

REVIEW

Eosinophilic Esophagitis: Asthma of the Esophagus?

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Eosinophilic esophagitis (EE) is rapidly emerging as a distinct disease entity in both pediatric and adult gastroenterology. The typical clinical presentation includes solid food dysphagia in young men who have an atopic predisposition. Food impaction necessitating endoscopic intervention is common. EE should be suspected, in particular, in patients with unexplained dysphagia or those with no response to antacid or anti-acid secretory therapy. Careful endoscopic and radiographic examinations reveal furrows, corrugations, rings, whitish plaques, fragile crêpe paper-like appearance, and a small-caliber esophagus. Mucosal erosion in the distal esophagus, characteristic to reflux esophagitis, is absent in EE. Marked eosinophil infiltration in the esophageal epithelia (>20 eosinophils per high-power field) is the diagnostic hallmark. Food antigens and aeroallergens may play a role in the pathogenesis of EE. The mechanisms may be dependent or independent of immunoglobulin E. Elimination diets, systemic and topical corticosteroids, leukotriene receptor antagonists, and, most recently, an anti-interleukin-5 monoclonal antibody have been used to treat EE. EE likely represents another example of eosinophil-associated inflammation of epithelia at the interface between external and internal milieu, similar to bronchial asthma and atopic dermatitis. This review summarizes recent progress in the diagnosis and management of EE and discusses future research directions.

The gastrointestinal tract is continuously exposed to foods, environmental allergens, toxins, and pathogens; eosinophils are typically present throughout. Interestingly, in healthy individuals, the esophagus is unique in that eosinophils are rarely seen.¹ A number of conditions, however, do predispose the esophagus to eosinophilic infiltration. These conditions include gastroesophageal reflux disease (GERD), parasitic infections, systemic eosinophilic syndromes, and, more recently, a condition known as eosinophilic esophagitis (EE).²⁻⁸

Although EE first was described by Landres et al.⁹ in 1978, studies on EE were virtually absent until the mid-1990s. However, since clinical features of EE have become well recognized by both gastroenterologists and

allergists,²⁻⁸ EE is now emerging as an important differential diagnosis in patients with esophageal symptoms. Indeed, there has been a marked increase in the number of EE-related publications in the past 5 years, currently surpassing those related to eosinophilic gastroenteritis (EGE), the representative eosinophil-associated disease of the gastrointestinal tract (Figure 1). As a distinct disease entity, EE poses considerable diagnostic and therapeutic challenges both in pediatric and adult gastroenterology.^{2,3}

This review highlights recent progress in the diagnosis and management of EE. We focus on adult patients with EE and discuss the immunopathogenesis of EE from a viewpoint of epithelial inflammation at an interface. Based on its clinical and immunologic characteristics, it is tempting to consider EE as "asthma of the esophagus."¹⁰ Readers are also referred to other reviews for detailed experimental information on EE.^{6,7}

Prevalence

EE has been thought to be a rare disease in the past. This may be attributed, however, to poor disease awareness and the lack of well-established diagnostic criteria. Although the epidemiology of EE still is obscure, data on pediatric EE provide some insights. EE was found in 3.4% of children with reflux symptoms¹¹ and 6.8% of children with esophagitis.² A hospital-based study¹² suggested that 20% of children with dysphagia and 50% of those with unexplained dysphagia may have EE. A high prevalence of EE has been reported in children with reflux symptoms who are unresponsive to proton pump inhibitors (68%–94%).^{13,14} The prevalence of EE in adults remains unknown; one report from Australia suggested that 19 adult patients with EE were diagnosed in a 21-month period in a geographically

Abbreviations used in this paper: EE, eosinophilic esophagitis; EGE, eosinophilic gastroenteritis; GERD, gastroesophageal reflux disease; HPF, high-power field; IgE, immunoglobulin E; IL, interleukin.

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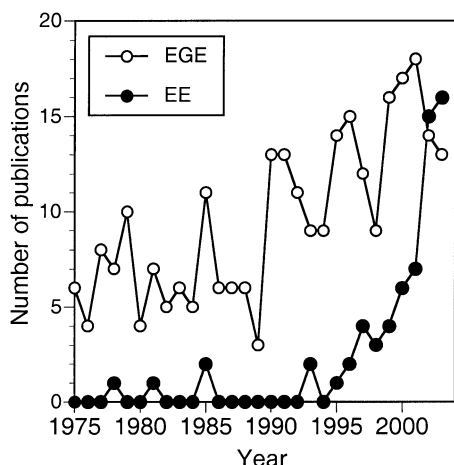


Figure 1. Number of English-language publications in the Medline database between 1975 and 2003 with the key words “eosinophilic esophagitis” and “eosinophilic gastroenteritis.”

isolated community of 198,000.¹⁵ A systematic investigation on the prevalence of EE in adults is urgently needed. EE should be included as a differential diagnosis, especially in patients with unexplained dysphagia or in those who are unresponsive to anti-acid secretory treatment. Clearly, by the number of reports in the recent literature, EE is an increasingly recognized condition. Whether this is caused by an increasing prevalence remains to be determined. Finally, Guajardo et al.¹⁶ recently initiated a world wide web-based registry for eosinophil-associated gastrointestinal disorders, including EE. Although this approach is interesting and may be useful in studying clinical features of EE, the data need to be interpreted with care because medical information provided by patients or family members may not always be accurate or sufficient and because sampling bias is inevitable.

Clinical Presentations

Clinical features of pediatric^{12–14,17} and adult^{10,15,18,19} patients with EE in 8 recent studies are summarized in Table 1. Male predominance was apparent. When these studies are combined, the percentage of boys was 73% (85 of 117)^{12–14,17} and the percentage of men was 75% (70 of 94).^{10,15,18,19} The majority of pediatric patients had atopic conditions including asthma, atopic dermatitis, and food allergy (51% to 84%). Adult patients also had an atopic predisposition (29% to 60%), although this may not be as strong as in the pediatric patients. Blood eosinophilia was seen in ~60% of the pediatric patients and between 5% to 50% of the adult patients. Increased serum immunoglobulin E (IgE) levels, positive skin prick test, and positive radioallergosorbent test could be found in a number of patients (40% to 73%). Thus, male sex, atopic predisposition, eosinophilia, increased IgE levels, positive skin prick tests, or radioallergosorbent tests seem to be useful clues to suspect EE. However, the absence of IgE-related features (e.g., negative skin prick tests or a negative radioallergosorbent test) does not exclude the possibility of EE because non-IgE-dependent EE does exist, as discussed later.

The clinical features of EE may be different between children and adults. In children, the predominant feature could be one of GERD: vomiting, dysphagia, and abdominal pain.^{13,20} However, in adult EE, dysphagia is often accompanied by solid food impaction.^{18,19,21,22} Dysphagia is long-standing^{10,19} and is often not associated with much weight loss. This suggests that the patients may have compensated for their dysphagia. Adults with EE are often very slow eaters, even as children.^{2,19}

Acid reflux is likely not important in children with EE; anti-acid therapy is generally ineffective.^{11,13,14} The

Table 1. Clinical Features of Eosinophilic Esophagitis

Study location	Year	Number of patients studied	Mean age (range)	Male	Dysphagia	Food impaction	Heartburn	Allergy ^a	Food allergy	Peripheral blood eosinophilia	Increased IgE levels	Positive skin-prick/radioallergosorbent test
Pediatric EE												
Boston ¹³	2002	19	8 (1–16)	74%	58%	11%	37%	84%	73%	58%	NA	53%
Philadelphia ¹⁷	2002	26	7 (2–14)	85%	NA	NA	NA	81%	73%	NA	NA	73% ^b
Australia ¹²	2003	21	10 (2–16)	76%	NA	67%	NA	67%	19%	NA	NA	NA
Philadelphia ¹⁴	2003	51	8 (3–16)	65%	14%	NA	53%	51%	NA	NA	NA	NA
Adult EE												
United Kingdom ¹⁸	2003	12	40 (22–64)	58%	100%	25%	50%	50%	NA	NA	NA	NA
Australia ¹⁵	2003	31	34 (14–77)	77%	89%	76%	48%	46%	25%	36%	56%	40%
Rochester, MN ¹⁹	2003	21	40 (28–55)	81%	100%	71%	19%	29%	NA	5%	NA	NA
Switzerland ¹⁰	2003	30	41 (16–71)	73%	100%	100%	7%	60%	13%	50%	69%	NA

NA, not available.

^aConcurrent allergic conditions, including asthma, atopic dermatitis, allergic rhinitis, and drug hypersensitivity.

^bPositive skin-prick test (skin patch test was positive in 81%; 96% were either skin-prick test- or patch test-positive).



Figure 2. Endoscopic and radiologic features of EE. (A) A typical ringed-appearing esophagus as seen at endoscopy. Reprinted with permission from Arora et al.¹⁹ (B) An esophagram of a patient with EE showing focal rings in the proximal to midesophagus.

results of ambulatory 24-hour esophageal pH monitoring are normal in >90%^{11,14} of children with EE who are unresponsive to acid-suppressing treatment. Although the role for reflux in adults with EE is less clear, recent reports suggest that 24-hour pH monitoring is normal in 85% to 100%.^{15,18,19} To date, there is no evidence that distal esophageal acid reflux is more prevalent in adult patients with EE. Esophageal manometry testing in adult patients with EE also has been unclear. Although there have been some reports of patients with a nutcracker-type phenomenon,^{9,21,23,24} other reports also have shown normal esophageal motility studies.^{13,19,24}

Endoscopic Features

Although endoscopic features for EE were considered to be subtle in early reports, recent studies have clearly established several features characteristic to EE.^{2,25} Careful endoscopic observations may reveal abnormalities in the majority (~90%) of patients.²⁵ The terms used include *furrows*,⁴ *vertical lines in esophageal mucosa*,²⁶ *corrugations*, *rings*,^{15,19,27} *adherent whitish plaques*,²⁸ and a *crêpe-paper mucosa*²⁹ in the mid- to distal esophagus (see Figure 2). Importantly, the presence of erosive distal esophageal changes, typical of GERD, have not been described in patients with EE to date. Although GERD lesions mostly are limited to the distal esophagus, EE appears to affect the more proximal esophagus. The term *small-caliber esophagus* also has been used to describe the endoscopic and radiographic findings.^{30,31} Vasilopoulos et al.³¹ reported that EE patients with a small-caliber esophagus showed long segments of rents that occurred after empiric dilatation. This study suggested that the clue to the diagnosis was in re-inspecting the esophagus after dilatation and finding the mucosal tears. The presence of mucosal tears has been described. Indeed, some endoscopists suggest that EE should be characterized by

a fragile esophageal mucosa, or the so-called *crêpe-paper mucosa*.²⁹ These mucosal rents are frightening during endoscopy; however, esophageal perforations occurring after dilatations rarely have been reported.³²

Multiple, nodular, whitish plaques in the esophagus, containing markedly increased numbers of eosinophils, have been reported in an EE patient with extreme hyper-eosinophilia.³³ Recent studies suggest, however, that adherent whitish plaques or whitish vesicles/exudates (0.5–2 mm in size) may be a common endoscopic feature of EE.^{2,25,28} Whitish plaques may be present in a few discrete areas or more diffusely.²⁸ Because these whitish plaques can mimic esophageal candidiasis, special care needs to be taken to avoid confusing these 2 conditions.^{2,28} The early reports of “congenital esophageal stenosis” are intriguing because they have reported a dense eosinophilic infiltrate and so also may be considered part of the spectrum of EE.^{34,35} Finally, the use of endoscopic ultrasound recently has been reported.^{36,37} By using high-resolution endoscopic ultrasound in 11 children with EE, Fox et al.³⁶ showed that the total thickness of the esophageal wall is increased significantly in EE (2.8 vs. 2.1 mm), mainly by the increase in the thickness of the mucosa and submucosa. Although the muscularis propria was slightly thickened, the circular muscle was not. One atypical elderly male patient, with an esophageal stricture, underwent an endoscopic ultrasound that showed asymmetric thickening of the muscularis propria of the distal esophagus.³⁷ These studies suggest that EE may involve more than just the epithelium of the esophagus.

Histologic Diagnosis

The diagnostic hallmark of EE is a marked eosinophil infiltration in the esophagus (Figure 3). Basal zone hyperplasia and increased papillary size appear to be nonspecific findings associated with epithelial inflammation. Because a lesser degree of eosinophil infiltration is also seen in GERD,³⁸ investigators have sought to establish a quantitative cut-off value for eosinophil infiltration to differentiate EE from GERD. Recent studies agree, both in children and adults, that EE is diagnostic if the eosinophil infiltration is >20 eosinophils per high-power field (HPF; 400×) in the squamous epithelium.^{3,4,19,20,38,39} In contrast, eosinophil infiltration in GERD is less than 5–10 eosinophils/HPF.^{3,4,32} Interestingly, 2 studies using less-strict histologic definition of EE (≥ 5 eosinophils/HPF) reported that patients with mild to moderate eosinophil infiltration (5–20/HPF) showed more GERD-like features as compared with those with intense eosinophil infiltration (>20/

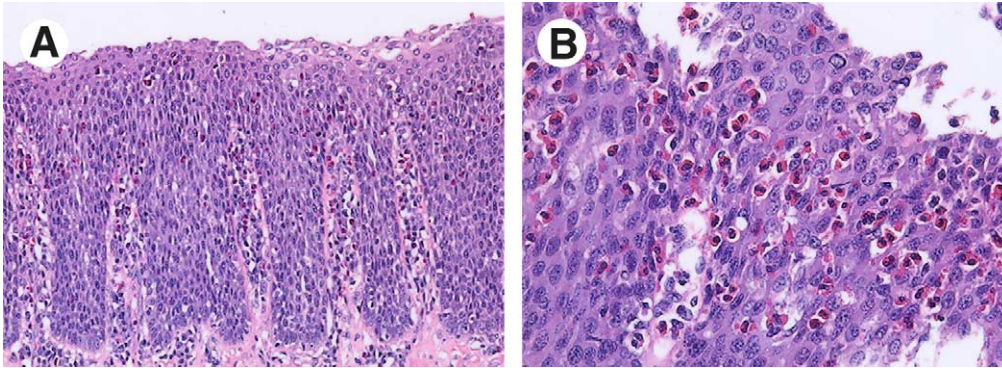


Figure 3. Pathologic features of esophageal mucosa in EE. (A) Thickened basal zone and intercellular edema. (B) Numerous intraepithelial eosinophils (H&E stains). Reprinted with permission from Arora et al.¹⁹

HPF).^{20,40} It should be noted, however, that the actual field area covered by HPF could vary, depending on the microscope used (0.166–0.307 mm²).^{10,13,18,19} Another histologic feature of EE is superficial layering of eosinophils.^{2,20} This is particularly evident in the form of eosinophil aggregates or a microabscess, burrowing through the esophageal epithelia.^{2,14,39} The eosinophil microabscess has been defined as the aggregate of 4 or more contiguous eosinophils at the surface of the esophageal epithelia.³⁹ Eosinophilic microabscesses were found in 25% to 45% of patients with EE,^{14,39} whereas none were seen in 292 GERD patients.¹⁴ Thus, superficial eosinophilic microabscess may be useful in the diagnosis of EE in patients with mild eosinophil infiltration.

Histologic studies provide intriguing information regarding disease involvement in EE. First, EE seems to affect the esophagus specifically. Concomitant eosinophil infiltration in the stomach or intestine has been found in only 4% to 13% of patients with EE.^{15,20} The patients with concurrent eosinophilic inflammation in the other parts of their gastrointestinal tract may represent secondary EE associated with EGE. Second, eosinophil infiltration in the esophagus in EE may not be homogenous (i.e., segmental,³ patchy,⁴¹ or even fluctuating⁴²), necessitating multiple biopsy specimens from different levels of the esophagus. A biopsy specimen of a whitish plaque may be useful in revealing intense eosinophilic infiltration and eosinophilic abscesses.^{25,28,33,41} Biopsies taken during an asymptomatic phase may show modest eosinophil infiltration in the esophagus.⁴² Conflicting data exist, however, regarding the magnitude of esophageal eosinophil infiltration: 2 recent studies, systematically examining the distal, middle, and proximal esophagus, suggested that the extent of eosinophil infiltration was similar irrespective of location in the esophagus in EE.^{13,15}

Prognosis

Straumann et al.¹⁰ recently reported the natural history of 30 adult patients with EE. During a mean

follow-up period of 7.2 years, dysphagia persisted in 97%. Eosinophilic inflammation was confined to the esophagus and did not progress into the stomach or duodenum. EE did not show malignant potential for cancer or hypereosinophilic syndrome. EE had a major negative impact on the social activities in only 3%. Although these data suggest that EE is likely a controllable and nondisabling disease, it should be remembered that 71% of adult EE patients¹⁹ and 24% of pediatric EE patients¹² experience serious food impaction, requiring endoscopic intervention for the removal of a food bolus. Patients with allergic disorders, such as food allergy and atopic dermatitis, often outgrow these allergies as they grow older. Unfortunately, the long-term prognosis for pediatric EE is unknown.

Immunopathogenesis

Eosinophils are tissue-dwelling cells with a tissue to blood ratio of 100–300:1. They are important effector cells in epithelial inflammation at the interface between external and internal milieu, such as skin (e.g., atopic dermatitis) and lung (e.g., bronchial asthma).^{43–45} The esophagus is another interface epithelium where the initial encounter with foreign antigens occurs. Eosinophils can cause epithelial injury via release of mediators such as cytotoxic granule proteins, reactive oxygen intermediates, lipid mediators, and cytokines.^{8,43–45} Previous studies have shown that eosinophils in EE are indeed activated in situ in the esophagus.^{46,47}

What, then, is the mechanism(s) for eosinophil recruitment and activation in the esophagus? Atopic predisposition, increased IgE levels, and positive skin-prick tests clearly suggest an IgE-mediated mechanism.^{2,13,17,20,48} Interestingly, Spergel et al.¹⁷ found that 73% of EE patients had positive skin-prick tests (i.e., IgE-dependent) and 81% had positive patch tests (i.e., non-IgE-dependent); 19% showed negative skin-prick and positive patch tests (pure non-IgE-dependent). These data suggest that both IgE-dependent (extrinsic, allergic) and

Table 2. Possible Routes of Allergen Exposure in EE

Possible routes of antigen exposure		
Initial sensitization	Secondary challenge	Responsible antigens
Esophagus	Esophagus	Food allergens (aeroallergens?)
Bronchus	Esophagus	Aeroallergens
Outside esophagus	Outside esophagus	Food- and aeroallergens

NOTE. The potential modes of antigen sensitization and challenge are listed. See text for details.

non-IgE-dependent (intrinsic, nonallergic) mechanisms may be operative in EE.

There are several possibilities for initial sensitization and subsequent challenge in EE. The possible routes of antigen exposure are summarized in Table 2. First, both initial sensitization and subsequent challenge may occur in the esophagus as antigens pass through in the form of foods, swallowed aeroallergens and pathogens, and secretions from upper and lower airways. Beneficial effects of an elemental diet in pediatric EE^{14,17,49} suggest food proteins as major responsible antigens. Second, an experimental model of EE shows that initial sensitization with aeroallergens in the bronchus is essential,^{6,7,50} with secondary challenge in the esophagus by passive ingestion of aeroallergens deposited in the naso-oral cavity. By using *Aspergillus fumigatus*, a ubiquitous fungal aeroallergen, Rothenberg et al.^{6,7} and Mishra et al.⁵⁰ have effectively shown that eosinophil infiltration in the esophagus only occurs when the animal is sensitized initially in the bronchus, but not in the nose or digestive tract. In this model, eosinophil recruitment in the gastrointestinal tract was limited to the esophagus.⁵⁰ Substantial immunologic interactions may occur between upper and lower airways (one airway hypothesis).⁵¹ This interaction may well extend to the esophagus, forming a unique aeroesophageal immune unit. This concept is interesting in view of the cross-reactivity between aeroallergens and plant-related food allergens,^{52,53} as seen in the pollen-food allergy syndrome, for example, the ragweed-banana-melon, birch-apple, and celery-mugwort-spice syndromes. Intriguingly, a case of pollen-induced EE recently has been reported.⁴² Third, EE may occur after sensitization and challenge outside the esophagus. This is possible if immune cells at the original site of antigen exposure can communicate specifically with those in the esophagus. It has been shown that exclusive sensitization and challenge in the bronchus can induce experimental EE without antigen exposure in the esophagus.^{6,7,50} There may be a possible interaction between the skin and esophagus also. Cutaneous lymphocyte-associated antigen is a skin-homing receptor for memory/effector T

cells, which recycle between skin-associated lymph nodes and squamous epithelia.⁵⁴ Cutaneous lymphocyte-associated antigen-positive T cells likely play a role in the food-allergen-induced exacerbation of atopic dermatitis. Interestingly, the esophagus is the only tissue in the gastrointestinal tract that has squamous, albeit nonkeratinized, epithelia. Teitelbaum et al.,¹³ however, showed that the number of cutaneous lymphocyte-associated antigen-positive cells in the esophagus was not increased in EE. Finally, the difference in eosinophilic inflammation seen in primary EE (without EGE) and secondary EE (with EGE) may be explained, at least in part, by the difference in the routes of antigen exposure. In an animal model, EE developed without other gastrointestinal involvement when sensitized and challenged in the lung,⁵⁰ whereas EE developed in conjunction with gastric and intestinal eosinophil inflammation when systemically sensitized and enterically challenged.⁵⁵

The roles for eosinophil-directed cytokines and chemokines in EE, in particular, interleukin (IL)-5 and eotaxin, have been studied extensively in mouse models.^{6,7,50,56} IL-5 likely plays a central role in trafficking eosinophils into the esophagus.^{50,56} Abolishing IL-5 resulted in complete disappearance of esophageal eosinophils, whereas abolishing eotaxin resulted in a significant, but partial, decrease in esophageal eosinophils.⁵⁰ Eotaxin seems more important in eosinophil chemotaxis into the stomach and intestine.⁵⁵ Intratracheal administration of IL-13, but not IL-4, induced eosinophil infiltration in the murine esophagus.⁵⁷

Unfortunately, immunologic studies on patients with EE have been sparse. The esophagus in EE shows increased infiltration of CD3⁺ T cells,^{13,48} CD8⁺ T cells,¹³ CD1a⁺ dendritic cells,¹³ and mast cells.⁴⁸ Augmented expressions of IL-5 in cells infiltrating the epithelial layer and tumor necrosis factor- α in the epithelia have been reported in EE, whereas eotaxin expression was minimal.⁴⁸ Marked expression of eotaxin in eosinophils in the esophagus was recorded in a case report.⁵⁸ Although these data are important, further immunologic characterization of EE is needed.

Treatment

There have been a number of interventions to treat EE. The premise of an elimination diet is based on the hypothesis that food allergens are the stimulus for the inflammatory response.^{4,14,49} Kelly et al.⁴⁹ first reported that 10 children with EE documented long-term improvement in their symptoms with an amino acid-based elemental diet. The efficacy of this strict elimination diet has been confirmed recently by a larger study^{4,14}: symp-

tomatic improvement occurred in 48 of 51 patients (94%) in 8.5 days. Overall, an elimination diet is a successful way to treat EE, especially in children. However, these studies do contend with the problem of compliance, because these elemental diets are difficult to continue on a long-term basis. Although food restriction based on allergen tests is more acceptable, the results are variable.^{13,17} Interestingly, the identification of responsible food allergens by the combination of a skin-prick and skin patch test¹⁷ seems to be more effective than allergen identification by skin-prick test alone.¹³ Practical approaches for diet therapy in EE were summarized by Markowitz and Liacouras.⁴ Elimination diets have not been systematically studied in adults.

The use of steroids has been found to be extremely helpful in the treatment of EE. Liacouras et al.¹¹ treated 21 children with oral steroids for 1 month, and all patients experienced near-total symptom relief within about 1 week. Faubion et al.²⁷ reported that topical steroid therapy with aerosolized corticosteroids induced complete resolution of symptoms within a week. Teitelbaum et al.¹³ used fluticasone propionate with marked improvement in symptoms and disappearance of eosinophilic infiltration in the esophagus. The only side effect was esophageal candidiasis, which was treated successfully with fluconazole. We reported our experience with topical steroids in 21 adults with EE, who had solid food dysphagia for at least 6 years.¹⁹ Therapy for 6 weeks resulted in complete dysphagia relief for a minimum of 4 months. The only adverse effect was a transient dry mouth, which was managed by oral intake of water. There were no cases of candidiasis. Although 3 patients had a relapse of dysphagia after 4 months, this responded well to a repeat topical corticosteroid treatment. About 50%–60% of adult patients develop recurrent symptoms after topical corticosteroid treatment at 12–18 months (personal observation). Most of these patients tolerate a shorter course of corticosteroid re-treatment, although this is not yet fully defined. Our standard protocol for topical steroid treatment (4 puffs twice a day [220 µg fluticasone per puff, total 1760 µg/day]) is shown in Table 3. This protocol was originally reported in the pediatric literature.²⁷ Fluticasone is safe and effective for bronchial asthma in adults; the maximum effect is achieved with a dose of around 500 µg/day.⁵⁹ Because esophageal delivery of the inhaled drug is limited (even without a spacer) and because the drug continuously is washed away toward the stomach, we believe that 1760 µg is a reasonable daily inhalation dose for adult patients with EE. The 6-week treatment period is reasonable to examine the initial responses to fluticasone inhalation

Table 3. Topical Steroid Treatment Protocol for EE Used at Mayo Clinic Rochester

Fluticasone is prescribed at a dose of 220 µg/puff with inhaler. Take 4 puffs twice a day after breakfast and evening meal (total, 1760 µg/day) for 6 weeks.
A spacer should not be used with the inhaler to maximize the drug delivery to the esophagus.
After shaking the inhaler, take a deep breath. At the point of maximum held inspiration, depress the inhaler and swallow the aerosol with each puff.
Rinse the mouth and spit the water out.
No food or drink for 3 hours after dispensing.

because most EE patients respond to fluticasone within 4 weeks (personal observation).

Attwood et al.¹⁸ described the use of montelukast to treat EE. Montelukast is a selective inhibitor of the leukotriene D₄ receptor, used successfully to treat asthma.⁶⁰ They studied 8 patients with EE, beginning montelukast 10 mg/day, and adjusted the dosage according to tolerance and symptoms up to 100 mg/day. Once symptom relief had been achieved, the dosage was reduced to a maintenance level between 20 to 40 mg/day. Seven patients (88%) showed complete improvement in dysphagia, although montelukast did not eradicate eosinophils themselves in the esophagus. The majority of patients were able to discontinue acid-suppression therapy. The only adverse effects included nausea and myalgia during the 14-month treatment. The difference between the topical corticosteroid and the leukotriene antagonist is that the former can be used in a pulse manner (for a 4–6-wk period), whereas the montelukast needs to be given daily.

Beneficial effects of anti-IL-5 treatment using mepolizumab, a humanized blocking antibody against IL-5, have been reported in 4 patients with various hypereosinophilic syndromes.⁶¹ This study included an 18-year-old man with severe EE who had been unresponsive to an elimination diet, topical fluticasone, and systemic prednisone. Intriguingly, 3 administrations of i.v. mepolizumab (10 mg/kg at 4-wk intervals) resulted in marked symptomatic and endoscopic improvement, as well as a >10-fold decrease in esophageal eosinophil infiltration in this patient. Long-term effects and safety need to be evaluated in a larger study of mepolizumab for intractable EE.

Finally, there have been a number of reports that mentioned the importance of dilatation, as well as a low-residue diet (a so-called *dysphagia diet*).^{29,31,32,62–64} These studies highlighted the fact that dilatation does improve symptoms, but they often recur.⁶⁴

Conclusions

An immense interest in EE in adults is developing, and research clearly defines a reasonably homogeneous group of patients: young men with atopic predispositions with solid food dysphagia and food impactions. EE likely represents another example of eosinophilic inflammation of epithelia at the interface between external and internal milieu, and may be considered as “asthma of the esophagus.”

Despite recent advances in EE research, a number of questions remain to be answered. Is the incidence of EE truly increasing in a similar fashion with other atopic diseases? Why is EE more prevalent in men? What are the responsible antigens and how important are aeroallergens? What is the actual route(s) of antigen exposure? Do pediatric patients outgrow EE as they become older? If so, is it host-dependent or antigen-dependent? Should extrinsic and intrinsic EE be treated similarly? Can eosinophil granule proteins directly affect neural transmission in the esophagus?⁶⁵ Finally, are eosinophils in the esophagus really all bad? An anti-inflammatory role for eosinophils has been reported recently.⁶⁶

Eos is the Greek word for the goddess of dawn. The eosinophil was so named by Paul Ehrlich in 1879 because its cytoplasmic granules stained red with eosin, similar to the colors of morning glow. Now, 125 years later, we may be witnessing the dawn of a new era of eosinophil research in gastroenterology. Hopefully, close collaborations among gastroenterologists, allergists, immunologists, and food and environmental chemists will lead to a better understanding and management of EE.

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