

# Current Management of Eosinophilic Esophagitis 2015

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**Abstract:** Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized by esophageal dysfunction and eosinophilic infiltrate ( $\geq 15/\text{hpf}$ ) in the esophageal epithelium and the absence of other potential causes of eosinophilia. The prevalence is increasing and is the most common cause of solid food dysphagia in children and young adults. This article will review the diagnosis and management of EoE based on consensus conferences, systematic reviews, and meta-analysis and highlights seminal studies in our evolving treatment of this disease. However, all answers are not available and I will remark about the lessons learned in my clinical practice seeing EoE patients over the last 25 years. The complicated etiology of the complaint of dysphagia in EoE patients will be reviewed. The importance of utilizing endoscopy, biopsies, and barium esophagram to help define the 2 phenotypes (inflammatory, fibrostenosis) of EoE will be highlighted. The controversy about PPI-responsive esophageal eosinophilia will be discussed and contrasted with idiopathic EoE. Finally, the 3 treatment options for EoE (drugs, diet, dilation) will be reviewed in detail and a useful clinical management algorithm presented.

**Key Words:** eosinophilic esophagitis, topical steroids, proton pump inhibitors, 6-food elimination diet, esophageal dilation

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Eosinophilic esophagitis (EoE) is a chronic inflammatory condition defined by symptoms of esophageal dysfunction, an eosinophilic infiltrate in the esophageal epithelium, and the absence of other potential causes of esophageal eosinophilia.<sup>1</sup> It is primarily seen in white males under the age of 40 years. First described in 1978,<sup>2</sup> EoE was only rarely reported for the subsequent 2 decades.<sup>3</sup> In the late 1990s, however, the condition was first recognized in children and then adults, with an explosion of the published literatures after the First Multidiscipline EoE Conference in Orlando, Florida, in 2005.<sup>4</sup> Current estimates suggest that the overall prevalence in the United States of EoE is approximately 57/100,000 persons.<sup>5</sup>

EoE is an immune-mediated disorder in which food and environmental antigens simulate a Th2-inflammatory response.<sup>6</sup> Key cytokines such as interleukin (IL)-4, IL-5, and IL-13 stimulate the production of eotaxin-3 in esophageal mucosa. Eotaxin-3 is markedly upregulated in EoE and a potent chemokine recruiting eosinophils to the esophageal mucosa. These activated eosinophils secrete proinflammatory and profibrotic mediators, cause local tissue damage, recruit additional cells (mast cells and

fibroblasts) that perpetuate the inflammatory response, and over time results in tissue fibrosis and remodeling.<sup>7</sup>

This article will review the diagnosis and management of EoE based on consensus conferences, systematic reviews, and meta-analyses and highlight seminal studies in our evolving treatment of this disease. However, all the answers are not available and I will remark about the lessons learned in my clinical practice seeing EoE patients over the last 25 years. Finally, a suggested clinical treatment algorithm will be proposed which has evolved in our esophageal center since 2006.

## CLINICAL PRESENTATIONS

EoE in children is more of an inflammatory process with common symptoms including failure to thrive, vomiting, abdominal pain, and heartburn. In adolescents and adults, the symptoms are primarily solid food dysphagia, heartburn, and chest pain that can be associated with food impaction with or without esophageal strictures.<sup>1</sup> Esophageal strictures are present in 30% to 80% of adult EoE patients, but are less commonly found in children (< 5%), even though food impactions occur in up to 30% of subjects.<sup>1</sup> The more severe the stricture disease, the longer duration of untreated disease suggesting an evolution from pure inflammation to fibrosis, strictures, and generalized esophageal narrowing.<sup>8,9</sup>

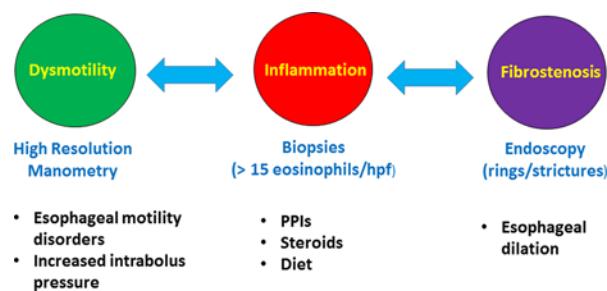
The complaint of solid food dysphagia in EoE patients is a complex pathophysiological process with both mechanical and psychological factors. Although the inciting event is the mucosal eosinophilic inflammation, the degree of mucosal eosinophilia does not correlate with the severity of dysphagia.<sup>10,11</sup> As illustrated in Figure 1, dysphagia is related to mechanical factors including the degree of dysmotility present, extent of mucosal inflammation, and fibrostenosis from esophageal remodeling. The contribution of each varies in the individual patient and often is incompletely evaluated if only endoscopy with biopsies is performed. More important, most treatments (diet, medications, or esophageal dilation) only address one of these mechanisms. For example, esophageal dilation improves dysphagia despite not addressing the mucosal eosinophilia especially in EoE patients with the fibrostenotic phenotype.<sup>12</sup> In contrast, patients with the inflammatory phenotype will do well with steroids or diet, but some have less than optimal outcomes because of unrecognized motility disturbances or subtle esophageal strictures.<sup>10,11</sup>

Psychological fears also contribute to the report of dysphagia. Impaired quality of life is related to the need for dietary changes, fear of social embarrassment while eating (rush from the table to vomit lodged food, inability to go out to restaurants to eat), anxiety created by choking episodes, and the frightening experience of having a food impaction. The latter is reported by 30% to 55% of adult EoE patients with other complications including risk of aspiration, esophageal tears, and esophageal perforation.<sup>11</sup>

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The author declares that there is nothing to disclose.

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**FIGURE 1.** Mechanical factors contributing to dysphagia in patients with eosinophilic esophagitis. One or more of these factors may contribute to the symptoms of dysphagia and occurrence of food impactions.

EoE patients drastically modify their eating habits by avoiding pleasurable foods (meats, bread), cutting their food up like you would for a small child, drinking large quantities of liquids with their meals, and being the last to leave the eating table.

## DIAGNOSTIC TESTING

### Barium Esophagram

The barium esophagram is a cheap available test to assess esophageal anatomy, especially focal strictures and diffuse esophageal narrowing. Before the new nomenclature, x-ray patterns were associated with a number of aliases for EoE including “ringed esophagus, corrugated esophagus, feline esophagus, small caliber or narrowed esophagus, and congenital esophageal stenosis.”<sup>12</sup> A recent study from the Mayo Clinic suggests the barium esophagram is the most accurate test for identifying esophageal narrowing. In the upright position, they found the maximal diameter of the esophagus with continuous drinking is  $> 21$  mm in healthy subjects and the minimal diameter is  $> 16$  mm with individual swallows. Among 58 EoE patients with endoscopy and barium esophagrams, endoscopy had poor sensitivity (14.7%) and only modest specificity (79.2%) for identifying esophageal strictures. Even at a cut-off diameter of  $< 15$  mm, endoscopy had a sensitivity of only 25% for a narrowed esophagus.<sup>13</sup> A 13 mm tablet may help better define the location of esophageal stenosis, but some EoE patients are frightened to swallow the tablet. In addition, other patients can only “sip” the barium rather than taking large swallows, thereby limiting the ability to distend the esophagus. I primarily use the barium esophagram in difficult-to-manage strictures or when the endoscopy is normal and dysphagia persists.

### Endoscopy

In practice, upper endoscopy is the first test performed in suspected EoE patients to inspect the esophagus, obtain esophageal biopsies, and evaluate for alternative causes. Endoscopic findings described in EoE include the primarily inflammatory features such as pale mucosa, decreased vascularity, white exudate sometimes confused with candida esophagitis, and longitudinal furrows running parallel to the axis of the esophagus. Features of fibrostenosis and esophageal remodeling include transient (feline) and fixed rings, narrow-caliber esophagus, and fragile esophageal mucosa, termed “crepe-paper mucosa,” where a tear occurs with passage of the endoscope.<sup>1,3</sup> However, 7% to 10% of patients with confirmed EoE have a normal esophagus, and

none of the endoscopic features of EoE are specific to this disease.<sup>14</sup> A new Endoscopic Reference Scoring System (ERES) was recently developed to improve endoscopic criteria for EoE.<sup>15</sup> Diagnostic reliability is variable—interobserver agreement for rings, furrows, and exudate was moderate (56% to 65% agreement), fair for narrowed caliber esophagus, and poor for edema and feline esophagus. Therefore, esophageal biopsies must be obtained in all patients with suspected EoE regardless of the endoscopic features.<sup>1,4</sup> As the eosinophilic infiltrate is patchy, it is recommended that at least 2 to 4 biopsies from both the distal and proximal esophagus be obtained.<sup>16</sup>

As noted, the ability of endoscopy to identify strictures is crude and not very reliable between 11 and 17 mm—the range at which many patients have symptomatic dysphagia for solids.<sup>17</sup> We have found that simple bougie sizing of suspected strictures is better than visual inspection and easy to perform. After obtaining biopsies, we carefully dilate all EoE patients to assess lumen diameter defined by the bougie size at which moderate resistance is noted with the passage of Savary or Maloney dilators. Using this simple technique, we found that one third of our EoE patients had subtle strictures between 10 and 17 mm which may not be detected by endoscopy alone.<sup>9</sup> Their dysphagia complaints reliably resolved with dilations to  $> 17$  mm where they can eat a regular diet and do not have to fear food impactions.<sup>18</sup>

### Histology

By consensus, an eosinophilic infiltrate in the esophageal mucosa with  $\geq 15$  eosinophils/high-power field (eos/hpf) suggests the diagnosis of EoE.<sup>1,4</sup> However, these eosinophil counts are not diagnostic for EoE and can be seen in other disorders especially gastroesophageal reflux disease (GERD) and the recently described proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE).<sup>1</sup> Other associated histologic features of EoE include eosinophil degranulation, eosinophil microabscesses defined by clusters of  $\geq 4$  eosinophils, basal zone hyperplasia, rete peg elongation, spongiosis (intercellular dilation), and fibrosis of the lamina propria. The mucosal eosinophilia is patchy and an interesting recent study found the highest concentration of eosinophils in the exudate and furrows and lowest values in the rings/strictures.<sup>19</sup>

### Esophageal Manometry and Reflux Testing

Abnormalities of esophageal motility are not uncommon in EoE patients and may contribute to their dysphagia. Reports using traditional esophageal manometry in 100 EoE adults found 53% of patients with motility disorders, usually nonspecific peristaltic abnormalities or low LES pressures.<sup>4</sup> High-resolution manometry has identified a novel finding in EoE patients characterized by abnormal esophageal pressurization not seen in GERD or control groups. These manometric patterns consist of pan-esophageal pressurization as seen in achalasia and distal esophageal pressurization (measured as high intrabolus pressure) in 34% to 48% of adult EoE patients.<sup>20,21</sup> Recently, we confirmed these findings in 29 EoE patients observing that average intrabolus pressure was significantly higher in fibrostenotic versus inflammatory EoE (18.6 vs. 12.6 mm Hg,  $P < 0.05$ ).<sup>22</sup> These esophageal pressurization events reflect reduced esophageal distensibility secondary to remodeling with strictures.<sup>23</sup>

The role of classic GERD in EoE is controversial with pH testing being positive in 20% to 71% of patients.<sup>1</sup>

However, the predictive role of acid or impedance-pH testing is limited and inconsistent because the 2 diseases can overlap, GERD can cause mucosal eosinophilia and the response to PPIs is not predicted by these tests either due to diagnostic inaccuracy or that PPIs improve esophageal eosinophilia by mechanisms unrelated to acid control.<sup>24</sup> I rarely perform reflux testing in my EoE patients unless heartburn is their dominant symptom, they have endoscopic features of GERD with hiatal hernia and erosive esophagitis, and especially, if antireflux surgery is being considered.

### Allergy Testing

Allergic diseases such as atopic dermatitis, atopic rhinitis, asthma, and food allergies are very common in EoE, reported in 50% to 80% of children with a somewhat lower rate in adults.<sup>3</sup> The most recent guidelines suggest referral to an allergist to help maximize therapy for nonesophageal allergic diseases and to assist with interplay between multiple allergic conditions.<sup>1</sup>

A recent review by Aceves<sup>25</sup> is useful for understanding allergy testing in EoE. There are 3 types of food allergy tests: skin prick which measures IgE-mediated hypersensitivity, patch testing which assesses non-IgE, cell-mediated reactions, and serum IgE tests. Dr Aceves<sup>25</sup> concludes the following:

- (1) Allergy testing for foods is most useful in children compared with adults, where the latter have more aeroallergen problems.
- (2) The negative predictive values for foods tend to be superior to the positive predictive values. An exception is milk allergies.
- (3) The presence of food-specific IgE can be due to cross-reactivity with environmental allergies (eg, wheat-specific IgE due to grass allergy).
- (4) There is little role for serum IgE-based dietary elimination diets or serum food allergy panels.
- (5) Positive allergy tests for foods may reveal a food EoE trigger, but is not an alternative to endoscopy with biopsies after food elimination and reintroduction to define the specific food allergies.

### GENERAL GOALS OF MEDICAL THERAPY FOR EoE

The treatment of EoE pursues several goals: (1) improvement of symptoms, especially dysphagia and fear of food impactions, (2) histologic remission of the mucosal eosinophilia, (3) correction of endoscopic activity, both inflammation and strictures, and (4) prevention of long-term sequelae (food impactions, strictures, and diffuse esophageal narrowing). This occurs in a setting where the disease has acute activity and frequently the need for chronic maintenance therapy. No one treatment can meet all these requirements (ie, anti-inflammatory drugs rarely relieve significant stenosis and esophageal dilation does not inhibit mucosal eosinophilia) and often multiple treatment modalities need to be used, especially in patients with the fibrostenotic phenotype. The natural history of EoE is slowly being understood. It appears to be a chronic benign disease, not associated with esophageal cancer, other malignancies, or the need for surgery, but one which relapses, requires periodic medical interventions, and importantly, most patients can expect excellent quality of life.<sup>18,26</sup> Furthermore, a balance needs to be established as

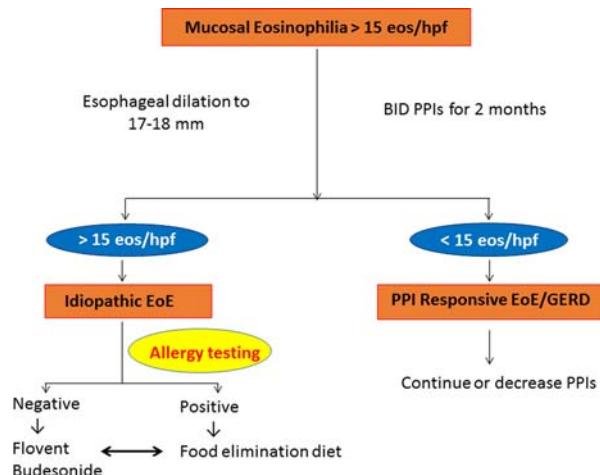
patients primarily desire symptom relief, mucosal eosinophil eradication is not easy or predictable, chronic drug use will be expensive with potential side effects, and the role of “aggressive” treatments to control mucosal eosinophilia needs to be tempered by the generally benign nature of EoE.

Consensus statements<sup>1,4</sup> and society guidelines<sup>27</sup> are evolving and being updated on the efficacy of various medical and endoscopic treatments for EoE. Interestingly, most suggested treatment algorithms are proposed from single centers that have extensive clinical experience and publish frequently on EoE. It is remarkable that each center has their preferred “treatment of choice” (eg, Chicago Northwestern, diet; University of North Carolina, steroids; Switzerland, steroids; and my group at the University of South Florida, PPIs and esophageal dilation), how well patients do with each particular approach and the intensity of debates on EoE treatment at national meetings. Not to be outdone, I will add our treatment algorithm for EoE (Fig. 2) currently used at the University of South Florida, which continues to evolve as we understand this disease better.

### PPIs

To this observer, one of the most remarkable stories in the EoE experience is the positioning of PPIs as the initial treatment of mucosal eosinophilia and the understanding this class of drugs has both anti-inflammatory as well as antacid mechanisms. The first EoE consensus published in 2007<sup>4</sup> stated: “acid suppression is useful to fulfill the diagnostic criteria for EoE by excluding GERD... and may be used in lieu of esophageal pH monitoring for patients with established EoE who have symptoms secondary to concomitant GERD. PPI therapy should not be considered as a primary treatment for patients with EoE”. Thus before this time, the assumption was that patients responding to PPIs had GERD, and those who did not had the diagnosis of EoE.

The first data contradicting this theme was a case series in 2006 of 3 children with typical symptoms of EoE and high eosinophil counts with complete symptom and



**FIGURE 2.** My treatment algorithm for mucosal eosinophilia and eosinophilic esophagitis. EoE indicates eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

histologic resolution when treated with PPIs.<sup>28</sup> Then in 2011, Molina-Infante et al<sup>24</sup> published the first prospective study on this issue. They found that 74% of patients with esophageal eosinophilia responded to a high-dose PPI trial (rabeprazole 20 mg bid for 2 mo) and first used the term “PPI-responsive esophageal eosinophilia” (PPI-REE). All their 17 patients with a GERD profile responded, 9/18 (50%) with an EoE profile responded and pH monitoring was poorly predictive of a PPI response. Subsequently, a number of studies in both children and adults have shown consistently that at least one third of all patients (range, 33% to 80%; 45% in my USF practice) with esophageal eosinophilia respond to PPI therapy.<sup>29</sup> Furthermore, no clinical, histologic, or endoscopic factors allows us to predict which patients will respond to PPIs.<sup>29,30</sup> Therefore, as shown in Figure 2, all gastroenterologists must conduct a full PPI trial followed by another endoscopy in patients with esophageal eosinophilia to differentiate between EoE and PPI-REE.<sup>3,27</sup> A positive response is considered a significant fall in the eosinophil count, typically <15 eos/hpf, paralleled by endoscopic resolution of inflammation and symptom improvement.

To date, EoE studies rarely compare treatment regimens directly in the same patient population. However, 2 small studies have randomized patients with esophageal eosinophilia to fluticasone (440 mcg bid) or esomeprazole 40 mg a day for 8 weeks. The first study<sup>31</sup> randomized 24 patients with similar improvement in dysphagia scores [3/12 (25%) in esomeprazole versus 6/12 (50%) in fluticasone group,  $P = 0.40$ ] and decrease in absolute eosinophil count ( $P = 0.70$  between groups). The second study<sup>32</sup> randomized 42 patients with no change in eosinophil count between groups and similar rates of resolution of esophageal eosinophilia (19% fluticasone versus 33% esomeprazole,  $P = 0.48$ ). However, the Mayo dysphagia questionnaire score significantly decreased after treatment with esomeprazole ( $19 \pm 21$  vs.  $1.4 \pm 4.5$ ,  $P < 0.001$ ) but not with fluticasone ( $17 \pm 18$  vs.  $12 \pm 16$ ,  $P = 0.162$ ). Unfortunately, both studies did not rigorously require a prior PPI trial and included a combination of GERD, PPI-REE, and EoE subjects whose differences may explain the underlying responses.

Three potential mechanisms have been identified by which PPIs can decrease mucosal eosinophilia. In cultures of esophageal squamous cells from GERD and EoE patients, omeprazole blocks the esophageal endothelium from secreting eotaxin-3 after being stimulated by allergic cytokines such as IL-4 or IL-13.<sup>33</sup> This occurred in an acid-free setting confirming that PPIs have an anti-inflammatory/antieosinophilic effect independent of their effects on gastric acid secretion. Another possible mechanism involves the effect of PPIs on esophageal barrier function. PPIs improve barrier function in PPI-REE but not EoE patients, making the barrier less leaky and possibly preventing allergens from driving an eosinophilic response upon entering the esophageal mucosa.<sup>34</sup> The third possibility is that, in some patients, the esophageal eosinophilia that responds to PPIs is actually due to acid reflux and by reducing the acid, the PPIs decrease esophageal injury and allows the eosinophilia to resolve.

The use of PPIs in patients with mucosal eosinophilia is still evolving. Although the dose and duration varies across studies, most recommend twice daily or high-dose PPIs for at least 2 months.<sup>13,14,35</sup> The intensity of the eosinophil count may effect the rapidity of the PPI response

as we recently observed in a patient with 400 eos/hpf, who took 4 months to normalize her eosinophil count on dexlansoprazole 60 mg. The durability of the PPI response in PPI-REE is currently being studied. The Molina-Infante group have data on approximately 50 patients with 20% to 30% having loss of PPI response over 1 to 2 years. In general, most lost their response when PPI dose was lowered and regained response when their PPI dose was increased.<sup>36</sup> However, a series of 4 children maintained on PPIs after a documented response experienced recurrent symptoms and eosinophilia after 1 to 2 years of treatment.<sup>37</sup> There was no seasonal variation or lack of PPI adherence to explain the return of mucosal eosinophilia. Similarly, I recently had a patient with excellent eosinophil control over 2 years of bid PPIs, whose mucosal eosinophilia recurred in association with exacerbation of her allergic rhinitis. Finally, the response to PPIs is a critical step in defining EoE and subsequent treatments with steroids or dietary modifications. It is well described that generalists and gastroenterologists prescribe PPIs inappropriately in up to 54% of patients.<sup>38</sup> Many factors contribute including confusion about timing related to meals, taking the PPI at bedtime, underdosing, expense of prescription medications, and poor compliance. We are finding that a detailed discussion about the importance of and appropriate way to take PPIs, followed by a 2-month PPI “retry” is helpful in nearly 30% of our patients, before declaring “failure” and moving on to diet therapy or topical steroids.

## SYSTEMIC AND TOPICAL STEROIDS

### Systemic Corticosteroids

Systemic corticosteroids were the first of the steroid preparations used for EoE.<sup>3</sup> A pediatric case series showed that treatment with methylprednisolone lead to symptom relief in 19/20 children, with a mean response time of 8 days.<sup>39</sup> However, 6 months later the children had disease relapse after the steroids were stopped. The only randomized trial compared prednisone with swallowed steroids in 80 children.<sup>40</sup> Prednisone was equivalent to the topical steroids for decreasing eosinophilia and improving symptoms, but had more adverse events (40% including weight gain and Cushingoid features). Systemic corticosteroids are now reserved as first-line therapy primarily in children with severe symptoms, malnutrition, and feeding intolerance where a rapid response is needed.<sup>1</sup>

### Topical Steroids

Topical steroids are the mainstay of EoE treatment in children and adults and first-line therapy for many cases. Two forms are commonly used—swallowed aerosolized fluticasone and budesonide administered as a liquid (in resuples) or as a powder which can be compounded. When using fluticasone, the patient is directed to puff the inhaler into the mouth during a breath hold, and then swallow it. After dosing, patients should avoid eating or drinking for 30 to 60 minutes. The dose in children is 88 to 440 mcg/day in divided doses and 880 to 1760 mcg/day in divided doses for adults. In the latter group, the most robust histologic response is with the 1760 mcg daily.<sup>3</sup> Budesonide is much easier to administer and was first used in children.<sup>41</sup> The compound is bitter and often mixed with a sweetener, such as sucralose, chocolate syrup, honey, to make a slurry called “oral viscous budesonide.” The dose in children is

1 mg/day, and 2 mg/day in divided doses for adults. Best timing is after breakfast and immediately before laying down at night. Contact time with the esophagus is a problem with both agents. Dellow et al<sup>42</sup> observed that the majority of swallowed fluticasone stays in the mouth or inadvertently entered the lungs; swallowed budesonide had better contact with the esophagus but this was not robust. Topical steroids in general are safe. About 1% of patients get oral candidiasis regardless of medication dose, formulation, or whether the mouth was rinsed after medication use.<sup>3</sup> Usually asymptomatic candida esophagitis is noted in 5% to 30% of patients undergoing endoscopy. To date, there is no evidence of adrenal suppression up to 2 months of treatment, but as EoE is a chronic disease and maintenance therapy may be required, this issue will need to be followed relevant to growth rates and bone density.<sup>27</sup>

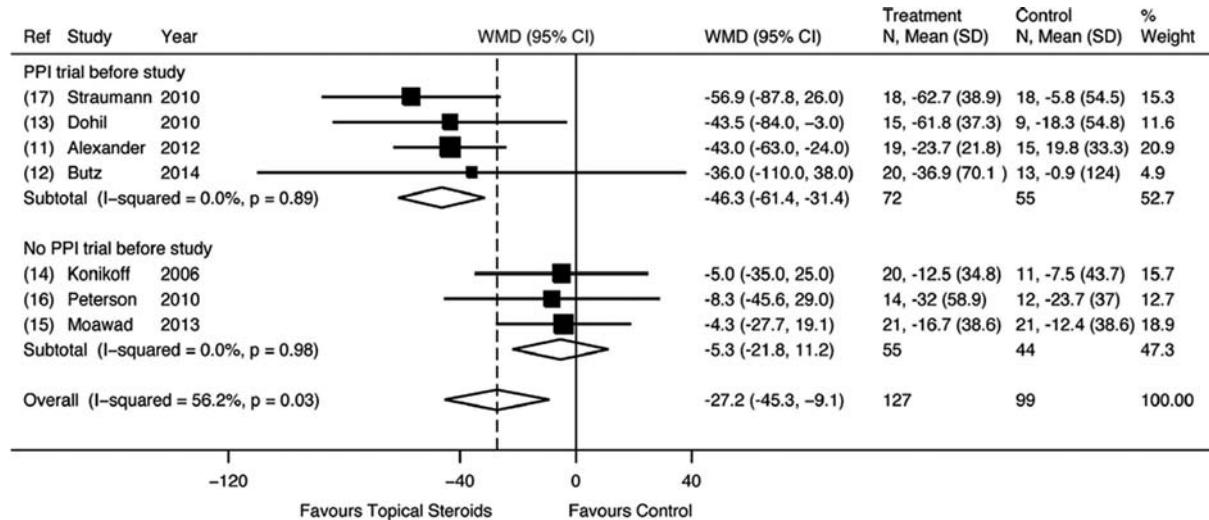
In children, randomized trials comparing fluticasone to prednisone<sup>40</sup> and to placebo<sup>43</sup> demonstrate an approximately 50% complete and 95% partial response of eosinophilia after 1 to 3 months of therapy. In contrast, the initial studies were not as encouraging in adults with EoE. The Mayo group initially reported a near 100% relief of dysphagia after 6 weeks of fluticasone lasting a minimum of 4 months.<sup>44</sup> However, after 2 to 3 years of follow-up, most had relapsed and 25% had further food impactions.<sup>45</sup> Alexander et al<sup>11</sup> reported a randomized study in which 21 adult EoE patients received fluticasone 1760 mcg/day divided twice daily and 15 received placebo for 6 weeks. Patients on fluticasone had 62% rate of eosinophilia resolution (>90%) as compared with 0% for placebo. However, the improvement in dysphagia was not significantly different between groups.

Budesonide studies were initially done in children with the oral viscous solution and universally was found effective.<sup>46,47</sup> An RCT in adults using nebulized budesonide and then swallowed (1 mg bid) for 15 days showed similar positive results.<sup>48</sup> Eosinophil counts decreased on active medication (68 to 5 eosinophils,  $P < 0.0001$ ) and dysphagia scores improved. White exudate and furrows resolved on endoscopy but rings and strictures persisted. A recent large

pediatric study found the best results with medium (2 mg) or high-dose (4 mg) oral budesonide for eosinophil reduction, but across all doses symptom relief was variable and no better than placebo.<sup>47</sup>

To date, 9 randomized clinical trials have been published examining the use of topical steroids for EoE; including fluticasone versus placebo,<sup>11,40</sup> fluticasone versus prednisone,<sup>40</sup> fluticasone versus esomeprazole,<sup>31,32</sup> budesonide versus placebo,<sup>46,48</sup> and a study of 2 forms of budesonide.<sup>42</sup> In the last year, 2 systematic reviews with meta-analysis were published combining most, if not all, of the above studies.<sup>49,50</sup> The results were similar and interesting, both show a robust (10- to 13-fold) reduction in mucosal eosinophilia, but the reduction in symptoms was less clear (1- to 3-fold improvement) and more striking with budesonide. Among studies that partially or fully excluded PPI responders, a significantly greater reduction in eosinophil count was observed with topical steroids compared with control treatment (Fig. 3). Several factors may be contributing to this dichotomy, including the poor detection of subtle strictures associated with diminished symptom response and the lack of a validated, symptom-scoring system for EoE. However, a new symptom-based activity index specific to EoE was recently published, which showed good correlation with symptom responses and eosinophil counts in EoE patients.<sup>51</sup> There have been no studies to date comparing the efficacy of fluticasone to budesonide.

If topical steroids are stopped after initial treatment, nearly all patients will relapse. This is a theme that is repeated for all treatment modalities. Therefore, like inflammatory bowel disease, maintenance therapy may be required for a subset of EoE patients. To date, there has been 1 trial of maintenance therapy for EoE. In this study, subjects previously responding to nebulized/swallowed budesonide<sup>48</sup> were randomized to low-dose budesonide (0.5 mg/d) or placebo for 1 year.<sup>52</sup> Histologic recurrence was universal in the placebo group compared with budesonide group (100% to 50%) and symptom recurrence was also more common (64% to 36%). Interestingly, signs of esophageal remodeling based on biopsies and endoscopic



**FIGURE 3.** Forest plot of all randomized controlled trials comparing the effect of topical steroid therapy on the reduction in eosinophilic count, subdivided on the exclusion of PPI responders. A significantly negative MD (WMD) indicates a significant reduction in eosinophil counts following topical steroids versus control treatment. CI indicates confidence interval; PPI, proton pump inhibitor; WMD, weighted mean difference. Used with permission from Chuang et al.<sup>50</sup>

ultrasound showed a trend toward normalization in the patients taking low-dose budesonide for 1 year.

Several unresolved issues exist in treating EoE patients with topical steroids. The most practical is the cost of these compounds and secondarily none of these agents are FDA approved for use in EoE. In Rochester, Minnesota, the formulation of budesonide respules (Pulmicort; AstraZeneca, Wilmington, DE) at 1 mg bid daily cost \$1613 for a 6-week therapy, and a fluticasone inhaler at 880 mcg bid cost \$967 for 6-week course. Oral viscous budesonide made by a compounding pharmacy was much cheaper at \$141 for 6 weeks; however, this product is not widely available.<sup>53</sup> Not all patients respond to steroids and some of this may be genetic rather than noncompliance. In a multicenter randomized study, 65% of EoE patients from 3 to 30 years had complete histologic remission on fluticasone 1760 mcg and an additional 12% had a partial response. When the daily dose was decreased by 50% at the end of 3 months, 73% and 20% remained in complete or partial histologic remission, respectively. Nonresponders had genetic evidence of steroid resistance with genetic transcript patterns predictive of fluticasone unresponsiveness.<sup>54</sup> In a second retrospective cohort study from the University of North Carolina,<sup>55</sup> 221 patients with EoE received topical steroids, 71% had endoscopic improvement, 79% had symptomatic improvement, but only 57% had a histologic response (< 15 eos/hpf). Baseline need for esophageal dilation and decreased tissue levels of mast cells and eotaxin-3 predicted which patients would not respond. Among 27 steroid-refractory patients, a mean of 2 additional therapies were tried and only 48% responded to any second-line therapy.

## OTHER BIOLOGICAL AGENTS

### Leukotriene Antagonists and Mast Cell Stabilizers

Leukotriene antagonists, useful in asthma, block the D4 receptor of cysteinyl leukotrienes reducing the inflammatory action of eosinophils. In a case series of 8 adult patients with EoE treated with high doses of montelukast (up to 100 mg/d), there was symptom resolution in 6 patients who remained asymptomatic on maintenance therapy over 4 to 28 months. However, histology did not improve.<sup>56</sup> In a study of 11 adults, montelukast was not effective for maintaining a steroid-induced remission.<sup>57</sup>

Mast cells are increasingly recognized as critical in the pathogenesis of EoE.<sup>6</sup> However, mast cell stabilizers such as cromolyn sodium are not effective based on case-series data and are not recommended for routine use in EoE.<sup>1</sup>

### Immunomodulators

A single case series of 3 steroid-refractory adults with EoE treated with azathioprine 2 to 2.5 mg/kg was reported.<sup>58</sup> All had excellent symptomatic and histologic response, but relapsed when treatment was discontinued. After relapse, they were successfully treated with corticosteroids and maintained on azathioprine with good success. Currently, potential side effects in a benign disease and few data limit the enthusiasm for routine use of this drug class.

### Biologics

Similar to treating inflammatory bowel disease, new biological therapies have been developed especially targeting IL-5, a central cytokine in eosinophil physiology and EoE pathophysiology. Mepolizumab was used in 2 trials,

1 in children and 1 in adults.<sup>59,60</sup> In both studies, the drugs reduced the eosinophil count, but complete remission was infrequent and in the adult trial, there was no change in symptoms. In the largest of the studies using the anti-IL-5 antibody reslizumab,<sup>61</sup> significant improvement in tissue eosinophilia was observed; however, symptom relief was better but not different than placebo.

IL-13 is upregulated 16-fold in EoE patients and mice deficient in IL-13 are protected against allergen-induced esophageal eosinophilia.<sup>6</sup> A recent study administered intravenous QAX576, a neutralizing IL-13 antibody, to 23 adult EoE patients in a randomized placebo study over 8 weeks with 6 months of follow-up.<sup>62</sup> The mean esophageal eosinophil count decreased by 60% on drug versus 23% increase on placebo ( $P = 0.004$ ), but the complete response was only 40%. The decrease was sustained for 6 months and a trend for dysphagia improvement was observed.

Omalizumab, an anti-IgE antibody, in an open-labeled study decreased tissue IgE levels in 13/15 EoE patients, but full remission defined as histologic and clinical improvement only occurred in 33% of patients.<sup>63</sup>

## DIETARY TREATMENT

From its earliest description, the origin of EoE has been linked to allergies; indeed both pediatric and adult patients commonly present concurrent family and/or personal atopic conditions including asthma, rhinitis, conjunctivitis, eczema, and IgE-mediated food allergies.<sup>4</sup> In a large study of 146 children, Spergel et al<sup>64</sup> found that nearly 50% had a causative food identified by skin testing. Results in adults are similar.<sup>65</sup> Since the early days of EoE, allergen avoidance by dietary measures has been an established treatment for this disease.<sup>1,4</sup> The most recent ACG guidelines consider dietary elimination as an initial treatment of pediatric and adult EoE.<sup>27</sup> Three strategies of dietary therapy have evolved: elemental diet, six-food elimination diet (SFED), and targeted elimination diet. The specific approach often depends on local allergy and nutrition support and expertise and patient/family preference and motivation. The literature in this area has grown rapidly and is summarized well in a recent systematic review and meta-analysis of 33 published studies.<sup>66</sup> Results vary with diet approaches, ranging from 90.8% for elemental diets to 45.5% for allergy testing-directed food elimination.

### Elemental Diet

An elemental diet composed of amino acids, basic carbohydrates, and medium-chained triglycerides is allergen free and shown to be very effective since first used in 1995.<sup>67</sup> It has been assessed in over 400 patients, usually children, from 13 different studies, yielding an overall combined efficacy of > 90% with resolution of symptoms and histology over 4 to 6 weeks.<sup>66</sup> Adult studies were not available until 2013, when a small 4-week study in 18 adults showed a 72% histologic response ( $\leq 10$  eos/hpf).<sup>68</sup> In practice, elemental diets are difficult: the formulas are expansive and unpalatable, usually need to be administered by enteral feeding tubes, are very restrictive as no table food can be eaten, and can adversely impact quality of life. Children are more amenable to this treatment because of parental influence and attention.

### SFED

In 2006, Kagalwalla et al<sup>69</sup> proposed the empiric SFED in an attempt to overcome the limitations of allergy

testing in directing food elimination, as well as make dietary therapy more palatable. This diet eliminates 6 of the most common food allergies in children: milk, eggs, wheat, soy, nuts, and fish/shellfish. It was first studied on a retrospective basis and compared favorably with an elemental diet, with 74% of patients having a histologic remission and 95% improving their symptoms.<sup>69</sup> Subsequent work from the same group showed after food reintroduction, the most common food triggers were milk, with wheat, eggs, and soy being less common.<sup>70</sup> Gonsalves et al<sup>71</sup> published a pivotal study in 50 adult EoE patients treated with SFED, with 64% having a complete histologic response ( $\leq 5$  eos/hpf) and 94% had symptom improvement. On the basis of reintroduction, the foods most frequently associated with EoE were wheat (60%) and milk (50%). Skin-prick testing predicted only 13% of food-associated EoE. As shown in Figure 4, a meta-analysis for the 7 published studies that evaluated an SFED were extremely homogenous, with a combined efficacy rate of 72%.<sup>66</sup> This analysis also included the first long-term study which showed that a SFED can maintain a clinical and histologic remission for up to 3 years.<sup>72</sup> Recently, a 4-food elimination diet (milk, wheat, eggs, legumes) published from Spain found that 54% of adult patients with EoE had a clinicopathologic remission.<sup>73</sup>

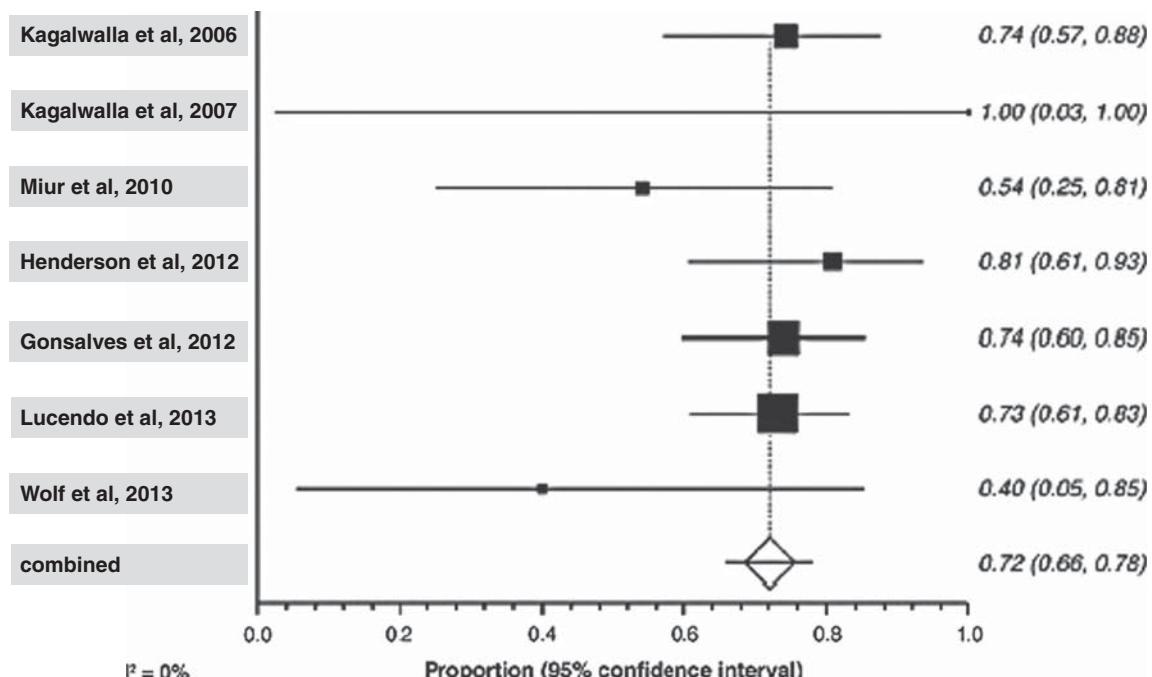
Although more palatable and practical, the SFED requires collaboration between gastroenterologists, allergists, dieticians, and informed dedicated patients and their families. The Chicago group recently published a detailed review of their approach to implementing dietary therapy in adults with EoE.<sup>74</sup> Important details reviewed included: a dietician must be involved in the program for initial training and subsequent follow-up sessions based on food logs. Patients must prepare their own meals separate from non-allergic family members, including segregated cook-top

surfaces, sponges, toasters, and utensils for allergy-free food. Most restaurants although familiar with gluten-free diets are a major source of cross-contamination for patients on SFED. Alcoholic beverages such as beer and wine can serve as source of allergens and limiting food groups can significantly impact serum levels of zinc, B vitamins, calcium, vitamin D, magnesium, and selenium as well as dietary fiber when taken long term.

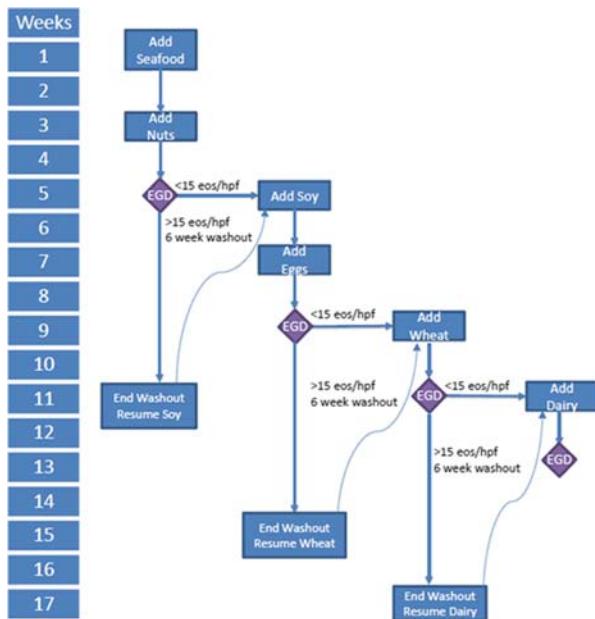
As shown in Figure 5, food reintroduction following a successful response to SFED requires time and multiple endoscopies with biopsies.<sup>74</sup> After 6 weeks on SFED, upper endoscopy with biopsies are repeated to assess the histologic remission. If successful ( $< 5$  eos/hpf by Chicago group criteria), food reintroduction begins with 1 new food group every 2 weeks with symptom monitoring. In their experience, most patients were symptomatic within 5 days of adding the trigger food.<sup>71</sup> If patients are doing well after 2 food groups are reintroduced, endoscopy and biopsies are repeated to monitor disease activity. Typically foods are reintroduced in order of the least to more likely cause of triggering EoE: seafood followed by nuts and wheat and milk at last. Sometimes endoscopy is repeated between the wheat and milk group additions, because of the high likelihood of either being a trigger. Overall, this process may take up to 12 weeks or longer with at least 4 endoscopies. A follow-up endoscopy at 1 year may be performed to assure histologic remission is maintained.

### Targeted Restrictive Diet

The last approach to dietary therapy is a targeted diet in which food allergens based on allergy testing are eliminated. This approach seems rationale, but unfortunately the reliability to detect specific food allergies with current testing is far from accurate.<sup>25</sup> This strategy has been assessed in 14 different studies (only 2 included adults)



**FIGURE 4.** Forest plot of efficacy of 6-food elimination diets in inducing histologic remission (<15 eosinophils/hpf) in patients with eosinophilic esophagitis. Used with permission from Arias et al.<sup>66</sup>



**FIGURE 5.** The Chicago food reintroduction algorithm following successful response to 6-food elimination diet. EGD indicates upper endoscopy. Used with permission from Doerfler et al.<sup>74</sup>

carried out in 626 patients (594 children and 32 adults). Overall efficacy was the lowest of the 3 dietary strategies at 45.5% with wide variability in the response rate (0% to 100%).<sup>66</sup> In the adult populations the results were even poorer, achieving remission rates between 22% and 32%.<sup>75,76</sup>

### ESOPHAGEAL DILATION

The final treatment for EoE and most controversial is esophageal dilation. In adult patients, it was a common treatment modality based on clinical experience with peptic strictures, even before the EoE syndrome was named. In 1993, Attwood et al<sup>77</sup> reported on a series of 12 patients with dysphagia and dense mucosal eosinophilic infiltration,

who did not have physiological evidence of GERD. Ten patients underwent esophageal dilation with symptom relief for 3 to 6 months. Morrow et al<sup>78</sup> at the Cleveland Clinic described 19 patients treated between 1995 and 1999 with the “ringed esophagus” and mucosal eosinophilia. All underwent esophageal dilation to 14 to 15 mm diameter and received PPIs, as was done for traditional reflux strictures. At telephone follow-up, 15/16 available patients were doing well with occasional dysphagia after an average of 19 months’ follow-up. No perforations occurred but deep tears were common and several patients required temporary narcotic analgesia after dilation. A similar report in 30 patients was published by Straumann et al<sup>26</sup> 2 years later describing successful symptom relief from 1 to 24 months, but the procedure caused “impressive lacerations” that were well tolerated by all patients.

These optimistic case series were soon followed by other reports in adults identifying symptom improvement with esophageal dilation, but highlighting the high rates of mucosal tears, need for hospitalization, and rare reports of esophageal perforation. In total, 84 adult EoE patients reported before 2008 underwent esophageal dilation with 5% experiencing esophageal perforation and 7% hospitalization for chest pain, rates substantially higher than for other esophageal diseases.<sup>79</sup> The first international EoE guidelines published in 2007 advised “whenever possible a diagnostic endoscopy with biopsy followed by medical or dietary therapy for EoE should be attempted prior to performing esophageal dilation.”<sup>4</sup> However, experienced esophagologists like myself, Walt Hogan, and Worth Boyce continued to safely dilate our EoE patients as primary therapy while developing thriving referral practices and patients seeking symptom relief after failing steroids or dietary treatments.<sup>18</sup>

The “renaissance period” for esophageal dilation began in 2010 with the publication of 3 papers from 4 groups with considerable experience with EoE patients.<sup>80–82</sup> They reported on a total of 109 adult EoE patients dilated with either Savory/Maloney bougies or through-the-scope (TTS) balloons. Dilations required a mean of 1.2 to 2.5 sessions to obtain an esophageal diameter of 16 to 17 mm. Most importantly, 91% of patients experienced dysphagia

**TABLE 1.** Esophageal Dilation for EoE in the Renaissance Era

References	No. Patients	Type of Dilators	Mean No. Sessions	Length of Sx Relief (mo)	Final Mean Lumen Size (mm)	Outcome
Schoepfer et al <sup>80</sup>	63 adults	46 Savary 17 TTS balloons	2.25	23	16	60/63 improved
Bohm et al <sup>81</sup>	10 adults	3 Savary 7 Maloney	1.2	22	17	8/10 improved at 2 y F/U
Dellon et al <sup>82</sup>	36 adults and children	12 Savary 58 TTS	1.9	N/A	16	20/24 at F/U doing well
Ally et al <sup>83</sup>	54 adults	29 Savary 24 Maloney 13 TTS	1.2	N/A	15	N/A
Saligram and McGarth <sup>84</sup>	30 adults	30 Savary	1.3	48	15	20 had F/U at 4 y: 10 intermittent dysphagia 10 assx
Lipka et al <sup>18</sup>	13 adults	12 Savary/ Maloney 2 TTS	3.2	14 y	16	11/13 assx with dilation average of every 2 y

assx indicates asymptomatic; EoE, eosinophilic esophagitis; F/U, follow-up; N/A, not assessed; TTS, through-the-scope.

relief for an average of 22 to 23 months (Table 1). Mucosal eosinophil counts did not change and complications were infrequent—3 mucosal tears, 2 requiring short hospitalization for pain, and no perforations. Since the initial 2010 series, 3 more US centers have reported their experiences with an additional 102 EoE patients with similar efficacy and safety.<sup>18,83,84</sup> The second international EoE consensus guidelines published in 2011<sup>1</sup> has begun to liberalize their recommendations—“Esophageal dilation with or without concomitant medical or dietary therapy can provide relief of dysphagia in selected patients. In the absence of high-grade esophageal stenosis, a trial of medical or dietary therapy before esophageal dilation is reasonable. For high-grade strictures, dilation before initiation of medical therapy has been well tolerated and effective.”

### Safety of Esophageal Dilation

Early reports of severe complications related to esophageal dilation in EoE patients generated great trepidation among gastroenterologists. Important factors contributing to these high complications rates included lack of disease awareness, overly aggressive dilation techniques, and associated Boerhaave syndrome. There are now 3 systematic reviews on dilation for patients with EoE.<sup>12,85,86</sup> Although these studies are retrospective, almost 500 patients representing nearly 100 dilations have been reported with only 3 esophageal perforations. This rate of 0.3% is not dissimilar to that quoted for standard endoscopy with dilation in non-EoE patients.<sup>87</sup> In addition, nearly all the reported perforations have been managed nonoperatively.

In contrast, mucosal tears associated with chest pain are quite common after dilating EoE patients.<sup>84</sup> In fact, many of us would argue that a mucosal tear is actually an indicator of effective esophageal dilation where the goal is to disrupt tissue and collagen.<sup>79</sup> Several reports have identified risk factors for esophageal complications after dilation in EoE patients.<sup>88,89</sup> Most are consistent with the concept that severe remodeling with scar tissue results in a more fragile, “crepe-paper” esophagus. These factors include strictures in the proximal and mid-esophagus, tight strictures, long duration of symptoms, and higher eosinophil counts.

### Guidelines for Safe Esophageal Dilation

Only recently have there been recommendations from our GI societies about esophageal dilation in EoE patients.<sup>27</sup> The guidelines summarized in Table 2 are based

on the retrospective series in the literature (Table 1) and my experiences dilating EoE patients over the last 25 years.<sup>12</sup>

All patients should be forewarned that pain, sometimes persisting for several days, is almost “expected” after esophageal dilation. I found this recognition lessens patient fears when pain occurs, help them tolerate it using mild analgesics, and rarely are narcotics required. As the esophageal lumen is frequently narrowed at multiple sites and sometimes diffusely, Savary-Guillard or Maloney bougies are my dilators of choice giving a better tactile assessment of lumen narrowing as the bougies of gradually increasing diameter are passed along the entire length of the esophagus. Strictures <15 mm are usually dilated with Savary bougies over a guidewire, than switching to Maloney bougies for larger diameters. The advocate of TTS balloon point to 2 theoretical advantages: radial rather than shearing dilating forces are applied during the procedure and one can immediately assess the degree of esophageal tearing.<sup>90</sup> The latter may be helpful for physician who do not do frequent esophageal dilations and are uncomfortable estimating the resistance tolerated for esophageal dilation. However, these balloons are cumbersome as they need repositioning several times during the procedure, the procedure is more time consuming, and TTS balloons are not reusable and more expensive. My goal is to start with a small diameter bougie or balloon, progress slowly, and gradually dilate to a bougie diameter of 15 to 18 mm to achieve symptom relief. This degree of lumen diameter will allow patients to eat a modified diet (15 mm, 45 Fr) or a full regular diet (18 mm, 54 Fr).<sup>17</sup> After reaching an optimal diameter, I dilate patients only when their symptoms begin to recur, approximately once a week or more. With this maintenance approach, many of my patients require dilation only every 2 to 3 years.<sup>18</sup>

### A PRACTICAL CLINICAL APPROACH TO TREATING EoE

As illustrated in Figure 2, my algorithm for treating EoE at the University of South Florida Swallowing Center has evolved over the last 8 to 10 years. My goals are to relieve symptoms and address both the inflammatory and possible fibrostenotic components of EoE in parallel treatments. All patients at initial endoscopy have biopsies and careful esophageal dilation if EoE is suspected. Patients with mucosal eosinophilia  $\geq 15$  eos/hpf receive high-dose PPIs, usually in a bid regimen for at least 2 to 3 months. If patients can be easily dilated to 17 to 18 mm initially, then their disease is considered the inflammatory phenotype and

**TABLE 2. Guidelines for Esophageal Dilation in Eosinophilic Esophagitis Patients**

Forewarn all patients that some degree of postdilation pain is to be expected
Endoscopy should be done before dilation to assess the location of strictures and estimate esophageal diameter
Start with a small diameter bougie and gradually dilate to 15 to 18 mm
If diameter <15 mm, we use Savary-Guillard bougies over a guidewire
If diameter $\geq 15$ mm, we use Maloney bougies which are easier to pass and give excellent tactile assessment of lumen narrowing
Gradual dilation is key with sessions separated by 3-4 wks
Limit the progression of dilation per session to 3 mm or less after resistance is noted. We stop with moderate resistance or blood on the dilator
Tight strictures <9 mm may require on average 2-3 dilations, whereas minimal strictures can be dilated to 17-18 mm at the first session
We do not routinely take a second look for mucosal tears
For postprocedure chest pain, mild analgesia is recommended and rarely narcotics (< 2% of patients). Expected chest pain is monitored during recovery period and by telephone, if necessary

anti-inflammatories are the key to their treatment. Those with strictures have a fibrostenotic phenotype and are gradually dilated simultaneously with PPI treatment, usually over 2 to 5 sessions to a goal of 15 to 18 mm allowing them to eat a regular diet and not be fearful of food impactions. All patients on PPI treatment have a second endoscopy with biopsies to assess the eosinophil count and define PPI-REE. If significant mucosal eosinophilia persists, then I do allergy testing to help direct the next choice of anti-inflammatory therapy. Those patients positive for food allergies by prick and patch testing are offered a SFED or a restricted diet based on history and test results. A dietitian gets involved with initial education about these complex diets, tips on managing this diet, and follow-ups with food logs. If tests are negative, then I prefer to initiate swallowed steroids using oral viscous budesonide at a dose of 1 mg after breakfast and immediately before going to bed. Endoscopies are repeated at appropriate intervals to monitor this therapy and at 1 year of maintenance therapy. Those with inflammatory phenotype rarely require further dilations, whereas the fibrostenotic patients are dilated when symptoms begin to recur, usually every 2 to 3 years.

With this approach, we have found that many of our healthy young adults find esophageal dilation as a primary therapy more “palatable” than dietary therapy and more reliable and cheaper than swallowed steroids. In contrast, monotherapy with dilation clearly does not improve the underlying inflammation.<sup>80,81</sup> I treat all my patients with PPIs being satisfied with this anti-inflammatory alone even if patients have mild persistent mucosal eosinophilia in the range of 15 to 30 to 40 eos/hpf. This is supported by our recent report of EoE patients treated with only PPIs and esophageal dilation doing well over an average of 14 years.<sup>18</sup> In contrast, more intensive mucosal eosinophilia persisting on PPIs is treated with steroids/diet in hopes of preventing stricture disease or reducing the need for frequent esophageal dilations.

While treating my EoE patients, I reassure them about the benign nature of EoE, emphasize my key goal is to relieve their dysphagia and prevent food impactions, while balancing the aggressiveness, cost, and inconvenience of treatments to normalize the mucosal eosinophilia. As new studies are conducted and additional data accumulate, my treatment algorithm of EoE will continue to evolve.

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