Treatment of eosinophilic esophagitis

Authors
Peter A L Bonis, MD
Glenn T Furuta, MD

Section Editor
Nicholas J Talley, MD, PhD

Deputy Editor
Shilpa Grover, MD, MPH

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INTRODUCTION — Esophageal eosinophilia has been described in association with eosinophilic gastroenteritis, an uncommon condition that can cause a range of symptoms, including malabsorption, dysmotility, and ascites, depending upon the layer of the intestinal tract that is involved [1,2]. When the gastrointestinal eosinophilia is limited to the esophagus and is accompanied by characteristic symptoms, it is termed eosinophilic esophagitis. Eosinophilic esophagitis is an increasingly recognized cause of dysphagia and possibly heartburn that is unresponsive to antireflux measures.

The management of eosinophilic esophagitis includes dietary, pharmacologic, and endoscopic interventions. The approach to patients with eosinophilic esophagitis is based primarily on clinical experience, case series, and small controlled trials [3-5]. In addition, it is uncertain whether treatment of symptoms alone is sufficient or if resolution of the eosinophilic inflammation is required.

Commonly used treatments include:

- Elimination and elemental diets to decrease allergen exposure
- Acid suppression to treat gastroesophageal reflux disease, which may mimic or contribute to eosinophilic esophagitis
- Topical glucocorticoids to decrease esophageal inflammation
- Esophageal dilation to treat strictures

Other treatments that have been studied include systemic glucocorticoids, antihistamines, immunosuppressants, and immunomodulators.

This topic will review the treatment of eosinophilic esophagitis. The approaches outlined are consistent with a 2011 consensus statement [6]. The pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis in adults and children are discussed separately. (See "Pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis".)

NATURAL HISTORY — There are limited data regarding the natural history of eosinophilic esophagitis. However, the available data suggest dysphagia persists in patients who do not receive treatment. In one study of 30 untreated patients followed for an average of 7.2 years, dysphagia persisted in 29 (97 percent) [7]. During follow-up, symptoms increased in 23 percent, were stable in 37 percent, and decreased in 37 percent. Attacks of dysphagia occurred more frequently in patients with blood eosinophilia or with pronounced findings on endoscopy. All patients maintained adequate caloric intake and body weight. Eleven patients were treated with esophageal dilation (seven had a single dilation and four had repeat dilations), which was at least partially successful in 10 (at least a 50 percent reduction in dysphagia).

DIETARY THERAPY — Dietary therapy is an effective treatment for eosinophilic esophagitis in children [8-10]. Dietary therapy is based upon the observation that patients with eosinophilic esophagitis have high rates of food allergies, and that those allergies may contribute to the development of eosinophilic esophagitis. (See "Pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis", section on 'Environmental factors

and T-cell immunity'.)

The appeal of the dietary approach is that it potentially offers an effective non-pharmacologic treatment. On the other hand, allergen avoidance with elimination and elemental diets poses a risk of nutritional deprivation, can be difficult for patients and families (particularly if nasogastric feedings are required), can lead to psychological problems, and may lead to unnecessary food aversion [11,12]. In addition, relapse upon discontinuation of the diet is common [9]. When used, elemental and elimination diets should be administered under the supervision of a registered dietician [13].

We refer both adults and children to an allergist with expertise in the evaluation of food allergies. We suggest avoidance of known allergens (both food and environmental) for patients in whom specific allergies can be identified after discussion of the pros and cons of the dietary approach. (See "Diagnostic evaluation of food allergy".)

Elimination diets — Three general approaches can be taken when implementing an elimination diet. The first is to perform testing for food allergies, with subsequent elimination of foods with positive test results. The second is to empirically eliminate foods to which patients are most likely to be allergic. Common food allergies in adults with eosinophilic esophagitis include peanuts, eggs, soy, cow's milk, wheat, and tree nuts [14-16]. The third involves the use of an elemental formula that eliminates all potential food proteins (see 'Elemental diets' below). Once symptoms are controlled, foods may be able to be sequentially reintroduced. Any foods that result in worsening of symptoms should be avoided indefinitely. (See "Diagnostic evaluation of food allergy".)

Elimination diets in children — A large series that looked at the use of elimination diets included 146 children who were treated with an elimination diet guided by the results of skin prick and patch testing [15,17]. Resolution of esophageal eosinophilia was observed in 77 percent (including 39 patients in whom esophageal eosinophilia returned upon reintroduction of the offending food) [15]. Egg, milk, and soy were identified most frequently with skin prick testing, while corn, soy, and wheat were identified most frequently with atopy patch testing. On average, four causative foods were identified per patient, although one patient had 11.

While this approach appears promising, food allergy testing (particularly patch testing) has not yet been standardized and additional follow-up is required to understand the long-term benefits. Furthermore, the above study was retrospective, uncontrolled, and not systematic, thus leaving considerable uncertainty regarding the predictive ability of the allergy testing [18].

An observational study compared outcomes in 98 children with eosinophilic esophagitis who had been treated with either an elemental diet (see 'Elemental diets' below), a diet in which six foods associated with allergy were eliminated (ie, cow-milk protein, soy, wheat, egg, peanut, and seafood), or a skin prick allergy testing-directed elimination diet [19]. Histologic remission occurred in children on all three diets (96, 81, and 65 percent, respectively). However, the odds of histologic remission were significantly higher in children on elemental diets compared with directed diets (OR 12.5, 95% CI 2.3-65.6). There was no significant difference in histologic remission rates between children on an elemental diet and a six-food elimination diet (OR 5.6, 95% CI 1.0-31.2). In another observational study in which 60 children were treated with either an elemental diet, or a six-food elimination diet, the authors found a similar degree of clinical and histologic improvement but improved acceptance, lower costs, and better compliance with the six-food elimination diet [20].

Elimination diets in adults — The six-food elimination diet has also been studied in adults [21,22]. In a study of 50 adults with eosinophilic esophagitis, patients were treated with the six-food elimination diet for six weeks [21]. This diet was based on excluding the six most common food allergens and was not based on specific food allergy testing. At the end of six weeks, a clinical response (decreased dysphagia) was seen in 94 percent of patients, the endoscopic appearance improved in 78 percent, and esophageal biopsies revealed at least a 50 percent reduction in eosinophils in 78 percent. A clinical response was more common in patients who initially had heartburn or who started the six-food elimination diet during the final three years of the study (possibly reflecting increasing experience in coaching patients to adhere to the diet). However, while 94 percent of patients showed clinical improvement, only 74 percent had a reduction in their eosinophil count to less than 15 eosinophils/hpf.

After six weeks, patients gradually reintroduced food groups and follow-up data were available in 20 patients. In all 20 patients, a specific food could be implicated in inciting the esophageal eosinophilia. The most common food triggers were wheat (60 percent) and milk (50 percent). Seafood was not a trigger for any patient. Skin-prick

allergy testing identified only 13 percent of the food triggers.

These studies suggest that six-food elimination diets for six weeks followed by individually tailored exclusion diets may be an option for motivated adults. However, successful implementation of such diets requires a dedicated and informed nutritionist and willingness on the part of the patient to make substantial lifestyle changes. In addition, patients will need to undergo multiple endoscopies to determine which food group is the trigger.

These observations also question the value of traditional allergy testing in identifying the implicated foods. Nevertheless, referring patients to an allergist may lead to an improvement in quality of life through treatment of patients with an overall allergic diathesis.

While it is unclear if adults will adhere to an elimination diet long-term, among the few patients who have been studied, clinical and histologic improvement (although not always normalization) appears to be sustained for up to three years [22].

Elemental diets — Consumption of an elemental diet provides another means to limit the intake of potential food allergens [23,24]. An elemental diet is composed of an elemental formula in which the protein source is comprised of synthetic amino acids. Elemental diets are unpalatable and expensive. They have been studied almost exclusively in children and data in adults are limited [25].

One of the largest series included 51 children and adolescents who were treated with an elemental diet that consisted of free amino acids, corn syrup solids, and medium-chain triglyceride oil (Neocate-1-Plus, SHS North America, Gaithersburg, MD) delivered orally (to three patients) or via a nasogastric tube (to 48 patients) [24]. Patients were allowed to consume water and one fruit (either grape or apple) and its corresponding pure juice. They were also maintained on a proton pump inhibitor.

Significant improvement in vomiting, abdominal pain, and dysphagia were observed an average of 8.5 days after beginning treatment in all but two patients. A repeat endoscopy with biopsies was performed one month after beginning treatment and revealed a corresponding significant decrease in esophageal eosinophils. The long-term efficacy of treatment was not described, although the authors suggested that they reintroduced single foods every five to seven days while simultaneously observing clinical symptoms and repeating an endoscopy with biopsy in ambiguous cases.

Symptomatic and histologic improvement was also observed in an earlier report using a similar approach in 10 children [23]. However, the median time to symptom relief was three weeks (range two to six weeks).

PHARMACOLOGIC THERAPY

Acid suppression — The relationship between gastroesophageal reflux disease (GERD) and eosinophilic esophagitis is unclear. GERD may be a mimic of eosinophilic esophagitis, coexist with it [26], or contribute to it. Conversely, eosinophilic esophagitis may contribute to GERD [27]. The diagnosis of eosinophilic esophagitis should generally include demonstration of persistent esophageal eosinophilia after treatment with a proton pump inhibitor (or with a normal pH study). (See "Pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis", section on 'Distinction from GERD'.)

Proton pump inhibitors may benefit patients with esophageal eosinophilia either by reducing acid production in patients with co-existent GERD, or by other yet undefined anti-inflammatory mechanisms [28]. Acid-suppressing therapy may also be helpful in patients with established eosinophilic esophagitis, since the already inflamed esophagus may be predisposed to injury and more sensitive to physiologic acid exposure [29,30].

Occasional patients have a good clinical and histologic response to proton pump inhibitors alone, suggesting that GERD, or a PPI-responsive form of esophageal eosinophilia, may be responsible [31,32]. In a randomized trial, 42 patients with newly diagnosed eosinophilic esophagitis were randomly assigned to treatment with aerosolized swallowed fluticasone (440 mcg twice daily) or esomeprazole (40 mg daily) for eight weeks followed by an upper endoscopy with biopsies [32]. In patients without coexisting GERD, there was no significant difference in resolution of esophageal eosinophilia between the esomeprazole and fluticasone treatment arms (18 versus 24 percent). In contrast, among patients with GERD, those treated with esomeprazole were significantly more likely to have resolution of esophageal eosinophilia as compared with fluticasone (100 versus 0 percent). However, regardless of the presence of GERD, treatment with esomeprazole, but not fluticasone, was associated with a significant

improvement in symptoms of dysphagia.

Topical glucocorticoids — Most patients with eosinophilic esophagitis respond to topical glucocorticoids as demonstrated by a decrease in eosinophil counts [26,33,34]. Fluticasone, budesonide, and ciclesonide have been studied. (See "Major side effects of inhaled glucocorticoids" and "Major side effects of systemic glucocorticoids".) No formulation of topical glucocorticoids has been approved specifically for eosinophilic esophagitis. We treat most adult patients with swallowed fluticasone [26,33,35-40].

Randomized controlled trials have not consistently demonstrated an improvement in dysphagia with topical glucocorticoids [34,41]. It is unclear if this is due to differences in patient selection, definitions of symptom response, steroid formulations and duration of treatment, or dietary modification that may have resulted in a higher placebo response rate [42]. Long-term steroid use is associated with side effects and symptoms often recur when steroids are discontinued [43].

Fluticasone propionate — Fluticasone is administered using a metered dose inhaler without a spacer. The medication is sprayed into the patient's mouth and then swallowed. Patients should **not** inhale when the medication is being delivered and they should not eat or drink for 30 minutes following administration.

The optimal dose has not been established. Our approach is based upon the patient's age:

- Children from 1 to 4 years of age: 44 mcg inhaler, two sprays twice daily
- Children from 5 to 10 years of age: 110 mcg inhaler, two sprays twice daily
- Patients ≥11 years of age (including adults): 220 mcg inhaler, two sprays twice daily

Treatment is generally well-tolerated and patients who are destined to respond tend to do so quickly (within one week and often within one to two days). Patients frequently relapse when treatment is stopped, with reported relapse rates of 14 to 91 percent [26,43-45]. For patients who relapse, we repeat treatment for four to six weeks.

Maintenance therapy has not yet been standardized. Because eosinophilic esophagitis is a chronic disease, we suggest ongoing treatment, whether medical or nutritional. Some authorities treat on an as-needed basis, while others will use the lowest dose possible of topical glucocorticoids that allow patients to remain asymptomatic. Our approach is to continue nutritional therapy, using topical glucocorticoids as needed in doses and intervals that keep patients asymptomatic (see 'Dietary therapy' above).

Representative studies of fluticasone for eosinophilic esophagitis have shown the following:

- A series in adults included 21 patients who were treated with fluticasone propionate 220 mcg twice daily [44]. All patients had relief of dysphagia that lasted a minimum of four months. Relief often occurred within a few days after beginning treatment. Three patients (14 percent) relapsed and required additional therapy. Histologic outcomes were not assessed. However, in a later series, clinical improvement was associated with a significant decrease in esophageal eosinophil counts [26]. The only adverse effect noted was dry mouth.
- Similar benefits have been observed in children, although different doses and dosing intervals have been used [33,36,40,45]. The largest controlled trial included 36 children who were randomly assigned to swallowed fluticasone (880 mcg/day in two divided doses) or placebo for three months [33]. Histologic remission was observed significantly more often in the fluticasone group (50 versus 9 percent).

Side effects that have been reported with the use of fluticasone for eosinophilic esophagitis include candidal esophagitis [36,45] and herpes esophagitis was noted in a case report [46]. In addition, in diseases other than eosinophilic esophagitis, inhaled doses of fluticasone higher than 440 mcg/day have been associated with systemic side effects including cataracts, impaired growth in children, and adrenal suppression [47,48]. It is not known if the risk of these side effects is reduced when fluticasone is swallowed and undergoes first-pass metabolism in the liver.

Budesonide — Budesonide has been evaluated in case series and randomized trials and appears to be effective for treating eosinophilic esophagitis [41,49-55]. Budesonide can be administered using a nebulizer and

patients are then instructed to swallow the accumulated liquid or as an oral viscous slurry (1 mg daily for children under the age of 10 years, and 2 mg daily for older children and adults). Viscous budesonide can be compounded by mixing two or four 0.5 mg/2mL Pulmicort Respules™ with sucralose (Splenda™; ten 1-gram packets per 1 mg of budesonide, creating a volume of approximately 8 mL) [41]. Patients should not eat or drink for 30 minutes after taking the budesonide suspension.

In a randomized trial, 22 patients with eosinophilic esophagitis were treated with budesonide either nebulized and then swallowed or as an oral viscous slurry [56]. Although patients who received the viscous slurry had a higher duration of mucosal contact with budesonide and lower eosinophil count, there was no significant difference in dysphagia symptom scores which improved in both groups.

Studies of budesonide for eosinophilic esophagitis have shown the following:

- In a randomized trial with 24 children, the response rate, defined as an eosinophilic count ≤6/hpf was significantly higher with oral viscous budesonide (87 versus 0 percent with placebo) [41]. Symptoms, endoscopic findings, and histologic features improved after treatment. Patients in both groups were also treated with a proton pump inhibitor. Since there were no responders in the placebo group, monotherapy with a proton pump inhibitor had no benefit.

- Similar benefits have been described in studies in adults [51,52,55]. In a randomized trial, 36 adults and adolescents with active eosinophilic esophagitis were randomized to budesonide 1 mg twice daily or placebo for 15 days [55]. The budesonide was administered using a nebulizer and patients were instructed to continuously swallow the accumulated liquid. Patients who received budesonide were more likely to have significant improvements in dysphagia compared with those who received placebo (72 versus 22 percent). In addition, patients treated with budesonide showed histologic improvement, whereas those treated with placebo did not.

Ciclesonide — Ciclesonide, a topical glucocorticoid with less systemic absorption than fluticasone, has been evaluated in small case series [57-59]. In one report, four children who had either failed therapy with fluticasone or dietary restriction, or whose parents were concerned about steroid exposure, were treated with swallowed topical ciclesonide (80 or 160 mcg, two sprays twice daily) for two months [58]. Symptoms resolved in all four patients and there was a significant decrease in eosinophil counts in both proximal and distal esophageal biopsy specimens at two months (proximal: 71± 25.5 versus 1.8 ± 2 eosinophils/hpf before and after treatment; distal: 76.3± 33 versus 0.75 ± 1.5 eosinophils/hpf before and after treatment). Further studies are needed before ciclesonide can be recommended for patients with eosinophilic esophagitis.

Maintenance therapy — The high relapse rate following discontinuation of treatment with topical glucocorticoids has led to investigations of maintenance therapy with topical steroids for patients with eosinophilic esophagitis. Low-dose budesonide was used in a randomized trial in 28 adults with eosinophilic esophagitis who were in clinical remission [54]. The patients were assigned to twice daily budesonide (0.25 mg) or placebo for a total of 50 weeks. The eosinophil load increased over the course of treatment in both groups, but the increase was less in those treated with budesonide (from 0.4 to 32 eosinophils/hpf) than in those treated with placebo (from 0.7 to 65 eosinophils/hpf).

Over the course of the study, patients treated with budesonide did not report a statistically significant increase in symptoms, whereas those who received placebo did. At the end of the study, patients who received budesonide were more likely to be in clinical remission (64 versus 36 percent). Patients treated with budesonide also showed evidence of esophageal remodelling. At baseline, patients with eosinophilic esophagitis had esophageal walls that were twice as thick as those seen in healthy controls (mean thickness 4.2 mm versus 2.2 mm). After treatment, patients in the budesonide group showed decreases in the thickness of all wall layers, though only the decrease in the thickness of the mucosa was statistically significant. No adverse events were noted.

Topical versus systemic glucocorticoids — Data suggest that oral prednisone may be slightly more effective than topical fluticasone for the treatment of eosinophilic esophagitis, but the degree of benefit probably does not justify routine use of prednisone considering the greater likelihood of side effects [17]. Furthermore, because of the high relapse rate, chronic or repeated therapy may be needed, which may also support the preferential use of swallowed fluticasone. If systemic steroids are used, the typical dose is 1 to 2 mg/kg/day in divided doses

(maximum 60 mg per day).

A randomized trial compared topical with systemic glucocorticoids [45]. The trial included 80 children with eosinophilic esophagitis who were randomly assigned to oral prednisone or swallowed fluticasone. Almost all of the patients, regardless of treatment, were symptom free by four weeks. Histologic improvement was seen to a greater degree in the prednisone group. Relapse was observed in 45 percent of patients in both groups within 24 weeks of stopping therapy. Glucocorticoid side effects occurred in 40 percent of patients in the prednisone arm, whereas candidal esophagitis was seen in 15 percent in the fluticasone arm.

ESOPHAGEAL DILATION — Dilation of esophageal strictures is effective for relieving dysphagia, but has no effect on underlying inflammation [60,61]. It is often reserved for patients who have failed more conservative therapy, but may be required as initial therapy in patients with high-grade strictures [62]. We generally reserve dilation for patients with strictures or rings who have not responded to medical therapy.

Dilation should be performed carefully since it has been associated with deep mucosal tears and esophageal perforation [63-66]. It has been recommended that the progression of dilation per session be limited to 3 mm or less [64]. Because of this, multiple dilations are often required to attain a goal esophageal diameter of 15 to 18 mm. Chest pain following the procedure is common and patients should be forewarned [60].

Whether patients with eosinophilic esophagitis are at higher risk of perforation due to esophageal dilation than other patients undergoing dilation is not clear. Older studies suggested that patients with eosinophilic esophagitis are at increased risk for perforation, with perforation rates of 5 to 7 percent [67]. More recent studies suggest that the rate of perforation is considerably lower and is closer to that seen with esophageal dilation for strictures due to causes other than eosinophilic esophagitis (approximately 0.1 to 0.2 percent). A 2010 meta-analysis that included 468 patients who underwent 671 dilations found that while mucosal tears were described in a majority of cases, there was only one perforation (0.1 percent) [68].

Studies subsequent to the meta-analysis have also shown lower perforation rates that originally reported:

- A study of 207 patients with eosinophilic esophagitis found no cases of perforation, though 74 percent of patients reported chest pain following the procedure [60].
- A large series included 293 dilations in 167 patients performed between 1990 and 2009 [64]. Three of the procedures (1 percent) were complicated by a perforation. Risk factors included luminal narrowing in the upper or middle third of the esophagus, the presence of a stricture that could not be traversed with a standard upper endoscope, and the use of Savory dilators. Deep mucosal tears occurred in 9 percent of procedures and major bleeding occurred in 0.3 percent.
- A study of 70 dilations carried out in 36 patients had an overall complication rate of 7 percent [69]. There were two deep mucosal rents and three episodes of chest pain, but there were no perforations reported.

Tearing and perforation can occur without perceived resistance when passing a dilator or the endoscope (picture 1) [63]. As a result, it may be reasonable to gently inspect the esophagus after passing each dilator. Rigid endoscopy has been associated with a high rate of perforation and should be avoided [11]. The use of glucocorticoids before dilation has not been extensively studied [70]; it may offer a small benefit prior to dilation by diminishing inflammation. (See "Management of benign esophageal strictures", section on 'Complex strictures'.)

EXPERIMENTAL AND INEFFECTIVE TREATMENTS — Other treatments for eosinophilic esophagitis have been examined. Many have been ineffective, whereas others have shown efficacy in small series.

Antihistamines and cromolyn — Little benefit has been seen in patients treated with medications aimed at controlling allergies, including antihistamines and cromolyn sodium (a mast cell stabilizer) [71,72].

Montelukast — Initial experience suggested that montelukast (a leukotriene inhibitor that has been used in eosinophilic gastroenteritis) may be helpful for symptom reduction in patients with eosinophilic esophagitis but subsequent experience has been mixed. Thus, trials are required to clarify whether montelukast has a role in the management of eosinophilic esophagitis.

The following are illustrative of the range of observations. Symptomatic improvement has been observed in small

case series of both adult and pediatric patients with isolated eosinophilic esophagitis:

- One series examined eight adults who were treated with montelukast [73]. The dose used was much higher than the standard 10 mg dose used for the treatment of asthma in adults. While patients started at a dose of 10 mg per day, the patient increased the dose up to a suprapharmacologic dose totaling 100 mg daily based upon symptom relief. Once symptom relief had been achieved, the dose was reduced to maintenance levels where symptom control was maintained (20 to 40 mg daily). Six of eight patients had complete symptom relief. However, there was no effect on esophageal eosinophilia. Several side effects were observed, including nausea and myalgias. The safety of the high doses used in this study is unclear.
- In a retrospective series of eight pediatric patients who were maintained on montelukast (4 to 10 mg daily), three patients had a clinical response that was attributed to montelukast (one complete response and two partial responses) [74]. Four patients responded clinically but had also been started on other therapies in addition to the montelukast. The study was not able to confirm if montelukast had an effect on esophageal histology. No side effects were reported related to the montelukast.

By contrast, montelukast was not helpful in a patient with eosinophilic gastroenteritis with esophageal involvement in one report [75], while in another it was not effective in maintaining the histopathological or clinical response achieved by topical steroids in adults with eosinophilic esophagitis [76].

Mepolizumab — Mepolizumab is a humanized monoclonal antibody against interleukin (IL)-5, which has a central role in eosinophil recruitment. (See "Pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis", section on 'Environmental factors and T-cell immunity'.)

Studies of mepolizumab have had variable results:

- A case series found clinical benefits in four patients with eosinophilic esophagitis [77].
- A placebo-controlled trial in 11 adults found a reduction in esophageal eosinophilia in patients treated with mepolizumab compared with those who received placebo [78]. Clinically, there was a small improvement in dysphagia in the mepolizumab arm, but it did not differ significantly from improvement also seen the placebo arm.
- A third report included 57 children with eosinophilic esophagitis who were randomly assigned to three infusions of mepolizumab at different doses (0.55, 2.5, or 10 mg/kg) [79]. There was a significant decrease in the peak and mean eosinophil counts and improvement in endoscopic findings in all three groups. However, symptoms did not improve, possibly because most patients did not have severe symptoms at baseline. Whether the observed histologic end endoscopic benefits could be attributed to mepolizumab is uncertain since the study did not include a placebo arm and because dietary interventions were permitted.

Reslizumab — Reslizumab is an IL-5 neutralizing antibody that is undergoing clinical trials in eosinophilic esophagitis. In a controlled trial involving 226 children and adolescents with eosinophilic esophagitis, there was a significant reduction in peak eosinophil counts compared with placebo (59, 67, and 64 percent for the three doses tested versus 24 percent for placebo) [80]. However, all treatment groups had significant improvement in symptoms as assessed by a physician global assessment score and the differences were not significantly different than placebo. Thus, its role remains uncertain.

Anti-IgE monoclonal antibody — In a report of two patients with multiple food allergies and eosinophilic esophagitis, treatment with the anti-IgE monoclonal antibody omalizumab was associated with an improvement in allergic symptoms but not in endoscopic or histologic features of eosinophilic esophagitis [81].

Purine analogues — A case report described a clinical and histologic response to azathioprine or 6-mercaptopurine in three adults with glucocorticoid-dependent eosinophilic esophagitis [52].

Anti-TNF therapy — Treatment with infliximab was not effective at resolving symptoms or eosinophilia in a case series of three adults with glucocorticoid-dependent eosinophilic esophagitis [82].

PROGNOSIS — The long-term prognosis of eosinophilic esophagitis is unclear. Untreated, patients may remain

symptomatic or have episodic symptoms. As noted above, symptoms frequently recur in patients treated with a short course of topical glucocorticoids [43].

Whether the disease persists into adulthood in affected children has not been extensively studied, although the available data suggest that it does. In a report of 620 children evaluated over a 14-year period, eosinophilic esophagitis persisted, with only 10 percent developing tolerance to their food allergies [9]. No children progressed to other gastrointestinal diseases.

In adults, anecdotal observations suggest that the disease may progress to a fibrostenotic stage in which the predominant symptom is intermittent dysphagia, but the proportion of patients with progressive disease is unknown [83].

The largest study on the natural history in adults focused on 30 adults who were followed for an average of seven years [7]. Patients underwent a follow-up examination consisting of a structured interview, laboratory testing, and an upper endoscopy with biopsies. The majority of patients had persistent dysphagia. Attacks of dysphagia were more common in patients who had peripheral eosinophilia. Eosinophilic infiltration persisted in all symptomatic patients, but the degree of tissue eosinophilia appeared to decrease. The inflammatory process remained confined to the esophagus without gastric or duodenal involvement. No cases of dysplasia or esophageal malignancy were observed.

PATIENT ADVOCACY — The American Partnership for Eosinophilic Disorders (apfed.org/drupal/drupal/index.php) is an advocacy group for patients with eosinophilic gastrointestinal diseases.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient information: Eosinophilic esophagitis (The Basics)")

SUMMARY AND RECOMMENDATIONS — The management of eosinophilic esophagitis includes pharmacologic, endoscopic, and dietary interventions. Our recommendations below are consistent with consensus guidelines (table 1).

- We refer both adults and children to an allergist with expertise in the evaluation of food allergies. We suggest avoidance of known allergens (both food and environmental) for patients in whom specific allergies can be identified after discussion of the pros and cons of the dietary approach as described above (**Grade 2C**). (See 'Dietary therapy' above.)

- Dietary approaches have been best studied in children, in whom they are used routinely as an option for primary therapy. Emerging data in adults suggest a six-food elimination diet can improve symptoms and esophageal eosinophilia and help identify causative foods. As a result, some authorities have begun recommending this approach as a primary option for their adult patients. If a dietary approach is taken, it is important to coordinate it with a nutritionist since elimination and elemental diets can result in important restrictions of calories and nutrients.

- In patients who opt for a pharmacologic approach, we suggest treatment with swallowed fluticasone (**Grade 2B**). (See 'Fluticasone propionate' above.)

  Fluticasone is administered using a metered dose inhaler without a spacer. The medication is sprayed into

the patient's mouth and then swallowed. Patients should not use a spacer or inhale while the medication is being delivered, and they should not eat or drink for 30 minutes following administration. The dose used varies with the age of the patient.

We suggest initial treatment for six to eight weeks (**Grade 2C**). Optimal strategies after initial treatment are unsettled. Thus, the decision to continue treatment should be individualized. Because symptoms and esophageal eosinophilia almost universally return when treatment is discontinued, we suggest ongoing treatment, whether medical or nutritional (**Grade 2C**). Some authorities treat on an as-needed basis. Such an approach is particularly useful in patients who have identifiable, seasonal triggers. Others use the lowest dose possible of topical glucocorticoids that allow patients to remain asymptomatic. Our approach is to continue nutritional therapy, using topical glucocorticoids as needed in doses and intervals that keep patients asymptomatic.

Treatment is generally well-tolerated. However, worsening of dysphagia during treatment should alert to the possibility of candidal esophagitis.

- In patients who do not respond to topical fluticasone, we suggest either an elimination diet (if not already tried) or a trial of topical budesonide (**Grade 2C**). (See 'Elimination diets' above and 'Budesonide' above.)
- Adult patients with esophageal rings or strictures may require dilation. Dilation is associated with mucosal tears and esophageal perforation and thus should be performed extremely cautiously. We suggest that, if possible, dilation be avoided until patients have been given a course of fluticasone, which may relieve dysphagia and thus avoid the need for dilation (**Grade 2C**). Dilation has generally not been needed in children in most reports. (See 'Esophageal dilation' above.)
- The role of acid suppression is unclear. Acid suppression is reasonable in patients in whom reflux is suspected to be contributing to symptoms and there are occasional patients who have a good clinical response to proton pump inhibitors. Thus, we suggest a trial of a proton pump inhibitor except in patients who have already tried one and did not respond (**Grade 2C**). (See 'Acid suppression' above.)
- Whether patients should undergo surveillance endoscopy is unclear. Although a malignant potential has not been reported, follow-up has generally been short. We generally repeat upper endoscopy for patients in whom symptoms have changed or who require esophageal dilation.

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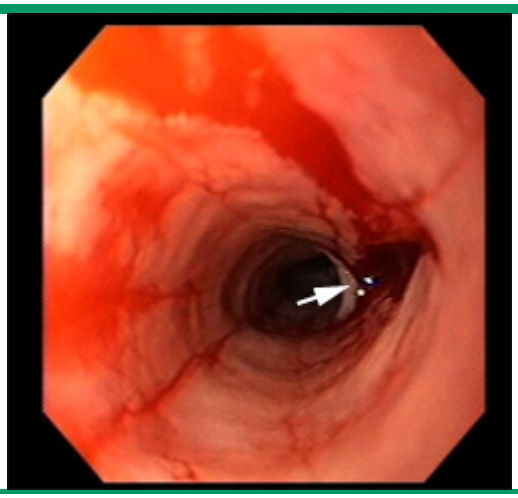
GRAPHICS

Eosinophilic esophagitis



Endoscopy performed after passing a dilator and prior to passage of the next size dilator. A deep mucosal tear is evident in the mid esophagus (arrow). There were no clinical signs of immediate perforation. Esophagography (initially with Gastrografin®, a water-soluble contrast agent, and then with barium) was negative for a perforation.
Courtesy of Andres Gelrud, MD and Anthony Lembo, MD.

The International Gastrointestinal Eosinophil Researchers (TIGERS) Summary of 2011 eosinophilic esophagitis updated consensus recommendations

Below is a summary version of the 2011 consensus recommendations for eosinophilic esophagitis (EoE) diagnosis and treatment.[1] Since 2007, the number of EoE publications doubled, providing new disease insight. A panel of 33 physicians with expertise in pediatric and adult allergy/immunology, gastroenterology and pathology conducted a systematic review of the EoE literature (since September 2006) using electronic databases. Based on the literature review and expertise of the panel, a summary of the recommendations is provided here.

Conceptual definition - To refine perceptions and hypotheses for future EoE studies, the following conceptual definition was developed: "Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."

Diagnostic guidelines - Taking into account increasing clinical experiences and research, the following guidelines were proposed: "Eosinophilic esophagitis is a clinico-pathological disease. Clinically, EoE is characterized by symptoms related to esophageal dysfunction. Pathologically, one or more biopsies must show eosinophil predominant inflammation.* With few exceptions, 15 eosinophils/hpf (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is isolated to the esophagus and other causes of esophageal eosinophilia should be excluded, specifically proton pump inhibitor (PPI)-responsive esophageal eosinophilia.• (Table A). The disease should remit with treatments of dietary exclusion and/or topical corticosteroids. EoE should be diagnosed by clinicians taking into consideration all clinical and pathologic information; neither of these parameters should be interpreted in isolation.

Summary statements

History and physical - History should focus on difficulties with eating and swallowing (Table B) and a thorough physical examination should focus on growth and nutrition parameters and to assess potential other causes of esophagitis (Table A).

Endoscopy - Endoscopy with esophageal biopsy is considered the only reliable EoE diagnostic. Two to four biopsies each from the proximal and distal esophagus should be obtained. Gastric and duodenal biopsies should be examined to exclude other potential causes of eosinophil associated gastrointestinal disease (Table A). Endoscopic features can suggest but cannot diagnose EoE.

Radiography - An upper gastrointestinal series is useful to characterize anatomic abnormalities that may escape endoscopic detection such as proximal strictures and long segment narrowing.

Histopathology - See Diagnostic guidelines and Table C.

Allergic evaluation - An evaluation by an allergist or immunologist is recommended to document aeroallergen sensitization and seasonal variability as it may pertain to EoE and to control concurrent atopic diseases. Serum IgE and/or skin prick testing for immediate type hypersensitivity reactions to foods are warranted to help identify food allergic disease in patients with EoE. Medically supervised food reintroduction may be necessary for patients with previous allergic reactions to a food or IgE-mediated sensitivity documented by IgE testing. Skin prick tests, serum IgE tests, and food patch tests may be used to help identify foods that are associated with EoE, but are **not** sufficient to make the diagnosis of food allergy driven EoE. Foods that trigger EoE can only be identified by documenting disease remission and recrudescence after specific food elimination and addition.

Genetics - EoE runs in families and although specific genes that pre-dispose to EoE susceptibility have been identified (thymic stromal lymphopoietin [TSLP], eotaxin-3), they are not yet ready for usage in clinical settings.

Treatments - (Table D).

Dietary therapy - Amino acid based formulas and dietary elimination are effective therapies for children with EoE and their use in adults requires further study. Patient's lifestyle, adherence to therapy and family resources should be considered when instituting these treatments. Consultation with a registered dietitian is strongly encouraged. EoE foods triggers may need to be restricted indefinitely.

Steroids - Topical corticosteroids are effective therapy for EoE in children and adults. Systemic corticosteroids may be used for emergent situations (severe dysphagia, hospitalization, weight loss) but caution is warranted for chronic management of EoE.

Other treatments - Cromolyn sodium, leukotriene receptor antagonists, and immunosuppressives (azathioprine or 6-mercaptopurine) are not recommended treatments for EoE. Biologic agents require further clinical studies and are currently not recommended for routine use.
Dilation - Esophageal dilation can provide relief of dysphagia in selected EoE patients. If high-grade esophageal stenosis is not present, a trial of medical or dietary therapy prior to esophageal dilation is reasonable.

Table A.[1] Conditions associated with esophageal eosinophilia

Gastroesophageal reflux disease (GERD)
Eosinophilic esophagitis (EoE)
Eosinophilic gastrointestinal diseases (EGIDs)
Celiac disease
Crohn's disease
Infection
Hypereosinophilic syndrome (HES)
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigoid vegetans
Connective tissue disease
Graft versus host disease

Table B.[1] Symptoms related to EoE

Dysphagia and feeding dysfunction
Coping mechanisms - Avoiding highly textured foods such as meats and bulky foods such as bagels, cutting food in small pieces, lubricating foods before eating with liquids or butter, extensive chewing of foods, washing food down with liquids, prolongation of mealtimes
Food impaction
Coping mechanisms - Drinking liquid to wash food down, raising hands above head, jumping up and down, waiting for food to dissolve or to pass
Chest pain
Coping mechanisms - Avoiding foods or liquids that exacerbate pain such as highly textured or bulky foods, alcohol or acidic drinks
GERD like symptoms recalcitrant to medical and surgical GERD management
Abdominal pain
Vomiting
Anorexia and early satiety

Table C.[1] Histological characteristics of EoE

Mucosal eosinophilia
Eosinophil microabscesses
Superficial layering of eosinophils
Extracellular eosinophil granules
Surface epithelial desquamation
Basal zone hyperplasia
Rete peg elongation

Dilated intercellular spaces
Subepithelial fibrosis/sclerosis/lamina propria fibrosis
Table D.[1] Recommended initial treatments for EoE
Topical swallowed corticosteroids (initial doses)[2-4]
Fluticasone (spray metered dose inhaler directly in mouth then swallow)
Adults: 440 to 880 mcg twice daily
Children: 88 to 440 mcg twice to four times daily (maximum 1760 mcg per day)
Budesonide (as a compounded viscous suspension$^{\Delta}$)
Children (<10 years): 1 mg daily
Older children and adults: 2 mg daily
Following administration, patients should not rinse the mouth or eat or drink for 30 minutes
Systemic corticosteroids (severe disease)
Prednisone: 1 to 2 mg/kg per day by mouth in one or two divided doses (maximum 60 mg per day), taper after week 4[4]
Education, advocacy, and/or research support resources:
American Academy of Allergy, Asthma, and Immunology: www.aaaai.org
American Partnership for Eosinophilic Disorders: www.apfed.org
Campaign Urging Research for Eosinophilic Disorders: www.curedfoundation.org
Children's Digestive Health and Nutrition Foundation: www.cdhnf.org
Food Allergy Initiative: www.faiusa.org
Food Allergy & Anaphylaxis Network: www.foodallergy.org
North American Society of Pediatric Gastroenterology and Nutrition: www.naspghan.org
Registry for Eosinophilic Gastrointestinal Disorders: www.regid.org
The International Gastrointestinal Eosinophil Researchers: www.tigers-egid.cdhnf.org
TIGERS is grateful to the American Partnership for Eosinophilic Disorders for providing financial support of this summary document. APFED (www.apfed.org) is a 501(c)3 non-profit dedicated to education, advocacy, support and advancing research to improve the lives of those with eosinophil associated diseases. Content summarized by TIGERS.

EoE: eosinophilic esophagitis.
* For optimal pathological evaluation, multiple biopsies from the proximal and distal esophagus should be obtained and evaluated for a variety of pathological features. Pathologists should report all abnormalities associated with EoE such as the peak eosinophil count (obtained from the area with the highest density of eosinophils), eosinophilic microabscesses, surface layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, and lamina propria fibrosis. In a few circumstances, patients may have strong clinical evidence for EoE and have less than 15 eosinophils/hpf with other histological features indicative of eosinophilic inflammation.
• An emerging body of literature and clinical experience describes a subset of patients whose symptoms and histopathologic findings are responsive to PPI treatment and who may, or may not, have well documented gastroesophageal reflux disease (GERD). Until more is known, these patients should be diagnosed as "PPI-responsive esophageal eosinophilia."
Δ Viscous budesonide can be compounded by mixing two 0.5 mg/2 mL budesonide inhalation (Pulmicort Respule®) ampules for nebulization with sucralose (Splenda™), ten 1-gram packets per 1 mg of budesonide, creating a volume of approximately 8 mL[3].

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