ME Levin, MB ChB, FCPaed, Dip Allergy, MMed (Paed), PhD
Asthma and Allergy Clinic, Red Cross War Memorial Children’s Hospital, School of Child and Adolescent Health, University of Cape Town, Rondebosch, South Africa

ABSTRACT

Eosinophilic oesophagitis (EO) is a mixed IgE-mediated and non-IgE (cell)-mediated food allergy. Adults present predominantly with dysphagia and food impaction. Children present predominantly with vomiting, gastro-oesophageal reflux that does not respond to medical treatment, food refusal and failure to thrive. The hallmark of the condition is oesophageal biopsy showing >15 eosinophils per high power field and exclusion of other similar disorders especially gastro-oesophageal reflux disease (GORD). Skin-prick and patch testing are useful to identify food allergens responsible for triggering EO. Dietary manipulation has the best long-term results but almost equivalent results can be achieved with topical steroid administration or systemic steroids. There is urgent need for study of EO in South Africa, assessing the prevalence in high-risk groups, the role of food allergies and the success of alternative methods of treatment.

INTRODUCTION

True food allergy is an immune-mediated adverse reaction to food. Food allergy is usually divided into IgE-mediated and non-IgE-mediated food allergy. IgE-mediated food allergy is more common, has well-defined pathological mechanisms and has a rapid onset and thus a clear link between exposure and symptoms. This, and the ready availability of validated tests results in a relatively easy diagnosis. Non-IgE-mediated food allergy, on the other hand, may have unclear mechanisms of initiation of response and has a delayed onset of symptoms. There may therefore be no clear link between exposure to the offending food and the adverse reaction. In addition, tests are not well validated for non-IgE food allergy and it is therefore far harder to diagnose.

Recent literature classifies the mechanisms of initiation of the symptoms of food allergy into (i) IgE-mediated, (ii) mixed IgE-mediated and non-IgE-mediated (cell-mediated) food allergy and (iii) non-IgE, entirely cell-mediated food allergy. Table I lists disorders in these categories. Eosinophilic oesophagitis (EO), an isolated eosinophilic inflammation of the oesophagus, is the most common of the eosinophilic gastrointestinal disorders. The incidence of these diseases has increased over recent years in both adults and children, and this seems to be a real increase rather than an increase in diagnosis due to increased awareness of the disorders.

Older children and adults may present with food impaction whereas children present with symptoms of gastro-oesophageal reflux that does not respond to anti-reflux treatment. In addition they may have feeding difficulties, food refusal and failure to thrive. Patients with EO have a higher risk of associated allergic disorders such as asthma and atopic dermatitis. The mechanism of EO is not clearly elucidated but both IgE- and non-IgE-mediated food allergy play a role. Foods such as cow’s milk, hen’s egg, soya and wheat are commonly implicated. A number of reports suggest familial clustering and preliminary evidence has emerged for a role of the gene encoding the eosinophil-specific chemo-attractant eotaxin-3.

<table>
<thead>
<tr>
<th>Table I. Food allergy disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE-mediated</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Generalised</td>
</tr>
<tr>
<td><strong>Mixed IgE- and cell-mediated</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td><strong>Cell-mediated</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
</tbody>
</table>

Correspondence: Dr M Levin, luvuyo@mweb.co.za

CASE VIGNETTE

HM presented to the asthma and allergy clinic at age 1½ years. Presenting problems were eczema, immediate food allergies and failure to thrive. Eczema had an early onset at the age of weaning, typical of that related to food allergies. She had experienced itching and flaring with ingestion of peanuts. She had been breastfed and her mother ate peanuts every day. Specific IgE to peanuts was 1.6 kU/l which is raised but not above the range at which it can be held to be strongly predictive of IgE-mediated food allergy (14 kU/l). She had experienced urticarial skin rashes within an hour of ingestion of milk. Specific IgE to milk was 24 kU/l and skin test was 4 mm to milk extract and 13 mm to fresh milk, both strongly suggestive of IgE-mediated food allergy (>5 kU/l and 6 mm respectively). She had never ingested egg, but a specific IgE to hen’s egg was 6.1 kU/l and skin testing was 13 mm to fresh egg white, confirming IgE-mediated food allergy (>2 kU/l and 5 mm respectively). She was on a diet excluding milk, egg and peanuts under the supervision of a dietician.
Feeding was a significant problem. The mother was struggling to get her to drink her soya milk. She was refusing to eat foods and when she did ingest solids she took a very long time to eat. She had occasional vomiting. Stools were normal.

At this stage the differential diagnosis was gastro-oesophageal reflux disease (GORD) and EO with resulting malnutrition and rickets. The following special investigations were performed. Blood chemistry tests showed normal electrolytes, calcium, magnesium and phosphate and a raised alkaline phosphatase level of 1430 (upper limit of normal up to 140 in children) with normal liver function tests, suggestive of early rickets. She had a white cell count of 11.3 with an eosinophil count of between 4% and 8% on repeated samples (normal range 0-4%).

A barium swallow revealed reflux to the thoracic inlet. An upper gastrointestinal endoscopy was normal macroscopically and biopsy of the oesophagus and stomach was performed. Oesophageal biopsy showed a peak concentration of 35 eosinophils per high power field (hpf). Figure 1 shows another oesophageal biopsy.

**EOSINOPHILIC OESOPHAGITIS**

Eosinophilic oesophagitis (EO) has been described in patients from all ethnic backgrounds in studies originating in all continents apart from Africa. There is no clear ethnic, racial or socioeconomic predilection. EO does have a male predilection and has been reported in paediatric and adult populations. In children, the mean age of presentation is 7-10 years and in adults 30-40 years, but these data may reflect the age at which the diagnosis is most commonly made as a result of patient complaints raising the possibility, rather than reflecting the true peak age of the condition. EO may occur in very young infants and toddlers. Adults often complain of dysphagia, food impaction, reflux symptoms, chest pain, abdominal pain and vomiting and 25-50% have concomitant allergies. Children experience abdominal pain, vomiting, gastro-oesophageal reflux that does not respond to medical treatment, and failure to thrive. Food refusal or intolerance is the presenting complaint in children too young to complain of symptoms. Other concomitant allergic diseases are present in 50-80%.

The differential diagnosis of oesophageal eosinophilia includes GORD, food allergy, candida oesophagitis, eosinophilic gastroenteritis, inflammatory bowel disease, coeliac disease and parasitic infection. Rarer causes include connective tissue disease, drug allergy, hyper-eosinophilic syndrome, autoimmune enteropathy, viral oesophagitis (herpes or cytomegalovirus) and Churg-Strauss syndrome.

**Endoscopy**

Endoscopic appearance may be grossly abnormal, have subtle abnormalities or be macroscopically normal. Common features include concentric rings and linear furrows. When these coexist a cobblestoned appearance is produced. White plaques of eosinophilic infiltration may be mistaken macroscopically for candidal infection. Aggregates of eosinophils may produce visible micro-abscesses. Normal endoscopy does not exclude EO, thus all endoscopic evaluation of EO must be followed up with biopsies even when endoscopy is macroscopically normal.

**Biopsies**

The hallmark of EO is eosinophilic infiltration of the squamous epithelium. There is no consensus as to what quantity of eosinophils is pathognomonic of the condition with some studies using as few as 5 per hpf and others up to 30 per hpf, but a recent consensus statement uses 15 as a cut-off level. Other minor features on biopsy may include basal zone hyperplasia, increased papillary size, intercellular oedema, lamina propria fibrosis and layering of eosinophils resulting in aggregates or micro-abscesses.

GORD can also result in eosinophilic infiltration but at a lower level of up to 10 per hpf. In addition the distribution of infiltration in the oesophagus will be predominantly distal, starting from the gastro-oesophageal junction spreading proximally with increased severity of disease, whereas in EO the histological abnormalities typically involve longer lengths of the oesophagus, affect the proximal equally, or even more, than the distal oesophagus, and the pathological findings are often patchy in distribution.

For this reason it is highly recommended to take biopsy specimens from the distal and proximal oesophagus to assess the distribution of pathology as well as from macroscopically normal and abnormal areas. Taking 1 biopsy specimen has a sensitivity of 55% in contrast to a sensitivity of 100% from 5 specimens. Biopsy specimens should also be taken from the duodenum and stomach to rule out other diseases such as eosinophilic gastroenteritis and inflammatory bowel disease.

The concept of a cut-off level for eosinophil count per hpf is therefore an oversimplification as the number of eosinophils varies according to the site of the biopsy. In addition there may be many patients whose symptoms are typical of EO, who respond to treatment for EO rather than GORD and who therefore should be considered as fulfilling the case definition for EO despite not qualifying according to the degree of eosinophilic infiltration on biopsy. Bigger et al. assessed the accuracy of histopathological diagnosis in distinguishing EO from GORD in children by repeating the assessment of biopsy specimens in 31 patients with EO, GORD or neither, with the pathologist blinded as to the clinical presentation and response to therapy. Diagnostic concurrence between the masked pathological diagnosis and the established clinicopathological diagnosis was 64% in children with EO, 70% in children with GORD, and 100% in children with neither.

---

**Fig. 1. Oesophageal biopsy of a different patient showing squamous epithelium (light pink) interspersed with many eosinophils (granular red cytoplasm and bilobed blue nuclei). (Material provided by Dr Komala Pillay, Department of Histopathology, National Health Laboratory Services and University of Cape Town).**
The distinction between EO and GORD can therefore not be reliably made on histopathological evidence alone. All biopsy specimens should be interpreted in the light of the clinical findings on history and examination and patients with typical findings whose biopsies do not reveal >15 eosinophils per hpf may also benefit from a trial of therapy. In addition biopsy specimens revealing isolated oesophageal eosinophilia while the patient is on an adequate dose of acid suppression is virtually pathognomonic of EO.

**Laboratory features**

The sensitivity and specificity of laboratory tests are not known. Peripheral eosinophilia is reported to be present in 10-50% of adults and 20-100% of children. This and raised total IgE may indicate background atopic predisposition and not be specific or sensitive for EO. Antigen specific IgE may be raised due to specific immediate food allergies or due to involvement of food as a trigger for EO, but no positive or negative predictive values for any foods have been elucidated. Skin-prick test and patch tests are commonly positive in subjects with EO.

**Skin-prick testing**

Approximately two-thirds of all paediatric patients have positive skin tests to at least one food. The number of foods tested in studies typically ranges from an average of 13 to a maximum of 42 foods. In adults, the presence of positive skin tests to foods is uncommon unless there is a history of immediate food hypersensitivity to a particular food. The most common foods reported to be positive by skin test include peanuts, eggs, soya, cow’s milk, wheat, beans, rye and beef.

**Patch testing**

Patch testing to foods has primarily been studied in eczema. Spergel’s group identified food allergens in 26 children with EO using skin-prick and patch testing. Skin-prick testing identified 68 suspect foods in 19 children and patch testing 67 suspect foods in 21 patients. Although overlap existed between foods identified in individual patients, skin-prick in combination with patch testing revealed more suspect foods (average 2.7) per patient. Patch testing is poorly standardised and the protocol used by Spergel et al. for patch testing differs from that of other investigators. Notably, larger (12 mm) Finn chambers are used and foods are prepared where available in dry powder form (milk, soy, potato, rice, oat, wheat, corn, egg, barley and rye) or jarred baby foods. This may result in a higher concentration of food allergen in the chamber, possibly accounting for the higher rate of positive foods identified by patch testing in their studies compared with results of other investigators.

**Treatment**

Gastric acid is not thought to be the primary cause of EO. Patients with oesophageal eosinophilia whose symptoms resolve with acid inhibition have GORD, not EO. Despite this, acid suppression may have a potential role in patients with EO. Lack of a response to adequate acid suppression with symptoms and isolated oesophageal eosinophilia is diagnostic of EO. In addition acid suppression may be considered as cotherapy to relieve symptoms of GORD that may occur secondary to established EO. Definitive treatment relies on avoidance of food triggers either with specific targeted food elimination or institution of an elemental diet, as well as immune modulation with oral steroids, topical steroids or leukotriene-receptor antagonists.

**Dietary modification**

Controversy exists over the choice of a targeted diet that eliminates suspected foodstuffs or a totally elemental diet. Because EO is a mixed IgE- and cell-mediated process, history, skin tests and allergen-specific IgE tests alone are insufficient to guide an elimination diet. Patch tests may give additional information about cell-mediated allergic food hypersensitivity.

**Targeted food avoidance**

Spergel et al.’s use of skin and patch tests to identify foods suspected of triggering EO allowed targeted food avoidance to be instituted in 18 patients experiencing complete resolution and 6 partial resolution. The most common foods were milk, egg, soya, chicken and wheat. A follow-up study identified 146 children with EO and eliminated foods based on skin and patch tests (including 14% who required elemental diets because of multiple positive food tests). Seventy-seven per cent of subjects in this study had resolution on biopsy and in a 10-year review a 98% clinical response rate to dietary restriction was observed.

**Elemental diet**

Kagalwalla et al. compared a standard 6-foods avoidance diet with elemental diet in 50 children with EO. Seventy-four per cent of children on the specific avoidance diet had symptom resolution and histological response, compared with 88% of the children on the elemental diet. The post-treatment eosinophil counts were much lower in the extensively hydrolysed group (3.7 per hpf vs. 13.6 per hpf), but the initial eosinophil count in this group was also somewhat lower at 58.8 per hpf vs. 30.2 per hpf. Kelly et al. placed 10 children on elemental (amino acid) formula for a minimum of 6 weeks with partial or complete resolution in all 10. On follow-up biopsies, median eosinophil counts decreased markedly. All children relapsed on open food challenge. Markowitz et al. used elemental formula on 51 children. Forty-nine had symptom resolution and reduced eosinophil counts on repeat biopsies. The median time to improvement was 8.5 days.

These data suggest that elemental diet may be superior, but that specific food avoidance guided by skin-prick and patch tests or specific ‘few-foods’ diets may be alternative options. Failure to respond to an elemental diet does not exclude food antigens as triggers, but establishes, at a minimum, that something besides food also triggers eosinophilic infiltration. The link between food allergens and EO is not clear in adults because of limited data. An abstract by Gonsalves reported a 50% response rate in adults to a 6-foods elimination diet and near 100% resolution on an elemental diet.

In children elemental formula may be necessary as a supplement to a few-food restricted diet to maintain nutritional adequacy. Because of poor palatability the formula may need to be administered via a nasogastric tube or even a gastrostomy. In selecting a diet, the patient’s lifestyle and family resources need to be considered and consultation with a dietician is necessary to aid in adherence to the diet and to ensure its nutritional adequacy.

**Topical steroids**

Swallowed steroids are used for the treatment of EO. In this modality of treatment inhaled steroids are given, usually by metered dose inhaler without a spacer, while the patient is not inhaling. The patient is instructed to avoid food or drink for half-an-hour after administration. Fluticasone is the most well-studied formulation in-
Fig. 2. Treatment flow algorithm. Reprinted from Putnam PE,23 with permission from Elsevier, Dr Putnam and the Cincinnati Center for Eosinophilic Disorders. (PPI – proton pump inhibitor).

including a randomised double-blinded placebo-controlled study.24

Arora et al.21 treated 21 adult patients with swallowed fluticasone for 6 weeks. All patients had complete symptomatic relief for at least 4 months. The only side-effect was dry mouth, with no oral candidiasis reported. Oral candidiasis has been reported in a small minority of patients.5 Remedios et al.25 treated 19 adult patients with dysphagia and food bolus obstruction with swallowed fluticasone propionate. All had symptom resolution and a histological response.

Budesonide may also be used26 and recently orally administered viscous budesonide27 (nebuliser solution mixed with sucralose) has been used. In 20 children treated with viscous budesonide,27 there were 16 responders, 1 partial responder, and 3 non-responders. Morning cortisol levels were within normal limits.

Oral steroids

The use of oral steroids was first documented in children by Liacoras et al.26 After 4 weeks of steroid therapy, 19 of 20 children responded and 13 had complete symptom resolution. Steroids and anti-reflux medications, such as proton pump inhibitors, were then tapered and withdrawn after 6 weeks. The average time to improvement was 8 days.

A prospective randomised trial comparing oral steroids to topical fluticasone29 showed excellent effectiveness of both modalities, with all of 32 and 35 of 36 patients being free of presenting symptoms at week 4. Histological improvement was seen in 30 of 32 patients on oral steroids and 34 of 36 patients taking topical fluticasone, with a greater degree of histological improvement in the group receiving oral steroids. Systemic adverse effects were noted in 40% of the subjects receiving oral steroids, whereas oesophageal candidal overgrowth was seen in 15% of the subjects receiving topical fluticasone. There was no statistical difference between the groups in terms of symptom resolution, relapse rates, or time to relapse. Symptoms relapse was common to both groups upon therapy discontinuation, highlighting the need for maintenance treatment protocols.

Leukotriene receptor antagonists

Schwartz et al.30 first documented the use of montelukast as a steroid-sparing therapy in a patient with recurrent relapsing EO, but some subsequent studies have been unsuccessful.31 Only 1 study has been published on a small series of 8 adult patients. Attwood et al.32 used higher than usual doses of montelukast starting at 10 mg orally once daily and titrated if necessary up to 100 mg daily. All patients had symptomatic improvement, with only 2 having residual discomfort. Once symptoms were relieved, the dose was reduced to 20-40 mg/day to maintain symptom resolution. Side-effects included nausea and myalgias and treatment did not change the density of eosinophils on repeat biopsy.

Comparison between strategies

A prospective trial has compared targeted dietary restriction and swallowed fluticasone in children.22 Dietary restriction did not induce clinical improvement in any patients, whereas all children who completed treatment with fluticasone had resolution of symptoms. Repeat biopsy in the fluticasone group showed a significant reduction in eosinophils.
Treatment flow algorithm

The algorithm (Fig. 2) describes the scheme followed for management of children who have EO at the Cincinnati Center for Eosinophilic Disorders. Many centres perform follow-up scope and repeat biopsies as the definitive method for assessing response to treatment, but there have been few studies to guide the biopsy protocol or to clarify baseline fluctuation in the density of eosinophils with time. Endoscopy and biopsy may also be associated with the potential for complications. If repeat endoscopy with biopsy is planned it should be performed no less than 4 weeks after the last therapeutic intervention. Repeat biopsies may not be practical in all settings because of cost constraints and patient refusal. Repeat biopsies may be better indicated after a change in symptoms or a change in therapy, rather than on a routine basis.

CASE VIGNETTE CONTINUED

A short course of oral prednisone (2 mg/kg daily) and maintenance swallowed fluticasone (125 µg twice daily) was commenced. In addition montelukast was added at a dose of 5 mg daily. Elemental diet was instituted with high protein and high calorie content. On follow up after 2 weeks symptomatic improvement was noted with less vomiting and better appetite. The patient was weaned off oral steroids. Fruit and vegetables were reintroduced into the diet and were eaten more easily and better tolerated. After 3 months growth had improved and eczema had improved substantially. Patch tests (Fig. 3) were performed which revealed additional suspect foods that had not been identified with specific IgE and skin-prick testing. This has allowed a targeted elimination diet and the re-introduction of other solid food.

CONCLUSION

Although EO is considered rare in South Africa, no large studies have been performed looking for EO in high-risk groups, such as children with reflux persisting despite medical management, children with reflux and other atopic diseases or failure to thrive, or adults and children with swallowing difficulties. A high index of suspicion must exist for investigating for EO in these subgroups. A consensus statement defines EO as being present where there are symptoms compatible with EO, >15 eosinophils per hpf and exclusion of other similar disorders especially GORD. Biopsy is the most important diagnostic modality and it is critical to take multiple biopsy specimens from different sites, both normal and abnormal in macroscopic appearance. It is highly recommended to perform biopsies after instituting acid suppression treatment to exclude the possibility of confounding biopsy results due to reflux. If expertise is present (or can be developed) in patch testing, this is recommended to broaden the range of possible dietary treatment strategies or at the very least to help guide the re-introduction of foods after the institution of an elemental diet. Dietary manipulation (with the help of a registered dietician) has the best long-term results but almost equivalent results can be achieved with topical steroid administration or systemic steroids. In either case a course of systemic steroids can be used at initiation of treatment to achieve rapid control. Treatment options should be guided by the wishes of the patient and family in order to achieve better adherence to the chosen strategy. Repeat biopsies are the gold standard for assessing response to treatment. Should one treatment option fail, another may be tried. There is urgent need for a study of EO in South Africa assessing the prevalence in high-risk groups, the role of food allergies and the success of alternative methods of treatment.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES


