients, only 11 were treated with endoscopic dilation; of these, 4 had repeated dilations and 7 required only a single dilation. The remaining 19 patients were monitored only. Patients who had peripheral blood eosinophilia and severe endoscopic abnormalities were more likely to relapse than those who did not. Although fibrosis of the lamina propria was noted in later biopsies, no progression to deeper layers or to other parts of the gastrointestinal tract was observed. No patient developed esophageal carcinoma or hypereosinophilic syndrome. Hence, EE does not appear to influence life expectancy. In another study, reported from the Mayo Clinic in abstract form [21], follow-up of 10 patients who had EE 3 years after diagnosis using a mailed questionnaire revealed recurrent solid food dysphagia occurring at least once a week in 60% of patients. All had received retreatment with inhaled steroids, and 70% had received endoscopic dilation despite medical treatment. The clinical course of patients who had EE in Olmsted County was characterized by recurrent symptoms in 40% of patients responding to medical or endoscopic treatment, with EE also appearing to be a recurrent relapsing disease in a substantial proportion of patients.

PATHOGENESIS

Debate continues on the etiopathogenesis of EE, with allergic and immunologic mechanisms being proposed and investigated [22–25], based on the substantial proportion of adult patients who have associated food, inhalant, and seasonal allergies (40%–60%) [12,26] (although this appears to be somewhat lower than in children, where up to 80% have been reported to have an allergic diathesis [27–29]). Specific IgE testing, skin prick testing, and atopy patch testing have been reported to be positive in variable (32%–80%) proportions of adults and children with EE [25,30]. On the basis of allergy testing results, it is thought that EE may be a result of IgE-mediated and non-IgE-mediated reactions [31]. In addition, the relationship between EE and GERD remains to be defined [32], given the presence of esophageal eosinophilia in patients who have GERD (albeit to a lesser degree).

Two possible mechanisms of antigen sensitization have been proposed in EE. One is an initial esophageal sensitization to a food antigen, resulting in EE when esophageal re-exposure to the same antigen results; an alternative hypothesis is that initial bronchial sensitization followed by esophageal re-exposure leads to EE. This latter mechanism was supported by experiments conducted by Mishra and colleagues [22], when they exposed mice to *Aspergillus fumigatus* intranasally and intragastrically. Only mice exposed to intragastric *A. fumigatus* developed esophageal eosinophilia. A bronchial esophageal connection was also supported by experiments in which airway delivery of interleukin (IL)-13 promoted the development of EE [33]. EE appears to be associated with a Th2-type immune response; increased levels of eosinophil-active Th2 cytokines (such as IL-4, IL-5, and IL-13) and mast cells have been described in the esophagus in patients who have EE. Experimental models of EE can be induced in mice by means of allergen exposure, especially in the respiratory tract after mucosal or epicutaneous sensitization, and by means of overexpression of Th2 cytokines (IL-5 and IL-13) [22,23,34].

The esophagus is normally devoid of eosinophils. In patients who have EE, recruitment of eosinophils to the esophagus is thought to be mediated by IL-5 and eotaxin. IL-5 is a cytokine produced by T-helper (type 2) lymphocytes, which can prime eosinophils to react to chemoattractants such as eotaxin (an eosinophil chemotactic factor, also known to be overexpressed in patients who have EE Ref. [35]) (Fig. 1). IL-13 has also been shown to be crucial in the development of EE. In sensitized individuals, allergen exposure can lead to IgE-mediated mast cell degranulation, which leads to the production of chemokines, histamine, and eosinophilic chemoattractants. These factors then induce eosinophil migration and degranulation, releasing products such as major basic protein (MBP), eosinophil cationic protein, and eosinophil-derived neurotoxin. These products can cause tissue damage, edema, and chronic inflammation, which, if prolonged, can lead to fibrosis [16]. In addition, these cationic proteins released by eosinophils set up a positive feedback loop by causing further mast cell degranulation, which leads to greater eosinophil recruitment to the esophagus and further release of eosinophil granule products [31]. The effect of eosinophil products such as MBP on smooth muscle has also been described, with muscarinic M2 receptors mediating smooth muscle contraction. This finding may explain the ability of eosinophilic infiltration of the esophagus to lead to dysphagia and FI, analogous to bronchoconstriction in asthma [28,36].

Familial clustering of EE has been reported by some investigators [9,19,37,38]. Whether this clustering reflects a true genetic predilection or a common environmental exposure remains unclear. Support for a genetic basis of EE comes from a study that found that the gene encoding for eotaxin 3 was the most highly induced gene in EE patients when compared with healthy controls [35]. Seasonal variations in the diagnosis and severity of symptoms of EE have been reported in adults [27] and children [39], rendering support to the hypothesis that environmental allergens play a role in the pathogenesis of EE.

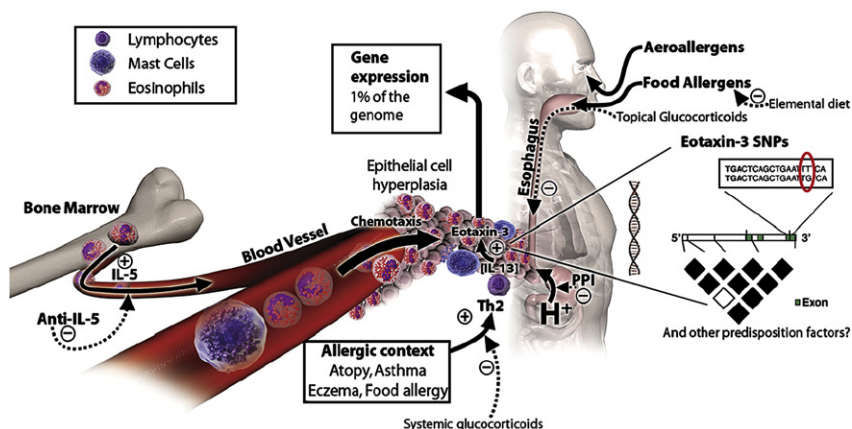


Fig. 1. A proposed mode to explain the molecular and cellular mechanisms involved in EE pathogenesis, eotaxin-3-associated eosinophil recruitment, and treatment. Aeroallergen, food allergen, and skin sensitization have been implicated in EE pathogenesis. Elemental diet, glucocorticoids, and anti-IL-5 treatments improve the microscopic features of EE acting at different levels on the disease pathogenesis. Proton pump inhibitors (PPI) inhibit H^+ secretion by parietal cells of the stomach and only partially improve EE features. Hyperplastic epithelial cells of the esophagus overexpress eotaxin-3, likely in response to IL-13. Eotaxin-3 overexpression allows chemoattraction of $CCR3^+$ cells. Inheritance of EE disease suggests a genetic predisposition. A single-nucleotide polymorphism (SNP) in the eotaxin-3 gene has been associated with EE. The linkage disequilibrium pattern (ID'I) of the SNPs in the eotaxin-3 gene, based on the genotype data in a European population from the HapMap database, is presented. ID'I is the measure of the correlation between two SNPs; it ranges from 0 (in linkage equilibrium) to 1 (in strong linkage disequilibrium). Except for the SNP pair +76 and -5419 with an ID'I of 0.71, the other SNP pairs (shown in black) are in strong linkage disequilibrium (ID'I = 1). As such, the genotype of one SNP speaks for the others. (From Blanchard C, Wang N, Rothenberg ME. Eosinophilic esophagitis: pathogenesis, genetics, and therapy. *J Allergy Clin Immunol* 2006;118:1054; with permission.)

CLINICAL MANIFESTATIONS

Patients who have EE tend to be young men, with a male gender preponderance (a male/female ratio of 3:1 was reported in one meta-analysis Ref. [8]). Most patients are diagnosed in the third or fourth decade of life. The most common presenting symptom in adults is dysphagia to solids (60%–90%). FI is also a common presenting manifestation, with 50% to 60% of patients reporting episodes. Two prospective studies have reported that 50% to 55% of patients presenting to the emergency room with FI have EE, based on esophageal biopsies [4,40]. In addition, symptoms of GERD (heartburn and acid regurgitation) are also common in adults who have EE, from 24% in a meta-analysis [8] to 50% in a prospective study of patients who had dysphagia [10]. Some patients who have EE may also present with acid reflux symptoms that do not respond to medical treatment with proton pump inhibitors. Despite the presence of acid reflux symptoms, most patients who have EE (82%) have normal or negative

ambulatory pH studies [11]. Chest pain, abdominal pain, diarrhea, and weight loss are some of the other symptoms reported by patients diagnosed with EE. This pattern of presenting symptoms in adults differs from that of children, who present with more nonspecific symptoms such as poor feeding, vomiting, regurgitation, and failure to thrive. Older children and adolescents present with symptoms similar to those of adults. Symptoms in adults are compared with those in children in [Box 1](#).

Ten percent to fifty percent of studies in adults have reported varying degrees of peripheral eosinophilia [16,36,41]. The degree of eosinophilia reported has been modest and is complicated by studies using different thresholds to define eosinophilia. A recent meta-analysis reported that 30% of patients (82/266 patients from 19 studies) had peripheral eosinophilia [8].

DIAGNOSIS

Endoscopic Manifestations

Several typical endoscopic manifestations of EE have been described in case series of EE, including esophageal rings, which lead to “trachealization” or “felinization” of the esophageal mucosa ([Fig. 2A](#)); raised white specks, which may represent eosinophilic microabscesses ([Fig. 2B](#)); longitudinal furrows ([Fig. 2C](#)); whitish exudates; and “crepe paper” mucosa, which refers to a friable mucosa that tears by the mere passage of the endoscope. Strictures can be located in the proximal, middle, or lower third of the esophagus. Case series also describe a substantial proportion of patients who have EE as having normal esophageal mucosa on endoscopy (10%–33%) [8,11,17]. A prospective study on outpatients presenting with dysphagia found that 10% of patients

Box 1: Comparison of presenting symptoms in adults and children with eosinophilic esophagitis

Adults

Dysphagia
Food impaction
Heartburn/acid reflux not responsive to medical treatment
Chest pain

Children

Feeding aversion
Vomiting, regurgitation
Failure to thrive
GERD symptoms not responsive to medical treatment
Abdominal pain
Chest pain
Dysphagia, food impaction

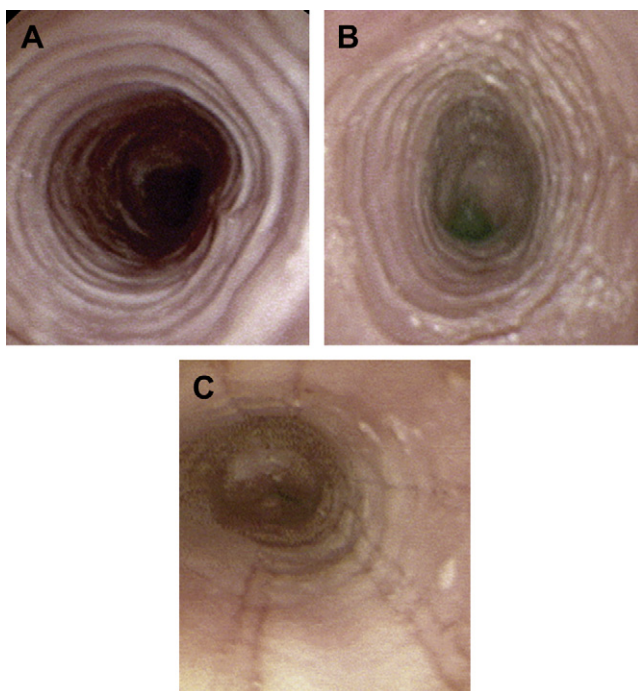


Fig. 2. (A) Endoscopy showing multiple rings in the esophagus. (B) Endoscopy showing multiple rings with white spots in the esophagus. (C) Endoscopy showing linear furrows in the esophagus.

who had a “normal endoscopy” had evidence of EE on midesophageal biopsies, supporting the argument for taking esophageal biopsies in all patients who have dysphagia and a “normal” endoscopic examination [10]. The same study also found that the typical endoscopic manifestations of EE have a poor predictive value for a diagnosis of EE, with only 38% of patients who had typical endoscopic features suggestive of EE meeting the histologic criteria for EE on midesophageal biopsies. However, the presence of more than one endoscopic feature of EE increased the likelihood of EE on esophageal biopsies in the same study [10].

Esophageal Biopsies

Site

The recent consensus statement on the diagnosis and management of EE states that “multiple biopsy specimens should be obtained from different esophageal locations along the length of the esophagus” to confirm a diagnosis of EE in all patients who have suspected EE, “regardless of the gross appearance of the esophageal mucosa” [11]. Multiple prior studies have based their diagnosis of EE on biopsies obtained from either the proximal or the distal esophagus.

These studies have demonstrated a marked variability in the degree of eosinophilia in biopsies taken from different levels of the esophagus, with levels from the distal esophagus being numerically greater than those from the proximal esophagus [17,42,43]. Gonsalves and colleagues [42] performed a subgroup analysis in 20 out of 61 patients who had proximal and distal biopsies available; they found that 4 patients (20%) met the histologic criteria for EE only on distal biopsies. In contrast, in a large pediatric study, proximal esophageal biopsies demonstrated 100% sensitivity in making a diagnosis of EE, when compared with distal esophageal biopsies.

Number

In an elegant study, investigators modeled the sensitivity of diagnosis by varying the number of biopsies [42], with a diagnostic threshold of 15 eosinophils/HPF. The sensitivity of one biopsy specimen was 55% and increased to 100% with five biopsy specimens (Fig. 3), which led the consensus statement on the diagnosis of EE to recommend that “multiple” biopsy specimens be taken. At the authors’ institution, they recommend that at least four biopsies be taken from the esophagus at different levels, to maximize sensitivity. Despite multiple biopsies, false-negative results may occur because of patchy distribution of the eosinophilic infiltrate, other medications the patient may be taking (such as systemic or inhaled steroids and leukotriene inhibitors), or involvement of deeper esophageal layers (muscularis propria) by the eosinophilic inflammation [44].

Processing

Bouin’s fluid was found to reduce the sensitivity of eosinophil detection in one study [45] and hence, it is recommended that mucosal biopsy samples be fixed in an alternative preservative (such as formalin).

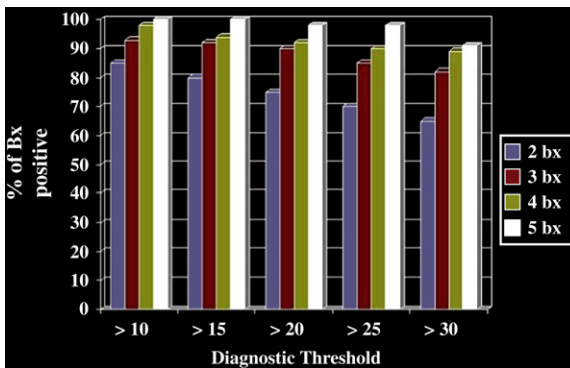


Fig. 3. Variable sensitivity of diagnosis, with varying number of biopsies from the esophagus with different diagnostic thresholds. Bx, biopsy. (From Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;64:313; with permission.)

Pathology

The diagnostic sine qua non of EE is eosinophilic infiltration of the esophageal mucosa (Fig. 4). The diagnostic threshold for EE has varied in different studies, given the lack of consensus on the precise threshold. The most commonly used thresholds are 15 [17,42,46,47], 20 [2,10,14,48], and 24 [9,13,20,35,49] eosinophils/HPF. In addition, variability has been enhanced by the use of mean, median, and maximal eosinophil counts in the diagnostic threshold, and by variation in the method of counting eosinophils, with some studies targeting the most densely infiltrated areas and other studies counting a set number of HPFs in a given area [50]. In addition, as pointed out by Dellon and colleagues [50], because of significant variation in eosinophil counts introduced by the use of different microscopes, the size of a single HPF can vary from 0.12 mm² to 0.44 mm². Given this background of significant variability, the North American consensus statement states that “intraepithelial eosinophils should be counted in the most intensely inflamed HPF of a biopsy ($\times 400$) to generate a peak count.” A peak count of greater than or equal to 15 eosinophils/HPF in at least one HPF, in the proper clinical context, was adopted in this statement as the diagnostic criterion for EE [11].

Other pathologic features that are not pathognomonic of EE but have been recognized to be characteristic of EE include eosinophilic microabscesses (defined as the presence of four or more eosinophils in a cluster), which are pathologic correlates of endoscopic mucosal specks and plaques; preferential superficial layering of the eosinophilic infiltrate in the upper half of the esophageal mucosa; basal zone hyperplasia (defined as the basal zone occupying greater than 20% of the epithelium, as seen in Fig. 5); papillary lengthening; and epithelial edema.

MBP has been proposed as a surrogate marker of eosinophil degranulation, with increased deposition of this protein being reported in the esophageal mucosa of patients who have EE compared with those who have GERD

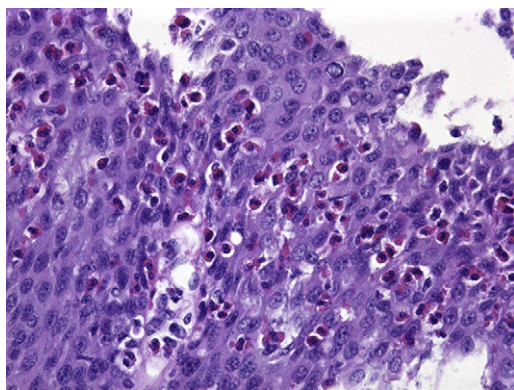


Fig. 4. Eosinophilic infiltration of the esophageal squamous mucosa.

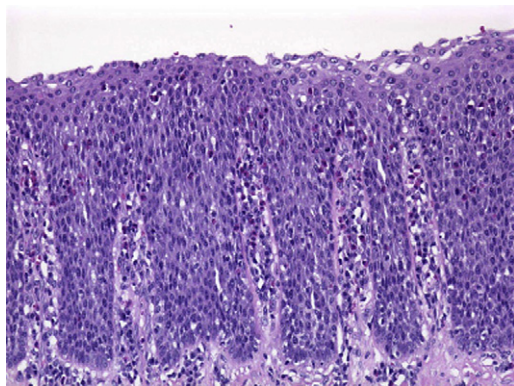


Fig. 5. Cross-section showing full thickness of the epithelium, demonstrating the striking basilar hyperplasia (elongated subepithelial papillae, thickened basal zone), commonly seen in EE.

[4,41]. It may be speculated that identification of increased levels of MBP in esophageal biopsies could increase the sensitivity of the diagnosis of EE. However, acquisition of biopsies and biopsy processing alone may cause eosinophil degranulation, releasing MBP, and possibly leading to a decrease in specificity.

Other Tests

Ambulatory pH testing

Multiple studies have reported on the results of pH monitoring in patients who have EE. In a meta-analysis, results were normal in 90% of patients [8]. Esophageal pH testing may be helpful in excluding abnormal distal esophageal reflux because it is occasionally difficult to distinguish between EE and GERD using symptoms, endoscopy, and biopsies. An alternative approach, as suggested by the recent consensus statement on EE, is to perform an upper endoscopy after 6 to 8 weeks of twice-a-day proton pump inhibitor therapy [11].

Esophageal manometry

Results of manometry in patients who have EE have been reported by a few investigators [14,51]. Most patients have normal results, with the most common abnormal findings being nonspecific peristaltic abnormalities [11] and incomplete lower esophageal sphincter relaxation [8]. Esophageal manometry does not appear to provide useful information in patients who have EE.

Radiology

Barium esophageal studies may demonstrate the presence of proximal and distal esophageal strictures, in addition to revealing diffuse narrowing of the esophagus [51–53]. A pediatric study reported the presence of EE in 8 of 18 children with Schatzki's rings [54]. Hence, radiologic studies may be helpful before endoscopy in patients who have prominent dysphagia with a high likelihood of

strictures and may provide valuable information in terms of planning endoscopy and possible endoscopic dilation.

ALLERGIC EVALUATION

Most studies evaluating the role of allergies in EE have been conducted in children. In this article, the authors attempt to summarize the results of studies performed in adults. Allergic responses have been implicated in the pathogenesis of EE, based on multiple immunologic studies. Food allergies have been documented in a substantial proportion of patients who have EE [28]; this proportion may be higher in pediatric patients than in adult patients. Despite positive tests for food allergies, however, some patients who have EE may not respond to withdrawal of the foods that cause a positive food allergy test [55]. Based on these studies and the coexistence of other allergic diseases such as allergic rhinitis, asthma, and skin or food allergies in patients who have EE, it has been recommended that patients who have EE be evaluated by an allergist [11].

Methods of allergy testing include determination of peripheral eosinophil counts (modestly elevated in some studies), assessment of specific IgE testing, skin prick testing, and skin patch testing. In addition, some studies have correlated the extent of peripheral and tissue eosinophilia with the severity and persistence of symptoms [16,56]. Eosinophil products such as eosinophil-derived neurotoxin may have potential as biomarkers of EE. Although total IgE levels have been reported to be elevated in adult patients who have EE, the significant confounding influence of coexisting atopic conditions makes the values difficult to interpret. Food-specific radioallergosorbent testing has also been reported in patients who have EE [57]. The results of these tests appear to have poor predictive value regarding the response of symptoms to the avoidance of the foods associated with positive tests. In vitro food allergy testing (using IgE levels) is not currently recommended [11].

Skin prick testing involves pricking the skin with a bifurcated needle through a drop of commercially available allergen extract; a wheal-and-flare reaction is measured after 15 minutes. Most of the studies reporting the results of this test in EE patients have been from pediatric patients [30]. Close to two thirds of patients have positive reactions to one or more foods; common foods include peanuts, eggs, soy, cow milk, and wheat. The significance of a positive skin test remains to be determined fully, however, because treatment correlates of a positive test are unclear [58].

Skin patch testing involves prolonged contact of the allergen to the skin surface and, unlike skin prick testing (which assesses type 1 or immediate hypersensitivity), it assesses delayed (or Th2-mediated) hypersensitivity. As with skin prick testing, most studies have reported results with skin patch testing in children, with most pediatric patients who have EE testing positive [25,59]. Spergel and colleagues [59,60] reported that 77% of patients who had EE had resolution of eosinophilic inflammation on biopsies when their diets were modified on the basis of positive skin tests and patch tests. The most commonly identified foods were milk, eggs, soy, chicken, and wheat. These results were

further confirmed when the investigators reintroduced the foods that tested positive, which led to recurrent esophageal eosinophilia. Because these results are from only one center, the consensus statement recommended the use of patch testing for EE in research settings until these results are confirmed by other investigators. The diagnostic criteria for EE, as per the recent American Gastroenterological Association consensus statement, are summarized as follows [11]:

- Clinical symptoms of esophageal dysfunction
- ≥ 15 eosinophils in one HPF
- Lack of responsiveness to high-dose proton pump inhibitor therapy
- Normal pH monitoring of the distal esophagus

TREATMENT

Medical Treatment

Corticosteroids

Because corticosteroids are able to control inflammation in other organs, systemic [51,61] and locally active corticosteroids have been used in EE, with success. Systemic corticosteroids are able to induce symptomatic and histologic remission. Their effectiveness has not been compared with other treatments. Doses used have been comparable to those used in other inflammatory diseases such as inflammatory bowel disease (1–2 mg/kg/d, tapered over 4–6 weeks). However, given the potential for significant systemic toxicity with prolonged use, and the availability of other effective alternatives, their use is now recommended only in patients who have severe disease manifestations necessitating rapid symptom relief, such as severe dysphagia associated with dehydration and weight loss, perhaps associated with refractory esophageal strictures. Given the toxicities associated with prolonged systemic steroid administration, maintenance therapy with systemic corticosteroids is not recommended because this is, unfortunately, associated with recurrent disease in a large proportion of patients. Recent reports have documented the ability of other immunosuppressants (such as azathioprine and 6 mercaptopurine) to exert a “steroid-sparing” effect, analogous to their use in inflammatory bowel disease, allowing the weaning of steroids and maintaining clinical and histologic remission [62].

Faubion and colleagues [48] first reported the ability of swallowed topical corticosteroids (fluticasone propionate, 880 μ g/d, or beclomethasone) to induce symptomatic remission in children who have EE. This symptomatic remission has been subsequently reported in adult patients [2,6]. Doses used in adults range from 440 to 500 μ g/d of fluticasone propionate twice a day for 4 to 6 weeks. Patients were asked to use the inhalers without a spacer, and to swallow afterwards. Patients were also instructed not to eat or drink for 30 minutes after swallowing the medication. Symptomatic remission was induced in all patients except one. Relapse of symptoms was noted in almost 50% of patients, most of whom were retreated with inhaled corticosteroids. A randomized placebo-controlled trial of inhaled fluticasone propionate in pediatric patients who

had EE showed that patients who had EE who received fluticasone were more likely to achieve symptomatic and histologic remission (50%) than those who received placebo (9%) ($P = .047$) [13]. Younger patients who have a nonallergic phenotype appeared to be more likely to respond to treatment. An alternative approach has been reported recently in the literature using swallowed budesonide suspension mixed in sucralose (a nonabsorbable sugar) to increase fluid viscosity; safety (no adverse effects with unaffected morning cortisol levels) and efficacy (80% histologic response) was reported in 20 children who had EE [63]. The most common adverse effect associated with inhaled topical corticosteroids appears to be oral candidiasis, perhaps as a result of the drug being deposited in the pharynx; oral candidiasis does not appear to be associated with the use of the viscous budesonide preparation. Inhaled topical corticosteroids may be associated with a risk for bone loss at higher doses (typically more than 750 $\mu\text{g}/\text{d}$) for prolonged periods [12]; this finding has not been reported in patients who have EE.

Leukotriene receptor antagonists

Because of the postulated involvement of eosinophil-derived leukotrienes in the inflammatory cascade causing EE, leukotriene receptor antagonists have been used in patients who have EE, with some success. However, the evidence is based on one case series only. Attwood and colleagues [14] reported the treatment of eight patients with montelukast, with six reporting complete symptomatic relief (the remainder experienced improvement in dysphagia). The doses of montelukast used were 10 to 40 mg/d. Histologic improvement was not observed. The investigators also reported continuing maintenance treatment with montelukast for a median duration of 14 months, with persistent symptomatic remission in these patients. The drug was reasonably well tolerated, with one patient developing nausea and myalgia at 40 mg/d. Contradictory data were reported by Gupta and colleagues [64], who measured cysteinyl leukotriene (eosinophil chemoattractants) levels in pediatric patients who had and did not have EE. They found that levels were comparable between the two groups and did not correlate with the degree of eosinophilic esophageal inflammation. The consensus statement on EE does not recommend treatment with leukotriene inhibitors at this time.

Endoscopic Treatment

Several earlier studies have reported the successful treatment of EE with dilations alone; these have mostly been in adult patients [16,54,65–67]. In one study, patients were managed with dilations alone (most needing only one dilation over a mean follow-up of 7 years), with minimal effect on quality of life [16]. Concern about mucosal friability leading to deep mucosal tears (sometimes with the mere passage of the endoscope) and perforation, in addition to recurrence of symptoms, remains a barrier to the widespread use of dilations as a primary means of treatment of EE. Even patients who do not have perforation have been reported to develop significant chest pain needing narcotic analgesics and hospitalization, raising the possibility of small, self-contained

perforations in these patients [66]. A recent audit of complications associated with endoscopy in EE from a single medical center reported an alarmingly high rate of endoscopic complications; 31% of patients (11/31) who had EE had these complications. The investigators reported seven mucosal lacerations, three perforations, and one emesis-induced rupture. They also attempted to identify the factors associated with an increased risk for complications and found that the presence of a stricture, a longer duration of symptoms, and a greater density of eosinophilic infiltration predicted an increased risk for complications. Because the density of eosinophilic infiltration cannot be determined before endoscopy, they suggested that the performance of endoscopy and subsequent dilatation be deferred until biopsy specimens are reviewed or treatment is completed [68]. Given this concern about perforation in patients who have EE, it has been recommended that patients who have esophageal eosinophilia have a diagnostic endoscopy with biopsies followed by medical treatment before endoscopic dilation, whenever possible. It remains unknown, however, whether dilation following medical treatment is safer than dilation upfront. It is imperative to recognize that dilation may be necessary in patients who are refractory to medical management with underlying strictures. No data are currently available on the durability of symptomatic response following endoscopic dilation alone in patients who have EE.

Dietary Treatment

Given the strong circumstantial evidence of the role of food allergy in the pathogenesis of EE, an argument can be made for the removal of offending foods/antigens as a strategy for the treatment of EE. Indeed, substantial evidence of the success of this strategy exists in the pediatric population. In children, success rates of 77% to 98% in inducing clinical and histologic remission have been reported through the elimination of all potential food antigens by using an elemental amino acid formula [55,69]; removing foods most likely to be associated with eosinophilia (such as dairy, eggs, wheat, soy, peanuts, and fish) [58]; and eliminating specific foods indicated by allergy testing by skin prick or skin patch testing [25,59].

Despite the success of dietary therapy in the pediatric population, instituting dietary changes, particularly on a long-term basis, is challenging in adults (given the poor tolerability of these significantly restricted diets), which explains the emphasis on anti-inflammatory medications and endoscopic approaches in treating EE in adult patients. A recent abstract reported the first clinical prospective trial of dietary modification in adults who had EE [70]. Adults with newly diagnosed EE (diagnosed with more than 20 eosinophils/HPF on esophageal biopsies), or those with relapsing symptoms and a prior diagnosis of EE, were recruited. All patients underwent 24-hour pH testing and were unresponsive to twice-a-day proton pump inhibitor therapy. Following skin prick testing for food and aeroallergens, patients completed a 6-week trial of a six-food elimination diet (milk, soy, eggs, wheat, nuts, and seafood were all excluded from the diet) in addition to any foods that tested positive

on skin prick testing. Repeat endoscopy with biopsies was performed after 6 weeks of the special diet, and remission was defined as the presence of fewer than 5 eosinophils/HPF on esophageal biopsies. Nine patients entered the trial, of which three had completed the trial at the time of publication of this article. Of the three patients, one had a complete response, one had a partial response (defined as significant resolution of esophageal eosinophilia without meeting the criteria for response), and one had no response. Symptom scores of dysphagia improved by 30% after dietary treatment. In addition, markers of epithelial proliferation (Ki-67 and p63 staining) also decreased significantly. Further detailed results of this study and other trials are needed before any recommendations can be made about dietary modifications in adults. Given the limited tolerability of exclusion diets in adults, this approach may be more appropriate for patients who remain refractory to medical and endoscopic therapy.

Acid Suppression

Acid reflux is also associated with esophageal eosinophilia and hence, remains in the differential diagnosis of eosinophilic infiltration of the esophagus. A recent elegant review speculated on the possible association between EE and GERD, raising four possible hypotheses to explain this interaction between acid and eosinophils in the esophagus: (1) GERD causes esophageal injury that results in a mild eosinophilic infiltration; (2) GERD and EE coexist but are unrelated; (3) EE contributes to, or causes, GERD; or (4) GERD contributes to, or causes, EE [32]. Studies in children appear to show that, although GERD may be associated with eosinophilic infiltration in the esophagus, the degree of esophageal eosinophilia is mild (<5 eosinophils/HPF) and does not reach the levels associated with a diagnosis of EE. In addition, studies in children who have EE have reported normal pH studies in most patients who have EE [71–73]. Another study correlated the likelihood of response to acid blockade and found that patients who had fewer than 3 eosinophils/HPF were more likely to respond than those who had more than 20 eosinophils/HPF [71]. Studies in adults provide more confusing results, with not only a substantial proportion of patients (23% in a meta-analysis) meeting the histologic criteria for EE reporting symptoms of GERD [10], but also a fair proportion of patients (as high as 42% in one study Ref. [6]) meeting the histologic criteria for EE having positive pH studies. This confusion is further confounded by reports of patients meeting the histologic and endoscopic criteria for EE, who respond to high-dose acid-suppressive therapy [65,74].

Biologic Agents

With greater understanding of the pathogenesis of EE, it is evident that certain cytokines, such as IL-5, play a crucial role in the production, recruitment, and activation of eosinophils in the esophagus. Preclinical studies have found that monoclonal antibodies to IL-5 or IL-5 gene deletion block the induction of EE in mice. It has also been shown that monthly administration of intravenous monoclonal antibody to IL-5 in a patient who had hypereosinophilic syndrome along with esophageal eosinophilia resulted in a resolution of esophageal and

systemic eosinophilia within 3 months [75], which raises the possibility of similar agents being tried in patients who have EE who are resistant to conventional medications.

UNRESOLVED ISSUES

Several issues remain unresolved in the diagnosis and management of EE because of limited available evidence. Controversy continues about whether the observed increase in cases of EE reflects a true increase in the incidence of EE [9,19] or is merely a reflection of increased recognition by endoscopists and pathologists and an increasing use of endoscopy [76]. Studies reaching both conclusions have appeared in the literature, although most of the available evidence appears to favor a true increase in the incidence of EE. Data are lacking on secular trends in the incidence of EE in a population-based setting in adults from the United States.

The interaction of GERD with esophageal eosinophilia remains to be defined fully. The overlap of findings (histologic and endoscopic) in patients who have GERD and EE opens up many theories [32] on the interaction between acid reflux and EE. Carefully performed, controlled studies are needed to delineate clearly the relationship between EE and GERD; it is possible that an overlap exists between the two diseases, with the clearer distinctions at both ends of the spectrum. The role of food allergy testing and dietary therapy in adults, with exclusion of foods likely to be inciting an allergic response in the esophagus, also remains unclear.

The number and location of biopsies needed for the diagnosis of EE also remains uncertain, although more evidence exists for the number of biopsies needed [42] than for their location (proximal versus distal). Even though the intensity of eosinophilic infiltration varies across the esophagus, the need for biopsies at multiple sites in the esophagus, although endorsed by the consensus statement on EE [11], remains to be proved in an evidence-based fashion; the largest pediatric study indicated that midesophageal biopsies alone missed only one case of EE when compared with distal esophageal biopsies [13]. The cost effectiveness of multiple biopsies at multiple locations also remains to be determined.

The best treatment of EE in adults also remains undefined, with the only randomized study showing efficacy for inhaled/swallowed fluticasone being reported in children [13]. Studies reporting the efficacy of inhaled topical steroids (fluticasone and budesonide) in adults are all uncontrolled case series with unclear end points. An important issue that is yet to be defined is the end point of treatment in EE. Is symptomatic improvement sufficient to classify patients as responders or is a stricter end point of histologic remission (fewer than 5 eosinophils/HPF) necessary? The answer to this question perhaps depends on another unanswered question: What is the significance of persistent esophageal eosinophilia, in the absence of symptoms? Does it act as a harbinger of symptoms and relapse and does it lead to long-term alterations in esophageal function? Treating asymptomatic or minimally symptomatic esophageal eosinophilia with currently available treatments can lead to impaired quality

of life (especially with elimination diets) and adverse effects (oral candidiasis and suppression of the pituitary hypothalamic axis with high-dose topical steroids, especially in children). Finally, whether the best method of monitoring patients who have EE who have responded to treatment is clinically, with symptom assessment alone; endoscopically, with assessment of the mucosa visually and with biopsies; or radiologically also remains to be delineated in an evidence-based fashion.

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