Eosinophilic oesophagitis and food allergy

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Abstract

Eosinophilic oesophagitis (EoE) is an allergic condition of the oesophagus. It is a clinico-pathological diagnosis in which intermittent dysphagia and/or food impaction in adults occurs in the presence of severe eosinophilic infiltration of the oesophagus. Symptoms can be less well defined in children, with feeding refusal, vomiting and failure to thrive. Patients tend to have a history of atopy, and both food and aero-allergens are implicated in EoE pathophysiology. EoE is defined as ≥15 eosinophils/high-power field in oesophageal biopsies. The reported prevalence of EoE is 4 per 1000 adult population. Its incidence is increasing, and it has a male predilection. Although original guidelines required acid reflux to be excluded before making a diagnosis of EoE, the two conditions can overlap. Clinical awareness is necessary for the condition to be diagnosed, by ensuring oesophageal biopsies are taken when patients present with symptoms suggestive of EoE even if the oesophagus looks normal. The main treatment options include proton pump inhibitors, topical corticosteroids and dietary therapy with elimination or exclusion diets in children, and more recently also in adults. Endoscopic dilatation of identified strictures is less commonly needed; this also carries a high risk of perforation.

Keywords Dysphagia; elimination/exclusion diet; eosinophilic oesophagitis; food allergy; food bolus obstruction; MRCP; topical corticosteroids

Key points

- Eosinophilic oesophagitis (EoE) is a progressive chronic inflammatory disease of the oesophagus
- EoE is characterized by oesophageal dysfunction and dysphagia, and oesophageal eosinophilia
- Endoscopic oesophageal biopsies are indicated in all patients with dysphagia
- Prevalence in children increases with age; adults <50 years old are more often affected
- The condition is more common in male patients
- EoE is associated with food allergies and atopy
- Proton pump inhibitors can be effective in management
- Topical corticosteroids and/or food elimination diets can achieve remission
- Oesophageal strictures can occur and require dilatation

Introduction

Eosinophilic oesophagitis (EoE) is a chronic, immune/antigen-mediated condition of the oesophagus. It is a clinico-pathological diagnosis in which symptoms of oesophageal dysfunction, most often dysphagia and food impaction in adults, occur in the presence of eosinophil-predominant inflammation of the oesophagus. In children, symptoms are less well defined, with feeding refusal, vomiting and failure to thrive. Symptoms of reflux, often described by both adult and paediatric patients, are typically unresponsive to acid suppression treatment. Patients tend to have a history of atopy, and both food and aero-allergens are implicated in the pathophysiology.

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The prevalence of EoE is reported to be 4 per 1000 population. Although increasing awareness of the condition is probably contributing to increased reporting, there appears to have been a genuine rise in the prevalence of EoE. The main treatment options include dietary therapy, and topical or systemic corticosteroids.

Diagnosis

In patients with clinical symptoms suggestive of EoE, oesophageal eosinophilia of >20 eosinophils per high-powered field (eos/HPF) has historically been taken as consistent with the diagnosis. Consensus guidelines, first published in 2007 and updated in 2011 and 2017,[1–3] required the presence of 15 or more eosinophils in 1 HPF in the presence of symptoms of oesophageal dysfunction not responding to proton pump inhibitors (PPIs) or occurring in the presence of normal pH monitoring of the oesophagus.

The 2013 American College of Gastroenterology clinical guidelines require clinical symptoms of oesophageal dysfunction in the presence of 15 or more eosinophils in 1 HPF on histology. Histology, rather than symptoms alone, was given more emphasis: mucosal eosinophilia should be isolated to the oesophagus and persist after a trial of PPIs. Exclusion of other systemic or local causes of oesophageal eosinophilia Table 1) was also required. A response to treatment with dietary exclusion and/or corticosteroids supported, but was not a prerequisite to make, the diagnosis.

These guidelines also introduced the concept of PPI-responsive oesophageal eosinophilia as a condition distinct from EoE. In these cases, symptoms and oesophageal eosinophilia respond to PPIs. This response should not be assumed to

Differential diagnoses of oesophageal eosinophilia

- Gastro-oesophageal reflux disease
- Inflammatory bowel disease
- Drug hypersensitivity reactions
- Parasitic infections
- Malignancy
- Connective tissue diseases
- Churg—Strauss syndrome
- Systemic lupus erythematosus
- Eosinophilic gastroenteritis (if there is clinical suspicion, gastric and duodenal biopsies may be needed to exclude it)
- Hyper-eosinophilic syndrome
- Graft-versus-host disease
- Food allergies

Table 1

be related to gastro-oesophageal reflux disease (GORD) and should be actively investigated, including use of ambulatory 24-hour pH studies.

In the latest European guidelines published in 2017, it was argued that PPI-responsive oesophageal eosinophilia was not a separate disease entity from EoE in view of its indistinguishable clinical, endoscopic, pH monitoring, histological and molecular characteristics. The term 'PPI-responsive oesophageal eosinophilia' was retracted and PPIs were accepted as therapeutic agents in EoE.

Presentation

Adults present primarily with symptoms of intermittent dysphagia (81—93%) and/or food bolus obstruction (55—62%). More than one-third of patients presenting with food bolus impaction have underlying EoE with other common causes of food impaction, including GORD, oesophageal stricture and Schatzki rings. Of all cases of dysphagia, 10—12% have been attributed to underlying EoE. Men are most commonly affected (male:female 4:1), with age at diagnosis usually <45 years, and highest prevalence at age 20—39 years. Symptoms of heartburn, atypical chest pain and odynophagia are also reported. Rarely, oesophageal perforation has been reported; this is often limited and may occur in the context of food bolus obstruction rather than being spontaneous rupture (Boerhaave's syndrome).

Children present with symptoms of reflux unresponsive to acid suppression and with non-specific symptoms of failure to thrive, food avoidance, abdominal pain, nausea and vomiting.

Endoscopy

Linear furrows, oesophageal rings (trachealization of the oesophagus), mucosal fragility, white papules or strictures can be present on endoscopy (Figure 1). However, up to 42% of cases have a normal endoscopy, and a high level of suspicion is needed by the endoscopist to ensure that oesophageal biopsies are taken even in the presence of a normal oesophagus, especially in younger individuals. EoE tends to be patchy, and eosinophilic infiltration in the lower oesophagus can occur in reflux; it is therefore recommended that at least six biopsies are obtained from both the proximal and distal oesophagus, and areas of endoscopic abnormality, to improve yield. Eosinophilic gastroenteritis and other differential diagnoses must be excluded, and gastric antrum and duodenal biopsies should be taken.

Histopathology

Eosinophils are seen under normal conditions in the remainder of the gastrointestinal tract but are usually absent from the normal oesophagus.

Aggregation of eosinophils is seen in gastro-oesophageal reflux, although generally in lower numbers (usually up to 6—10 eos/HPF) than in EoE (Figure 1). The two conditions cannot be distinguished on histological criteria alone, and showing a correlation between symptoms and histological findings is paramount. Other features often present in EoE include extensive basal cell hyperplasia, dilatation of intracellular spaces, superficial layering of eosinophils, eosinophil degranulation and eosinophil clustering to form micro-abscesses. However, it might be that GORD and EoE can coexist, especially in adults, in whom GORD is a common condition. It has been speculated that four possibilities might exist:

1. High numbers of eosinophils in the oesophagus can indeed exist in GORD.
2. GORD can occur in patients with EoE by chance.
3. EoE can predispose to or worsen GORD.
4. GORD can predispose to or worsen EoE.

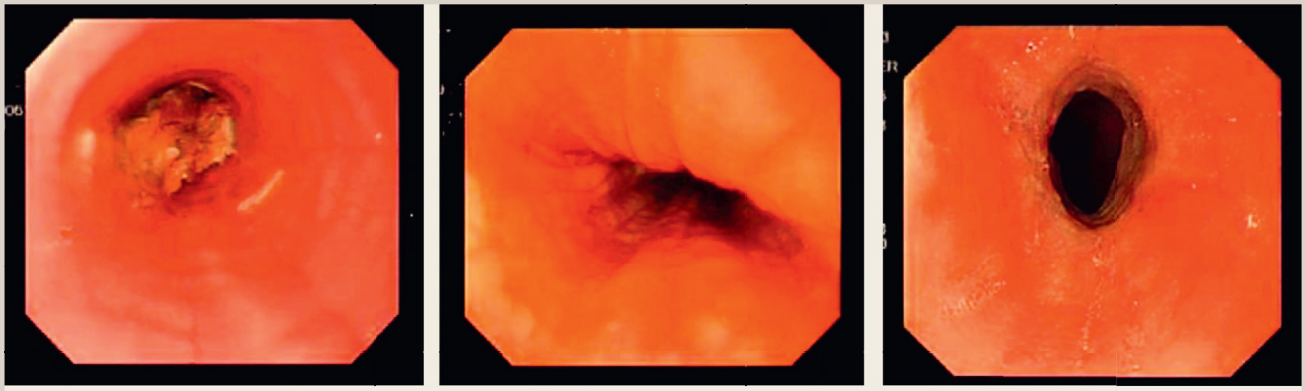
Pathophysiology

Patients with EoE often have a concomitant history of allergic disease (asthma, allergic rhinitis, eczema) and sensitization to allergens, demonstrated by positive radioallergosorbent testing or skin prick testing. Elevated serum immunoglobulin (Ig)E and peripheral eosinophilia may be seen. EoE appears to be directly linked to an immunological response to food allergens, especially in the paediatric population. A mixture of IgE (type I) and cell-mediated (type IV) hypersensitivity responses is involved. More recently, a role for IgG4-related food atopy and inflammation has been identified in both adult and paediatric populations.

In active EoE, defects in desmosomal and tight junction adhesion proteins result in disrupted oesophageal mucosal integrity. It is unclear whether this is due to non-specific inflammation or whether there is a predisposition in patients with EoE. Loss of the oesophageal mucosal barrier function allows allergens to breach the oesophageal epithelium and trigger an inflammatory response. This appears to be driven by type 2 T helper cells, with increased expression of interleukin (IL)-5, IL-13 and tumour necrosis factor-α, and accumulation of IgE receptor-rich eosinophils and mast cells. IL-5 is a specific eosinophil differentiation and survival factor, generated in chronic allergic conditions. Induction of eotaxin 3 facilitates eosinophilic migration to the oesophagus.

There is no correlation between the number of eosinophils and the severity of endoscopic findings, suggesting that eosinophil aggregation alone is not the cause of epithelial damage. Tissue damage results from eosinophil aggregation and degranulation with release of chemo-active agents. These agents include major basic protein, an antagonist at muscarinic M_2 receptors that increases smooth muscle reactivity. Expression of

Endoscopic findings:

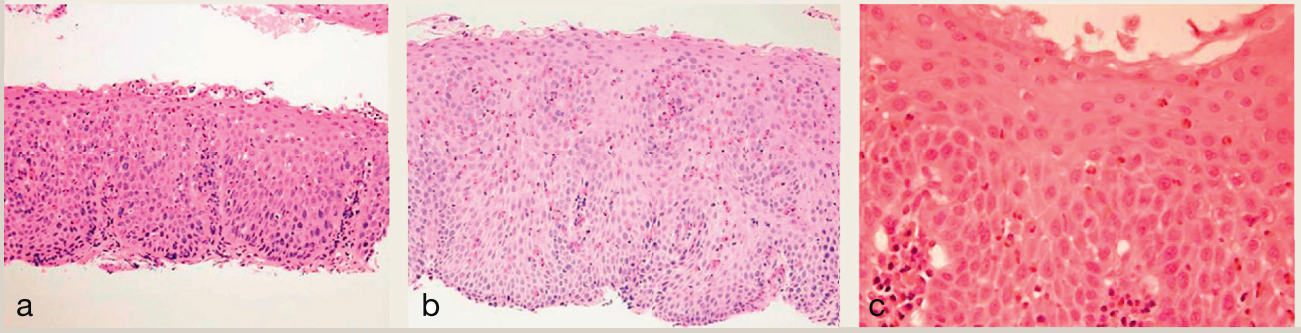


Food bolus obstruction in a ringed oesophagus

Thickened folds

Linear furrows and white papules in lower oesophagus

Histologic findings:



a. Prominent superficial eosinophilic microabscesses, patient presented with long standing intermittent dysphagia, initially dismissed as functional.

b. Diffuse eosinophilic infiltration in a patient with dysphagia and history of asthma who had partial response on swallowed fluticasone. A pH study identified severe acid reflux, with partial improvement of symptoms on standard dose PPI and resolution on high dose.

c. Eosinophil infiltration in oesophageal biopsies taken at time of FBO.

FBO, food bolus obstruction; PPI, proton pump inhibitor.

Figure 1

transforming growth factor-β1 by both eosinophils and mast cells is also increased in patients with EoE and is associated with tissue remodelling and fibrosis. Persistent and chronic inflammation, eventually leads to oesophageal wall stricturing.

On endoscopic ultrasonography, there can be thickening of the oesophageal wall, while dynamic studies using concurrent high-frequency intraluminal ultrasound and manometry suggest that asynchrony between oesophageal circular and longitudinal muscle might be one of the mechanisms of early dysphagia in patients with EoE. Manometric findings are pleomorphic and have demonstrated non-specific variable oesophageal dysmotility, hyperkinetic peristalsis and diffuse oesophageal spasm, or aperistalsis.

Endoluminal functional luminal imaging (EndoFLIP®), which uses high-resolution impedance to measure the distensibility of the oesophageal wall, can provide complementary information of underlying fibrosis and hence disease progression, response to treatment and prognosis.

Treatment

Untreated EoE is associated with persistent symptoms, inflammation and, over time, oesophageal remodelling with stricture formation and functional abnormalities. Effective anti-inflammatory treatment can limit progression. The choice of therapy should consider the individual age, co-morbidities and

preferences (Figure 2). Effectiveness should be assessed with repeat endoscopy after 6–12 weeks of treatment.

Food allergens and dietary modifications

The utility of dietary therapy with elemental or exclusion diets has been extensively assessed in the paediatric population. Children frequently have food allergies and are better at tolerating dietary treatment options. More recently, evidence has been accumulating to support a role for early dietary intervention in adults as well. Prolonged avoidance of trigger foods can lead to drug-free sustained clinical and histological remission of EoE.

Dietary interventions include the following:

- **Amino acid-based elemental diet** – this induces histological remission in up to 90% of children and adults. However, it is poorly tolerated because of poor palatability or need for administration via nasogastric feeding tube in children, resulting in low adherence.

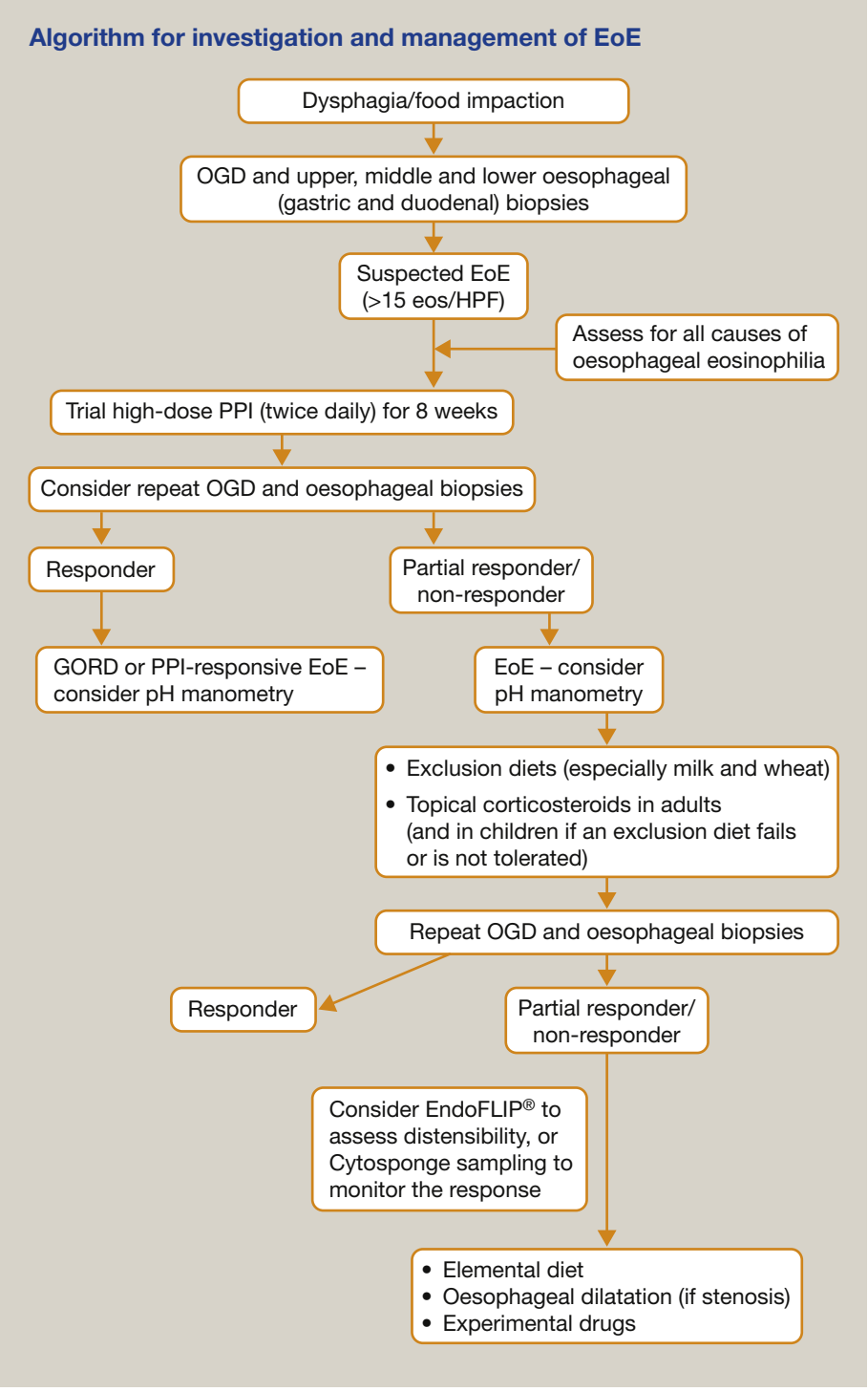


Figure 2

- **Specific food elimination** – this is guided by identified food allergens using skin-prick and patch-testing. It induces histological remission in less than one-third of adult patients but the rate can be higher in paediatric patients. Overall utility of allergy tests in the identification of food triggers is low.
- **Empirical six-food elimination diet** (SFED) – introduced for 6 weeks, this is based on known common food allergens, namely cow's milk, egg, soy, wheat, peanut and seafood.

Studies looking into the effectiveness of various therapies to treat EoE in the paediatric population have illustrated the effectiveness of dietary modifications, which have a more favourable adverse effect profile than corticosteroids. Awareness of nutritional and calorific needs, supervision of their provision and issues with compliance can make implementation difficult.

In adults with EoE, skin-prick and patch-testing appear to be even less sensitive than in children, with positive tests to wheat and rye suspected to result from cross-reactivity with grass pollen allergy and thus not able to guide dietary modifications. In a study by Gonsalves, an empirical SFED was reported to produce histological improvement in 70% and clinical improvement in 94% of patients, the most common allergens being milk and wheat. In a recent systematic review, SFED showed homogeneous effectiveness in both children and adults, inducing responses in 72.8% and 71.3%, respectively.

More recently the 2–4–6 study has looked at a step-up approach in which 56 patients with EoE initially avoided milk and cereals (gluten), escalating to four- or six-food elimination diets if there was no response. In the two-food elimination diet, triggers in responders were milk in 52% of cases, gluten (16%) or both (28%). An EoE response to only milk exclusion was present in 18% and 33% of adults and children, respectively. Remission rates with a four-food elimination diet (milk, gluten, eggs, vegetables) and an SFED (seafood/fish and nuts also being excluded) were 60% and 79%, respectively. This step-up approach tends to be better tolerated by patients.[4]

An *in vitro* study has implicated aero-allergens as well as food as possible triggers of inflammation in EoE, with greater IL-5 production in EoE patients but not in controls. Further studies into the role of allergens in the pathogenesis of EoE are needed, as well as into the effectiveness of dietary modification in adults, especially as implementation in adults may be even less practical than it is in children.

Medical treatments

Proton pump inhibitors: due to their safety profile, ease of administration and high response rates (up to 50%), PPIs can be considered a first-line treatment for EoE, before diet and topical corticosteroids. A sufficiently long (e.g. 8-week) course of any of the available agents at a regular dose given twice daily has been proposed as sufficient to assess the response to PPI therapy.

Corticosteroids: *Systemic* – the use of systemic corticosteroids has been reported to result in near-resolution of symptoms within a week of treatment. Short courses can be used for acute exacerbations, but regular use is undesirable and not recommended, in view of the extensive adverse effect profile and relative mild symptomatology in most EoE patients.

Topical – swallowed inhaled corticosteroids, in the form of fluticasone, 44–110 micrograms/puff, 2–4 puffs twice daily has been reported to be well tolerated in children, with improved clinical, endoscopic and histological parameters, minimal systemic absorption and only occasional oesophageal candidiasis. Similarly, in adults, clinical, endoscopic and histological improvements were seen with the use of fluticasone, 220 μg, 2–4 puffs twice daily for 1 month; this too is only occasionally complicated by asymptomatic oesophageal candidiasis.

Likewise, oral viscous budesonide has also been shown to be effective therapy in randomized trials in children, mixed in with a sugar substitute (budesonide 1 mg/2 ml, with 5 g sucralose). In adolescents and adults, Straumann et al. demonstrated that nebulized budesonide also produces a response, although viscous budesonide is likely to be a more effective topical formulation.[5] More recently, an oro-dispersible formulation of budesonide has been shown to have prolonged adhesion to the oesophageal mucosa than the inhaled forms, which was associated with improved clinicohistological response rates of 57.6% after 6 weeks of treatment, significantly higher than placebo.

Long-term use of oro-dispersible budesonide, with the co-prescription of PPIs if GORD is also present, is likely to be needed, at the lowest dose that will maintain remission, as symptoms tend to recur on discontinuation of treatment.

Experimental drugs: other treatment options for long-term management such as montelukast and sodium cromoglicate, used in asthma, have not been shown to be particularly effective in EoE.

Immunomodulators such as azathioprine and 6-mercaptopurine, which have a corticosteroid-sparing effect, are used in eosinophilic gastroenteritis and may have a role in EoE, although this has not yet been objectively evaluated.

Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, approved for the treatment of atopic dermatitis and asthma, has also shown encouraging results in phase II studies in patients with EoE. Improvement occurred in both symptoms of dysphagia and histological activity scores at 12 weeks of treatment, but more data on long-term efficacy are required before dupilumab can enter clinical practice.

Endoscopic treatment

Oesophageal dilatation is indicated in the presence of established strictures with symptomatic food impaction. Concerns regarding potential oesophageal perforation in the presence of the fragile oesophageal mucosa have triggered caution in terms of this intervention. Although the risk of perforation remains low (<1%), the recommendation is that medical or dietary therapy is instituted before dilatation is undertaken, to reduce the risk. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 45-year-old man presented for review after an endoscopy. Six weeks previously, he had presented with food bolus obstruction requiring emergency endoscopy for removal. He had had no previous food bolus obstruction but had had intermittent feelings of food getting stuck at the back of the throat, although this was not limiting. There was no heartburn.

Investigation

- Endoscopy appearances were normal
- Biopsies showed eosinophilia at 25 eosinophils per high-power field

What is the most appropriate management?

A. Symptoms are mild, so a watch-and-wait approach could suffice
B. Undertake a trial of proton pump inhibitor therapy, with repeat endoscopy at 3 months
C. Give a trial of an elemental diet, with repeat endoscopy at 8 weeks
D. Reassure and explain this is likely to be a food allergy that might benefit from avoiding milk and gluten
E. Proceed to pH manometry to investigate for dysmotility

Question 2

A 48-year-old man presented with worsening symptoms of eosinophilic oesophagitis, diagnosed on endoscopy 4 months earlier. These had initially been controlled using once-daily omeprazole but then recurred and persisted despite increasing PPI to twice daily.

What is the most appropriate next action?

A Repeat endoscopy
B Refer to dietitian for exclusion diet
C Prescribe course of systemic corticosteroids
D Perform pH monitoring
E Continue omeprazole for longer

Question 3

A 55-year-old patient re-presented, 5 years after a diagnosis of eosinophilic oesophagitis, with worsening dysphagia. He was now finding difficulty eating steak and toast. Weight was steady. He was on omeprazole 20 mg 12-hourly, and had previously found exclusion of seafood helpful in alleviating symptoms. He was unkeen to have a repeat endoscopy and wondered if steroids, which he had previously found beneficial, should be tried.

What is the next best action?

A. Dietetic review for trial of an elemental diet
B. Repeat trial of topical corticosteroids
C. Repeat endoscopy
D. Barium swallow and pH manometry
E. Increase Omeprazole to 40 mg 12-hourly