

ANNOTATION

Eosinophilic oesophagitis: A paediatric updateKatrina J Allen^{1,2,3} and Ralf G Heine^{1,2,3}¹Department of Allergy, Gastroenterology and Immunology, Royal Children's Hospital, ²Department of Paediatrics, University of Melbourne and ³Centre of Food and Allergy Research, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia

Abstract: Eosinophilic oesophagitis (EoE) is a key differential for gastro-oesophageal reflux (GOR) in children. It can be difficult for clinicians to decide which patients need referral for the assessment of EoE, which can only be confirmed by histological analysis of endoscopic biopsies. Recent guidelines recommend that EoE can only be diagnosed following the exclusion of GOR through empiric treatment with proton pump inhibitors prior to endoscopy. Some aspects of history are strongly suggestive of EoE: red flags for referral include poor weight gain in the context of reflux symptoms, choking during eating or food impaction. Therapeutic options include dietary allergen elimination or swallowed aerosolised corticosteroids. Other novel therapies have failed to demonstrate benefit, but novel diagnostic biomarkers to enable non-invasive disease ascertainment and follow-up show some promise.

Key words: corticosteroids; elimination diet; eosinophil; gastro-oesophageal reflux disease; proton-pump inhibitor.

Eosinophilic oesophagitis is an immune-mediated disorder with eosinophilic inflammation of the oesophagus, in conjunction with symptoms attributable to oesophageal dysfunction.¹ Histological changes are usually pan-oesophageal but can be patchy. The diagnosis can only be made by endoscopy with oesophageal biopsies, and is defined as more than 15 eosinophils per high powered field (HPF) at 400 times magnification by light microscopy. Although eosinophilic oesophagitis was only described relatively recently, most experts agree that both the prevalence and ascertainment appear to have increased over the last 20–30 years, for as yet unknown reasons.² Because the macroscopic endoscopic features (which include longitudinal furrowing,

white plaques (eosinophilic microabscesses), concentric rings ('trachealisation') and strictures) are often striking, they are unlikely to be missed, and so it is believed that the increase is over and above that of increased ascertainment. Moreover, paediatric endoscopists, unlike their adult counterparts, have over the past decades routinely obtained oesophageal biopsies during gastroscopy, irrespective of whether macroscopic findings were present or not.

One of the most difficult aspects in the management of eosinophilic oesophagitis is deciding which child should be referred for endoscopic assessment. As yet, no study has systematically and prospectively investigated which clinical features are predictive of eosinophilic oesophagitis, although it has been reported in many retrospective studies that there is a male predominance and co-association with other allergic diseases, such as eczema and immunoglobulin E-mediated food allergy.³ Although eosinophilic oesophagitis is a condition that should be considered in children and infants who present with upper gastrointestinal signs and symptoms, it can be difficult for general paediatricians and practitioners to decide when referral to a gastroenterologist is required to either confirm or rule out this condition, particularly since non-specific symptoms such as regurgitation and abdominal pain are so common in the general community. To date, there is little evidence to help inform this decision.

Age appears to have a significant impact on how eosinophilic oesophagitis presents. In infancy, irritability, feeding refusal and failure to thrive are classic presenting features, while dysphagia and food bolus impaction are the most characteristic symptoms in school-aged children and young adults.¹ 'Red flags' for urgent investigation include persistent swallowing difficulties, food bolus impaction or reflux-like symptoms that have not responded to standard antireflux therapy. Some useful screening questions include: 'Does the child take a long time to eat?'; 'Do they use a lot of water to wash down food?'; 'Do they avoid chunky food such as meat or bread?'; or 'Does food stick or does the child choke when eating?' The diagnosis of eosinophilic

Key Points

- 1 Eosinophilic oesophagitis is an immune-mediated condition with eosinophilic inflammation in the oesophagus, in association with symptoms attributable to oesophageal dysfunction.
- 2 Identification of eosinophilic oesophagitis by paediatricians requires a high index of suspicion, and better non-invasive clinical indicators are needed.
- 3 The treatment of eosinophilic oesophagitis involves either elimination diets, swallowed corticosteroid aerosols or slurries, and in some patients cautious endoscopic dilatation of oesophageal strictures.

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oesophagitis requires a high index of clinical suspicion in order to undertake an endoscopy for histological confirmation.

There is considerable diagnostic overlap with gastro-oesophageal reflux disease, and recently, a second clinical condition has been distinguished from eosinophilic oesophagitis: proton pump inhibitor-responsive oesophageal eosinophilia (PPI-ROE).⁴ In PPI-ROE, eosinophilia resolves after high-dose treatment with omeprazole or a similar PPI. This diagnostic step is important in order to delineate PPI-ROE from eosinophilic oesophagitis, which would be treated differently. If tissue eosinophilia has resolved on repeat biopsy after an 8-week course of omeprazole, a diagnosis of PPI-ROE is assumed, and the patient is treated with PPI on an ongoing basis.^{3,5} The exact mechanisms by which PPIs reduce mucosal eosinophil counts are not clear. Apart from acid suppression, a direct anti-inflammatory effect is possible.

There is currently no consensus on the exact diagnostic procedure. For example, the number and sites of oesophageal biopsies are not standardised. Generally, three to four biopsies both from the upper and lower oesophagus are required. Given the patchy nature of inflammatory changes, a higher numbers of biopsies will improve the diagnostic accuracy of a procedure. This is particularly important when the mucosal changes are not pathognomonic and 'random' biopsies are obtained. While endoscopic findings often stand out, an apparently normal appearance does not rule out eosinophilic oesophagitis, and multiple biopsies should be routinely obtained.^{1,5} The interpretation of histological findings may also be somewhat subjective, and methods for the quantification of eosinophil numbers per HPF or surface area are not standardised. More objective diagnostic methods or markers of disease activity are needed with new research supporting the potential to develop a molecular diagnostic approach.⁶

Recently, the American Academy of Allergy, Asthma, and Immunology recommended that dietary elimination therapy (removal of common food allergens) should be trialled in all patients with eosinophilic oesophagitis, including adults. Importantly, the response to swallowed corticosteroid aerosols has been shown to be worse in patients who also have underlying food allergies.⁷ This fact provides further incentive to trial dietary interventions before resorting to topical steroid treatment. However, elimination diets can often be complex to follow and are associated with poor long-term compliance. This is due to the low palatability of an elemental or highly restricted diet. In our experience, young teenagers and adults are often not motivated to go through the rigorous process of long-term dietary elimination and repeated endoscopic re-examination to assess the effect of the diet on symptoms. In these patients, many physicians choose corticosteroid treatment as the initial therapy.

In older children, targeted elimination diets (based on skin prick testing) have been used in treatment. However, a recent systematic review found that targeted elimination diets had a similar efficacy compared with empirical diets outlined below.⁸ As long-term use of elemental diets is impractical and skin prick testing availability for targeted elimination can be limited because of long allergy waiting lists, many gastroenterologists and even allergists have now moved to the use of empirical elimination diets of the most commonly implicated food allergens in children as first-line therapy.⁸ These include the six-food elimination diet (removal of cows milk, soy, wheat, egg,

nuts and seafood)⁹ and more recently the four-food elimination diet (cows milk, soy, wheat and egg).¹⁰ The latter limits the number of endoscopies required when liberation of the diet is attempted. For those in whom either the diet is refused for life-style reasons or has been unsuccessfully attempted, administration of swallowed corticosteroid aerosols or slurries is a well-tolerated and efficacious option.^{7,11} This can take the form of fluticasone inhalers or budesonide respules – the latter made into a slurry with sucralose powder (Splenda) to improve delivery by increasing exposure of drug coating of the oesophagus. In both cases, the liver provides an ample first pass effect, and systemic absorption of steroids is believed to be low. Other steroid-sparing and novel therapeutics have been investigated (including anti-interleukin 5), but trials have been disappointing and there are no other therapies other than systemic steroids that are currently recommended.¹⁰

Debate rages as to how often to monitor children with eosinophilic oesophagitis, and whether endoscopes should be undertaken after each eliminated food is introduced, although there is consensus that an initial endoscopic follow-up is required after initiation of therapy to ensure mucosal remission has been attained.¹² More recently, some centres have moved to less aggressive use of endoscopic follow-up and once remission has been established, liberate diet and follow symptom recurrence to guide whether a new introduction of food has resulted in a flare. It should be noted that seasonal fluctuation in disease flares related to pollen count has been noted for some patient and therefore consideration of timing of endoscopy should attempt to control for this.¹⁰

Currently, there is little information available to inform how often these children should be followed or indeed whether asymptomatic eosinophilic oesophagitis requires treatment. The major long-term complication of concern is oesophageal stricture, which can be difficult to treat because of the high risk of perforation. Some series suggests stricture occurs in up to 10% of cases but better longitudinal data are required, and some evidence suggests that structuring disease may represent a more severely progressing disease.¹ To date, there have been no prospective longitudinal studies – either treated or untreated – and therefore neither the efficacy of long-term treatment nor the natural history of disease progression is fully understood. In general, eosinophilic oesophagitis often appears to follow a chronic or relapsing course, and complete resolution of the disease is thought to be uncommon. One retrospective analysis has suggested that even the persistence of small numbers of oesophageal eosinophils >5/HPF may have prognostic significance, although this remains controversial. A handful of observational studies have found a progression of symptoms in untreated disease, but these studies have been limited by biased follow-up of those who remain symptomatic.

In conclusion, there is significant research required to better understand both the natural history and response to treatment for this disease. Referral guidelines would be greatly enhanced by the development of reliable, non-invasive biomarkers that could be used in the diagnosis, as well as monitoring of therapy, and thus minimise the requirement for invasive endoscopies. Studies currently underway are likely to herald new therapeutic regimens and improved clinical outcomes for patients with eosinophilic oesophagitis.

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