Treatment of eosinophilic esophagitis (EoE)

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INTRODUCTION

Esophageal eosinophilia has been described in association with other eosinophilic gastrointestinal disorders collectively known as EGIDs. Of these, eosinophilic gastroenteritis is the most common, and yet 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. When the gastrointestinal eosinophilia is limited to the esophagus and is accompanied by characteristic symptoms, it is termed eosinophilic esophagitis (EoE). EoE is an increasingly recognized cause of dysphagia and possibly heartburn that is unresponsive to antireflux measures.

The management of EoE includes dietary, pharmacologic, and endoscopic interventions. The approach to patients with EoE is based on clinical experience and data from observational studies and a few randomized controlled trials. It is becoming increasingly known that management based solely on subjectively self-reported symptoms is insufficient, and additional assessment tools are required. These tools are advancing from primarily resolution of eosinophilic inflammation to objective patient-reported outcomes and attention to other histologic parameters. Regardless, the primary goal of therapy in patients with EoE is histologic improvement in esophageal eosinophilia. In addition, for pediatric patients, therapy aims to restore normal growth and development.

Commonly used treatments include dietary therapy, acid suppression, and topical glucocorticoids. Experience is evolving with dupilumab.

This topic will review the pharmacologic and endoscopic treatment of EoE. The approaches outlined are generally consistent with guidelines from the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy, an Appraisal of Guidelines for Research and Evaluation consensus statement, and international expert recommendations [1-4].

Other aspects of EoE are discussed separately:

- Disease pathogenesis - (See "Eosinophilic esophagitis (EoE): Genetics and immunopathogenesis".)
- Clinical manifestations, and diagnosis - (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)".)
- Testing for allergies - (See "Allergy testing in eosinophilic esophagitis".)
- Dietary management - (See "Dietary management of eosinophilic esophagitis".)

DIETARY THERAPY

Dietary therapy is an effective first-line treatment for eosinophilic esophagitis (EoE) in children and adults. Dietary therapy is based upon the observation that patients with EoE have high rates of food allergies, and that those allergies may contribute to the development of EoE. (See "Eosinophilic esophagitis (EoE): Genetics and immunopathogenesis", section on 'Role of the immune system and environmental factors'.)

The appeal of the dietary approach is that it potentially offers an effective nonpharmacologic 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 or gastrostomy tubes are required), can lead to psychologic problems, and may lead to unnecessary food aversion. Other important factors that may influence the decision include costs (often not borne by insurance providers), convenience, ease of adherence, and patient/family preferences. In addition, relapse upon discontinuation of the diet is common. When used, elemental and elimination diets should be administered in consultation with a registered dietician.

We refer both adults and children to an allergist with expertise in the evaluation of food allergies to guide dietary therapy, assist in the treatment of EoE, and identify and treat extraesophageal atopic conditions. Thus, consultation with an allergist is often an important part of disease management. (See "Allergy testing in eosinophilic esophagitis".)

We suggest avoidance of known food allergens for patients in whom specific allergies can be identified, in addition to discussion of the pros and cons of the dietary approach. The role of environmental allergen avoidance is unclear, and the practical aspects of this are also discussed with patients and their families. Dietary management of EoE is discussed in detail, separately. (See "Diagnostic evaluation of IgE-mediated food allergy" and "Dietary management of eosinophilic esophagitis".)

PHARMACOLOGIC THERAPY

Acid suppression — Proton pump inhibitors (PPIs) are among first line treatment options, together with dietary modification and topical glucocorticoids.

For patients treated with a PPI, we suggest initial treatment for eight weeks. For most patients, we begin standard full-dose PPI once daily and, if symptoms fail to improve after four weeks of therapy, we increase the dose to twice daily. An alternative dosing regimen is to initiate PPI with a twice-daily dose.

Patients are assessed for symptomatic improvement following an eight-week course of PPI treatment [5]. We perform upper endoscopy eight weeks after initiating therapy to assess for endoscopic and histologic improvement [4]. For patients who respond, we continue the PPI at the lowest dose successful at controlling symptoms. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Dose and timing of administration' and "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Defining disease severity'.)

For patients with persistent symptoms and/or esophageal eosinophilia, alternative therapy can be pursued (eg, dietary modification or topical glucocorticoid). (See 'Topical glucocorticoids' below.)

The relationship between gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE) is unclear. GERD may be a mimic of EoE, coexist with it, or contribute to it [6]. Conversely, EoE may contribute to GERD [7].

Data comparing PPIs to topical glucocorticoids or dietary therapy in patients with EoE are limited to small case series [8]. However, PPIs have been used to treat esophageal eosinophilia in patients with suspected EoE. In a meta-analysis of 33 studies that included 619 patients with symptomatic esophageal eosinophilia, PPI therapy was associated with pooled clinical response and histologic remission rates of 61 and 51 percent, respectively [9]. However, there was wide variability in response rates and significant heterogeneity between studies.

Similar findings were observed in a subsequent multicenter observational study including 630 patients with EoE [10]; PPI therapy was associated with clinical response and histologic remission rates of 71 and 49 percent, respectively. On multivariate analysis, factors associated with symptom improvement and histologic remission were inflammatory phenotype (odds ratio [OR] 3.7, 95% CI 1.4-9.5) and treatment duration of 10 to 12 weeks (OR 2.7, 95% CI 1.3-5.3). A stricturing phenotype was associated with lower response rates, both initially and in the long term.

PPIs may benefit patients with esophageal eosinophilia either by reducing acid production in patients with coexistent GERD, or by other anti-inflammatory mechanisms [11,12]. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Distinction from GERD'.)

Topical glucocorticoids — Most patients with EoE respond to topical glucocorticoids, as demonstrated by a decrease in eosinophil counts [6,13,14]. No formulation of topical glucocorticoids has been approved specifically for EoE in the United States, while the European Medicines Agency (EMA) and Health Canada approved budesonide in an orodispersible tablet formulation for adults with EoE [15,16]. Among topical glucocorticoids, fluticasone and budesonide have been best studied.

For most patients treated with a topical glucocorticoid, we use fluticasone or swallowed budesonide [6,13,17-22]. (See 'Fluticasone propionate' below and 'Budesonide' below.)

Symptoms and histologic changes often recur when glucocorticoids are discontinued [23]. (See "Major side effects of inhaled glucocorticoids" and "Major side effects of systemic glucocorticoids".)

Data from randomized trials suggested that topical glucocorticoid therapy was effective for achieving clinical and histologic improvement in patients with EoE. In a meta-analysis of six trials comparing topical glucocorticoids with placebo in 583 adult and pediatric patients with active EoE, patients who were treated with topical glucocorticoids were more likely to have symptomatic improvement after 2 to 12 weeks of therapy (risk ratio [RR] 1.74, 95% CI 1.08-2.80) [24]. Similarly, in a meta-analysis of 12 trials including 978 patients with active EoE, patients who

were treated with topical glucocorticoids were more likely to have histologic improvement (RR 11.94, 95% CI 6.56-21.75).

In trials limited to pediatric patients with EoE, topical glucocorticoid therapy resulted in histologic improvement, while symptomatic response was mixed. In a meta-analysis of five trials including 206 children with EoE, topical glucocorticoid therapy resulted in higher rates of histologic response compared with placebo (49 versus 4 percent; RR 11.05, 95% CI 3.8-32.15), while there was a nonsignificant trend toward higher rates of symptomatic response (34 versus 22 percent; RR 1.62, 95% CI 0.84-2.79) [25]. There were no major adverse effects.

Predictors of response to glucocorticoids are poorly understood [26,27]. In a retrospective cohort study that included 221 patients with EoE who received topical glucocorticoids, endoscopic, symptomatic, and histologic improvement were noted in 71, 79, and 57 percent of patients who underwent a repeat endoscopy approximately eight weeks after treatment, respectively [26]. On multivariate logistic regression analysis, esophageal narrowing that required dilation at baseline endoscopy was an independent predictor of a lack of response to topical glucocorticoid therapy, and abdominal pain was a predictor of response to therapy (OR nonresponse 2.9, 95% CI 1.4-6.3 and 0.3, 95% CI 0.1-0.8, respectively). Higher baseline levels of tryptase and eotaxin-3, but not major basic protein, were associated with a response to topical glucocorticoids.

Fluticasone propionate — Fluticasone propionate 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 general approach for fluticasone propionate induction dosing is based upon patient age [28,29]:

- Children ages 1 to 11 years – 110 mcg/spray, eight sprays daily in divided doses. We instruct patients to divide the total daily dose as two to four times daily.
- Children ages ≥12 years and adolescents – 220 mcg/spray, eight sprays daily in divided doses. We instruct patients to divide the total daily dose as two to four times daily.
- Patients ≥18 years of age – 220 mcg/spray, four sprays daily in divided doses. We instruct patients to divide the total daily dose as twice daily.

Treatment with fluticasone propionate 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) [30].

Symptom improvement, however, does not correlate well with resolution of esophageal eosinophilia. Fluticasone induction therapy is given for four to eight weeks, followed by assessment of symptomatic response (eg, dysphagia) [5]. We perform upper endoscopy 8 to 12 weeks after initiating therapy to assess for endoscopic and histologic improvement [4]. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Defining disease severity'.)

Patients frequently relapse when treatment is stopped, with reported relapse rates of 14 to 91 percent [6,23,31,32]. Thus, we lower the dose gradually after clinical remission has been achieved, and we continue to monitor symptoms as the dose is gradually lowered to a maintenance level. Specific tapering schedules are individualized and depend on several factors including starting dose, patient age, response to dose reduction, and clinician preference. As an example, the tapering schedule for children who achieved endoscopic and histologic remission after four to eight weeks of fluticasone therapy typically includes reducing the dose by 50 percent over a period of eight to 12 weeks (eg, gradual lowering the dose from eight to four sprays daily in divided doses), and then reassessing response, including upper endoscopy with biopsies. (See "Deprescribing", section on 'Tapering doses' and 'Maintenance therapy' below.)

For patients with episodic or seasonal flares, fluticasone may be given as needed during the maintenance phase (rather than as daily therapy).

For patients who do not respond to fluticasone, options include a higher dose of fluticasone, a change to oral viscous budesonide, a trial of PPI, or a dietary approach.

Representative studies of fluticasone for EoE have shown the following [33]:

- A series in adults included 21 patients who were treated with fluticasone propionate 220 mcg twice daily [31]. 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 [6]. The only adverse effect noted was dry mouth.

- Similar benefits have been observed in children, although different doses and dosing intervals have been used [13,18,22,32,34]. 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 [13]. 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 EoE include esophageal candidiasis [18,32], and herpes esophagitis was noted in a case report [35]. In addition, in diseases other than EoE, inhaled doses of fluticasone higher than 440 mcg per day have been associated with systemic side effects including cataracts, impaired growth in children, and adrenal suppression [36-39]. 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 [40]. Limited data suggest that orally administered fluticasone powder may be effective in improving histopathology, symptoms, and endoscopic features of inflammation in adult patients with EoE [33,41]. However, studies are needed to compare its efficacy with fluticasone administered using a metered dose inhaler in order to determine the optimal formulation for esophageal delivery.

Budesonide — Budesonide can be administered as an oral viscous slurry (1 mg daily for children under the age of 10 years, and up to 2 mg twice daily for older children and adults; the total daily dose is often divided into twice daily). In some studies, the total daily dose for adolescents and adults was 4 mg per day divided into two doses. Viscous budesonide can be compounded by mixing two or four 0.5 mg/2 mL Pulmicort Respules with sucralose (Splenda; 10 1-gram packets per 1 mg of budesonide, creating a volume of approximately 8 mL) or another carrier vehicle that is not liquid [42]. Patients should take the budesonide slowly, over 5 to 10 minutes, and not eat or drink for 30 minutes after taking the budesonide suspension. A commercially prepared budesonide oral suspension has not been approved for use in the United States [43]. Budesonide can also be administered as an effervescent tablet; however, its availability is limited [15]. (See 'Topical glucocorticoids' above.)

Treatment with budesonide is generally well tolerated, and patients who respond will typically have symptomatic improvement within several days [44]. Budesonide induction therapy is generally given for 12 weeks, followed by assessment of symptomatic response (eg, dysphagia) [5]. We perform upper endoscopy 8 to 12 weeks after initiating therapy to assess for endoscopic and histologic improvement [4]. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Defining disease severity'.)

Data from case series and randomized trials suggest that budesonide can reduce esophageal eosinophilia and improve symptoms [42,44-51]. In a phase 3 trial including 318 adolescent and adult patients with EoE, budesonide oral suspension (2 mg twice daily) resulted in significantly higher rates of histologic remission (53 versus 1 percent; absolute risk difference [ARD] 52 percent, 95% CI 43-59 percent) and higher rates of symptomatic response (52 versus 39 percent; ARD 13 percent, 95% CI 2-24 percent) after 12 weeks compared with placebo [51]. In another trial including 93 adolescent and adult patients with EoE and dysphagia, budesonide

oral suspension 2 mg twice daily resulted in higher rates of symptomatic, endoscopic, and histologic response compared with placebo [50]. In both trials, treatment-related adverse events were similar in the two groups.

Budesonide also appears to be comparable with fluticasone in treatment efficacy. In a randomized trial in which 129 adult patients with a new diagnosis of EoE were assigned to either oral viscous budesonide plus a placebo inhaler or swallowed fluticasone administered via metered dose inhaler plus a placebo slurry for eight weeks, both groups had similar improvements in symptoms of dysphagia, endoscopic features, and reduction in esophageal eosinophil counts [52].

Other options — Small studies and case series have examined other topical glucocorticoids for treating EoE:

- Ciclesonide – Ciclesonide, a topical glucocorticoid with less systemic absorption than fluticasone, has been evaluated in small case series [53-55]. 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 [54]. 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/high-power field (HPF) before and after treatment; distal: 76.3±33 versus 0.75±1.5 eosinophils/HPF before and after treatment). Further studies are needed.

- Mometasone furoate – Mometasone furoate, a topical glucocorticoid with limited systemic bioavailability (ie, approximately 1 percent), has been studied for treating children and adolescents with EoE [56,57]. In a retrospective study including 34 patients with EoE (median age, nine years), topical mometasone furoate was associated with histologic improvement in 26 patients (76 percent) and histologic remission in 23 patients (68 percent) after a minimum of one month of therapy [57]. Mometasone was formulated as a viscous suspension with dosing based on patient height. All patients maintained their position on the growth curve during the study, while laboratory monitoring of adrenal function was not available for most patients.

Maintenance therapy — Maintenance therapy with topical glucocorticoids and/or dietary restriction should be considered for all patients, but particularly in those with severe dysphagia or food impaction, high-grade esophageal stricture, and rapid symptomatic/histologic relapse following initial therapy [58]. The lack of symptoms does not reliably predict the absence of disease activity [59-62].

Optimal approaches to maintenance therapy have not been well established. Thus, the approach should consider the clinical setting, patient preferences, and available resources. Long-term dietary restriction is effective in maintaining remission in patients in whom dietary triggers have been identified. In patients unwilling to maintain a dietary approach and those in whom a trigger cannot be identified, topical glucocorticoids can be used at the lowest dose that allows patients to remain asymptomatic, and for pediatric patients, in endoscopic and histologic remission. In adults, a guideline issued by the American College of Gastroenterology suggests a maintenance dose of fluticasone (880 mcg daily in divided doses) or oral viscous budesonide (1 mg daily) [58]. (See 'Dietary therapy' above and 'Fluticasone propionate' above.)

For adults with EoE, maintenance therapy with a topical glucocorticoid resulted in higher rates of sustained remission [48,63]. In a trial including 204 adults with EoE in remission, patients treated with budesonide orodispersible tablet (0.5 or 1 mg twice daily) had higher rates of sustained clinical and histologic remission compared with placebo after 48 weeks (74, 75, and 4 percent, respectively) [63]. No serious adverse events were reported, while rates of esophageal candidiasis were higher for patients given budesonide (0.5 or 1 mg twice daily) compared with placebo (16, 12, and 0 percent, respectively). In another trial including 28 adults with EoE in clinical and histologic remission (defined as <5 eosinophils/HPF), budesonide (0.25 mg twice daily) resulted in higher rates of sustained clinical remission compared with placebo after 50 weeks (64 versus 36 percent) [48]. While the eosinophil burden increased during the maintenance phase in both groups, the magnitude was less in those treated with budesonide (from 0.4 to 32 eosinophils/HPF) compared with placebo (from 0.7 to 65 eosinophils/HPF). Patients treated with budesonide also showed improvement in esophageal remodeling. At baseline, patients with EoE had esophageal walls that were twice as thick as those seen in healthy controls (mean thickness 4.2 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.

The optimal dose of topical glucocorticoids for maintenance therapy has not been studied extensively. A retrospective study of 82 adults suggested longer time to relapse with higher doses of maintenance therapy during 2.2 years of follow-up, although relapse rates were not significantly different [64].

Maintenance therapy has been associated with benefit in children with EoE. In a prospective study including 20 children with EoE, oral viscous budesonide demonstrated efficacy in sustaining remission when used as 12-week maintenance therapy [65].

Topical versus systemic glucocorticoids — Systemic glucocorticoids have a limited role in EoE, except possibly in patients with severe disease in whom other approaches are not feasible [58]. Oral prednisone may be slightly more effective than topical fluticasone for the treatment of EoE, but the degree of benefit probably does not justify routine use of prednisone considering the greater likelihood of side effects [66]. 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 per day in divided doses (maximum 60 mg per day).

A randomized trial compared topical with systemic glucocorticoids [32]. The trial included 80 children with EoE 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 esophageal candidiasis was seen in 15 percent in the fluticasone arm.

Options for nonresponders — Dupilumab is an interleukin (IL)-4 receptor alpha antagonist that has been approved for use in the United States for the treatment of EoE in adults and in pediatric patients who are 12 years of age and older and weigh at least 40 kilograms.

Approval of dupilumab was based on randomized trials evaluating clinical and histologic improvement [67-69]. A two-part trial included patients with EoE who had not responded to PPI therapy (part A and B with 81 and 240 patients, respectively). In part A, patients were treated with dupilumab 300 mg weekly and in part B, patients were treated with dupilumab 300 mg weekly or every two weeks. After 24 weeks, dupilumab resulted in higher rates of histologic improvement compared with placebo (for part A: 60 versus 5 percent and for part B: 59 and 60 percent, respectively, versus 6 percent) [69]. Dupilumab given weekly resulted in improvement in dysphagia scores as measured by the Dysphagia Symptom Questionnaire. Reported adverse reactions with dupilumab included injection-site reaction/pain and upper respiratory tract infection.

Dupilumab inhibits signaling of IL-4 and IL-13 cytokines, which is important in the generation of inflammation mediated by T helper type 2 (Th2) cells and is involved in other inflammatory diseases (eg, asthma, atopic dermatitis). For EoE, dupilumab is administered at a dose of 300 mg by subcutaneous injection once weekly [68]. Laboratory monitoring is not required. (See "Treatment of severe asthma in adolescents and adults", section on 'Anti-lL-4 receptor alpha subunit antibody (dupilumab)' and "Treatment of atopic dermatitis (eczema)", section on 'Dupilumab'.)

Its role in the management of EoE remains to be fully defined compared with other options such as dietary therapy and topical glucocorticoids. While no US Food and Drug Administration (FDA)-approved formulation of the latter is available in the United States or in some other regions, many studies have demonstrated a clinical benefit and clarified its safety profile (see 'Topical glucocorticoids' above). That, combined with the high expense of dupilumab, suggests that dupilumab may be best reserved for patients who are refractory to or decline other options. In addition, patients with EoE plus one or more atopic conditions (eg, severe asthma, eczema, sinus disease) may be candidates for dupilumab because it may consolidate their medical therapies.

Long-term safety of dupilumab is still being established. The most common side effects occurring more often than placebo in trials of EoE included injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections, but additional side effects have been described in trials using dupilumab for other indications. Preliminary data suggest that dupilumab use may be linked to an increased risk for developing other cytokine-mediated conditions including seronegative inflammatory arthritis, enthesitis, iridocyclitis (iritis with adjacent ciliary body inflammation), and psoriasis, possibly by shifting immune responses toward alternative cytokine pathways [70]. Additional studies may help to describe the underlying mechanism and confirm these findings.

The manufacturer lists several precautions, which should be considered before initiating, and while monitoring, therapy [68].

Long-term monitoring — We clinically monitor patients with stable disease (ie, stable clinical features and endoscopic and histologic remission [<15 eosinophils per high power field]) for the development of recurrent symptoms at least every 12 to 24 months [4]. The decision to perform periodic endoscopic evaluation is individualized and informed by patient symptoms, history of esophageal pathology, medication adjustments, and clinician and patient preferences. As examples, we generally repeat upper endoscopy for patients in whom symptoms have changed, who require changes in therapy, or who required esophageal dilation.

ESOPHAGEAL DILATION

Dilation of esophageal strictures is effective for relieving dysphagia, but has no effect on underlying inflammation [3,71,72]. 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 [2,58]. 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 [73-76]. It has been recommended that the progression of dilation per session be limited to 3 mm or less [74]. Because of this, multiple dilations are often required to attain a goal esophageal diameter of 15 to 18 mm [71,77,78]. A combination of medical therapy with dilation can usually achieve a diameter of 13 mm or more even for patients with severe esophageal stenosis [79]. Patients should be forewarned of the risks of esophageal dilation including chest pain and bleeding [71,80].

Whether patients with eosinophilic esophagitis (EoE) are at higher risk of perforation due to esophageal dilation than other patients undergoing dilation is not clear. Older studies suggested that patients with EoE are at increased risk for perforation, with perforation rates of 5 to 7 percent [81]. Subsequent studies have suggested that the rate of perforation is considerably lower [71,74,79,82-84]. A 2017 meta-analysis of 37 studies that included 977 patients and a total of 2034 dilations found that perforation and postprocedure hospitalization occurred in 0.03 and 0.7 percent of dilations, respectively [80]. Rates of perforation did not differ significantly by the method of dilation employed. Clinically significant chest pain and hemorrhage occurred in 3.6 and 0.03 percent of procedures, respectively. Similar findings have been reported in children [85].

Tearing and perforation can occur without perceived resistance when passing a dilator or the endoscope (picture 1) [73]. 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 [86]. The use of glucocorticoids before dilation has not been extensively studied [87]; it may offer a small benefit prior to dilation by diminishing inflammation.

EXPERIMENTAL TREATMENTS

Biologic agents

- **Monoclonal antibody against IL-13** – IL-13 has been implicated as an important cytokine in the pathogenesis of eosinophilic esophagitis (EoE). In a randomized trial, 99 adults with active EoE were assigned to weekly recombinant humanized monoclonal antibodies against IL-13 (180 or 360 mg) or placebo for 16 weeks [88]. Both treatment groups had a significant reduction in esophageal eosinophil count, endoscopic severity, and histologic grade compared with placebo. Although there was no significant improvement in dysphagia symptom scores, the study may have lacked power to detect a difference. The frequency of treatment-emergent adverse events was similar in the three groups. Further

studies are needed to validate these results and clarify the role of IL-13 blockade in the management of EoE.

- Mepolizumab – Mepolizumab is a humanized monoclonal antibody against interleukin (IL)-5, which has a central role in eosinophil recruitment. Studies of mepolizumab have had variable results [89-91]. As a result, its role is uncertain. (See "Eosinophilic esophagitis (EoE): Genetics and immunopathogenesis", section on 'Role of the immune system and environmental factors'.)

- Reslizumab – Reslizumab is an IL-5 neutralizing antibody that is undergoing clinical trials in EoE. In a controlled trial involving 226 children and adolescents with EoE, 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) [92]. 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.

Prostaglandin D2 receptor antagonist — Chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) is a receptor expressed by Th2 cells, eosinophils, and other inflammatory cells that mediates chemotaxis of these cells in response to prostaglandin D2. OC000459 is a selective, orally bioavailable, CRTH2 antagonist. In a randomized controlled trial, 26 adults with steroid-dependent or steroid-refractory EoE were randomly assigned to treatment with OC000459 (100 mg twice daily) or placebo [93]. At eight weeks, treatment with OC000459, but not placebo, was associated with a modest but significant reduction in esophageal eosinophil counts and an improvement in symptoms as compared with baseline.

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 EoE, but subsequent experience has been mixed for either induction or maintenance of remission [94-99]. Thus, its role, if any, remains unclear.

Purine analogues — A case report described a clinical and histologic response to azathioprine or 6-mercaptopurine in three adults with glucocorticoid-dependent EoE [47].

PROGNOSIS

While there are limited data regarding the natural history of eosinophilic esophagitis (EoE), patients should be counseled that the disease is chronic. If left untreated, patients may remain symptomatic or have episodic symptoms. Following treatment, there is a high likelihood of

symptom recurrence after discontinuing treatment [23,58,100]. The long-term prognosis of EoE is unclear, but EoE does not appear to significantly shorten lifespan.

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, EoE persisted, with only 10 percent developing tolerance to their food allergies [101]. No children progressed to other gastrointestinal diseases.

In adults, long-term observations suggest that the disease may progress to a fibrostenotic stage in which the predominant symptom is intermittent dysphagia [102]. Patients with extreme narrow-caliber esophagus, a subtype of EoE in which the esophagus cannot be traversed with an adult endoscope, often require multiple dilations, are more refractory to treatment with glucocorticoids, and have lower response rates to treatment [103]. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Subtypes'.)

However, the proportion of patients with progressive disease is unknown. One of the largest natural history studies in adults focused on 30 adults who were followed for an average of seven years [104]. 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 and Campaign Urging Research for Eosinophilic Disease (CURED) are advocacy groups 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 education: Eosinophilic esophagitis (The Basics)")

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Eosinophilic esophagitis".)

SUMMARY AND RECOMMENDATIONS

- **Dietary therapy** – 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 (**Grade 2C**). (See 'Dietary therapy' above.)

  The role of food allergies in eosinophilic esophagitis and types of dietary therapy (eg, elimination diets) are discussed in detail separately. (See "Dietary management of eosinophilic esophagitis".)

- **Initial pharmacologic therapy** – In patients who opt for a pharmacologic approach, initial treatment with a proton pump inhibitor (PPI) or with a topical glucocorticoid are both acceptable alternatives.

  For patients who opt for a PPI, the clinical response should be evaluated after an eight-week course of treatment. We perform upper endoscopy after 8 to 12 weeks of therapy to assess endoscopic and histologic response.

  For patients who opt for a topical glucocorticoid, we suggest treatment with swallowed fluticasone (**Grade 2B**), although preparations containing swallowed budesonide (where available) are good alternatives. (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 fluticasone treatment for four to eight weeks (**Grade 2C**). Subsequent therapy depends on patient age and clinical, endoscopic, and histologic response. Some authorities treat on an as-needed basis. Such an approach is particularly useful in patients who have identifiable, seasonal triggers.

Treatment is generally well tolerated. However, worsening of dysphagia during treatment should alert to the possibility of esophageal candidiasis. (See 'Topical glucocorticoids' above.)

- **Subsequent therapy** – For patients who do not respond to topical fluticasone, treatment options include an elimination diet (if not already tried), topical budesonide, or dupilumab. (See 'Budesonide' above and 'Dietary therapy' above and "Dietary management of eosinophilic esophagitis", section on 'Choosing an elimination diet'.)

- **Maintenance therapy** – Maintenance therapy with topical glucocorticoids and/or dietary restriction should be considered for all patients, but particularly in those with severe dysphagia or food impaction, high-grade esophageal stricture, and rapid symptomatic/histologic relapse following initial therapy. (See 'Maintenance therapy' above.)

- **Patients with esophageal stricture** – Patients with esophageal rings or strictures may require dilation. Dilation is associated with mucosal tears and esophageal perforation and thus should be performed cautiously. We suggest that, if possible, dilation be avoided until patients have been given a course of fluticasone or budesonide, which may relieve dysphagia and thus avoid the need for dilation (**Grade 2C**). Dilation has generally not been needed in children in most reports due to the inflammatory nature of disease in this age group. (See 'Esophageal dilation' above.)

- **Role of acid suppression** – In patients treated with topical glucocorticoids or with a dietary approach, acid suppression is reasonable if reflux is suspected to be contributing to symptoms. (See 'Acid suppression' above and "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Diagnosis'.)

- **Long-term monitoring** – We monitor patients with stable disease (ie, stable clinical features, and endoscopic and histologic remission) for the development of recurrent symptoms at least every 12 to 24 months. The decision to perform periodic endoscopic evaluation is individualized and informed by patient symptoms, history of esophageal pathology, medication adjustments, and clinician and patient preferences. As examples, we generally repeat upper endoscopy for patients in whom symptoms have changed, who require changes in therapy, or who required esophageal dilation. (See 'Long-term monitoring' above.)

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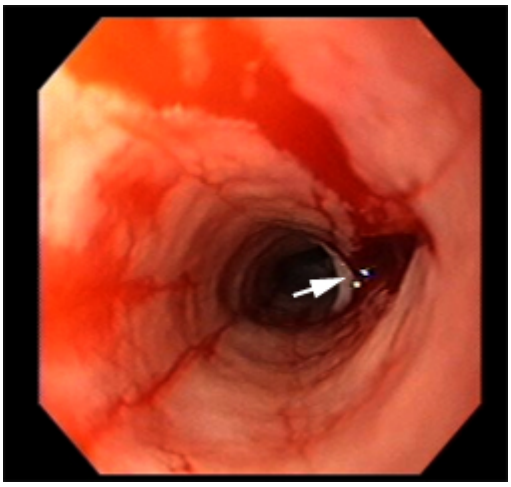
GRAPHICS

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.

Graphic 50953 Version 4.0

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