

# Esophageal dilation in eosinophilic esophagitis: risks, benefits, and when to do it

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#### **Purpose of review**

For patients with eosinophilic esophagitis (EoE), endoscopic dilation has been used primarily to provide immediate symptomatic relief of dysphagia. This report reviews the current position of esophageal dilation in the therapeutic algorithm for EoE, including effectiveness and safety issues.

#### **Recent findings**

Esophageal strictures in EoE develop as a consequence of long-lasting esophageal eosinophilia, with patient age and diagnostic delay as well established risk factors. Endoscopic dilation leads to immediate symptomatic improvement in 95% of EoE patients who have strictures or narrow caliber esophagus. As dilation has no effect on the underlying eosinophil inflammation, repeated procedures are usually needed to maintain symptoms in remission. Adding an effective drug or dietary-based EoE therapy reduces the need of further dilation. The high rate of severe complications from dilation reported in early literature has not been reproduced in most recent series, with mild postprocedural chest pain as the most common side effect. Current data suggest that the risk of esophageal perforation is less than 1%. Mucosal tears after dilation should no longer be considered a complication, but rather a marker of procedural success.

#### Summary

Esophageal dilation should be considered in EoE patients with esophageal strictures or narrow caliber esophagus who have persistent dysphagia/food impaction despite an effective anti-inflammatory treatment.

#### Keywords

dilation, endoscopy, eosinophilic esophagitis, therapy, treatment

## INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, local, immune-mediated disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1<sup>••</sup>]. After almost 3 decades since identification of the disease [2], the prevalence of EoE has sharply increased to constitute currently the second leading cause of chronic esophagitis after gastroesophageal reflux disease (GERD) [3] and the most frequent cause of dysphagia in young patients in Westernized countries [4]. Currently, EoE affects up to one patient per 2000 inhabitants in Europe and the USA, with an increasing trend developing [5,6]. An important diagnostic delay has been described for patients suffering from EoE in multiple settings [7,8], in part because the endoscopic abnormalities can be subtle enough to be missed in a proportion of cases [9,10]. However, remarkable abnormalities can be detected in the majority of patients [11], affecting either the esophageal caliber or the mucosal surface, with a prevalence that has varied substantially among available studies [12].

EoE is considered a form of food allergy, triggered and maintained by protein antigens contained in the diet. Dietary therapy currently constitutes one of the first-line therapies in patients of all ages with EoE, reducing the eosinophil infiltrate until the histology of the esophagus is normalized and symptoms are controlled [13]. Antiinflammatory agents, including proton pump inhibitors (PPIs) [14,15] and swallowed topical steroids also lead to disease remission [16,17]. The chronic nature of EoE and the frequent diagnostic

Curr Opin Gastroenterol 2018, 34:226-232 DOI:10.1097/MOG.000000000000442

Volume 34 • Number 4 • July 2018

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# **KEY POINTS**

- Esophageal dilation should be considered in EoE patients with esophageal strictures or narrow caliber esophagus who have persistent dysphagia/food impaction despite an effective antiinflammatory treatment.
- Current evidence shows that when esophageal dilation is performed carefully and gradually in multiple sessions with the goal of achieving a lumen of 16– 18 mm, it is a highly effective and safe procedure.
- As the effectiveness of esophageal dilation tends to decrease over time when there is persistent esophageal eosinophilia, patients should receive effective long-term anti-inflammatory treatment with drugs or diets to maintain their disease in histological remission.
- Increasing evidence supports the predictive value of esophageal distensibility measured by Endoluminal Functional Lumen Imaging Probe in the assessment of clinical activity of EoE; this measure could also have a role in selecting the best candidates for esophageal dilation.

delay [7,8] contribute to the fibrous remodeling of the esophagus, characterized by collagen deposition beneath the epithelial layer [18] and altered mechanical properties of the organ with reduced distensibility [19,20]. As a consequence, narrowing of the esophageal lumen, either diffusely of focally, constitutes an EoE complication that was deemed to require esophageal dilation in the earliest documented cases.

The current article aims to comprehensively review current evidence on the role of endoscopic dilation in the therapeutic approach to patients with EoE, in terms of dysphagia relief and changes in esophageal caliber. Safety of dilation will be assessed according to current systematic reviews, and advice to maximize the benefits of esophageal dilation in patients with EoE will be provided.

# ESOPHAGEAL REMODELING IN EOSINOPHILIC ESOPHAGITIS AND ITS CLINICAL IMPLICATIONS

Subepithelial fibrous remodeling as a consequence of chronic esophageal inflammation has been demonstrated in children and adults with EoE, and reproduced in animal models [21]. Eosinophil-associated tissue remodeling is a common process found in several conditions in which chronic eosinophilic inflammation is the common hallmark, including bronchial asthma [22], hypereosinophilic syndrome [23], eosinophilic gastroenteritis [24], and lastly, EoE [21]. All share structural changes within the affected tissue, including subepithelial fibrosis, which ultimately alter the functionality of the affected organs. Several mediators released from inflammatory cells are involved in driving esophageal remodeling in EoE, with a particular role for transforming growth factor (TGF)- $\beta$ 1 [25], analogous to the one observed in airway remodeling associated with asthma [26]. In addition to TGF- $\beta$ 1 signaling, other mechanisms involved in EoE remodeling include epithelium-mesenchymal transition and angiogenesis [27]. Uncontrolled remodeling due to ongoing inflammation in EoE may adversely affect esophageal function, leading to dysmotility [28], esophageal rigidity [29], progressive dysphagia and food impaction and, finally, stricture formation.

The increased mucosal fragility in EoE has been directly related to the cytotoxic proteins released from the cytoplasmatic granules of eosinophils in the inflammatory infiltrate. These eosinophil products are capable of damaging tissues, and the risk of esophageal damage has been shown to increase with the density of eosinophils in the esophagus and with symptom duration [30]. In EoE, eosinophils penetrate deeply into the esophageal wall, involving the lamina propria, submucosa and even the muscularis propria [31,32]. The resultant fibrous remodeling reduces the elasticity of the esophagus, impairing its mechanical functionality [19]. This reduced esophageal compliance leads to increased fragility, which can be manifested during endoscopic dilation procedures and in traction movements around the esophagogastric junction associated with nausea and vomiting. Thus, a simple brush of the endoscope may give rise to mucosal rents, and there are reports of spontaneous esophageal perforation [33] and Boerhaave's syndrome occurring in EoE patients after the mere passage of an endoscope [33,34] or following biopsy sampling [35].

# IMMEDIATE AND SUSTAINED EFFICACY OF ESOPHAGEAL DILATION IN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS

Esophageal strictures developing as a result of longstanding, untreated eosinophilic inflammation are severe and common complications of EoE. Patient age [18,36] and diagnostic delay [7,37<sup>••</sup>] are their main determining factors, but not every patient with prolonged EoE evolution develops such strictures. Proposed additional risk factors for finding a smallcaliber esophagus at baseline include the use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), as well as smoking and alcohol consumption, according to a single-center, comparative study conducted on 64 adults with more than 7 years of diagnostic delay [37<sup>••</sup>]. Esophageal strictures are less

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commonly found in pediatric patients with EoE, likely due to limited disease duration that is insufficient for fibrotic progression [38–40].

Esophageal dilation with through-the-scope balloons, Maloney or Savary bougies has been used as a treatment option to provide immediate symptomatic relief for EoE patients from the earliest documented cases [41,42]. This approach is similar to that used for esophageal strictures resulting from GERD (peptic stricutres) or the ingestion of caustic substances. A notable degree of symptomatic improvement was achieved in 75% [95% confidence interval (CI) 58–93%] of the 525 adult patients with EoE who underwent 992 dilation procedures, as summarized in a first meta-analysis published in 2013 [43]. An updated meta-analysis retrieved subsequent publications up to 2016 and overall included 27 studies assessing 845 individual patients undergoing 1820 dilation procedures [44\*\*]: Dysphagia improved in 95% of patients following dilation (95% CI 90-98%), with no significant heterogeneity among the studies considered. However, specific scores to objectively quantify improvements in dysphagia induced by dilation were not included in the studies retrieved in the previous meta-analyses; instead, a dichotomous outcome variable (improvement of dysphagia yes or no) was used. As an additional limitation, a proportion of patients undergoing dilation also received concomitant drug [45,46<sup>•</sup>] or dietary therapy [40,47<sup>•</sup>], potentially obscuring the clinical effect of the endoscopic therapy itself [45,48].

Differences in the effectiveness of dilation related to the dilation device used have not been reported, so symptomatic improvements can only be attributed to the increase induced in the esophageal caliber. Few studies have reported objective measurements to document that increase, with an average predilation caliber of 9.9 mm rising to 16.1 mm after the procedure [44<sup>••</sup>].

Unlike dietary or drug-based therapies in EoE, endoscopic dilation is a mechanical procedure with no effect on the underlying inflammatory process [49], and its efficacy declines over time. Short followup durations in most studies on EoE dilation published to date (ranging from 1 to 36 months in the most recent systematic review [44\*\*]) preclude meaningful conclusions regarding the long-term efficacy of dilation procedure in EoE patients. Nevertheless, it is common for patients with EoE to undergo repeated dilations to control their dysphagia. In steroid-naïve patients treated exclusively with PPIs who had dilations scheduled based on symptoms, an average of 3.2 dilations were required over the first year (range 1-6) to achieve a luminal size ranging from 14 to 18 mm, and control of dysphagia was maintained with dilations every 2 years, on average [45]. However, the wide variability in dilation requirements is highlighted by one patient who underwent 35 separate endoscopic esophageal dilations [45]. Effective control of the underlying eosinophil inflammation improves these rates. The likelihood and frequency of esophageal dilation in patients with EoE was reduced by 65% in those who received swallowed topical steroids and achieved a histologic remission, as recently shown in a retrospective cohort study [50<sup>••</sup>].

A growing interest has appeared in trying to define the profile of patients who would benefit most from esophageal dilation, using technical developments that identify functional behavior of the esophagus including the location of esophageal narrowing and localized strictures. The classification of EoE patients into fibrostenotic and inflammatory phenotypes currently relies on endoscopic assessment of the esophageal caliber. However, endoscopy has been demonstrated to underestimate reductions in esophageal caliber when compared with barium esophagram in adults [51]. In parallel, esophageal strictures are identified by barium esophagram, and not endoscopy, in half of children [38], thus hindering the ability of endoscopic assessment to identify a narrow caliber esophagus. In contrast, inflammatory features are better assessed by endoscopy than by radiology, so both techniques may provide complementary information in selected patients [52]. The recent release of the Endoluminal Functional Lumen Imaging Probe (EndoFLIP; Crospon, Inc, Carlsbad, California, USA), a device that has demonstrated a significant reduction in esophageal distensibility in patients with EoE [19], may change this scenario in the future. A lack of correlation between eosinophil counts and esophageal distensibility has been shown with EndoFLIP, partially explaining the dissociation between inflammatory activity and symptoms in EoE [53]. Reduced esophageal distensibility found by EndoFLIP predicted the risk for food impaction and correlated with endoscopically-identified ring severity [54]; improvements in esophageal body distensibility are achieved with medical and diet therapies without dilation [55"]. Whether the addition of the EndoFLIP system to patient reported outcome measures can enhance the accuracy of predicting the biological activity of EoE and improve results of endoscopic dilation warrants further investigation [56].

# PERFORATION RISK AND OTHER COMPLICATIONS DURING EOSINOPHILIC ESOPHAGITIS ENDOSCOPY

As endoscopic dilation was used in early studies to provide immediate relief of symptoms for EoE patients [57,58], concerns regarding EoE dilation safety were raised in multiple reports of severe complications, including chest pain requiring hospitalization in 7% of procedures, frequent deep esophageal tears, and esophageal perforations in up to 5% of patients [59]. All these complications were substantially more frequent in EoE than in dilations performed for benign esophageal strictures of other causes. Perforations also appeared during endoscopic treatments for food impactions and even during diagnostic endoscopies, which raised concerns about the marked esophageal fragility (crepe paper esophagus) that characterizes EoE. Most of the perforations reported (spontaneously or after endoscopic procedures) only led to pneumomediastinum [60,61] that resolved with conservative management in most cases [34], with a minority of patients requiring esophagectomy or esophagogastroplasty [31,34,62,63]. In contrast to these data, the good effectiveness and safety profile for dietary modifications and swallowed topical steroids led some researchers to recommend these treatments first, avoiding dilation until active eosinophilic inflammation was under control [64,65].

In contrast to the early literature, perforation rates for dilation in EoE described in more recent studies did not differ from those for dilation in other esophageal conditions [48,49]. Two systematic reviews published in 2017 assessed complication rates from large numbers of patients with EoE undergoing esophageal dilation [44<sup>••</sup>,66<sup>••</sup>]: the pooled proportion of patients with postprocedural perforation ranged from 0.38 to 0.61%; hemorrhage was observed in 0.05 to 0.38% of patients, and 0.675 to 4.4% of cases required hospitalization after the procedure. No death occurred as a consequence of esophageal dilation in EoE, overall indicating that the rate of major complications for dilation in EoE is similar to that reported for endoscopic dilation in other esophageal diseases [67]. However, mucosal tears occurring with dilation are reported in up to 22.3% of patients, but they are deep enough to involve the muscularis propria in only the minority of cases [66"]. Indeed, mucosal tears in EoE are so common that they should no longer be considered a complication of esophageal dilation, but rather a marker of procedural success in achieving its goal of widening a fibrotic stricture [68<sup>•</sup>]. Chest pain probably constitutes the most common side effect of esophageal dilation, and almost all patients will feel some degree of discomfort after a dilation procedure, especially while swallowing and if mucosal tears are produced. Most cases will respond readily to reassurance and NSAIDs. A multicenter study found self-declared chest pain after dilation in 74% of patients, who usually considered the pain to be mild [49].

Predictive factors for complications during esophageal dilation of EoE patients were provided in early studies with larger patient numbers, and included long-lasting dysphagia, fixed esophageal strictures blocking the passage of an endoscope, and a high density of esophageal eosinophils [69]. Repeated procedures and younger age were also significantly associated with higher complication rates [48], but the latter factor was not been confirmed as a perforation risk factor in a recent pediatric series [46<sup>•</sup>]. A luminal narrowing located in the upper-third and middle-third of the esophagus (compared with the distal-third) has been identified as an additional risk factor [70]. No differences in perforation risk related to the dilation device were found in the most recent systematic review [44<sup>•••</sup>].

The safety of esophageal dilation in children has been evaluated only recently in a large, single-center series [46<sup>•</sup>]: Forty children underwent endoscopic dilation during a 5-year period, with 40% requiring repeated procedures. Any grade of chest pain was reported in 14.7% of EoE dilations, and was independent of the dilation method, final dilator size, medical therapy, or esophageal eosinophil density. No significant differences were found between EoE and non-EoE children in dilation-related adverse event rates, with no perforations or significant hemorrhages reported.

# WHEN TO CONSIDER ENDOSCOPIC DILATION IN A PATIENT WITH EOSINOPHILIC ESOPHAGITIS

Due to the safety and moderate durability of esophageal dilation in EoE, some authors consider it a primary therapy in selected EoE patients [59,71], because it allows avoiding food restrictions imposed by dietary therapy and is more reliable than topic steroid therapy in adults [71]. The lack of effect of esophageal dilation on the eosinophil inflammation and ongoing fibrous remodeling process, and the frequent need for repeated procedures to avoid recurrent dysphagia raise doubts regarding this recommendation. Dietary treatment regimens recently proposed allow faster identification of foods responsible for triggering EoE [72,73], and novel topical steroid preparations targeted to the esophageal mucosa are highly effective in achieving sustained clinical-histological remission of EoE [74]. Therefore, esophageal dilation as the only primary therapy for EoE [75] likely will be replaced by the practice of combining dilation with a treatment that has the possibility of inducing a sustained clinicalhistological remission.

Recent research has shown that, for patients without esophageal strictures at the time of

diagnosis, esophageal dilation did not provide improvement in dysphagia scores beyond that of treatment with PPIs and fluticasone alone [76<sup>••</sup>]. In addition, cost-effectiveness analyses indicate that swallowed fluticasone treatment (followed by esophageal dilation if necessary) is the more economical initial strategy when compared with dilation first in patients with biopsy-proven EoE who continues to be symptomatic despite initial PPI therapy [77].

According to recent, evidence-based recommendations [1<sup>••</sup>], endoscopic dilation should not be the only therapeutic intervention, as it has no effect on the underlying esophageal inflammation [49]. Even for patients with severe symptomatic esophageal strictures, initial therapy with topical steroids and endoscopic dilation might rapidly achieve remission of their clinical, endoscopic, and histologic features. Esophageal dilation should be considered for patients who have symptoms of EoE (dysphagia/ food impaction) and esophageal strictures after other measures have failed, and esophageal dilation should be used together with an eosinophil-reducing therapy to avoid complications of active eosinophil inflammation of the esophagus.

# HOW TO PERFORM ESOPHAGEAL DILATION IN A PATIENT WITH EOSINOPHILIC ESOPHAGITIS

As described above, endoscopic dilation constitutes an effective and safe treatment that should be considered in EoE patients who have esophageal narrowing and persistent dysphagia despite effective medical (i.e., topical steroids or PPIs) and/or dietary therapy. Whenever possible, dilation should preferably be done when the active inflammatory infiltrate has been eliminated or significantly reduced after an anti-inflammatory or dietary-based medical treatment [65]; after dilation, treating the underlying inflammation will also contribute to reduce the rate of stricture recurrence.

Endoscopic dilation should also be carried out preferably by experienced endoscopists and under sedation to avoid provoking Boherhaave's syndrome if the technique is not well tolerated [78]. To minimize complications and maximize the beneficial results of the technique, the following aspects should be considered:

First, the entire esophagus should be examined to assess the location and length of strictures (sometimes they are multiple) and estimate esophageal diameter. Consider barium esophagram if stricture blocks the passage of the endoscope, and consider having a pediatric or 5-mm endoscope available when endoscopy is scheduled.

Second, when dilating the focal strictures and small caliber esophagus of EoE, endoscopists should consider features of EoE patients that distinguish them from patients with an esophagus narrowed by fibrotic strictures of other origin or by Schatzki rings [75]. Pain is uncommon following dilation of non-EoE strictures and Schatzki rings, and Schatzki rings are dilated abruptly to a large diameter to break the ring. In contrast, the mucosal fragility that characterizes EoE frequently results in pain after dilation, and abrupt dilation of any fibrotic stricture can result in perforation. An EoE dilation practice of 'starting low and going slow' has been recommended [79,80]: small-diameter bougies or balloons should be used to gradually dilate initially to 13 mm (this caliber will alleviate dysphagia to most patients [51]) with the goal of achieving 16–18 mm (the size that usually allows a full regular diet [81]). This may require multiple dilation sessions separated by 3-4 weeks.

Third, there is no 'preferred' dilation method for patients with EoE: Savary-Guillard or Maloney bougies are capable of dilating the entire length of the esophagus, and provide tactile assessment of the location and degree of esophageal narrowing, so they may be preferred in an esophagus with narrowings at multiple sites. In contrast, through-the-scope balloons have the potential advantage of allowing endoscopists an immediate assessment of the degree of esophageal tearing. Multiple strictures can be treated by inflating the balloon segmentally in multiple areas to dilate the entire esophagus quickly if necessary while maintaining direct visualization at all times [48]. As no differences have been documented between through-the-scope balloons and bougies, the final choice of dilator should depend on the endoscopists' preferences and experience.

Fourth, the appearance of tears can be used as a sign to terminate a dilation session by demonstrating that an adequate dilation has been achieved. Moderate resistance to bougie passage or abundant bleeding should also end the procedure.

Fifth, patient should be forewarned that some degree of pain after the procedure can be expected; adequate pain management and dietary modifications may be necessary, including the avoidance of alcoholic beverages.

# CONCLUSION

Esophageal dilation is an effective, safe, and easy to perform procedure capable of providing immediate relief of dysphagia for EoE patients who have a narrowed esophagus. Esophageal dilation does not seem to provide additional benefit for patients with a normal caliber esophagus. As it does not alter eosinophil inflammation or eosinophil-induced fibrous remodeling, esophageal dilation should not be the only therapy for EoE. In fact, effective control of eosinophil inflammation significantly reduces the need for repeated dilation procedures.

### Acknowledgements

*The article has been seen, reviewed, and approved by all contributing authors.* 

### **Financial support and sponsorship**

None.

### **Conflicts of interest**

*There are no conflicts of interest.* 

### REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

of special interest

- of outstanding interest
- 1. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic
- esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017; 5:335–358.

First evidence-based guidelines for the diagnosis and management of eosinophilic esophagitis (EoE) patients, recognizing that esophageal dilation should not be the only therapeutic intervention for EoE. Combined with topical steroids, dilation rapidly achieve remission of clinical, endoscopic, and histologic features in patient with symptomatic small caliber esophagus. Esophageal dilation also should be used in patients with symptoms persisting despite an effective anti-inflammatory drug or dietary treatment.

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