Mistakes in eosinophilic oesophagitis and how to avoid them

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Eosinophilic oesophagitis (EoE) is a chronic immune-mediated inflammatory condition that is confined to the oesophagus. Clinically, EoE is characterized by symptoms of oesophageal dysfunction; histologically, by eosinophil-predominant inflammation. At present, EoE is the second-most frequent cause of chronic oesophagitis (after gastro-oesophageal reflux disease [GORD]) and the foremost cause of dysphagia and food impaction in children and young adults.

The first descriptions of EoE date back to the early 1990s, but at that time the condition was largely underappreciated and treated as GORD. Recognition of EoE grew with the rapid increase of paediatric and adult patients diagnosed since 2003, but so did confusion surrounding diagnostic criteria and treatment. The first consensus guidelines for the diagnosis and management of EoE were published in 2007 and were instrumental in bringing EoE to light as a distinct new condition.

Since 2007, the diagnostic criteria for EoE have constantly and rapidly changed. New evidence for therapeutic agents has mounted, especially during the past 5 years. Here, we discuss the critical pitfalls that frequently occur in daily practice when dealing with EoE patients. The discussion is evidence based and in line with the recommendations included in the updated guidelines for diagnosis and management of EoE in children and adults.

Mistake 1 Assuming a diagnosis of EoE whenever ≥15 eosinophils per high-power field are present in oesophageal biopsy samples

EoE is a clinicopathologic disorder and neither clinical nor pathologic information should be interpreted in isolation. Identification of dense eosinophilia in the squamous oesophageal epithelium is clearly an abnormal finding and the underlying cause should be identified; however, oesophageal eosinophilia ≥15 eosinophils per high-power field (HPP) alone does not define EoE. Indeed, objective oesophageal eosinophilia in the absence of symptoms of oesophageal dysfunction (e.g. an incidental finding in patients with diarrhoea or in biopsy samples taken from patients with Barrett oesophagus) should be monitored, but a diagnosis of EoE should not be given without an adequate clinical context. In addition, several local and systemic diseases that have different clinical and histological features can be associated with oesophageal eosinophilia (e.g. eosinophilic gastroenteritis, achalasia, parasitic infection, hypereosinophilic syndrome, drug hypersensitivity, vasculitis, pemphigus, connective tissue disorders, graft versus host disease) and should be ruled out before a diagnosis of EoE is made.

Mistake 2 Performing oesophageal pH monitoring to rule out EoE

Aside from clinical and histological features, the original 2007 diagnostic criteria for EoE included a proton-pump inhibitor (PPI) trial and/or oesophageal pH monitoring. Only patients who were unresponsive to PPI therapy, or alternatively those in whom oesophageal pH monitoring was normal, could be diagnosed with EoE. Conversely, responders to PPI therapy or those with pathological acid exposure were given a diagnosis of GORD. However, GORD and EoE are not mutually exclusive disorders. Both conditions are predominantly present in young males and GORD affects up to 1 in 3 people, so the likelihood of coexistence is high. Indeed, several series have reported the presence of GORD (defined either as heartburn or pathological pH monitoring) in 30–40% of EoE patients.

A prospective study in 2011 was the first to shed light on the inaccuracy of oesophageal pH monitoring for predicting response to PPI therapy in adult EoE patients. Response to PPI therapy was present in 80% of EoE patients who had pathological acid exposure, but also in 33% of those with normal pH monitoring. These results have been confirmed in a recent meta-analysis in both children and adults. Therefore, pH monitoring can confirm the presence of GORD, but it cannot rule out EoE, establish a causative role for acid exposure or predict further response to PPIs. Consequently, oesophageal pH monitoring was withdrawn as a diagnostic criterion in 2011 and it should not be performed for diagnostic purposes.

Mistake 3 Performing food allergy testing to discern food antigens triggering EoE

EoE is a chronic inflammatory oesophageal disease that is triggered predominantly, but not exclusively, by food antigens. Therefore, it seems intuitive to perform food allergy testing to identify the triggering foods.
Unfortunately, a testing-directed elimination diet had the lowest effectiveness rate in a meta-analysis of dietary interventions.\textsuperscript{10} These results were consistently low for studies performed in adults and variable among paediatric studies.\textsuperscript{10} Unlike IgE-mediated food allergy, EoE is a distinct form of food allergy that is largely driven by non-IgE delayed cell-mediated hypersensitivity.\textsuperscript{11} Most skin and blood food allergy tests detect IgE-mediated responses. An atopy patch test can be used to elucidate delayed-type reactions to foods, but this test has not been standardized or validated for food allergy, including EoE. The accuracy of five different skin and blood food allergy tests to detect causative foods in adult EoE patients has lately been assessed.\textsuperscript{12} None of the evaluated tests, measuring both IgE and non-IgE hypersensitivity, could accurately predict the causative foods previously identified in responders to an empiric six-food elimination diet (SFED).\textsuperscript{13} Therefore, this diagnostic strategy should be discouraged in adults. For children, the highest efficacy (up to 53%) was reported in one single centre,\textsuperscript{14} but these results have not been replicated in other paediatric and adult studies.\textsuperscript{8}

**Mistake 4 Considering EoE as a mild nonprogressive disease**

Untreated EoE is frequently associated with persistent oesophageal inflammation over time, leading to oesophageal remodelling that gives rise to stricture formation and functional abnormalities in the majority of patients. In a retrospective series of 200 Swiss adult EoE patients, the prevalence of fibrostricturing oesophageal features increased from 46.5\% to 87.5\% when the diagnostic delay increased from ≤2 years to >20 years.\textsuperscript{15} Similarly, diagnostic delay led to significant differences in oesophageal diameter in adult EoE patients, from <10mm with a mean delay of 14.8 years to ≥17mm with a delay <5 years.\textsuperscript{16} These results have been corroborated in a series from the US, in which the odds of having fibrostenotic features more than doubled for every 10-year increase in age.\textsuperscript{10}

All these findings suggest that the natural history of untreated EoE is a continuum from an inflammatory to a fibrostenotic disease. Whether anti-inflammatory therapy (e.g. PPI, topical steroids or dietary therapy) can reverse the natural history of the disease remains to be elucidated. Recent studies have shown the ability of topical steroids and dietary treatment to reverse oesophageal fibrotic remodelling in children.\textsuperscript{17-20}

**Mistake 5 Monitoring response to treatment via symptoms alone**

Contrary to the necessity for clinical and histological information to be interpreted together, most clinicians usually rate EoE activity after treatment on a symptom basis rather than on histological findings,\textsuperscript{21} most likely to try to reduce the need for endoscopic procedures. However, clinicopathologic dissociation in EoE has been largely reported after pharmacological therapy with a PPI or topical corticosteroids.\textsuperscript{16,22} Symptoms may improve without histological remission and, conversely, dysphagia and/or food impaction may persist despite the absence of inflammation in patients who have fibrostricturing features. In addition, children may have difficulties reporting symptoms, clinical manifestations typically change during the transition to adulthood and dysphagia might be minimized by behavioural modifications, such as food avoidance or by altering the consistency of the ingested food or the eating pace.

An advance in this field is the development and validation of an activity index for adult EoE patients (EESAI) that quantifies the difficulties foreseen by the patients in eating different food consistencies, along with the dietary or behavioural modifications for the same food consistencies.\textsuperscript{23} Unfortunately, a prospective multicentre study has lately shown a modest predictive capacity of the EESAI tool to predict either histological or endoscopic remission in adult EoE patients.\textsuperscript{24} Therefore, clinicians should not make assumptions about the biological activity of EoE solely on a symptom basis and endoscopic oesophageal biopsy samples are currently still required for accurate monitoring of the disease activity.

**Mistake 6 Considering responders to PPI therapy as just GORD patients**

As it was explicitly included in the 2007 and 2011 guidelines, many people still think that response to PPI therapy rules out EoE. GORD develops when the chronic reflux of stomach contents causes symptoms and/or complications, promoting a Th1 inflammatory response with recruitment of neutrophils and lymphocytes and a mild eosinophilic infiltration. The endoscopic appearance of the oesophagus may be normal in up to 80\% of GORD patients. By contrast, EoE is a chronic immunological disorder caused mainly by food allergens that promotes an aberrant Th2 inflammatory response, with eosinophil recruitment into the oesophageal mucosa. Typical endoscopic findings (e.g. rings, furrows, exudates, oedema and strictures) are present in up to 90\% of EoE patients.

Evolving knowledge, mostly from adults, has demonstrated that patients with clinical and histological features of EoE that remit with PPI treatment (formerly called PPI-responsive oesophageal eosinophilia [PPI-REE]) are clinically, endoscopically, histologically, molecularly and genetically indistinguishable from EoE patients.\textsuperscript{25} Aside from its anti-inflammatory effects, PPI monotherapy in PPI-REE patients also reverses the EoE abnormal gene expression signature, similar to the effects of topical steroids in patients with EoE. Some EoE patients who are responders to diet or topical steroids have also been shown to be responders to PPI therapy.\textsuperscript{26,27} Accordingly, it seems counterintuitive to differentiate responders to PPI therapy from EoE patients based on a differential response to a drug (PPI therapy), when their phenotypic, molecular, mechanistic and therapeutic features cannot be reliably distinguished.

The recent description of EoE patients as responders to voroprazan underscores the importance of acid reflux as a trigger of the disease.\textsuperscript{28} Regardless of what drug patients are responsive to, responders to PPI therapy exhibit the clinical, endoscopic, histological, molecular and genetic features of EoE, (which are radically different from those of conventional GORD). These patients should not be labelled and treated as GORD patients, but rather as EoE patients.

**Mistake 7 Using inhalers to deliver topical steroid treatment into the oesophagus**

Topical steroid formulations currently used in clinical practice are neither designed for oesophageal delivery nor approved for use in EoE patients by regulatory authorities. Although the use of inhalers is frequent, nebulized formulations may not be an adequate drug delivery method. Nebulized and viscous oral preparations of budesonide 1 mg given twice a day for 8 weeks were compared in a randomized trial in adult EoE patients.\textsuperscript{29} Histological remission was significantly higher for the swallowed formulation than the nebulized formulation and this correlated with longer mucosal contact time, as measured by nuclear scintigraphy, particularly in the distal oesophagus.

Swallowed formulations of either fluticasone or budesonide are the more logical delivery system compared with the aerosolized modality, which might be mixed with sucralose, maltodextrin or honey to increase viscosity. An alternative might be using a diskus formulation of fluticasone or budesonide, in which...
individual doses of fluticasone or budesonide powder can be easily released from the foil strip, dropped directly onto the tongue and swallowed.

The current difficulties in clinical practice with ‘do-it-yourself’ formulations will probably be overcome with the advent of the topical corticosteroids specifically designed for oesophageal delivery. A phase II trial has shown cure rates closer to 100% after only 2 weeks of treatment with budesonide given either as an effervescent tablet or viscous suspension.30

Mistake 8 Combining an elimination diet with pharmacological therapy

Similar to that expected in inflammatory bowel disease, the ideal treatment endpoint for EoE would be complete resolution of clinical, endoscopic and histological features (deep remission) in order to prevent remodeling and related complications.14–16 For this purpose, an induction phase, in which clinical and histological remission is achieved, should be followed by a maintenance phase, which is intended to prevent disease relapse and restore quality of life through sustained disease remission.31

A single therapeutic intervention should attempt to fulfil all the aforementioned therapeutic targets. Patients taking topical corticosteroids do not need dietary restrictions to be put in place, and topical steroid therapy should not be added for patients choosing dietary therapy. In addition to the potential unnecessary additive side effects and impairment of quality of life, an effective combination therapy may hinder getting to know which treatment was ultimately responsible for remission and which of the two treatments should be continued/discontinued for maintenance therapy. Likewise, combining different therapies in EoE studies might lead to results that are misleading and cannot be replicated.32 Evaluation of individual therapeutic interventions in EoE (e.g. PPI therapy or the SFED)33 has produced consistent results in both children and adults.

Mistake 9 Discarding empiric elimination diets because of the high indefinite level of dietary restriction

Treatment of EoE with an empiric elimination diet—the SFED—was first tested in Chicago in 2006.33 This diet eliminated the six food groups most commonly associated with food allergy in the paediatric population in Chicago (cow’s milk protein, wheat, egg, soy, peanut/tree nuts, fish and seafood) for 6 weeks and led to clinical and histological remission in 74% of children.33 Similar results have since been obtained in patients of all ages, as shown in a meta-analysis published in 2014.34 The effectiveness and wide reproducibility of the SFED are counteracted by the high level of dietary restriction and the large number of endoscopies required after reintroduction of individual foods. Less-restrictive empiric diets are therefore being evaluated.

Since three quarters of responders to the SFED have been found to have just one or two food triggers,35 a four-food elimination diet (FFED), which avoids the most common food triggers (milk, wheat, egg and, to a lesser extent, soy/legumes) was developed. In the first prospective multicentre study in adult patients, the FFED achieved 54% remission,36 whereas an abstract reporting the use of the FFED in a paediatric population revealed 71% efficacy.37 Half of the responders to the FFED had one or two food triggers—cow’s milk and wheat were the most common.36 Preliminary results have shown that a two-food elimination diet (cow’s milk and wheat) might achieve remission in 43% of children and adults, with one single food trigger identified in 70% of patients.37 At present, most people still believe that the food groups included in empiric diets are removed from their regular diet indefinitely. In responders to any empiric 6-week diet, all food groups are reintroduced individually, with an endoscopy performed following each food challenge. The final goal is to provide a personalized maintenance therapy, with long-term removal solely of food triggers, namely, foods proven to induce oesophageal inflammation after individual reintroduction.

Mistake 10 Avoiding endoscopic dilation because of the risk of oesophageal perforation

Early findings for oesophageal dilation in EoE patients reported a high rate of complications, mainly oesophageal perforation and chest pain.38,39 These findings were not confirmed in the first systematic review and metaanalysis of the literature, comprising 525 adult EoE patients and 992 endoscopic dilations.40 Only three oesophageal perforations (0.3%) and one haemorrhage (0.1%) were reported, all at the same institution. Accordingly, the rate of major complications is consistent with that reported for endoscopic dilation in other oesophageal diseases (<1%).

Endoscopic dilation should be recommended to all EoE patients who have dysphagia/food impaction that is related to fibrostenotic abnormalities (either narrow-calibre oesophagus or strictures) and unresponsive to medical or dietary therapy.4 Endoscopic dilation is highly effective, with clinical improvement documented in 75% of patients in the aforementioned meta-analysis.40 Mucosal lacerations after dilation should not be considered complications, but rather the intended outcome of the endoscopic procedure.

References


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Your eosinophilic oesophagitis briefing

**UEG Week**


- “Eosinophilic oesophagitis: Overlooked too often or searched for too fanatically?” session at UEG Week 2016. [https://www.ueg.eu/education/session-files/?session=1646&action=conference=144]

- Therapy update: Eosinophilic oesophagitis’ session at UEG Week 2015. [https://www.ueg.eu/education/session-files/?session=1431&action=conference=109]

- “The immune invaders in GI diseases” session at UEG Week 2015. [https://www.ueg.eu/education/session-files/?session=1392&action=conference=109]

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** Standards and Guidelines**


**Online resources**

- “Eosinophilic esophagitis: The use of fluticasone powder” video by Dr Mark Holbreich on the use of fluticasone powder for the treatment of eosinophilic esophagitis. [https://www.youtube.com/watch?v=b8tD_jyKLmI]