During the last decade, clinical practice saw a rapid increase of patients with esophageal eosinophilia who were thought to have gastroesophageal reflux disease (GERD) but who did not respond to medical and/or surgical GERD management. Subsequent studies demonstrated that these patients had a “new” disease termed eosinophilic esophagitis (EE). As recognition of EE grew, so did confusion surrounding diagnostic criteria and treatment. To address these issues, a multidisciplinary task force of 31 physicians assembled with the goal of determining diagnostic criteria and making recommendations for evaluation and treatment of children and adults with suspected EE. Consensus recommendations were based upon a systematic review of the literature and expert opinion. EE is a clinicopathological disease characterized by (1) Symptoms including but not restricted to food impaction and dysphagia in adults, and feeding intolerance and GERD symptoms in children; (2) ≥ 15 eosinophils/HPF; (3) Exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially GERD. (Use of high dose proton pump inhibitor treatment or normal pH monitoring). Appropriate treatments include dietary approaches based upon eliminating exposure to food allergens, or topical corticosteroids. Since EE is a relatively new disease, the intent of this report is to provide current recommendations for care of affected patients and defining gaps in knowledge for future research studies.

Eosinophilic esophagitis (EE) is a disease of the esophagus that has become increasingly recognized in children and adults over the last decade. It is a clinicopathologic disorder characterized by a dense esophageal eosinophilia with severe squamous epithelial hyperplasia generally occurring in association with upper gastrointestinal symptoms, primarily esophageal. In EE, the gastric and duodenal mucosae are normal. The esophageal abnormalities do not respond to treatment with high-dose proton pump inhibitor (PPI) therapy.

Although an increasing number of children and adults are presenting with EE, few controlled trials have been performed to guide management. As a result, clinical practice is largely based on limited data and expert opinion. This review was conducted in preparation for The First International Gastrointestinal Eosinophil Research Symposium held in Orlando, FL, on October 17 and 18, 2006. The clinical recommendations made herein are based on a systematic review of the published literature and on expert opinion in which there are gaps or controversy. The purpose of this review is to document the current state of knowledge in EE and to determine how to advance the field by expanding knowledge and defining priorities and strategies for future research.

Definition

A number of names and acronyms have been applied to this disease, including the following: eosino-
philic esophagitis (EE and EoE), primary eosinophilic esophagitis (PEE), allergic eosinophilic esophagitis (AEE), and idiopathic eosinophilic esophagitis (IEE). For the purposes of this review, we will use the acronym EE. Defining EE presents some problems because the presenting symptoms are similar to those of gastroesophageal reflux disease (GERD) and include heartburn, chest pain, feeding intolerance, dysphagia, odynophagia, and food impaction. However, although GERD may coexist with EE, the symptoms and pathologic features intrinsic to EE do not respond to acid suppression treatment. Although basal cell hyperplasia of esophageal mucosa often occurs in EE, as it does in GERD, the distinguishing primary histologic feature of EE is a striking eosinophilia of esophageal mucosa, often with eosinophil microabcesses. However, esophageal eosinophilia is not exclusively found in EE. Among other diseases that are associated with esophageal eosinophilia are GERD, Crohn’s disease, collagen vascular disease, infectious esophagitis (herpes, Candida), drug-associated esophagitis, hyper eosinophilic syndrome, and eosinophilic gastroenteritis1 (see Table 1). Therefore, careful consideration was given to excluding these conditions as diagnostic possibilities in the review. For example, one case series described 2 children and 1 adult with clinicopathologic features consistent with EE (gross evidence of furrowing, white plaques, and >20 eosinophils per high-power field [eos/HPF] in the squamous mucosa) in whom symptoms and histopathology resolved with intensive PPI medication.2 This is a somewhat unusual example, but, given that it is not uncommon for patients with EE to have some symptoms of GERD that respond to acid suppression treatment, our review focuses on those articles in which EE was clearly the primary diagnosis.

For the purposes of this review, EE is defined as a primary clinicopathologic disorder of the esophagus, characterized by esophageal and/or upper gastrointestinal (GI) tract symptoms in association with esophageal mucosal biopsy specimens containing ≥15 intraepithelial eos/HPF in 1 or more biopsy specimens and absence of pathologic GERD as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to high-dose PPI medication (see Table 2).

### Methodology of Review

A task force of 31 physicians who participated in the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) performed this review. The reviewers were divided into subcommittees along the lines of their recognized expertise in clinical evaluation, endoscopy, histopathology, allergy, and treatment. A systematic review of the English language medical literature through September 2006 was performed using electronic databases (MEDLINE, PubMed, and Ovid), with the key words “eosinophilic esophagitis,” “allergic esophagitis,” and “eosinophilic esophagitis.” Review articles, letters to the editor, most case reports of <3 patients, and abstracts were excluded. Several relevant articles on EE have been published since the Symposium, and a summary of these is provided at the end of this review.

Relevant data were discussed among committee members in conference calls. Critical evaluations included study design, numbers of patients, definitions used, outcomes reported, and potential biases. The chair of each committee synthesized the data, and inconsistencies were resolved by discussion until consensus was achieved. The quality of evidence supporting the recommendations contained in this review was assessed as follows: grade A: homogeneous evidence from multiple, well-designed, randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power; grade B: evidence from at least 1, large, well-designed clinical trial with or without randomization from cohort or case-control analytic studies or well-designed meta-analysis; grade C: evidence based on clinical experience, descriptive studies, or reports of expert committees.

The committees determined that the quality of evidence in these articles fell primarily into the grade C category. This finding speaks to the relative recent recognition of EE and therefore the need for current guidelines and future well-designed, randomized studies.

A total of 80 studies met the inclusion criteria and serve as the basis of this report. They include a total of 754 children (age range, 4 months to 20 years) and 323 adults (age range, 22–89 years). The sample sizes varied from 7 to 381 patients (mean, 37 years). The studies were conducted in academic centers in the United States, Canada, Europe, and Australia. The following is a review of the literature, with critical comments and consensus recommendations on selected topics.

### Table 1. Differential Diagnosis of Esophageal Eosinophilia

<table>
<thead>
<tr>
<th>Gastroesophageal reflux disease</th>
<th>Eosinophilic esophagitis</th>
<th>Eosinophilic gastroenteritis</th>
<th>Crohn’s disease</th>
<th>Connective tissue disease</th>
<th>Hypereosinophilic syndrome</th>
<th>Infection</th>
<th>Drug hypersensitivity response</th>
</tr>
</thead>
</table>

### Table 2. Diagnostic Guidelines

- Clinical symptoms of esophageal dysfunction
  - ≥15 Eosinophils in 1 high-power field
- Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day) or
- Normal pH monitoring of the distal esophagus
Epidemiology

Males are more commonly affected than females. Thirteen studies provided detailed information regarding 323 adult patients (76% males; mean age, 38 years; range, 14–89 years).16–31 Sixteen studies identified 754 pediatric patients (66% males; mean age, 8.6 years; range, 0.5–21.1 years).16–31

Geographically, patients with EE have now been identified throughout the United States and Canada, and reports in the literature have originated on all continents except Africa. Although there is frequent discussion about geographic variations of prevalence, at this time, there are no controlled data to support this.

EE has been described in patients with a variety of ethnic backgrounds, including white, African-American, Latin, and Asian, but few studies provided details. Thus, it remains unclear whether EE is associated with an ethnic or racial predilection. Socioeconomic distribution and seasonal variation in EE have not been systematically examined.

Two studies addressed the increasing prevalence of EE. Noel et al identified a 4-fold increase in disease prevalence in children with EE in the Midwest United States occurring over a period from 2000 to 2003.32 In addition, they reported an incidence of ~1:10,000 children per year, and this incidence remained constant over the course of the 4-year study. Given the lack of mortality associated with EE, the prevalence over time will increase even if the incidence remains the same. Similarly, Straumann and Simon found an increase in EE prevalence in Switzerland from 2 per 100,000 to 27 per 100,000 inhabitants over a 16-year period.33 It is unlikely that this increase can be entirely accounted for by increased recognition because the areas examined were geographically stable and recording practices were consistent.

A number of reports suggest familial clustering of the disease, but it is difficult to determine whether this observation represents genetic predisposition or similar environmental exposure.33–35 One study showed that the gene encoding the eosinophil-specific chemoattractant eotaxin-3 was the most highly induced gene in EE patients compared with its expression level in healthy individuals and may be an indicator of a potential genetic predisposition to EE.29

Clinical Manifestations

Children

As with many other diseases, some age-related differences were noted between presenting symptoms in children and adults.3,5–23,25–30,36 For instance, feeding refusal or intolerance is a common symptom of EE in children who are perhaps too young to relate the feeling of dysphagia. Children most commonly had GERD-like symptoms (including heartburn and regurgitation), although estimates varied widely across studies (range, 5%–82%). Emesis and abdominal pain were also commonly reported (range, 8%–100% for emesis; 5%–68% for abdominal pain). Dysphagia and food impaction were also reported (range, 16%–100% for dysphagia; 10%–50% for food impaction). These symptoms tended to be increasingly common with age. Other presenting symptoms in children included failure to thrive (range, 5%–19%), chest pain (range, 17%–20%), and diarrhea (range, 1%–24%).

Adults

In adults, the most common presenting symptoms were intermittent dysphagia (range, 29%–100%) and food impaction (range, 25%–100%). One report found that EE was responsible for 50% of cases of esophageal food impaction in one institution.10 Although less common than in children, GERD-like symptoms were also reported (range, 7%–100%) as were chest pain (range, 1%–58%) and abdominal pain (range, 3%–25%). Diarrhea and weight loss were reported in some patients. Many adults had long-standing symptoms including recurrent food impactions prior to the diagnosis of EE.10,37

Recommendations. EE should be considered in young children with GERD-like symptoms, including feeding problems, and in older children and adults with GERD-like symptoms, especially in those with dysphagia or esophageal food impaction. When the primary diagnosis is EE, symptoms are unresponsive or only partially responsive to acid blockade (Grade B).

Natural History

Three studies examined the natural history of EE in 90 adults, with follow-up ranging from 1 to 11.5 years.4,7,11 Potter et al followed 29 patients (21 men; mean age, 35 years; range, 16–71 years) who primarily presented with dysphagia and “refractory GERD” symptoms. The majority of patients showed evidence of tissue remodeling at endoscopy. Rings, strictures, or small caliber esophagus were found in 86% of patients, whereas radiographic studies showed narrowing in 67%. Importantly, the small caliber esophagus that was observed endoscopically was missed radiographically in 4 patients. Croese et al reported their experience with 31 patients with EE (24 men; mean age, 34 years; range, 14–77 years) who most commonly presented with bolus impaction or dysphagia (Table 3).11 Diagnosis was delayed a mean of 54 months (range, 0–180 months), and, in retrospect, highly suggestive features of EE were not recognized in 7 patients, leading to a delay in diagnosis. Strictures were present in 57% and were described as localized to the proximal esophagus, measuring several centimeters in length and extending in a longitudinal fashion. Dilation resulted in longitudinal tears in 77% of patients. No patient had a perforation. Straumann et al describe the longest follow-up of 30 adults with EE (22 men; mean age, 40.6 years; range, 16–71 years).3 The presenting
symptom was almost exclusively dysphagia with food impaction, and the diagnosis was delayed an average of 4.6 years (range, 0–17 years). During the follow-up period of 1.4–11.5 years, 23% of patients reported increasing dysphagia, and 36.7% reported stable symptoms. No change in endoscopic features was identified in 6 of 7 patients in whom a subepithelial component could be analyzed, but an increase in fibrosis and thickening was documented.

Liacouras et al reported the largest longitudinal study of 381 children with EE (66% male; mean age, 9 years).22 Most presented with symptoms of GERD refractory to acid suppression treatment or with dysphagia. Upper GI contrast studies demonstrated esophageal narrowing in 6% of children. Endoscopy showed rings in 12%, and 1 patient required esophageal dilation. In a subset of patients, medical treatment with systemic corticosteroids induced clinicopathologic remission in all but 1 patient, whereas 32% of patients treated with topical fluticasone showed improvement, with 2 developing esophageal candidiasis. Following discontinuation of medical treatment, almost all patients had recurring symptoms and esophageal eosinophilia. Dietary treatment in the form of either dietary restriction or amino acid-based formula was highly effective (97.6% showed clinicopathologic response) in inducing and maintaining remission. Barium studies normalized in 21 of 22 patients with esophageal narrowing.

Eosinophilic inflammation seems to persist over time. Clinical experience dictates that some patients may be asymptomatic and have esophageal eosinophilia. No data exist as to the best management of these patients, but it is suggested that they be followed closely for the development of clinical symptoms.

The disease does not appear to limit life expectancy. Esophageal metaplasia, (that is Barrett’s esophagus or cardia-type metaplasia or esophageal adenocarcinoma36) has not been reported in patients with EE, even in adults with severe disease. EE is not a disease characterized by mucosal ulceration or destruction. Therefore, it seems likely that the pathologic process of EE is different from that of GERD and that adenocarcinoma or squamous cancer of the esophagus are not part of the spectrum of EE, other than perhaps as coincidental occurrences. Natural history and basic studies will provide insights into the validity of this speculation.

**Recommendations.** EE tends to be a chronic disease with persistent or relapsing symptoms. To date, esophageal strictures and small caliber esophagus, often resulting in food impaction, have been the major complications identified. When these findings are encountered, either radiologically or at endoscopy, a high index of suspicion should be raised for EE, and mucosal biopsy specimens should be obtained (Grade B). Although esophageal metaplasia (Barrett’s esophagus or cardia-type metaplasia) has not been described as an associated finding in patients with EE, careful long-term follow-up is advised. Other chronic problems include failure to thrive and feeding intolerance in children. At present, it is unclear whether persistent esophageal eosinophilia is always accompanied by symptoms. See Monitoring section below.

**Diagnostic Testing**

**Endoscopy**

At endoscopy, a number of gross mucosal abnormalities have been identified including longitudinal furrowing, friability, edema, longitudinal shearing, raised white specks, whitish exudates, “crépe paper mucosa,” narrow caliber esophagus, Schatzki ring, felinization, and transient or fixed rings3,6,7,9-12,22,36,39-49 (See Table 4 and Figures 1 and 2). All listed findings except longitudinal shearing and “crépe paper” mucosa have been reported in other esophageal diseases. An earlier report described features such as circular rings that were primarily attributed to GERD but in retrospect likely were related to EE.50 This report further emphasizes that a high index of suspicion for EE must be maintained in any patient with GERD-like symptoms who has an abnormal appearing mucosa as described above.

Although none of the features can be classified as pathognomonic for EE, in the appropriate clinical context, the presence of more than 1 of these findings is strongly suggestive of the diagnosis of EE. In contrast, some studies have reported normal appearing mucosa. As experience has accumulated, particularly in centers focusing on endoscopic analysis of children and adults with EE, subtle abnormalities are now being detected that may

**Table 3. Symptoms Suggestive of Eosinophilic Esophagitis**

<table>
<thead>
<tr>
<th>Children</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding aversion/intolerance</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Vomiting/regurgitation</td>
<td>Food impaction</td>
</tr>
<tr>
<td>“GERD refractory to medical management”</td>
<td>“GERD refractory to surgical management”</td>
</tr>
<tr>
<td>Food impaction/foreign body impaction</td>
<td>Epigastric abdominal pain</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Failure to thrive</td>
</tr>
</tbody>
</table>

**Table 4. Endoscopic Features Associated With EE**

| Linear furrowing, vertical lines of the esophageal mucosa |
| White exudates, white specks, nodules, granularity |
| Circular rings, transient or fixed, felinization |
| Linear shearing/crepe paper mucosa with passage of endoscope or dilator |
| Stricture: proximal, middle, or distal |

**NOTE.** None of the features are pathognomonic of EE.
have been previously overlooked in earlier series. This may be related to different endoscopic techniques or older equipment.

**Biopsy Procurement and Evaluation**

Many earlier studies reported on endoscopic biopsy specimens that were taken primarily or solely from the distal esophagus. However, over the last several years, an increasing number of studies have included the findings on biopsy specimens from the middle and upper esophagus.6 – 8,10,11,14,16 –18,20,22–25,28,29,32,36,45,48,51–57 Three important points emerge from these studies. First, several studies show that histopathologic abnormalities are common in biopsy specimens obtained from endoscopically normal appearing mucosa. For example, in a study of 381 children with EE, 30% had a normal appearance endoscopically.22 However, over the last decade, as literature has developed and endoscopists have become increasingly aware of EE, the subtle features have become more fully recognized. Second, Bouin’s preservative was used in one study, and its use resulted in reduced ability to identify eosinophils. Therefore, fixing mucosal samples in preservatives other than Bouin’s is preferable. Third, to determine how the number of biopsy samples impacted diagnostic ability, Gonsalves et al performed a retrospective analysis of 341 biopsy specimens from 66 adults with EE. The results showed that, with a threshold of 15 eos/HPF, the procurement of 1 biopsy specimen had a sensitivity of 55%, in contrast to a sensitivity of 100% with 5 biopsy specimens.57 Clinical experience suggests that areas of gross endoscopic abnormalities, as well as proximal and distal esophageal mucosa (even if macroscopically unremarkable), should be assessed histologically.

**Recommendations.** The preceding discussion provides the rationale for histological assessment of EE. Endoscopic appearances should be documented and photographed. Mucosal pinch biopsy specimens should be obtained from all patients in whom EE is in the differential diagnosis. Biopsy specimens should be obtained regardless of the gross appearance of the mucosa, and multiple biopsy specimens should be obtained from different esophageal locations along the length of the esophagus. Biopsy specimens should also be obtained from stomach and duodenum to rule out other diseases such as eosinophilic gastroenteritis and, when appropriate, inflammatory bowel disease. Optimal fixation is accomplished by using fixative such as formalin or paraformaldehyde (Grade C). The cost-effectiveness of these recommendations has not been evaluated but deserves further study.

**Intraesophageal pH Testing**

Data regarding pH monitoring were reported in 9 studies involving adults and 11 involving children.3 – 6,9,11–20,23,25,27,28,57 Of 228 adults, pH monitoring was performed in 91 (40%) patients, with normal results in 75 (82%) patients. Of 223 children, pH monitoring was performed in 173 (78%) patients, with normal results in 156 (90%) patients.

**Esophageal Impedance**

No impedance monitoring studies have been reported in patients with EE.

**Intraesophageal pH Testing**

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**Esophageal Impedance**

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Esophageal Manometry

Esophageal manometry results were reported in 10 studies (7 adult and 3 pediatric) and were performed on 77 adults and 14 children. Of the 77 adults, the lower esophageal sphincter was normotensive in 66, hypotensive in 10, and hypertensive in 1 patient. Peristaltic abnormalities were reported in 30 of the 77 patients, with 28 of the 30 patients having nonspecific peristaltic abnormalities, and 1 each having distal esophageal spasms and nutcracker esophagus. Esophageal manometry, overall, was abnormal in 41 of the 77 adult patients (53%). All 14 children had a normal esophageal manometry.

Endoscopic Ultrasound

Endoscopic ultrasound was performed in one study of 11 children. The study reported significant thickening of the esophageal wall and individual tissue layers, including the combined mucosa and submucosal layer, and the muscularis propria, as compared with normal controls.

Recommendations. When the diagnosis of GERD vs EE is not apparent despite endoscopy and biopsy, intraesophageal pH monitoring may be of use in excluding pathologic reflux as either the primary or a concomitant cause for esophageal eosinophilia (Grade B). Alternatively, an upper endoscopy after 6–8 weeks of high-dose PPI treatment can help determine the etiology of esophageal eosinophilia (see Treatment section). Esophageal manometry does not provide diagnostic value in patients with EE.

Radiography

Some of the initial case series describing EE reported esophageal narrowing. Since then, it is well recognized that proximal and distal strictures are associated with EE. In addition, long segment narrowing and decreased compliance of the esophagus have also been described; these dynamic findings must be sought carefully because they may not be apparent on routine study. Schatzki ring has been described in some patients with EE. A series of 18 children with Schatzki ring, 8 were found to have EE. At endoscopy, none of these children showed gross evidence of a ring, suggesting that the radiograph had shown a transient contraction. These findings suggest that narrowing observed at endoscopy may or may not be seen radiographically and vice versa. When an esophageal contrast study is performed, close attention needs to be paid to esophageal distensibility and evidence of proximal or transient narrowing. In patients with a history of chronic vomiting, upper GI series may be useful to investigate other possible anatomic causes of vomiting (eg, malrotation, hiatal hernia).

Recommendations. In patients with dysphagia, an upper GI contrast study may identify the presence of a stricture, as well as its caliber and length. A contrast study may be beneficial for children who present with vomiting to rule out anatomic etiologies such as malrotation (Grade C). This information is also potentially helpful for a subsequent upper endoscopy because it may alert the endoscopist to use a smaller caliber endoscope or to proceed particularly cautiously with passage of the instrument so as to lessen the likelihood of a mucosal tear. In addition, it prepares the endoscopist for the possible need for a dilatation. An upper GI contrast study is generally not useful in patients presenting with symptoms typical of GERD, eg, heartburn.

Histopathology

History of Esophageal Eosinophilia

In 1977, the first report of eosinophilic inflammation of the esophageal epithelium in an adult with dysphagia and no GERD symptoms was published. Over the following few years, isolated case reports described additional similar findings in adults and children.

Throughout the 1980s, a number of reports associated intraepithelial eosinophils in esophageal biopsy specimens with GERD. Interestingly, Leape et al and Hyams et al recognized that a number of patients who had intraepithelial eosinophils in esophageal biopsy specimens failed to respond to medical treatment for GERD. A distinguishing feature of these patients was a dense eosinophilic infiltrate in their esophageal mucosa (see Figure 3). From 1982 until 1995, the significance of numerous esophageal eosinophils was underappreciated. Most pathologists viewed the presence of intraepithelial esophageal eosinophils as pathognomonic for GERD.

During this time, several investigators began to suggest that GERD might not be the etiology in patients presenting with a severe esophageal eosinophilia. In 1985, Lee reported a series of children and adults whose esophageal biopsy specimens showed “marked eosinophilia,” defined
as >10 intraepithelial eosinophils in 2 HPFs (Table 5).70 One patient, a 15-year-old girl presented with abdominal pain, asthma, and peripheral eosinophilia and showed no evidence of GERD. Lee considered this case to be an example of “idiopathic eosinophilic esophagitis.” In 1993, 11 adults with dysphagia, normal pH monitoring, and dense esophageal eosinophilia (>20 eos/HPF) were reported.14 Importantly, control patients with GERD had a mean of 3.3 eos/HPF in their esophageal mucosa. Seven patients had food hypersensitivity, and all required advanced intervention (dilation and/or steroids in one case) for resolution of symptoms. The authors cautioned about automatically attributing esophageal eosinophilia to GERD.14

In 1995, a seminal article by Kelly et al reported 10 children with GERD-like symptoms with intense esophageal eosinophilia despite antireflux therapy.23 Two of these patients had already received fundoplication, and all responded well to amino acid formulas, suggesting an allergic etiology. Subsequently, the degree of intraepithelial eosinophilic infiltration was correlated with response to conventional GERD treatment in children.16,54 During the 1990s, a number of studies described children with dense esophageal eosinophilia (>15–20 eos/HPF) who showed clinicopathologic response to dietary restriction with an amino acid-based formula23,54 oral corticosteroids,54,56,71 and topical corticosteroids.72 Additionally, Steiner et al showed an inverse correlation between epithelial eosinophil counts and reflex index, ie, 1–5 eos/HPF correlated with an elevated reflex index.18 These studies provided additional confirmation that patients with intractable GERD symptoms and dense eosinophilic esophageal infiltration appear to have a unique non-GERD disorder, which in some cases seemed related to allergy.

**Quantitative of Eosinophils**

The key diagnostic criterion for diagnosing EE in all studies has been an increased number of intraepithelial eosinophils. All studies used a threshold number of eos/HPF for the diagnosis of EE, but the number and method used to generate that number was not uniform. Peak count, the highest number of eosinophils within a HPF, was the method most commonly used.31,14,22,23,25,28,29,52,55,73 A mean number of eos/HPF was generated in some studies based on counting the number of eosinophils in several representative HPFs6,8,10,16,17,36,43 or in all HPFs.32,48,51,54,56 Most studies did not report the magnification and/or dimensions of the HPF in which eosinophils were counted. Those that did reported a wide variance in surface area, from 0.196 mm² to 0.44 mm².6,16,17,22,36

**Number of Eosinophils That Define EE**

The number of eos/HPF used to establish a diagnosis of EE varied among studies. For example, 10 studies required >15 eos/HPF based on peak count7,23–25,45,73 or mean number from a defined number of fields examined6,17,43,56; 8 studies required >20 eos/HPF based on peak count3,14,15,22,28,52,55 or mean number10; 2 studies required >24 eos/HPF peak count29 or mean number12; and 1 study required a peak count >30 eos/HPF.11 One study took a novel approach and set threshold numbers at >20 eosinophils in 1 HPF or >15 in 2 HPFs.8 The lowest number density of eosinophils reported for a diagnosis of EE was 15 eos/HPF for either peak or mean counts. The maximal number of eos/HPF that is associated with GERD-related esophagitis is still under investigation.2,14

**Mucosal Biopsy Specimens From Other Parts of the GI Tract**

In most studies, investigators identified histologically normal biopsy specimens from stomach (generally antrum) and duodenum.3,4,6–8,10,11,14–17,19,20,22–24,28,30,43,51,53–56 Four studies specifically excluded patients with eosinophilia of nonsophageal sites in their analysis of EE.10,11,56,73

**Eosinophil Morphology and Associated Histopathologic Features Observed in EE**

**Degranulation.** Major basic protein has been used as a marker for eosinophil degranulation in studies of asthma and atopic dermatitis. Increased extracellular major basic protein deposition in the esophageal mucosa of adults with EE compared with those with GERD has been reported.8,10 Other studies identified extracellular eosinophil granules in the mucosa affected by EE, but controls were not examined.8,14,25,28 A caveat in interpreting eosinophil degranulation is the fact that biopsy procurement and processing may cause eosinophil degranulation.74,75

**Microabscesses.** Three studies determined that eosinophilic microabscesses, defined as aggregates of 4 or more eosinophils in a cluster, were found exclusively in patients affected by EE and not in those with GERD8,10,16 (see Figure 4).

**Superficial layering.** Another histologic feature associated with EE is the preferential superficial distribution of eosinophilic inflammation in the upper one third to half of the squamous epithelium7,8,10,14,16,17,19,20,25,28,43,55 (see Figure 4). Surface layering was not found in biopsy specimens from reference groups10,16,55

**Basal zone hyperplasia.** Most investigators defined basal zone hyperplasia as a basal zone that occupied

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**Table 5. Histologic Features Associated With EE**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 Intraepithelial eos/HPF (peak count)</td>
<td></td>
</tr>
<tr>
<td>Eosinophil microabscess</td>
<td></td>
</tr>
<tr>
<td>Superficial layering of eosinophils</td>
<td></td>
</tr>
<tr>
<td>Basal zone hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** None of the features are pathognomonic of EE.
more than 20% of the epithelium\(^8,10,14,16-18,20,23,36,43\) (see Figures 3 and 4). Some studies reported less prevalent or less marked basal layer hyperplasia in a reference group compared with patients with EE\(^8,14,16,19,20,23,36\). Papillary lengthening was variably defined and was reported in 50%–100% of cases of EE in which it was evaluated.\(^8,14,16,19,20,23,36\) Some reports described papillary lengthening that was less prevalent\(^8\) or milder\(^16,23\) in a reference group compared with EE biopsy specimens. Basal zone hyperplasia and papillary elongation require well-oriented sections and therefore can be evaluated in only a minority of EE patients. Quantification of basal zone hyperplasia can be accomplished by staining for the proliferating cell antigen Ki-67 (MIB1 antibody); indeed, patients with EE have increased Ki-67 staining compared with reference control groups.\(^21\)

Epithelial edema was occasionally described in histologic evaluations of EE,\(^7,8\) whereas epithelial ulcers were rarely reported.\(^8,16\) Lamina propria fibrosis was described in only 2 reports.\(^8,36\) A limitation in evaluating this finding is the absence of lamina propria in most esophageal pinch biopsy specimens.

**Other inflammatory cells.** Cell types other than eosinophils were evaluated in some studies. Lymphocytes were increased in EE biopsy specimens\(^10,16,17,21,51\) compared with a reference group\(^17,21,29,51\) and in biopsy specimens obtained prior to therapy compared with biopsy specimens following therapy.\(^17,21\) Polymorphonuclear leukocytes were reported in some studies of EE biopsy specimens\(^8,14,16,48\) and were more\(^8\) or less\(^16,48\) abundant in reference groups. Mast cells were described as scattered as opposed to aggregated\(^14\) and were increased in EE biopsy specimens compared with a reference group.\(^24,29,51\) Numbers of mast cells positively correlated with numbers of eosinophils in one study.\(^29\)
Recommendations. EE is a clinicopathologic disease defined by esophageal symptoms associated with a severe isolated esophageal eosinophilia and absence of pathologic GERD as evidenced by normal pH monitoring of the distal esophagus or lack of response to high-dose PPI treatment. Intraepithelial eosinophils should be counted in the most intensely inflamed HPF of the biopsy (×400) to generate a peak count. Setting a fixed number of eosinophils as the sole cut-off criterion to distinguish EE from GERD is contentious, possibly misleading, and probably unwise based on current knowledge. On the basis of this literature review and collective clinical experience, we conclude that a peak count of ≥15 intraepithelial eos/HPF is an absolute minimum number to make the diagnosis of EE in the proper clinical context (Grade B). If all HPFs are counted, the mean eosinophil number may be less than 15 because of focal inflammation in the biopsy specimens, but at least 1 HPF must contain at least 15 intraepithelial eosinophils. For research purposes, defining EE with a higher threshold of peak eosinophils may be advisable to increase the specificity of the diagnosis.

Additional features that are not pathognomonic but may be helpful to the pathologist in recognizing EE include eosinophil microabscesses (correlate of endoscopic mucosal with specks and plaques), surface layering of eosinophils, basal layer hyperplasia, papillary lengthening, degranulating eosinophils, and lamina propria fibrosis and inflammation. These features should be assessed in all biopsy specimens and included in pathology reports in addition to the number of eosinophils. The diagnostic criteria for adults are the same as for children. Gastroenterologists treating adults and children with symptoms of esophageal dysfunction and numerous intraepithelial eosinophils in esophageal biopsy specimens should ensure that the disease cannot be attributed solely to GERD before making a diagnosis of EE.

Allergic Evaluation

History, Physical Examination, and Testing for Other Atopic Diatheses

Most studies characterizing the allergic phenotype have been performed in children. Allergic responses have been strongly implicated in the etiology of EE based on several lines of evidence. The majority of patients with EE (50%–80%)22 is atopic based on the coexistence of atopic dermatitis, allergic rhinitis, and/or asthma and the presence of allergic antigen sensitization based on skin prick testing or measurement of plasma antigen-specific IgE. Importantly, most patients improve on allergen-free diets, providing supportive evidence that antigen is eliciting the disease. Substantial evidence is accumulating that EE is associated with T helper cell (Th) 2 type immune responses (the type of T helper cell polarization seen in allergic individuals). In particular, elevated levels of eosinophil-active Th2 cytokines (eg, interleukin (IL)-4, IL-5, and IL-13) as well as mast cells are present in the esophagus of EE patients.5,24,51 In addition, experimental models of EE can be induced in mice by allergen exposure, especially in the respiratory tract following mucosal or epicutaneous sensitization, as well as by overexpression of Th2 cytokines (IL-5 and IL-13).76–79 Collectively, these experimental systems demonstrate an intimate connection between the development of eosinophilic inflammation in the respiratory tract and esophagus not only in response to external allergic triggers but also to intrinsic Th2 cytokines. It is interesting to note that patients with EE sometimes report seasonal variations in their symptoms; case reports recently documented seasonal changes in esophageal eosinophil levels, especially in the proximal esophagus.80,81

Recommendations. Because of the high rate of allergic rhinitis, asthma, and/or eczema in EE patients, a complete evaluation by a well-informed allergist for other atopic diatheses is recommended (Grade C).

Assessment of Atopy by Analysis of Blood Samples

Peripheral eosinophil count and eosinophil granule proteins. Seven pediatric16,17,19–21,26,47 and 4 adult38,51,80 studies document the number of peripheral eosinophils, the percentage of EE patients with peripheral eosinophilia, and the levels of eosinophil granule proteins. All were retrospective studies or case reports except for one prospective cross-sectional study. There was a significant amount of variability in the defining level for “peripheral eosinophilia” (range of eosinophils reported as abnormal ranged from greater than 350 eosinophils per mm³ to greater than 800 eosinophils per mm³). Some reports did not define the number of blood eosinophils that constituted a diagnosis of blood eosinophilia. Overall, 10%–50% of adults and 20%–100% of children had elevated peripheral eosinophil counts but usually only modestly elevated (<2-fold). In all studies, there was a high percentage of concurrent allergic sensitization, and it is likely that concurrent allergic diatheses in conjunction with EE play a role in the elevated eosinophil counts found in these patients. One study demonstrated that persistent blood eosinophilia correlated with persistent dysphagia.4 In another study, the degree of elevation of serum eosinophils correlated with the severity of EE.82

Two studies document decreases in blood eosinophil counts following therapy. Following treatment with fluticasone, 88% of patients demonstrated decreased blood eosinophil counts.26 In another study of oral corticosteroids, most patients demonstrated decreased blood eosinophils following treatment.56

Compared with other eosinophil products, plasma eosinophil-derived neurotoxin (EDN) (but not stool EDN) was also elevated in EE patients but had less predictive
value than circulating eosinophil counts. When elevated levels of EDN and peripheral eosinophil counts were used together, sensitivity, specificity, and positive and negative predictive values were 63%, 92%, 83%, and 79%, respectively.

**Recommendations.** Evaluation of peripheral blood eosinophils may provide supportive evidence for the presence of EE and the degree of tissue involvement but are not diagnostic, and correlation with disease activity is unknown (Grade C). In future studies, if eosinophil levels are to be followed, it is important that (1) blood eosinophil levels be drawn at diagnosis and again at each evaluation for response to treatment (dietary or medical) and (2) notation is made regarding the control of concurrent atopic diatheses and the extent of aeroallergen exposure at each time when eosinophil count is evaluated. Absolute eosinophil counts and defining criteria for “blood eosinophilia” should be reported in publications that document peripheral eosinophilia. Further studies are needed to evaluate whether eosinophils constitute an adequate surrogate disease marker either alone or in combination with other surrogate disease markers such as EDN.

**Total IgE.** Five pediatric and 3 adult studies report levels of total IgE in EE patients. All of the studies are retrospective and/or case reports/series. As with peripheral eosinophil counts, the defining criteria for abnormal values varied among studies, thus making broad conclusions difficult. One pediatric study correlated response of total IgE levels to oral corticosteroid therapy and found an almost 5-fold decrease, but the mean IgE level remained above normal. Overall, 71%–78% of pediatric EE patients and 60%–69% of adult EE patients had elevated total IgE levels. One adult study demonstrates that peripheral IgE levels remained elevated for years in EE patients not undergoing pharmacologic intervention. The high rate of concurrent atopic diatheses in these patients suggests that elevated IgE levels were likely not linked specifically to EE.

**Recommendations.** No published studies document whether or not total IgE can serve as a surrogate marker for disease progression or resolution. If total IgE levels are to be followed, it is imperative that (1) an evaluation is done regarding whether or not the patient has adequate aeroallergen avoidance and the pollen season at each time when the total IgE level is evaluated and (2) an evaluation is done regarding whether or not concurrent atopic diatheses are adequately controlled at the time that the total IgE is evaluated. If IgE levels are followed, it is recommended that levels be checked at diagnosis and at each endoscopic evaluation of disease response to intervention (Grade C). It is important that total IgE levels be interpreted within the context of age-defined normal values and that the total IgE level that is considered “normal” be clearly stated in any publication.

**Aeroallergen-specific IgE.** Although the presence of allergic rhinitis is cited in multiple studies, only one adult study specifically delineates the presence of antigen-specific IgE to specific allergens (grass, a potential cross-reacting allergen to wheat and rye) in a patient with EE. In addition, one case report suggests that EE is driven by aeroallergens, and one case series reports esophageal eosinophilia (up to 20 eos/HPF in the proximal esophagus and up to 12 in the distal esophagus) in patients with pollen allergies. Animal models have proposed that EE can be induced by aeroallergens.

**Recommendations.** Given the high rate of other allergic diatheses (50%–80%) in EE patients and the potential of aeroallergens to have a role in the instigation of EE, it may be important to evaluate EE patients for aeroallergen sensitivity (Grade C). Allergy testing may predict the response to pharmacotherapy or dietary avoidance in EE patients and thus warrants evaluation.

**Food-specific IgE.** Three pediatric studies report levels of total IgE in EE patients. One study utilized partial elimination diet (without success) based on food-specific IgE testing in addition to skin prick testing. No other studies used a clearly defined food specific-based elimination diet. Studies using empiric elemental formula or empiric elimination diet in children without any allergy testing (skin prick and/or patch, antigen-specific IgE) documented a 77%–98% disease improvement or eradication, suggesting that any allergy testing utilized for foods may not identify the inciting food allergen. It is currently unclear why more patients with food-specific IgE do not have anaphylaxis to those foods for which they have positive tests.

**Recommendations.** There are no positive or negative predictive values for food-specific IgE level testing in EE. In vitro food allergy testing is not supported in the evaluation of EE patients at this time, and empiric food testing should utilize skin prick tests (see below; Grade B).

**Peripheral cytokines.** Three studies, 1 adult and 2 pediatric evaluated peripheral cytokine production in EE patients. IL-13 release was elevated in 50% of adult patients (n = 3 patients with increased IL-13) with EE as compared with controls; no differences in IL-5 or interferon γ were observed. In one study, eotaxin-3 levels were found to be elevated 2-fold in the peripheral blood of EE (n = 12) as compared with normal (n = 6) and chronic esophagitis patients (n = 5). In another study involving 47 EE pediatric patients, eotaxin-3 was shown to be elevated in EE and correlated with esophageal eosinophil levels (37.7 vs 11.5 pg/mL, respectively, P = .01). In the same study, levels of plasma eotaxin-1, eotaxin-2, and IL-5 had no predictive value. Genetic analysis of single nucleotide polymorphism (SNPs) in the eotaxin-3 gene demonstrated that SNP 2496 GG in the
3′-untranslated region was overrepresented in EE patients independent of atopic status.

**Recommendations.** Eotaxin-3 expression and its genetic variation are promising markers of distinguishing EE from other causes of esophagitis (Grade B). Future research concerning the reversibility of eotaxin-3 levels with therapy and their prognostic significance deserve further investigation.

**Gene expression.** Two pediatric studies and one adult study evaluated changes in the level of esophageal genes in EE vs non-EE patients. Using a genome-wide transcript expression profile analysis, EE patients have been demonstrated to have dysregulation of ~1% of the human genome, with >50 genes changing over 10-fold. In contrast, patients with chronic esophagitis were much more similar to normal individuals. In fact, a number of these genes appear to be epithelial gene products, suggesting that the primary defect in EE may be secondary to an altered epithelial cell phenotype.

Using a genome-wide approach, followed by polymerase chain reaction-based verification and assessment of protein elevations, eotaxin-3 has been identified as markedly elevated in EE patients (50- to 100-fold) compared with normal individuals and those with chronic esophagitis. Although one study did not find elevated levels of eotaxin-3, the same study failed to find any gene elevated >2-fold, suggesting technical limitations. Two studies showed low or no difference in esophageal RANTES expression; both showed increased esophageal IL-5 expression. One study has shown increased levels of tumor necrosis factor α in affected tissue. There have been no demonstrable increases in cysteinyl leukotriene expression in EE patients.

**Recommendations.** Although the results of eotaxin-3 expression in EE vs non-EE patients are highly promising, assessment of eotaxin-3 remains a research tool, and correlations with disease severity and activity remain to be evaluated (Grade B). The identified EE transcriptome may indeed have promising value for disease diagnosis, assessment of therapeutic responsiveness, and prognosis.

**Skin prick testing for antigen sensitization.** Fifteen studies involving 12 case series and 3 case reports have examined skin prick testing in EE patients. In adults, positive skin tests to food allergens were difficult to elicit, except when there was a history of a reaction to a food (1 case). Positive skin tests to environmental allergens were more frequently found than positive reactions to food antigens. In pediatric patients, more comprehensive studies have been reported, including a retrospective case series with a total of 786 patients. Collectively, these studies have shown that approximately two thirds of patients have positive skin tests to at least one food allergen, whereas one third do not have any positive skin tests. The number of foods tested were not always reported but varied from an average of 13 foods to a panel of 42 foods. When larger panels were used, the foods tested included the common food allergens—cow milk, eggs, peanuts, soy, wheat, and fish—as well as representative members of classes of foods including grains, meats, seafood, tree nuts, fruits, and vegetables. The mean number of positive skin tests to foods when the larger panels were used varied from 2.7 ± 3.3 to 6 ± 4.2. The most common foods reported to be positive by skin prick tests included common food allergens—peanuts, eggs, soy, cow milk, and wheat—in addition to beans, rye, and beef.

**Recommendations.** Skin prick testing for foods and environmental allergens should be considered so that potential allergens and the atopic status of EE patients are identified (Grade C).

**Atopy patch testing in EE.** Patch tests were first described for contact dermatitis in the late 1890s for “allergy” to fabric. The earliest publication on patch testing in eczema was described in 1937, with the earliest controlled trial in 1982. Atopy patch testing (APT) has been used for the diagnosis of non-IgE, cell-mediated immune responses in which T cells are thought to play a prominent role. APT involves prolonged contact of the allergen to the skin with the goal of mimicking a similar immune response to atopic dermatitis. In fact, biopsy specimens of the patch test sites were found to have initial Th2 cell infiltration followed by a predominance of Th1 cytokines and eosinophils similar to the biopsy findings that have been observed in the skin of atopic dermatitis patients during acute and chronic lesions.

APT has been most extensively studied in atopic dermatitis. Most studies find that APT was better in identifying late reactions and GI reactions in children with atopic dermatitis. APT has been studied primarily in atopic dermatitis. The food to be tested is typically placed in aluminum cups (Finn Chambers on Scanpor; Allerderm Laboratories, Inc. Petaluma, CA) and then applied to uninvolved areas of the patient’s back in the 12-mm chambers. Similar to patch testing for contact dermatitis, a 48-hour occlusion time is used, and the patches are subsequently read at 20 minutes and 24 hours after removal of the Finn chamber, examining for erythema, papules, and induration. Any food can be assessed with patch testing, although cow’s milk, hen’s egg, wheat, and soy have been studied most extensively.

**Application of APT in EE**

APT has been used for the diagnosis of food allergies in two published studies by Spergel et al. They examined 146 children with biopsy specimen-diagnosed EE and eliminated foods based on positive skin test and atopy patch test. The authors found that 77% of the patients had resolution of their biopsy specimens based on these results (including 14% that required elemental formulas because of the multiple positive food
Allergies). Greater than 98% of their population responded to an elemental diet, indicating that patients who failed testing did not identify the correct foods. Spergel et al also identified foods that were apparently causative based on reintroduction of single foods or elimination resulting in normalization of biopsy specimens on elimination or significant eosinophilia on reintroduction. The most common foods were milk, egg, soy, chicken, and wheat.

**Recommendations.** The combination of prick skin tests and APT has been successful in one center and is being examined at other centers to verify these results. In addition, APT has shown promise in atopic dermatitis with good predictive values, high specificity, and low sensitivity, and APT has shown highly promising results with regard to food elimination diet and food reintroduction in patients with EE. However, its use should be reserved until additional data from multiple research teams emerge that clearly establish its value for diagnosing and/or managing EE (Grade B). In addition, further data regarding the types of cells and immune response that is occurring at the site of patch testing are needed (e.g., skin biopsy studies).

**Treatment of EE**

It is not known whether treatment will impact long-term outcomes of the disease, and the exact end points (reversal of symptoms and/or endoscopically or histologically normal mucosa) are not certain. The lack of evidence makes decisions regarding choice and duration of treatment difficult. Here, we present the evaluation of the data regarding efficacy and safety of known treatments.

**Acid Suppression**

**Rationale.** Gastric acid is not thought to be the primary mediator associated with the pathogenesis of EE. Patients with esophageal eosinophilia who are treated with PPI with resolution of their symptoms have GERD and not EE. Basic studies suggest that gastric acid inhibition may predispose to an allergic phenotype but population-based research has not yet been done to confirm this hypothesis.

**Studies.** PPIs play 2 potential roles for patients with EE. First, they are useful as part of the diagnostic evaluation in patients suspected of having EE. Lack of evidence makes decisions regarding choice and duration of treatment difficult. Here, we present the evaluation of the data regarding efficacy and safety of known treatments.

**Esophageal Dilatation**

**Rationale.** A number of studies document the presence of esophageal narrowing in patients with EE. The incidence of this complication is not certain. By the time this complication arises, medical management alone may not suffice, and thus mechanical dilatation may be necessary.

**Studies.** Several studies have reported the use of esophageal dilatation of EE strictures in adults. Morrow et al described 19 patients who underwent dilatation: 15 of 16 reported overall improvement in their dysphagia after multiple sessions of dilatation. No perforations occurred; however, deep mucosal tears, increased postendoscopy analgesia, and difficulty inserting the endoscope were reported in several patients. Straumann et al studied 11 EE patients who required esophageal dilatation. Of these, only 4 patients required repeat dilatation. Although the procedure caused severe mucosal tearing, no perforations occurred. Over 50% became asymptomatic, and one patient reported no improvement in symptoms. Vasilopoulos et al described 5 patients with small caliber esophagus. Of these patients, all received esophageal bougienage; 2 experienced extensive esophageal tearing associated with chest pain and overnight hospitalization. Cantu et al reported successful esophageal balloon dilatation in 2 cases. In the only pediatric study, Nurko et al described 7 EE patients who underwent dilatation. Five of the 7 patients had total symptom relief, whereas the other 2 only had a partial response. Despite successful esophageal dilatation, a significant number of patients developed a recurrence of their stricture requiring repeat dilatation. The recurrence rate ranged from 7% to 50% and occurred between 2 and 24 months. Additionally, as mentioned above, there have been a number of reports of esophageal mucosal tearing, significant pain, and rare reports of esophageal perforation.
Moreover, there has been an association with linear esophageal tearing or tearing simply with the introduction of the endoscope through the stricture.

Although dilatation may not alter the underlying abnormal esophageal histology, it may be required to facilitate esophageal function. Whether medical therapy should always be considered prior to performing dilatation of strictures secondary to EE is not certain. No studies have demonstrated normal esophageal histology after dilatation without additional medical or dietary therapy. Unless a critical stricture exists, a diagnostic procedure should be performed. If esophageal eosinophilia exists, patients not previously treated with acid suppression should be started on PPI therapy. If EE persists, medical or dietary therapy should be initiated. The approach to the untreated patient with narrowing is not certain. Approaches include pretreatment with nutritional or medical treatments or immediate dilatation. Whether medical treatment before dilatation leads to a better outcome is not known. Although not proven, concern exists that the use of steroids (systemic or topical) may exacerbate the risk of a perforation related to dilatation. Expert opinion suggests that residual strictures, unresponsive to medical therapy, may be more safely dilated, thereby reducing the risk of esophageal tearing.

**Recommendations.** Esophageal dilatation is useful for symptomatic patients who present with symptomatic esophageal narrowing secondary to fixed strictures causing food impaction (Grade C). However, because of the risk of mucosal tearing and perforation, whenever possible, a diagnostic esophagostomy with biopsy followed by medical or dietary therapy for EE should be attempted prior to performing esophageal dilatation. Inspection of the esophageal mucosa (radiographic or very gentle endoscopic examination) should be considered following esophageal dilatation to assess for laceration injury prior to the performance of sequential, larger caliber dilatation.

**Corticosteroids**

**Rationale.** Eosinophilic inflammation acutely resolves with the use of systemic corticosteroids in a number of allergic diseases including asthma and eczema. Proposed mechanisms in which corticosteroids impact eosinophils include induction of apoptosis, down-regulation of chemotactic factors, and inhibition of proinflammatory mediators. As such, a number of studies have shown that corticosteroids significantly improve esophageal eosinophilia in patients with EE. Although systemic corticosteroids are effective, they are associated with significant adverse effects. In contrast, swallowed topical steroids administered by a metered dose inhaler (or in a viscous solution) provide several advantages compared with systemic steroids. The dose of topical steroid is significantly less, the liver rapidly metabolizes the topical steroid, and the delivery of the medication is directly to the esophageal mucosa.

**Studies: systemic steroids.** Two early studies have demonstrated that systemic glucocorticoids (prednisone) are an effective pharmacologic treatment in resolving the clinicopathologic features of EE. In 1998, Liacouras et al demonstrated that the use of systemic corticosteroids significantly improved both clinical symptoms (within 7 days) and esophageal histology (within 4 weeks) in 20 of 21 children with EE. No published studies to date have compared the impact of systemic corticosteroids with other treatments.

Clinical experience dictates that systemic corticosteroids are useful when urgent symptom relief is required. These patients include those with severe dysphagia, dehydration, significant weight loss, or esophageal strictures. Additionally, steroids may be useful for EE patients presenting with a small caliber esophagus or for those patients deemed at high risk for esophageal perforation when undergoing esophageal dilatation. Dosages effective in relieving clinicopathologic abnormalities were similar to those used for inflammatory bowel disease (1–2 mg/kg/day of prednisone; maximum 60 mg), although lower doses have not been reported. Risk factors associated with long-term use of systemic corticosteroids include growth abnormalities, bone abnormalities, mood disturbances, and adrenal axis suppression among others. Corticosteroids were weaned similar to a schedule followed for patients with inflammatory bowel disease. Typically, when the medication was discontinued, the clinicopathologic signs and symptoms recurred.

**Studies: topical steroids.** Beginning in 1998, multiple studies demonstrated the effectiveness of swallowed topical corticosteroids delivered from a metered dose inhaler unit in treating clinical symptoms and abnormal histology associated with EE in adults and children. The first such study was reported by Faubion et al who prescribed swallowed fluticasone propionate (up to 880 μg/day) or beclomethasone twice a day to 4 patients with EE. All 4 patients demonstrated an improvement in clinical symptoms; 1 patient underwent repeat posttreatment biopsy and showed resolution of mucosal eosinophilia.

Since that initial study, 47 adults and 33 children were studied in 4 separate studies. With regard to the adults studied, 440–500 μg twice daily of fluticasone propionate was administered for 4–6 weeks. Clinical symptoms improved in all but 1 patient; complete resolution occurred in 75% of cases. Reported adverse effects included esophageal candidiasis in 3 patients and severe dry mouth in 1 patient. Follow-up evaluation revealed a recurrence in symptoms in 17 of 37 patients between 3 and 18 months after therapy was discontinued. With regard to the pediatric patients studied, 220–440 μg twice daily of fluticasone propionate was administered for 6–12 weeks. Clinical and histologic symptoms improved in 31 of 33 patients; 2 patients had no significant improvement. Esophageal candidiasis developed in 6 pa-
tients. Long-term follow-up and recurrence of symptoms after therapy was discontinued was not reported.

Details regarding the exact method of administration were not always presented, but clinical experience and documented protocols recommend that patients spray the metered dose inhaler in the mouth with lips sealed around the device. Following administration, patients should not eat, drink, or rinse for 30 minutes. In an attempt to provide easier delivery of this form of medication, Aceves et al used a preparation of viscous budesonide. Two patients were studied and swallowed 500 μg of oral budesonide mixed in a sucralfate suspension twice a day. The patients’ symptoms as well as histopathology normalized within 3 months of initiating therapy.

A meta-analysis of the risk of inhaled corticosteroids found that fluticasone might lead to bone loss at total daily doses higher than 750 μg each day. This risk may not be as great with swallowed topical steroids because they are rapidly metabolized by the first pass effect not present with inhaled steroids. Although this study evaluated inhaled steroids in patients with asthma, it should be noted that total daily doses of 1760 μg each day have been reported in patients with EE.

**Recommendations.** Systemic and topical corticosteroids effectively resolve acute clinicopathologic features of EE; however, when discontinued, the disease generally recurs. Systemic corticosteroids may be utilized in emergent cases such as dysphagia requiring hospitalization, dehydration because of swallowing difficulties, and weight loss. However, because of the potential for significant toxicity, their long-term use is not recommended (Grade B). For many patients, topical corticosteroids are also effective in inducing EE remission. Although the incidence of adverse effects with this form of administration has not been formally studied, several studies have documented its safety, except for local fungal infections.

The use of topical corticosteroids for maintenance treatment has not been studied. Age adjusted doses and administration frequency of topical corticosteroids, ie, fluticasone, budesonide, for children and adults with EE have not been established and these formulations were not designed for esophageal administration. One study extrapolated doses from those utilized in the treatment of asthma. Since then, others have utilized higher doses without significant complications. On the basis of expert opinion and the current literature, suggested starting doses range from 440–880 μg per day for children and 880–1760 μg per day for adolescents/adults. Drug has been administered by mouth and can be split into twice or 4 times daily doses. Equally important is the method of administration; patients should be instructed to administer the MDI without the use of a spacer. The MDI should be inserted into the mouth, sprayed with lips sealed around the device. The powder should then be swallowed and not rinsed. Patients should not eat or drink for at least 30 minutes. This regimen is continued for 6–8 weeks and then patients followed as described in Monitoring section (Grade B). More studies are needed to clarify specifics of topical steroid treatment plans. Also see Update section for information on alternative method of administration.

**Leukotriene Receptor Antagonists and Mast Cell Stabilizers**

**Rationale.** Inflammatory mediators such as cysteinyl leukotrienes or preformed mediators found in granules released by mast cells have been theorized to cause esophageal inflammation and tissue eosinophilia that occurs in patients with EE.

**Studies: Cromolyn Sodium.** The use of oral cromolyn sodium has never been formally studied in patients with EE. In a 10-year review, Liacouras et al presented information on 14 EE patients treated with 100 mg oral cromolyn, 4 times daily for 1 month. The study demonstrated that no patient improved either clinically or histologically.

**Studies: Leukotriene Receptor Antagonists.** Two studies have addressed the role of leukotriene receptor antagonists in patients with EE. Attwood et al utilized up to 100 mg in 8 patients diagnosed with EE manifested by dysphagia and symptoms of gastroesophageal reflux. After several weeks of treatment, 7 of the 8 patients showed complete symptomatic resolution; the other patient improved but did not completely resolve. The medication was maintained for a median of 14 months at doses ranging from 20 to 40 mg per day. Once discontinued, 6 of 8 patients had a recurrence of symptoms within 3 weeks. Minimal adverse effects (nausea, myalgia) occurred; however, no significant improvement in histology was appreciated. Gupta et al determined esophageal mucosal levels of cysteinyl leukotrienes in children with EE and normal controls and found that they were similar in both groups.

**Recommendations.** Although cromolyn sodium has no significant adverse effects, it has no apparent therapeutic effect for patients with EE. Leukotriene receptor antagonists have been shown to induce symptomatic relief at high dosages; however, its use has not been shown to have any effect on esophageal eosinophilia. Measurements of mucosal leukotriene levels do not suggest potential for a therapeutic benefit. The use of these drugs for the treatment of EE is not supported by the current literature (Grade C).

**Dietary Treatment**

**Rationale.** There is strong circumstantial but not definitive evidence that food allergens contribute to the pathogenesis of EE in children. The removal of food antigens has clearly been demonstrated to treat successfully both the symptoms and the underlying histopathology in the majority of patients with EE.
of causative foods can follow several therapeutic regimens. First, specific food elimination can be based on allergy testing and clinical history. Second, the decision to limit foods can be based on simply removing the foods deemed to be the most likely to cause EE. Finally, an amino acid-based formula can be utilized, thus removing all potential food allergens. The effectiveness of dietary therapy in adults has not been studied.

**Studies: specific food elimination.** As was mentioned in the section entitled Allergy Testing, diagnostic tests consisting of radioallergosorbent testing and IgE skin prick tests are limited and may have poor predictive value in implicating those antigens that provoke an inflammatory response in the esophageal mucosa. Several studies have demonstrated poor correlation of these tests to improvement of either symptoms or tissue inflammation. However, in one academic center, the introduction of APT used in combination with IgE skin prick testing significantly increased the ability to identify potential food allergens. Spiegel et al described the use of combination skin prick and APT in 146 patients with EE. Of these, 112 patients (77%) demonstrated clinical and histologic improvement after 6 weeks of dietary restriction based on allergy testing utilizing skin prick tests and APT.

**Studies: removal of selected causative foods.** In an attempt to minimize allergy testing and determine etiologic food allergens, Kagawalla et al demonstrated that the removal of the 6 most common allergenic foods (dairy, eggs, wheat, soy, peanuts, fish/shellfish), without the aid of allergy testing, demonstrated significant efficacy. Approximately 74% of the 35 patients who received the 6-food elimination diet demonstrated significant improvement both clinically and histologically. The study also compared the 6-food elimination diet to 25 patients who received a strict amino acid-based diet with no other added foods. The comparison revealed that, although both diets significantly improved the clinicopathologic features of the disease, the elemental diet was more effective with regard to the number of patients who responded (22 of 25) and with regard to the residual number of eosinophils per HPF (13.6 in the 6-food group; 3.7 in the amino acid formula group).

**Studies: amino acid-based formula.** The use of an amino acid-based formula is currently the gold standard in determining whether food antigens are responsible for EE in those patients who do not respond to diet elimination of specific antigens. In children, the use of an elemental formula has been shown to be extremely effective in 92%-98% of patients. Patients' symptoms resolved within 7 to 10 days followed by almost complete histologic resolution of the esophageal eosinophilia within 4 to 5 weeks. After the symptoms and histology normalized, a slow reintroduction of select foods was initiated. Because of poor palatability, the use of a strict amino acid-based formula frequently required enteral feeding via a nasogastric or gastrostomy tube as reported in these studies. Additionally, the administration of these formulas can be costly.

**Recommendations.** Dietary therapy (the specific antigens removal or elemental formula) should be considered as an effective therapy in all children diagnosed with EE (Grade B). When deciding on the use of a specific dietary therapy, the patient’s lifestyle and family resources also need to be considered. Consultation with a registered dietitian is strongly encouraged to ensure that proper calories, vitamins, and micronutrients are maintained. The use of dietary therapy in adults requires further study.

**Biologics**

**Rationale.** Potential future treatment includes the use of monoclonal antibodies such as anti-IL-5. Biologic treatments, like anti-IL-5, specifically target the molecule receptors that influence the production, migration, and activation of the eosinophil, subsequently reducing esophageal tissue inflammation. Notably, anti-IL-5 or IL-5 gene deletion blocks induction of experimental EE in mice, including esophageal epithelial hyperplasia, providing preclinical evidence that this strategy may be effective in EE.

**Studies.** Garrett et al demonstrated the effectiveness of anti-IL-5 antibodies in an adolescent male who had hypereosinophilic syndrome manifested by significant esophageal eosinophilia. Anti-IL-5 was administered via an intravenous infusion monthly. Within 3 months of treatment, the patient’s symptoms and esophageal eosinophilia dramatically improved (Grade C). Novel biologic agents present a unique opportunity for certain patients with EE. These molecules await clinical trials and cannot be recommended for routine use at the present time (Grade C).

**Treatment Panel Discussion**

Treatment recommendations are based on the potential unknown deleterious impact of chronic esophageal eosinophilia. Minimizing treatment adverse effects and maintenance of a high quality of life are additional treatment goals. Drug treatments are less restrictive, placing no compromises on the patient’s diet, but carry potential adverse effects and unknown duration of treatment. Dietary treatments give the prospect of prolonged remission but entail significant lifestyle modification. Despite the advances that have been made, controversy continues regarding treatment end points. Should treatment be aimed at symptomatic improvement or toward histologic resolution of eosinophilia? An analogy with inflammatory bowel disease may be made: the treatment of inflammatory bowel disease and celiac disease is aimed at symptomatic relief and not histological normalcy. In contrast, chronic esophageal inflammation secondary to acid reflux has been shown to contribute to Barrett’s
esophagus and potential esophageal cancer. Because we do not yet know the impact of chronic, untreated esophageal eosinophilia, there is an urgent need to determine, or even estimate, the natural history of EE so that we can better weigh the morbidity of chronic therapy against the risk of future complications.

**Treatment end points.** The goal of therapy remains unsettled. At the minimum, treatment should be aimed at relieving symptoms, which would ideally be accompanied by resolution of esophageal eosinophilia. However, resolution of symptoms and esophageal eosinophilia may not occur concordantly. Substantial esophageal eosinophilia persists in some patients who are asymptomatic or have only minimal symptoms. The optimal approach to such patients is unclear. On the one hand, more aggressive treatment may help prevent progression to permanent esophageal dysfunction and possibly improve symptoms that may not have been fully appreciated by the patient or parents. On the other hand, the natural history of esophageal eosinophilia has not been well established, and it is thus not clear whether all patients with persistent esophageal eosinophilia are destined to develop complications. There are no well-established markers to predict patients at increased risk, although those who have already developed esophageal morphologic abnormalities (such as rings, strictures, or narrowing) have already established themselves as being at increased risk.

At the same time, more aggressive treatment may have implication on quality of life and/or adverse effects. Elimination of foods in children, for example, can decrease quality of life in the patients and their family members. Corticosteroids, even if given topically, have been associated with esophageal candidiasis, and the long-term safety of strategies involving such treatment is unknown.

Thus, we suggest that treatment be initially aimed at improving symptoms. In those with persistent esophageal eosinophilia, the decision to advance treatment should be based on the degree of symptoms, the age of the patient, the presence of esophageal morphologic abnormalities, the results of monitoring (see below), and the patient’s and family’s values and preferences (Grade C).

**Monitoring.** Optimal strategies for monitoring patients with EE have not been established, and there continues to be variability among experts. EE has not been associated with the development of esophageal malignancy, although follow-up has been short. Thus, the main aim of monitoring is to prevent progressive esophageal dysfunction and detect complications from therapy.

In children with EE, many experts perform periodic endoscopy and/or barium studies to evaluate for persistent esophageal eosinophilia and/or the development of esophageal morphologic abnormalities. However, as noted above, whether the detection of persistent esophageal eosinophilia in asymptomatic patients warrants more aggressive therapy is unclear. Furthermore, there have been few studies to guide the biopsy protocol and the optimal interval for surveillance and to clarify baseline fluctuation in the density of esophageal eosinophilia with time. Whether surveillance (and the subsequent response to findings on surveillance) improves outcomes is unclear. Surveillance endoscopies are also associated with the potential for complications. In particular, patients with EE are at increased risk for esophageal tears and perforation.

Similar issues apply to adults with EE. Adults are more capable than younger children to report accurately their symptoms; however, whether monitoring symptoms alone is sufficient to guide treatment decisions remains uncertain. Some experts suggest periodic, regular, upper endoscopy regardless of symptoms, whereas others suggest upper endoscopy guided mainly by changes in symptoms.

**Recommendations.** In children and adults with EE, we suggest regular clinic visits during which the patient and parents should be questioned about symptoms, compliance with therapy, and adverse effects (Grade C). This suggestion is based on improving the recognition of long-term complications associated with chronic esophageal eosinophilia; presently, the incidence of complications is unknown.

In children, options for endoscopic and radiographic monitoring should be discussed considering the issues above. One approach might be to perform repeated upper endoscopies until settling on a treatment regimen that has controlled symptoms and ideally resolved esophageal eosinophilia. Repeat examinations can be based on change in symptoms or compliance with therapy. If repeat endoscopy with biopsy is planned, it should be performed no sooner than 4 weeks after the last therapeutic intervention. These suggestions are based on improving the recognition of long-term complications associated with chronic esophageal eosinophilia; currently, data are not available to determine the optimal method to follow patients.

In asymptomatic patients with persistent esophageal eosinophilia, a repeat upper endoscopy can be performed following institution of additional treatment. For those in whom additional treatment is deferred, a repeat upper endoscopy and/or barium swallow can be obtained every 2 to 3 years to evaluate for progressive disease, but the risks of this approach outside of a clinical research protocol need to be weighed against the unknown benefits; this is especially important because the accuracy of histologic and radiologic predictors of disease progression is unclear.

The approach to adults with EE should consider similar principles as described above for children. However, clinical experience suggests that adults may be inclined to guide treatment based mainly on symptoms. Thus, the need for surveillance should also consider willingness to accept more aggressive treatment based on the results.
Future Research

Today, the care of patients with EE stands at a crossroad (see Table 6). Clinical experience and the current literature dictate that EE is a chronic disease with few patients, if any, outgrowing their illness. Whether merely a subset or a majority of these patients is at risk to develop irreversible fibrotic changes is not known. If a stricture develops, the timetable is also unknown. These dilemmas complicate the question: What are appropriate treatment end points: symptom resolution, histologic remission, or both? Natural history studies will be key to determining whether treatment alters the disease progression. Basic studies directed at understanding the mechanisms by which eosinophils contribute to esophageal injury will be critical.

Currently, clinicians are limited to endoscopic biopsies in making the proper diagnosis and, in many circumstances, establishing disease remission. The identification of novel methods to assess disease activity, by reducing reliance on repeated endoscopies, will significantly improve the quality of life of patients and likely reduce the economic burden of the disease. Mechanistic pathways must be further delineated to identify target molecules for intervention. Results of these studies will also lead to novel therapeutic approaches (such as anti-IL-5 antibody, anti-eotaxin-3 antibody) that will be particularly important for patients who cannot comply with current medical and nutritional approaches, those with recalcitrant disease, and those with fibrotic changes.

Finally, instituting appropriate treatment has become a challenging and time-consuming clinical process. Nutritional (dietary antigen elimination, elemental diet) and steroid treatments are both effective in inducing clinical-pathologic remission in most patients, but some patients are still recalcitrant or encumbered by nonadherence or intolerable adverse effects. The definition and recognition of disease subtypes, using clinical phenotypes and/or biomarker profiles, holds promise for future identification of at-risk (for fibrosis and stricture formation) subgroups for more aggressive therapeutic intervention and monitoring. For instance, recent studies suggest that there are allergic and nonallergic phenotypes, and this information may guide future treatment into different approaches. The challenge will be to develop appropriate translational studies that define valid phenotypic subsets.

The past decade has witnessed the emergence and recognition of a new disease entity with unique features that differentiate it from gastroesophageal reflux disease, with which it had been confused. The joint efforts of clinical scientists and basic scientists to undertake studies on natural history, pathophysiology, biomarkers, and therapeutic approaches will be critical to developing novel diagnostic tools and therapeutic options that will improve the lives of affected children and adults.

Table 6. Unresolved Issues

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<thead>
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<th>Maintenance medical management</th>
<th>Treatment end points</th>
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<tr>
<td>Natural history</td>
<td>Best method to identify food/aeroallergens</td>
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<tr>
<td>Degree of eosinophilia associated with GERD</td>
<td>Evaluation and management of the asymptomatic patient with esophageal eosinophilia</td>
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<td>Etiology and pathogenesis</td>
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Update Since the First International Gastrointestinal Eosinophil Research Symposium

At the time of acceptance of this article (July 2007), there has already been a remarkable 25% growth of PubMed articles concerning EE including high-quality articles about epidemiology, diagnosis, pathogenesis, and treatment (including the first controlled clinical trial and early results with a novel targeted biotherapeutic agent). Notably, these studies were contributed by investigators in 3 continents, including Europe (Sweden, Switzerland, and Spain), America (United States and Canada), and Australia; this highlights the expanded global health burden of EE. Interestingly, a recent comprehensive literature review about the diagnostic criteria for EE indicated the need for a consensus standard,103 highlighting the value of our current report.

In the area of diagnostics, the striking association of EE with food impaction,104 dysphagia,105 and multi ringed esophagus was reported in several papers.105 Interestingly, the familial association of EE was expanded to include the cooccurrence of dysphagia and Schatzki rings in family members of EE patients.106 Furthermore, preliminary studies concerning cooccurrence of EE with celiac disease, erythema nodusum, and anticonvulsant hypersensitivity syndrome were reported.107–109 One long-term history study in pediatrics reported the chronic and relapsing nature of EE and a strong predominance among whites.110

In the area of diagnostics, an important surveillance endoscopy study in 1000 healthy individuals in Sweden revealed the presence of esophageal eosinophilia in 5% of endoscopic biopsy specimens, with 1% of individuals meeting diagnostic criteria for EE.111 This raises the possibility that the prevalence of EE may be substantially higher than expected, especially in view of the chronic and relapsing nature recently reported.110 A retrospective study reported that the incidence of EE in a pathology database in Iowa was similar in 1990 and 2005, suggesting that the recent recognition of EE is not due to increased disease awareness rather than increased incidence.112 In addition, 2 early studies reported the potential utility of noninvasive biomarkers based on the levels of peripheral blood eosinophils, EDN, eotaxin-3, and mononuclear cell Th2 cytokine production in response to food and/or aeroallergens.82,113
Several major advances in the area of therapy were reported, including an early provocative study demonstrating the ability of a humanized anti-IL-5 monoclonal antibody markedly to reduce esophageal eosinophilia and improve clinical symptoms in adult patients with long-standing disease. Positive and negative predictive values for skin testing and patch testing for EE were determined for the most common foods in EE. Furthermore, the first double-blind, placebo-controlled trial in EE was reported. In particular, the investigators evaluated the effect of swallowed fluticasone (880 μg daily) vs placebo in a 3-month trial. Notably, they were able to demonstrate strong efficacy of fluticasone compared with placebo, but only 50% of patients responded to the study drug, likely because of the existence of corticosteroid resistance in a substantial number of EE patients. In addition, the investigators defined the first placebo effect in EE at ~10%; this will have significant impact on the design of future clinical trials. A retrospective study reported the success of oral viscous budesonide in 20 pediatric patients.

In a retrospective study of 20 children, median age 4.1 years (1.7–17.6), some 85% responded within 3–4 months resolution or improvement of symptoms and histopathology to use of topical steroid administered as a slurry of oral viscous budesonide (OVB). They had previously failed PPI treatment alone. This form of treatment is particularly suitable for younger children who may have difficulty with taking medication by inhaler. Patients received OVB 1–2 mg daily and were instructed not to ingest any solid or liquid food for 30 minutes after its administration. Children under the age of 10 years received OVB 1 mg daily and those who were 10 years or older received 2 mg/day. Viscous budesonide was made by mixing each 0.5 mg Pulmicort Repulse with 5 g (5 packets) or sacralose (Splenda) to create a volume of 8–12 mL. A Pulmicort Respule is liquid budesonide intended for nebulized administration (0.5 mg budesonide/2 mL).

Finally, advances in understanding disease pathogenesis included an important paper describing the role of adaptive immunity in a murine model of EE (consistent with the view that EE is an antigen-driven disease) and a compelling paper that demonstrated the presence of extensive tissue remodeling (including deposition of collagen and evidence of angiogenesis) in EE biopsy specimens from pediatric patients. Of note, the investigators provided evidence for the overexpression of transforming growth factor β and its signaling molecule, phosphorylated SMAD2. The level of esophageal remodeling as well as the presence of activated IgE-bearing mast cells distinguished EE from GERD patients. Additionally, evidence for cooperation between systemic Th2 immunity and local eotaxin-3 production was reported.

Appendix 1. FIGERS Subcommittees

Clinical Features and Diagnostic Testing

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References


