

Emerging clinical evidence in the treatment of eosinophilic esophagitis

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Primary eosinophilic esophagitis (EoE) is no longer rare. The treatment is currently *ad hoc* with no licensed medications available. Symptom improvements occur with diet, drugs or esophageal dilatation and these have been applied to patients depending on their age, severity of illness and their need for continuing symptom relief. Problems in treating EoE include difficulties in assessing disease severity and lack of prognostic markers of disease progression. This article describes the current status of diet and topical steroid therapy. The evidence from randomized trials of biologic agents such as infliximab, mepolizumab, reslizumab and omalizumab show disappointing symptom benefit, despite changes to the immunobiology of the esophageal epithelium. Concerns regarding perforation during dilatation are discussed, and the use of EndoFLIP® to measure esophageal compliance is presented. CRTH-2 antagonists and montelukast are discussed. EoE will continue to require scientific and clinical research until an effective therapy suitable for all is found.

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Primary eosinophilic esophagitis (EoE) is no longer a rare diagnosis. First described in 1993 by Attwood *et al.* [1] and Straumann *et al.* [2], it is being increasingly recognized, diagnosed and studied worldwide. Due to its high prevalence, it is now considered the most common cause of dysphagia after gastroesophageal reflux disease. EoE represents a chronic, immune/antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [3]. The purpose of this article is to discuss challenges in the treatment of EoE, followed by a review of emerging therapeutics in both adults and children.

Clinical presentation

In the adult population, the typical patient presenting with EoE has a long history of dysphagia, mostly intermittent. However, in severe cases, the patient may have continuous dysphagia, as well as chest pain and odynophagia [4]. Males are affected three-times more often than females [3]. Research suggests that EoE accounts for half of all the acute esophageal food bolus obstruction presenting to hospitals [4,5]. Symptoms of EoE in children vary with age. Infants and toddlers present with feeding difficulties, prolonged feeding time or denial to eat food. School-aged children tend to present with vomiting or pain. Other allergic diseases such as food allergy, asthma, eczema, chronic rhinitis and environmental allergies can be associated with these patients, more so in children than in adolescents [3]. Atypically, pediatric patients may present with failure to thrive and weight loss. Presentation with eosinophilic gastroenteritis (abdominal pain and diarrhea) is a rare association with EoE [2]. EoE is often missed or misinterpreted due to lack of awareness of

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this pathology by physicians. Patients are often treated for a long period with a working diagnosis of gastro-esophageal reflux disease. However, only after failure of long-term treatment with proton pump therapy, is other pathology sought [4].

Endoscopic findings of the disease vary from normal in 25% of the patients to a variety of mucosal patterns and narrowing that are typical of EoE but not pathognomonic [4,6,7]. The abnormalities include white speckles or microabscesses, muscular ridges and fibrous rings (trachealization), longitudinal furrows, cobblestone nodularity, tissue fragility, loss of vascularity, impaction of food bolus or, in more severe cases, strictures (Figure 1) [4,6,7]. Barium study findings may vary from short to long strictures of the esophagus, narrow caliber whole esophagus or trachealization [4]. The established histological sign is dense eosinophilic infiltration (>15 in a high-power field) of the

esophageal epithelium on hematoxylin and eosin staining [3]. At least six biopsies are advised, two from each of the upper, middle and lower esophagus [6,8].

EoE has also been termed 'esophageal asthma' as research demonstrated that this disease had atopic association. Up to 50% of patients with EoE have bronchial asthma and/or allergic rhinitis and 20% have atopic dermatitis [4]. Pathophysiology of EoE suggests that besides eosinophils, T-helper cells (Th2), mast cells, IL-13, IL-15 and eotaxin-3 have a role in the disease. Blanchard *et al.* have shown that patients with EoE display higher than average expression of the gene encoding the eosinophil specific chemoattractant eotaxin-3 [9].

■ Challenges in therapy of EoE

There are a number of problems with treating EoE:

- Difficulty in assessing disease severity;
 - There are no licensed treatments;
 - There is no prognostic marker of disease progression.

The treatment of EoE is currently *ad hoc*, with no licensed medications or treatments available. Symptom improvements have been shown with diet, drugs or dilatation and these have been applied to patients depending on their age, severity of illness and their need for continuing symptomatic relief. One of the great problems with assessing the value of therapy for EoE is that the condition itself has intermittent symptoms of variable severity. Therefore, any treatment that is offered needs to be assessed over a significant period of time and with a good quality symptom diary in order to identify if there has been improvement. There is poor correlation of the symptoms of dysphagia or chest pain with histopathology or endoscopy findings [10–12]. In particular, there is no clear relationship between the severity of symptoms and the density of eosinophilic involvement in the epithelium, as patients with low eosinophil concentrations, in the order of 15–20 eosinophils per high power field (eos/hpf), may have very severe symptoms, while patients with 100 eos/hpf or more,

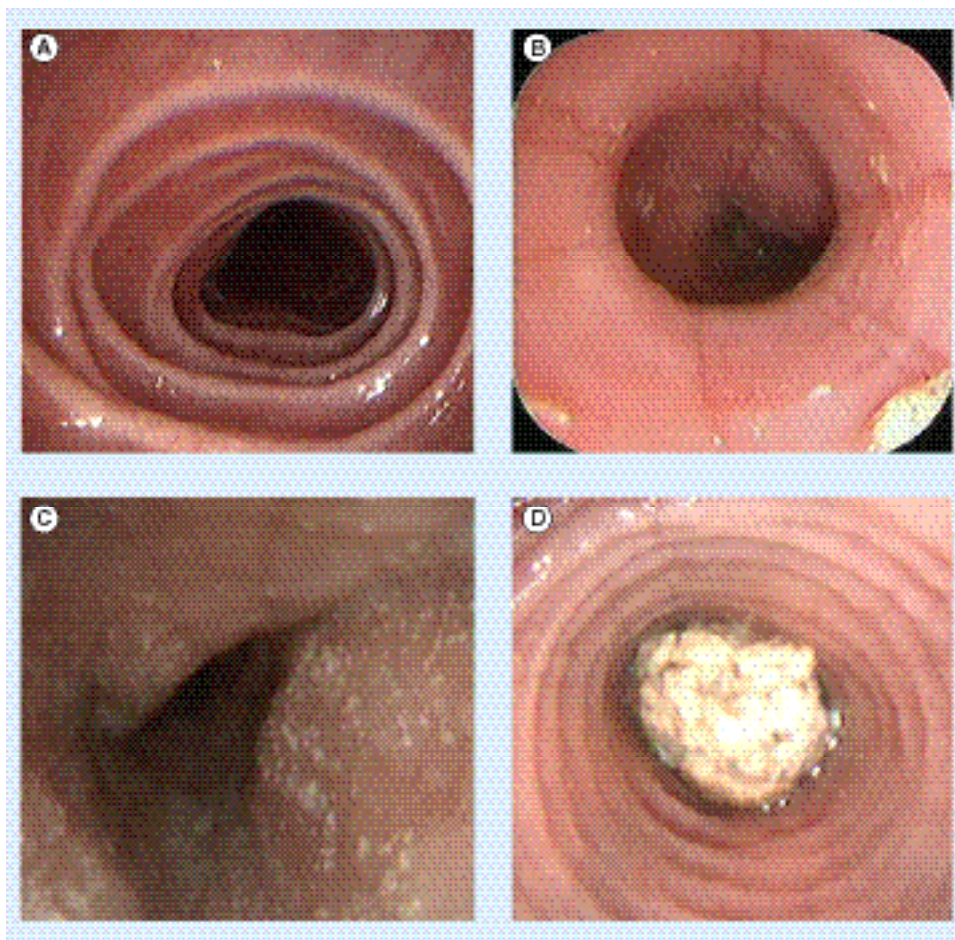


Figure 1. Endoscopic appearance of eosinophilic esophagitis. (A) Fixed rings or trachealization, **(B)** linear furrows **(C)** white exudates or microabscesses of eosinophils and **(D)** muscular rings and food bolus obstruction. Note that in some patients endoscopic appearances are normal. Reproduced with permission from [6].

may have mild, intermittent symptoms.

A panel of experts has recently published recommendations pertaining to the diagnosis and treatment of patients with EoE [3]. Endoscopy findings are quite variable, which has been discussed above, and the variation of appearance of the pathology at endoscopy some of the patterns, such as microabscesses or linear furrows, have no specific correlation with a symptom pattern. Fibrotic rings in the esophagus, however, are associated with regular symptoms of dysphagia because if the lumen of the esophagus is significantly narrowed, for example to a lumen of <7 mm, then swallowing any normal bolus becomes difficult and the patient will have dysphagia with every meal. Bolus obstruction can occur in patients with varied endoscopic findings, from stricture to simply trachealization or circular ridges.

Not only is there a poor correlation of the symptoms with histopathology and endoscopic findings, but there is also a poor correlation of pathology with symptom improvement after therapy. A number of studies, which will be described later, show that significant symptom improvements can occur without significant change in the eosinophil concentration in the esophagus. Conversely, dramatic improvements in the eosinophil concentration can occur with topical steroids where sometimes the symptoms will persist.

The third problem with assessing therapy is that we have no prognostic factors for disease progression. In particular we do not have specific prognostic factors for stricture development and treatments that are aimed to reduce the development of complications of EoE do not have clear indications because of the lack of this ability to predict the behavior of the disease. What is required is a measure of disease activity. Up until now, there has been no useful disease activity index. Aceves *et al.* published a symptom scoring tool for pediatrics in 2009, but this has not found value in adult practice [13]. There are research projects underway to try and develop a disease activity index that would incorporate elements of symptoms from a symptom diary, structured assessment of endoscopic findings, histopathological findings and response to treatment. Such a disease-activity index would be very useful in helping to define the place of the various therapeutic approaches to EoE and we await the outcome of such studies with interest.

Distensibility of the esophagus may be a better measure of the degree of obstruction. The EndoFLIP® (Crospan Ltd, Galway, Ireland) is a form of balloon barostat that is inflated in the esophagus, it measures compliance and distensibility of the muscle wall of the esophagus and gives a measure of cross-sectional area change with pressure (Figure 2). Kwiatek *et al.* have shown that in patients with EoE there is an inflection on the slope of the curve of distensibility as measured by the EndoFLIP in the lower esophagus of patients with EoE, and this compares with a linear change in patients with stricture of gastroesophageal reflux disease [14]. Until now, measuring the pressure of esophageal peristalsis by manometry has, in the majority of cases, failed to demonstrate any specific measure of therapeutic success in motility disorders, with the exception of the case series by Lucendo in 2007 [15], which demonstrated an improvement in motor disorders with swallowed fluticasone propionate. Recently, Fox *et al.* described the use of high-resolution manometry, which showed some increase in the intra-bolus pressure in patients with EoE [16], but again this identification of a high intra-bolus pressure has yet to be applied in the setting of decision making therapy or its outcomes.

Dietary therapy

It has been known for some time that the use of an elemental diet significantly improves the esophageal inflammation (reducing eosinophil concentrations)

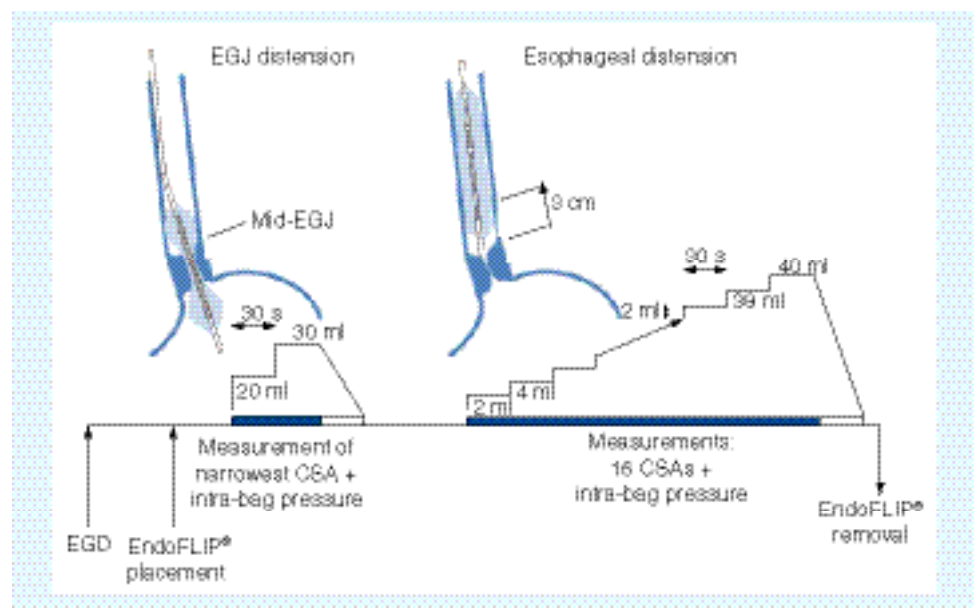


Figure 2. Measuring esophageal wall compliance. Changes in compliance of the esophageal wall measured by the EndoFLIP® device. CSA: Cross-sectional area; EGD: Esophagogastroduodenoscopy; EGJ: Esophagogastric junction. Reproduced with permission from [14].

and improving patients' symptoms, particularly in children. The great problem with elemental diets is that they are so unpalatable that they are not feasible as a long-term treatment. They have been very useful for the development of remission of symptoms in children, where the elemental diet has been given with nasogastric intubation [17]. Recurrence after remission from dieting is common. Elemental diet had not been used in adults until recently, but Peterson *et al.* have shown a partial response in adults to elemental diet [18]. The partial response seen in this study is not likely to be transferable to routine practice for the treatment of EoE due to the difficulties in maintaining this diet in the long term. Exclusion diets have been tried, where attempts have been made by skin-prick testing to identify specific foods, but these have also not proven of great help in improving patients' symptoms of dysphagia. In order to get around the problem of a directed exclusion diet, Gonsalves *et al.* created a six-food elimination diet, which in the acute setting of a 6- to 12-week program was able to improve patients' symptoms and reduce their epithelial eosinophilic inflammation [19]. The six-food elimination diet involves complete avoidance of wheat, milk, eggs, peanuts, soy and rice. In the western world this creates a diet that is very socially restrictive and adherence to this diet requires a lot of attention to detail. Subsequent work on maintaining this six-food elimination diet have shown the difficulty in trying to maintain a normal lifestyle for patients when they are excluding common food items that would normally be used in their community [20]. However, recent work by Kagalwalla *et al.* in the pediatric setting has demonstrated some success with single-food reintroduction after implementation of the six-food elimination. This has enabled the identification of specific causative food antigens in EoE, with milk being the most common causative food antigen [21]. The work of Liacouras *et al.* in use of diets for pediatric EoE has shown that it is useful in the acute setting and is a help to patients and their families to help modify the symptoms of EoE without curing the underlying abnormality [3]. Support is needed from dietitians and from psychologists because maintaining quality of life and normal social development of children in this circumstance is one that requires great attention to the detail of the diet and the way it affects the child's normal development [21]. There has been significant research on whether dietary changes have a fundamental effect on the progression of the underlying disease. Hsu Blatman *et al.* showed that the expression of mast-cell-associated genes is reduced along with eosinophil concentrations in patients who are

on successful exclusion diets [22]. Abu-Sultaneh *et al.* recently showed that there is potential for reversal of subepithelial fibrosis in patients who are on exclusion diets, as well as those on topical steroids [23]. Rea *et al.* looked at mesenchyme remodeling and showed that there is a significant change in the subepithelial connective tissue processes that occur in EoE and there is not yet a specific therapy that clearly makes improvement in mesenchymal remodeling [24]. If mesenchymal remodeling is a process of removal of fibrosis and creation of more compliant connective tissue (allowing the esophagus to distend more easily) then the EndoFLIP, described above, may be able to detect changes in the esophageal fibrosis by detecting changes in the wall distensibility after medical therapies [25].

Topical steroids

Currently the main-stay of symptomatic treatment of EoE is the use of topical steroids. As there are no dedicated or licensed formulations of topical steroids, most clinicians have used the topical steroidal inhalers, manufactured for bronchial asthma adapted for the purpose of EoE. With fluticasone, inhaler patients are advised to spray the back of the throat and swallow without making any attempt to inhale the topical steroid. Such an approach using fluticasone 300–500 µg twice daily, applied last-thing at night and after breakfast in the morning does allow a patient to have topical steroid affecting the mucosa of their esophagus for approximately 12 in each 24-h period. This approach can produce significant improvement in patients' dysphagia [26,27]. An alternative formulation is to use budesonide, and it is possible to use the budesonide powder formulated with a viscous liquid medium for improved adhesion to the esophageal epithelium. This has been shown to be effective in acute therapy of EoE [28]. However, in maintenance therapy, ability to control patients' symptoms is only partially effective [29]. Gupta *et al.* have also recently shown that swallowed viscous budesonide is effective in children [10,30]. They used a low, medium and a high dose in their patient population and they found that the high dose produced the best response reducing the eos/hpf to <6 in >90% of their patients, regardless of age, compared with the median dose, which was only 40–60% effective at reducing eosinophil concentration. However, there was no benefit in symptom improvement with the high dose and indeed the symptom improvement was seen in 53% of patients on the median dose and 47% on the high dose. This discrepancy between histological response and symptom response is, however, typical of all of the previous studies of therapies for EoE. Krishna *et al.* have shown that this viscous oral

preparation may be superior to swallowed fluticasone spray but currently the treatment offered to patients locally depends on what is available, and fluticasone spray is easily available as it is a routine treatment for bronchial asthma [31].

Drug therapy modulators of inflammatory processes

The cellular molecular mediators of EoE are thought to be the chemotaxins and leukotrienes involved in eosinophil and mast-cell biology. The cytokines include eotaxin-3 and the inflammatory process involves IL-4, IL-5 and IL-13 [9]. Unfortunately, there have been no effective therapies based on these mechanisms and no inhibitors of eotaxin-3 or the interleukins have so far been shown to be effective. The work of Straumann *et al.* has shown that infliximab is not effective in reducing either the symptoms or histology of EoE [32]. In contrast, mepolizumab showed some promise because in a randomized controlled trial there was a reduction in eos/hpf with this medication [11]. However, there was no effect in symptom reduction, and despite the improvement histologically there is no justification for using mepolizumab because of the lack of symptom improvement. Similarly, reslizumab and omalizumab have also produced little symptom improvement, despite some change in histology [12,33].

The histological and immunological mechanisms of inflammation in EoE seem to parallel those of the same cellular changes in bronchial asthma. Figure 3 is an example of the appearance of eosinophils in the esophagus in this condition. Without special staining the presence of other cell types (such as Th2 cells or mast cells) are not evident. Pettipher *et al.* have shown how the mast cell and eosinophils are activated in bronchial asthma [34]. Figure 4 shows that the activation of mast cells is dependent on prostaglandin D₂ activation via Th2 lymphocytes. Within this pathway of bronchial inflammation it is known that the leukotriene D₄ antagonist montelukast is effective. Montelukast has been shown in observational studies to be beneficial in

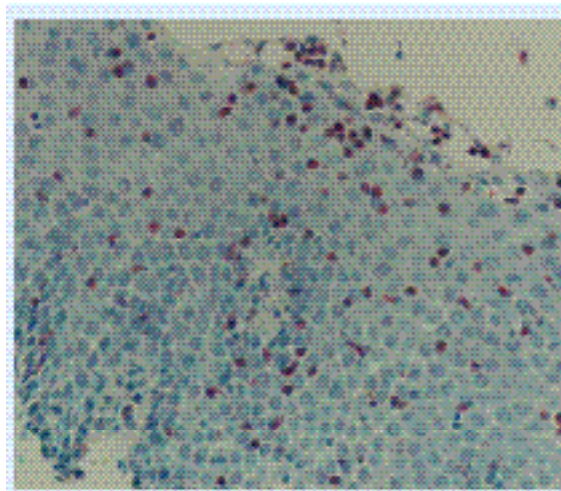


Figure 3. Histopathology of eosinophilic esophagitis. An esophageal biopsy of eosinophilic esophagitis showing the high concentration of eosinophils in the mucosa and surface aggregation of eosinophils into microabscesses.

EoE [35]. In that study 12 patients took daily montelukast at doses of between 10 and 30 mgs per day, and significant improvements in their dysphagia scores and reduced frequency of bolus obstruction occurred. Although there was some reduction in eosinophil

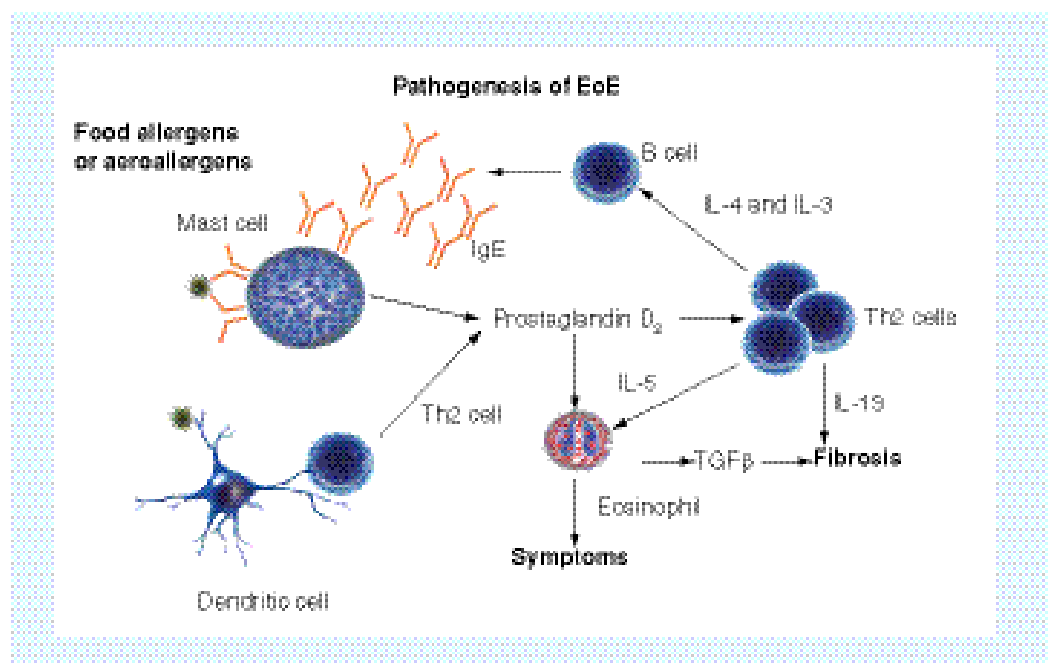


Figure 4. Mast cell activation in eosinophilic inflammation. Mechanisms of inflammatory stimulation and activation of eosinophils and mast cells that may provide opportunities for therapeutic blockade by CRTH-2 antagonists. Reproduced with permission from [34].

concentration in some of the patients, this was not seen universally in the group and this study showed better symptomatic response, but less significant histopathological response in eosinophil concentration. A similar observational study of improved symptoms with montelukast has been shown in a pediatric population of eight patients published by Stumphy *et al.* [36]. Both of these montelukast studies were not placebo-controlled, but there is a need for placebo-controlled randomized trials to identify the potential merit of this approach. Currently, this approach is used by patients who suffer the problem of oropharyngeal candida with long-term topical steroids or who only have a partial symptom response to topical steroids. However, montelukast has also been shown to be inefficient in maintaining steroid-reduced remission in EoE [37]. The activation of prostaglandin D_2 by Th2 cells in bronchial asthma has provided the opportunity of the receptor of the CRTH2 to be blocked using a specific blocker (OCR459). CRTH2 is a chemo-attracted receptor homologous molecule expressed on Th2 cells that binds prostaglandin D_2 [34]. Phase II clinical trials are now in progress to identify if this drug may be effective in reducing both the inflammatory process and symptoms of EoE.

Dilatation

Dilatation for EoE has been shown to be effective both in the acute setting of relieving bolus obstruction and also with long-term benefit in maintaining symptom relief over months or even years. It obviously does not change the underlying nature of the inflammatory process or antigen-driven reaction in the esophageal wall, but effective dilatation to an adequate gauge reduces bolus obstruction and can improve daily symptoms of patients who have persistent dysphagia [38]. The process of performing balloon dilatation can be modified by using a pull-through technique [39]. The process of dilating the whole of the esophagus may well provide a better symptom relief than simply dilating the lower esophagus or the esophagogastric junction. The safety of dilatation in EoE has been questioned because some years ago EoE had the reputation of being likely to cause more perforations at the time of dilatation than peptic esophageal strictures. This came about because of the practice of patients being referred to ear, nose and throat surgeons with bolus obstruction and having a rigid laryngoscopy and esophagoscopy performed. Attempting to dilate an esophagus or remove a bolus obstruction using a rigid laryngoscope or esophagoscope has greater inherent risk

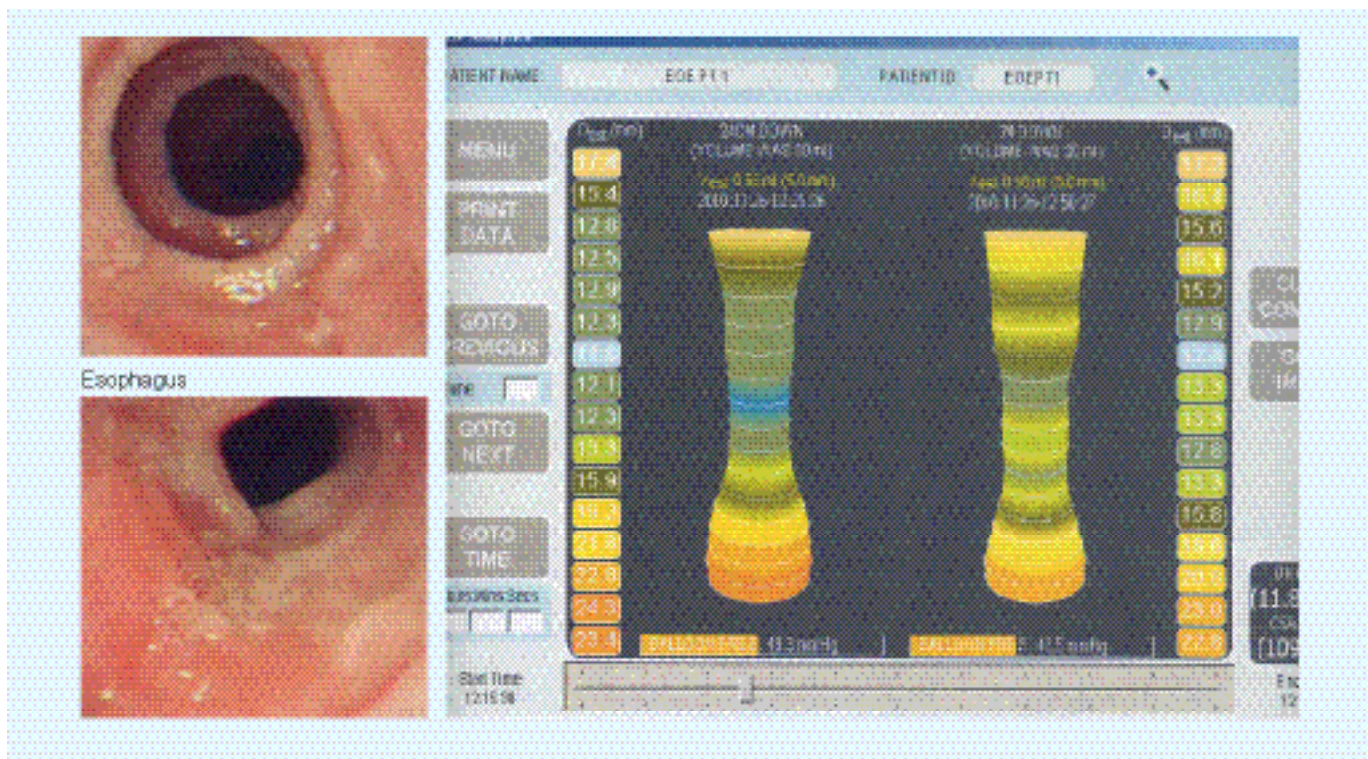


Figure 5. Compliance testing of strictures in eosinophilic esophagitis. Use of the EndFLIP® device to assess strictures in eosinophilic esophagitis and to document response to dilatation.

[40]. However, since the condition has been taken on by gastroenterologists, the safety of flexible endoscopy and balloon dilatation under observation has now been well established. Recent work by Hirano *et al.* [41], Schoepfer *et al.* [42], Jacobs and Spechler [43], Bohm *et al.* [44] and Dellon *et al.* [45] has identified that there is no greater risk of esophageal perforation at the time of dilatation than in other disorders. It may be possible that the EndoFLIP might be used to calibrate dilatation and help to judge the size to which an esophagus can safely be stretched (Figure 5). In the recent consensus guidelines it has also been highlighted that perforation is as likely, if not more likely, to occur from an obstructed bolus where a patient continually retches to try and regurgitate, and a subsequent partial perforation or partial tear of the esophageal wall is now known to be relatively common [3].

Conclusion

Current treatment of EoE relies on diet, unlicensed use of drugs, or dilatation. The outcomes are not sufficiently well studied to provide a clear evidence-based algorithm of management.

Future perspective

There is much work to be done to reach consensus on an evidence-based treatment strategy for EoE. Clear end points need to be established for measuring therapy outcomes. In dietary therapy, improved identification of food antigens and ways to improve quality of life for those on diets need to be explored. In the use of topical steroid therapy, the benefit of viscous oral budesonide needs to be established and a licensed formulation developed. Other therapeutic avenues, such as immune modulation with montelukast or CRTH2 antagonists or IL-13 antagonists need to be assessed in randomized control studies. The future of patients

Executive summary

Epidemiology

- Eosinophilic esophagitis (EoE) is becoming increasingly common and is now an important diagnosis for patients of all ages with dysphagia.
- Defined by the presence of obstructive esophageal symptoms with >15 eosinophils per high power field in any of six esophageal biopsies.

Clinical presentation

- Mild or severe and intermittent or continuous dysphagia.
- Commonest cause of acute food bolus obstruction, and may lead to partial rupture of the esophagus.
- Patients may also suffer asthma or other forms of atopic disease.

Pathology

- EoE is an antigen-driven disorder, but the causative agents or allergens are not often found, despite immunological testing.
- Eotaxin-3 and IL-4, IL-5 and IL-13 are known cytokines involved in the eosinophil chemoattraction within the esophageal mucosa. Mast cell activation may also be involved in the pathogenesis of the disease.
- Oesophageal muscle discoordination may occur and endoscopic findings vary between normal in some, mucosal abnormalities such as furrows, rings and hyperplasia in others, through to strictures and narrow caliber esophageal lumen in severe cases.

Clinical investigations

- Endoscopy and biopsy is the cornerstone of diagnosis and management.
- Biopsies should be taken during proton pump-inhibitor therapy.
- Barium contrast radiography assessing anatomy and swallow function of the esophagus is useful.
- Physiology testing with high-resolution manometry and 24 h pH testing is mainly to exclude acid reflux as a component of the symptom development.
- Tests of esophageal distensibility using the EndoFLIP® balloon device may prove useful in determining which patients will respond to esophageal dilatation therapy.
- Patients are encouraged to keep long-term symptom diaries to help assess the temporal variability of their symptoms.

Therapy

- Dietary restriction has proven useful in short-term studies and particularly in children. Adults do not show good long-term response to diets.
- Topical steroids (swallowed fluticasone or budesonide) are effective in both symptom reduction and in resolving eosinophilic inflammation.
- Systemic steroids should be avoided due to side effects.
- Medical therapies such as montelukast, or CRTH-2 antagonists, are under investigation.
- Acid suppression with proton pump inhibitors is useful when acid reflux is a proven component of the condition.
- Monoclonal antibody therapies including infliximab, reslizumab and mepolizumab have proven ineffective.
- Dilatation, although painful, may produce long-lasting benefits for selected patients.

with EoE is optimistic because better disease severity assessment tools and better management strategies will improve the outcomes for patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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