The Journal of Laryngology & Otology (2015), ***129***, *1156–1166.*

doi:10.1017/S0022215115002777

REVIEW ARTICLE

Eosinophilic oesophagitis: a systematic review for otolaryngologists

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Abstract

Background: Eosinophilic oesophagitis is a chronic, immune/antigen-mediated oesophageal disease, only recently, but increasingly, recognised in the world literature. It is diagnosed and managed primarily by medical gastroenterologists and allergy specialists, and is a distinct disease entity, affecting both children and adults. Few studies have been published in otolaryngology journals, although otolaryngologists will encounter patients with undiagnosed eosinophilic oesophagitis. Patients may present with dysphagia, bolus obstruction or with other ENT disorders, such as atopic rhinitis, reflecting the underlying systemic allergic disorder.

Objective: This paper systematically reviews the evidence base published on the epidemiology, clinical presentation, diagnosis, treatment and prognosis of eosinophilic oesophagitis, particularly as it relates to otolaryngology practice.

Key words: Eosinophilic Esophagitis; Esophagitis; Dysphagia; Gastro-Esophageal Reflux; Allergy; Otolaryngology; Review, Systematic; Randomized Controlled Trials as Topic; Meta-Analysis as Topic

Introduction

Eosinophilic oesophagitis is a chronic, immune/antigen-mediated clinicopathological condition, only recently considered an important cause of upper gastrointestinal morbidity in adults and children.[1–3] Before the 1990s, the abnormal presence of oesophageal intraepithelial eosinophils was simply attributed to reflux.[4] The first case series in adults appeared in 1993,[5] and in children in 1995.[6] Increasing incidence and prevalence was reported in US[7] and European[8] population-based studies, and in Asian[9] and Australasian[10] cohort analyses. Whilst initially attributed to rising endoscopy rates,[11] a 20-year, prospective, Swiss population-based study confirmed a true increase.[8] Reported prevalence varies widely,[12] estimated in adults at 56.7 cases per 100 000 population.[13] In children, a meta-analysis reported an incidence of 0.7–10 cases per 100 000 population, and prevalence of 0.2–43 cases per 100 000 population.[14]

In 2007, a multidisciplinary task force of 31 physicians defined diagnostic criteria and recommendations for the evaluation and treatment of suspected eosinophilic oesophagitis. Their systematic literature review and expert opinion achieved a consensus.[1] They recognised that eosinophilic oesophagitis manifests mainly in the child with vomiting, a failure to gain weight or a feeding disorder, but in older patients it manifests with abdominal pain, dysphagia and food impaction. It is strongly associated with atopy, with an estimated coincidence of 50–80 per cent, suggesting eosinophilic oesophagitis is a manifestation of an allergic response.[15,16] An updated consensus statement in 2011 added recommendations for diagnostics, genetics, allergy testing and therapeutics.[2] The 2013 American College of Gastroenterology clinical guidelines provide an additional evidence-based approach to diagnostics.[3]

Despite mucosal inflammation limited to the oesophagus, eosinophilic oesophagitis appears to be an immune-mediated aerodigestive tract disorder that is also associated with ENT symptoms. An otolaryngologists' review indicated that 10–15 per cent of paediatric patients present to ENT prior to gastroenterology referral, and the disease remains under-recognised by our specialty.[17] Furthermore, eosinophilic oesophagitis histological changes compare to those seen in the airway mucosa in chronic rhinosinusitis and asthma.[18] The spectrum of paediatric eosinophilic oesophagitis includes upper airway disease, and eosinophilic oesophagitis should be considered in patients with atopy and unexplained upper airway findings that are refractory to reflux treatment.[18] A cohort study reported otolaryngological surgery in nearly one-third of children with eosinophilic oesophagitis, often prior to this diagnosis.[19] There is an increased prevalence of grommet insertion, and, in one series,

Accepted for publication 24 July 2015 First published online 15 October 2015

five patients with eosinophilic oesophagitis required airway reconstruction for inflammatory stenosis.[19] However, most otolaryngologists are less aware of eosinophilic oesophagitis than of gastroesophageal reflux disease.[20] Care is multidisciplinary, involving gastroenterologists, otolaryngologists, allergists, pathologists and dieticians. We present an evidence-based systematic literature review, particularly relevant to the otolaryngologist.

Search strategy

We searched Medline, Embase and Cochrane Library databases, from their creation to 30th June 2015, using the following search term combinations: (1) 'eosinophilic esophagitis', (2) 'eosinophilic oesophagitis', (3) 1 or 2 (i.e. 'eosinophilic esophagitis' or 'eosinophilic oesophagitis'), and 'otolaryngology', (4) 1 or 2, and 'review', (5) 1 or 2, and 'systematic review', (6) 1 or 2, and 'meta-analysis', and (7) 1 or 2, and 'controlled trial'.

We sought high-quality, ideally prospective, clinical studies, reviews or laboratory work relevant to the diagnosis, pathophysiology and management of eosinophilic oesophagitis, especially those pertaining to ENT. Abstracts, identified from a review of article titles, were evaluated for inclusion by two authors (MB and LF) working independently, with consensus if opinions differed. Two authors (ND and LF) reviewed and revised the systematic process. Papers were chosen if the abstracts suggested systematic reviews or meta-analyses, prospective controlled studies, original basic science findings from laboratory studies, or publication in the otolaryngology literature. Abstracts were excluded if they suggested isolated case reports or presented no novelty; in the interests of brevity, these are not tabled. Non-English language papers were excluded, unless they significantly contributed to the evidence base.

Results

A search for (1) 'eosinophilic esophagitis' and (2) 'eosinophilic oesophagitis' identified 1357 and 1402 titles respectively. The search term combination (3), that is, 1 or 2 (i.e. 'eosinophilic esophagitis' or 'eosinophilic oesophagitis'), and 'otolaryngology', identified 24 titles; (4) 1 or 2, and 'review' identified 368 titles; (5) 1 or 2, and 'review, systematic' identified 26 titles; (6) 1 or 2, and 'meta-analysis' identified 7 titles, and (7) 1 or 2, and 'controlled trial' identified 21 titles.

We selected 1 Cochrane review,[21] 6 meta-analyses,[14,22–26] 11 systematic reviews,[1–3,12,18,27–32] 12 non-systematic reviews,[16,17,33–42] 11 randomised trials,[43–53] 15 other controlled trials,[54–68] 58 case series and cohort studies,[4–8,10,11,13,15,19,20,69–115] 1 qualitative study,[116] 1 case report,[117] 1 published guideline,[118] and 5 published abstracts.[9,119–122] Eighteen of these articles were selected from the otolaryngology literature.[17–20,32,40,60,95,103–110,112,117]

Clinical picture

Features in children

Children typically present with one or more symptoms such as: vomiting; regurgitation; nausea; refractory gastroesophageal reflux disease; epigastric, abdominal or chest pain; water brash; globus; decreased appetite; or growth failure.[1,69] Haematemesis is rare. Infants and toddlers tend to present with difficulty feeding, manifesting as gagging, choking, food refusal and vomiting. Dysphagia and food impaction are uncommon until adolescence.[1,70,33] Pooled prevalence was 3.7 per cent in children undergoing oesophagoscopy for any indication.[14] In a 14-year study, 68 per cent of 620 patients presented at younger than 6 years, commonly with reflux symptoms, feeding issues or failure to thrive. Systemic symptoms such as fever or weight loss suggest another diagnosis.[71]

An allergic component to oesophageal eosinophilia was recognised in 11 cases associated with refractory gastroesophageal reflux disease and stricture.[72] Genomic analysis has established several genetic origins to the allergic response,[54,73] though twin and family studies suggest environmental factors predominate.[55] Children with eosinophilic oesophagitis show increased prevalence of atopy (asthma, eczema or rhinitis), environmental allergies and immunoglobulin E (IgE)-mediated food allergy (urticaria and anaphylaxis) (Table I).[15,70,74,103,108] It is estimated that 30–50 per cent have asthma and 50–75 per cent have allergic rhinitis, compared to 10 and 30 per cent, respectively, in the general paediatric population.[16] Over 50 per cent have a family history of allergy.[15] Nevertheless, the literature remains unclear on testing to guide food elimination diets.[27] Moreover, eosinophilic oesophagitis is strongly associated with inherited connective tissue disease, with a cohort study comprising 42 cases reporting an 8-fold risk of eosinophilic oesophagitis.[75] Crohn's disease can show a similar eosinophil-predominant oesophageal inflammation.[2,75] Treatment of such presumed primary aetiology requires monitoring of oesophageal inflammation. If eosinophilia persists after primary disease control, eosinophilic oesophagitis may co-exist. Eosinophilic oesophagitis inevitably occurs by chance in children with other syndromes.[2]

Features in adults

In contrast to children, the commonest adult presentation of eosinophilic oesophagitis is solid food dysphagia, reported in 60–100 per cent of cases.[70,71,76] Eosinophilic oesophagitis can account for over 50 per cent of adult emergency food impaction cases, and over a quarter of adults with eosinophilic oesophagitis report this history. Eosinophilic oesophagitis is the strongest predictor of multiple food bolus impactions (odds ratio = 3.5; 95 per cent confidence interval (CI) = 1.8–7.0)[77] and non-obstructive dysphagia.[78]

Many adult sufferers adapt their eating behaviour and deny dysphagia, but will recount being the last

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TABLE I
REPORTED RATES OF ATOPY*

Symptom	Noel *et al.*[70] (*n* = 103)	Simon *et al.*[15] (*n* = 31)	Assa'ad *et al.*[74] (*n* = 89)	Dauer *et al.*[103] (*n* = 71)	Otteson *et al.*[108] (*n* = 92)
Rhinoconjunctivitis	57.4				
Wheezing	36.8				
Asthma					43
Rhinitis/ bronchial asthma/ allergic dermatitis		68			
Environmental allergen sensitivity			79		
Food allergen sensitivity	46		75	60	

Data represent percentages. *In children with eosinophilic oesophagitis.

diner to finish, lubricating or chewing food into a mush, drinking copious amounts of water after each bite, swallowing repeatedly to push food down, avoiding foods that tend to stick, and crushing or avoiding pills.[76] Heartburn is experienced by 30–60 per cent and non-cardiac chest pain by 8–44 per cent of patients with eosinophilic oesophagitis.[70,76] Abdominal pain, nausea, vomiting, diarrhoea and weight loss are atypical in adult eosinophilic oesophagitis, and suggest a more diffuse eosinophilic gastrointestinal disorder. Atopic diseases, such as food allergies, asthma, allergic rhinosinusitis and atopic dermatitis, frequently coexist.[15] As in children, atopy is reported in 20–80 per cent of adults with eosinophilic oesophagitis, with even higher rates of allergen sensitisation,[76] as supported by genomic analysis.[56]

Diagnosis

Eosinophilic oesophagitis is suggested by a history of allergy, typical symptoms and endoscopic features, but confirmation relies on histopathology. The updated 2011 consensus report,[2] and separate American College of Gastroenterology clinical guidelines,[3] provide evolving evidence-based recommendations on diagnostic criteria. A systematic literature review found a significant increase in studies using 15 or more eosinophils per high-power field as the histological diagnostic cut-off,[119] as recommended by the consensus.[2] However, variability in biopsy protocols and eosinophil count methodology suggests that early work, published prior to the first 2007 consensus document, be interpreted with caution.[119]

Endoscopic features

Oesophageal structural changes associated with eosinophilic oesophagitis include fixed oesophageal rings (corrugations or trachealisation) (Figure 1),[123] which is the prototypical finding. These rings can be transient, termed 'felinisation'.[22,79,80] Strictures often develop as a result of chronic inflammation and fibrosis.[81,82] In the 'small-calibre' oesophagus, the lumen appears diffusely narrowed; this is difficult to appreciate endoscopically, but can be demonstrated using contrast swallow.[83] Linear furrows, white plaques or exudates are frequent (Figure 2).[96] A subtler finding is a decrease in the normal vascular pattern and oedema due to mucosal congestion. 'Crêpe paper mucosa' describes the tendency of the oesophageal mucosa to split with passage of the endoscope. None of these features are universal, and Sgouros *et al.*[28] report normal endoscopy in 8.8 per cent of eosinophilic oesophagitis.

Endoscopic findings differ between children and adults.[57,80] Children are more likely to show either a normal-appearing oesophagus or plaques and oedema, whereas adults show rings and strictures (Figures 3 and 4).[96,124] The earlier features of eosinophilic oesophagitis result from acute inflammation (furrows, plaques and oedema), whilst the later features represent fibrosis (rings, strictures and narrowing), which occurs with longer-standing inflammation.[81,82]

No endoscopic finding diagnoses oesophageal eosinophilia or eosinophilic oesophagitis with a high degree of sensitivity or specificity.[80] Narrow-band imaging offers no further benefit.[58] Endoscopy alone therefore cannot confirm or refute a diagnosis. This was reported in a meta-analysis of 4678 patients with eosinophilic oesophagitis and 2742 controls,[22] and in

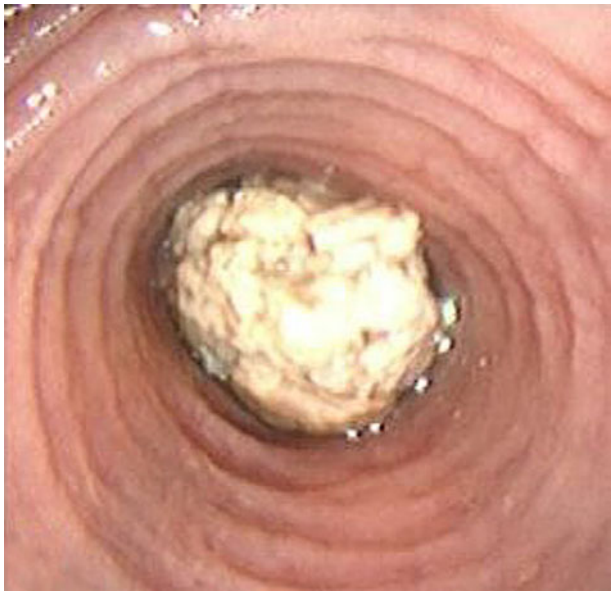

FIG. 1
Food impaction in the mid oesophagus with concentric mucosal rings and evidence of subtle linear furrowing. Reproduced with permission.[123]

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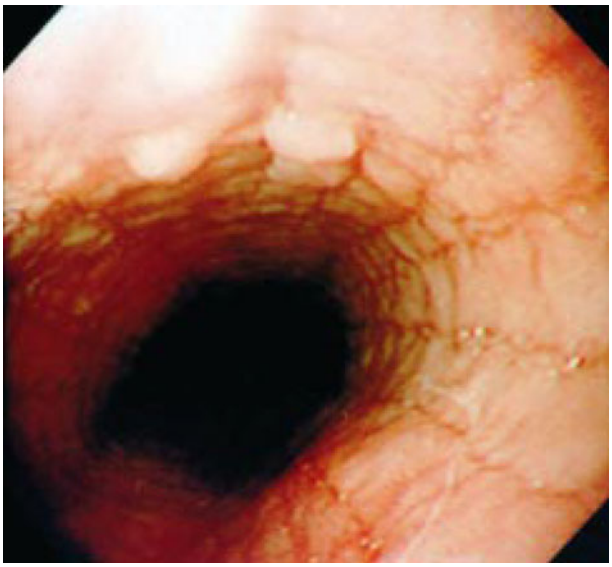

FIG. 2
Furrows and rings in combination, creating a cobblestone appearance. Reproduced with permission.[96]

a subsequent prospective, single-centre analysis of 2545 cases.[84] Kim *et al.*[22] concluded that, although findings associated with eosinophilic oesophagitis are not universal, 83 per cent of cases had at least one abnormality. A proposed novel classification system for standardising such endoscopic findings and severity has been validated.[59] Termed the eosinophilic oesophagitis endoscopic reference score, its acronym ('EREFS') reflects the components: Exudates, Rings, Edema, Furrows and Strictures.[57]

Histological features

The histological features of eosinophilic oesophagitis are similar in children and adults. The oesophageal epithelium shows prominent infiltration of eosinophils, cells which are absent in healthy mucosa.[35] Eosinophilic infiltration is, however, recognised in gastroesophageal reflux disease, eosinophilic gastroenteritis with oesophageal involvement, collagen vascular disease, achalasia, and parasitic infections.[36,85] At least 15 eosinophils per high-power field, following an initial proton pump inhibitor (PPI) trial, suggests a diagnosis of eosinophilic oesophagitis.[1–3] No other associated histopathological findings are pathognomonic for eosinophilic oesophagitis. The disease remains defined by both clinical and pathological features.[60,79]

In a cohort of 222 adults with dysphagia and normal endoscopy findings, 9.8 per cent had histological features of eosinophilic oesophagitis.[79] Only 38 per cent of patients with suggestive endoscopic changes had the typical biopsy findings of eosinophilic oesophagitis. Routine biopsies in that study identified eosinophilic oesophagitis in 10 per cent of cases presenting with unexplained solid food dysphagia.

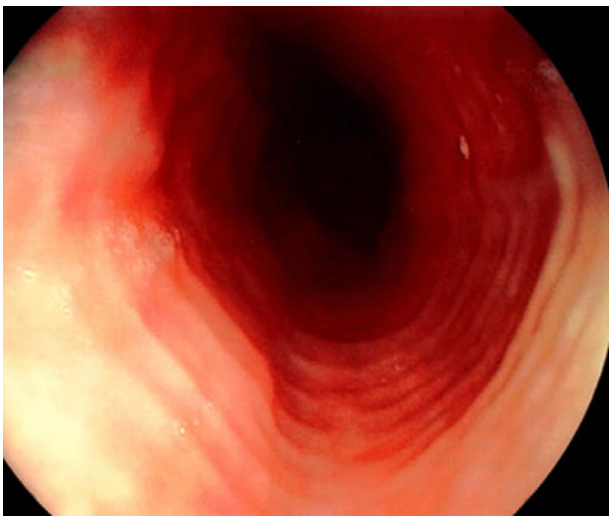

FIG. 3
Concentric oesophageal rings without associated mucosal change – referred to as 'trachealisation'. Reproduced with permission.[96]

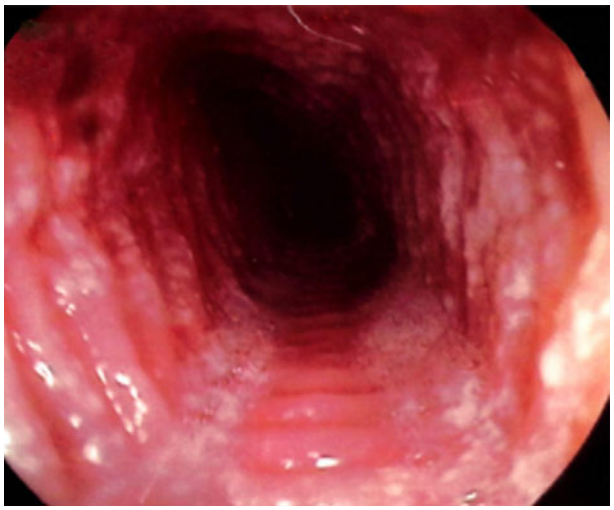

FIG. 4
Trachealisation with associated hyperplasia of the mucosa. Reproduced with permission.[124]

Biopsy recommendations

Endoscopic biopsy samples the oesophageal epithelium and rarely obtains tissue deeper than the lamina propria. The histological diagnosis of eosinophilic oesophagitis therefore relies on surface mucosal findings. Dellon *et al.*[120] identified a high variation in eosinophil counts throughout the oesophagus in eosinophilic oesophagitis, with only one-third of high-power fields meeting the 2011 consensus recommendations.[2] A localised and less symptomatic eosinophilic oesophagitis variant arises in the distal oesophagus.[86] Nielsen *et al.*[87] reviewed 102 cases of eosinophilic oesophagitis biopsied from the mid and distal oesophagus to determine best practice in sampling. They recommended at least four and no more than six biopsies (after which sensitivity reaches 100

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per cent) from the mid or proximal oesophagus, to ensure distinction from distal oesophageal biopsies that possibly represent gastroesophageal reflux disease. The American Society for Gastrointestinal Endoscopy acknowledges that the patchy microscopic and macroscopic distribution characteristic of eosinophilic oesophagitis compromises biopsy standardisation.[118] Pharyngeal biopsies proved unnecessary in a small series of 10 eosinophilic oesophagitis cases, as none showed eosinophilia.[88]

Both the 2013 American College of Gastroenterology clinical guidelines,[3] and 2011 consensus statement,[2] recommend two to four separate biopsies from both the proximal and distal oesophagus, with additional biopsies from the antrum and/or duodenum only in patients with atypical gastric or small intestinal symptoms or endoscopic abnormalities.

Differential diagnoses

Despite established diagnostic criteria for eosinophilic oesophagitis, there are confounding differential diagnoses. Gastroesophageal reflux disease and PPI-responsive eosinophilic oesophagitis also cause oesophageal eosinophilia.[85,89] Gastroesophageal reflux disease and eosinophilic oesophagitis show symptom overlap. Moreover, eosinophilic oesophagitis could cause gastroesophageal reflux disease (because of impaired oesophageal clearance of physiological refluxate), and gastroesophageal reflux disease could cause acid-mediated eosinophilic oesophagitis (if reflux leads to a leaky epithelial barrier, through which antigens induce an allergic response).[89] Eosinophilic oesophagitis and gastroesophageal reflux disease may demonstrate histological differences in eosinophil infiltration and secondary changes to the squamous epithelium.[90]

Proton pump inhibitor responsive eosinophilic oesophagitis is now recognised as a distinct disease entity, though ill-understood.[2,29,91] A proportion of patients with confirmed eosinophilic oesophagitis experience complete clinical and histological resolution following PPI therapy. The clinical, endoscopic and histological features of eosinophilic oesophagitis and PPI-responsive eosinophilic oesophagitis overlap, and the conditions cannot be distinguished by pH monitoring.[61] Furthermore, they are associated with the production of similar cytokines and tissue biomarkers. The immunohistochemical evidence of inflammation is similar in patients with eosinophilic oesophagitis and PPI-responsive eosinophilic oesophagitis,[62] being driven by allergy rather than reflux injury.[63] In retrospective studies, 23–75 per cent of patients with eosinophilic oesophagitis demonstrated a histological response to PPI therapy,[29] which correlated with cytokine down-regulation in PPI-responsive eosinophilic oesophagitis.[64] Proton pump inhibitor responsive eosinophilic oesophagitis is currently recognised as a variant of eosinophilic oesophagitis, distinct from gastroesophageal reflux disease, though this area of research is developing rapidly.[37,38]

The current American College of Gastroenterology guidelines make specific recommendations on distinguishing eosinophilic oesophagitis from gastroesophageal reflux disease or PPI-responsive eosinophilic oesophagitis.[3] The limited evidence suggests patients with suspected eosinophilic oesophagitis should receive a two-month course of PPI, followed by endoscopy and biopsies. A response to PPIs may still warrant further evaluation, such as pH monitoring.

Treatment

The literature summarises three treatment approaches to eosinophilic oesophagitis: drugs, dietary therapy (primarily targeting the inflammatory response), and dilatation (for fibrosis and stricture).

Drugs

Corticosteroids. Although oral corticosteroids improved symptoms and resolved eosinophilia,[65] they have now been abandoned because of concerns of long-term systemic administration.[2] Arora *et al*.[92] presented the first series describing the role of topical steroids for dysphagia in adult eosinophilic oesophagitis. Topical steroids do reduce eosinophil counts; however, evidence for symptom response is inconsistent.[30] Only one published randomised, controlled trial (RCT) included a recommended pre-treatment PPI trial. Dosage reduction can lead to rapid relapse.[43]

A case series showed that fluticasone or beclomethasone, swallowed rather than inhaled using a multi-dose inhaler, proved highly effective.[93] Randomised, controlled trials have studied fluticasone and budesonide, administered either as viscous slurry or as a swallowed nebulised vapour. There have been three RCTs of fluticasone versus placebo (one in children,[44] one in adults,[45] and one enrolling children and young adults[46]), and one RCT of fluticasone versus prednisone in children.[47] In each of these placebo-controlled trials, patients in the topical steroid group had statistically significant reductions in oesophageal eosinophil counts.

Two RCTs reported on budesonide versus placebo in children,[48,49] and one investigated swallowed nebulised budesonide versus placebo in adults.[50] These showed significant efficacy for budesonide in decreasing or normalising eosinophil counts.

Long-term data have shown budesonide to be more effective than placebo.[51] A five-year follow-up cohort analysis reported that increased swallowed topical steroid also lowered the risk of bolus impaction;[94] however, quality-of-life (QoL) analyses remain limited to pilot data.[95] A 2010 Cochrane review of non-surgical interventions[21] reported on three RCTs, two of which investigated topical corticosteroids, and found limited evidence to compare the benefits and harms of current medical treatments.

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No study has shown significant adrenal axis suppression.[2] Gastrointestinal inflammation of eosinophilic oesophagitis may increase budesonide absorption[48,49] and impair systemic elimination.[66] Oesophageal candidiasis was identified in follow-up endoscopies of 15–20 per cent of patients treated with topical steroids.[44–46,93] Herpes esophagitis has been reported in a single case.[93]

Leukotriene D4 antagonist, mast cell stabiliser and other biological drugs. Montelukast, a selective inhibitor of the leukotriene D4 receptor, is used to treat adult asthma. In a study of eight adults with eosinophilic oesophagitis treated with montelukast, six patients reported complete subjective improvement and five remained asymptomatic, but eosinophil infiltration was incompletely reversed.[96] Cromolyn sodium, a mast cell stabiliser, was ineffective in treating eosinophilic oesophagitis.[2] Mepolizumab, an interleukin (IL)-5 monoclonal antibody, apparently improved histological findings, but long-term data are lacking,[52] and the effects on clinical symptoms and endoscopic appearances vary.[53,67] Anti-IL-13 monoclonal antibodies, anti-eotaxin-3, anti-IgE antibodies and anti-inflammatory drugs hold early promise in research.

Dietary therapy

The identification and elimination of potential food antigens, which cause an antibody response and eosinophilic infiltration, is the mainstay of treatment for eosinophilic oesophagitis.[2] Corticosteroid benefit is temporary, but many patients experience long-term remission with food elimination (without medication).

A meta-analysis of 33 studies concluded that elemental diets (amino acid based formulas) and the six-food elimination diet (eliminating milk, egg, soy, wheat, nuts and seafood) were the most effective, achieving histological improvement in 90.8 and 72.1 per cent of cases respectively.[23] Early data from a four-food elimination diet (eliminating milk, wheat, egg and soy) have shown comparable efficacy to the six-food elimination diet; histology, symptoms and endoscopic features significantly improved in children and adults, but QoL scores were unchanged.[121] A meta-analysis of food elimination directed by skin allergy test results showed limited efficacy, with 45.5 per cent improvement (95 per cent CI = 35.4–55.7 per cent).[23] In this approach, if no allergens were identified, the commonest were empirically eliminated.

Dietary therapy improves oesophageal fibrosis and remodelling.[2] An association between the onset of eosinophilic oesophagitis during oral immunotherapy for IgE-mediated food allergy has been reported in 2.7 per cent of cases, which reversed after discontinuation of the challenge.[24] Successful dietary therapy requires a multidisciplinary approach to avoid dietary deficiencies.[39]

Dilatation

Early case reports and small series of oesophageal dilatation performed in patients with eosinophilic oesophagitis described a higher risk of perforation, deep mucosal tears and hospitalisation for post-operative chest pain.[97,98] The 2007 First International Gastrointestinal Eosinophil Research Symposium Subcommittee guidelines mentioned above cautiously recommended that dilatation be considered only after failed drug or dietary therapy.[1] However, a subsequent meta-analysis of 9 studies and 992 procedures calculated the risk of perforation from dilatation in eosinophilic oesophagitis to be 0.3 per cent, which is similar to the rate for any oesophagoscopy procedure.[25] Overall, short-term clinical improvement was seen in 75 per cent of cases (95 per cent CI = 57–93 per cent). An earlier review described longer-term benefits in 92 per cent of cases; these benefits were sustained for one to two years, and clinical improvement occurred independently of eosinophil counts.[31] Swallowed fluticasone via an inhaler (followed by oesophagoscopy with dilation if necessary) remains the more cost-effective initial strategy when compared with first-line oesophagoscopy and dilatation.[26]

Symptomatic and histological responses are often dissociated.[99] Dilatation can rapidly correct dysphagia, but, without dietary or pharmacological therapy, oesophageal eosinophilia persists. In contrast, a patient with a stricture, treated with steroids or diet, may achieve histological normalisation, but experience persisting dysphagia. The goal of the dilation is a mucosal tear, a break in the oesophageal mucosa at the level of the stricture. This is not considered a complication, as highlighted by Croese *et al.*,[100] who reported a mucosal tear in 13 of 17 cases. A single-centre retrospective analysis found no variation in outcomes between dilatation techniques.[101]

Otolaryngology perspectives

Pharyngolaryngeal symptoms often accompany eosinophilic oesophagitis. Despite the likelihood that otolaryngologists will encounter eosinophilic oesophagitis patients, and the close association with aerodigestive symptoms, atopy and overlap with gastroesophageal reflux disease, it remains under-reported in our literature.[32] Whilst gastroenterology, paediatrics and pathology journals have seen over 1400 publications, those in otolaryngology-specific journals number only 24. Otolaryngology interest stems from 2002, and a single case reporting a potential association between eosinophilic oesophagitis and a failed airway reconstruction for subglottic stenosis.[117] Several case series and cohort studies followed, but no randomised, controlled trials or meta-analyses have been performed, limiting our contribution to level III evidence.

Several studies have recognised an association between eosinophilic oesophagitis and ENT symptoms (Table II). Clinical features (Table III) vary and

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TABLE II
REPORTED RATES OF ENT MANIFESTATIONS*

Symptom	Dauer *et al.*[103] (*n* = 71)	Hill *et al.*[104] (*n* = 14)	Liacouras *et al.*[69] (*n* = 381)	Noel *et al.*[70] (*n* = 103)	Otteson *et al.*[108] (*n* = 92)
Rhinosinusitis	25				
Cough		42.9			46
Hoarseness					38
Throat clearing					30
Choking & vomiting		42.9			
GERD	54		82		17
Dysphagia			18	28	
Food bolus obstruction	51			7	

Data represent percentages. *In children with eosinophilic oesophagitis. GERD = gastroesophageal reflux disease

overlap with airway and reflux symptomatology.[102] Rhinosinusitis was reported in 25 per cent of patients, food bolus impaction in 51 per cent and gastroesophageal reflux disease in 54 per cent, of whom four subjects had undergone fundoplication.[103] A range of refractory upper airway and gastrointestinal symptoms is typical.[104] Flexible endoscope examinations conducted during airway evaluation for croup identified eosinophilic oesophagitis in 7.2 per cent of patients,[105] and eosinophilic oesophagitis was present in 10 per cent of patients in a select cohort.[106] A case–control study identified eosinophilic oesophagitis in 36 per cent of 101 children with cow's milk protein intolerance,[107] with 60 per cent showing improvement in ENT symptoms following dietary elimination. Otolaryngology interventions were more common in the cow's milk protein intolerance cohort than in controls (odds ratio = 33.78; 95 per cent CI = 7.55, 151.03).

Otolaryngologists will encounter both paediatric and adult eosinophilic oesophagitis patients. In a retrospective analysis, up to 20 per cent of paediatric eosinophilic oesophagitis cases had undergone ENT evaluation for a range of diagnoses.[20] In 144 patients seen by otolaryngologists, only 32 per cent of those ultimately diagnosed with eosinophilic oesophagitis were referred onwards as suspicious at early consultation, leaving 68 per cent that our specialty initially failed to recognise.[20] A 5-year review of 362 patients with confirmed eosinophilic oesophagitis diagnosis revealed that 33 per cent had undergone at least one, and 16.6 per cent had undergone multiple, ENT procedures.[19] Contrary to other reports, a diagnosis of eosinophilic oesophagitis was achieved in 75.6 per cent of cases by onward referral by ENT after their first procedure (12.6 per cent had biopsies confirming eosinophilic oesophagitis as part of their ENT assessment). Patients presented to ENT, on average, four years prior to gastroenterological diagnosis of eosinophilic oesophagitis.

TABLE III
TYPICAL FEATURES OF EOSINOPHILIC OESOPHAGITIS

Feeding difficulties in infants & toddlers
Dysphagia & bolus impaction in adolescents & adults
Atopic disorders
Characteristic endoscopic appearance
Stricture formation

Eosinophilic oesophagitis must be considered in children undergoing diagnostic aerodigestive endoscopy. A tertiary multidisciplinary centre reported a prevalence of 3.7 per cent in 372 children undergoing endoscopy for refractory aerodigestive symptoms.[104] This is comparable to the prevalence of 3.8 per cent reported in the largest study, which comprised 2429 patients who were managed through a paediatric otolaryngology-led service;[108] the mean age of 4.4 years is younger than that in the literature, suggesting increased awareness in a multidisciplinary service. Published multidisciplinary approaches to croup and chronic cough,[109] and aerodigestive dysfunction,[110] used in children, highlight an increasing recognition.

However, the literature highlights the ongoing failure of otolaryngology to consider the diagnosis.[77,111] Williams *et al.*[111] found eosinophilic oesophagitis more prevalent in food bolus obstruction cases, yet ENT departments never performed mucosal biopsies (despite eosinophilic oesophagitis being involved in 25 per cent of 572 cases of paediatric food bolus obstruction retrieval). One ENT series identified 18 cases of eosinophilic oesophagitis in 27 patients biopsied, from a series of 271 paediatric food bolus obstruction cases.[112]

Increased adoption of transnasal oesophagoscopy by otolaryngologists may increase exposure to eosinophilic oesophagitis and allow biopsy.[17,40,113] The specialty of ENT should maintain awareness and ensure that patients with clinical features of eosinophilic oesophagitis are referred to gastroenterology, recognising the importance of histology.

Otolaryngology series report significant delays to diagnosis. A mean diagnostic delay of 6 years in a series of 200 patients led to increased rates of fibrosis and stricture formation. Even delays of up to 2 years produced fibrosis and stricture formation rates of 46.5 and 17.2 per cent, respectively; delays of over 20 years produced rates of 87.5 and 70.8 per cent.[82]

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Natural history and prognosis

Eosinophilic oesophagitis is a chronic disease, which commonly relapses following the cessation of beneficial treatment.[76] There is no evidence that the disease process limits life expectancy, but it can impair QoL.[121,122] The Pediatric Eosinophilic Esophagitis Symptom Score ('PEESS', version 2.0) explored the QoL impact in children, reporting patient and parent-proxy reported outcomes.[116] This validated tool has yet to demonstrate improved treatment outcomes. Quality of life and symptom questionnaires are applied in clinical practice in adults, and clinicians broadly judge severity based on endoscopic features and symptoms.[68]

Eosinophilic oesophagitis has not been associated with an increased risk of malignancy. It is suggested to be the commonest cause of spontaneous oesophageal perforation, through a process distinct from that of Boerhaave syndrome.[41] In an 11.5-year follow-up study, the inflammatory process remained confined to the oesophagus, without transition to eosinophilic gastroenteritis or other disease.[76] The evidence base for the diagnosis and management of eosinophilic oesophagitis is limited, and provides opportunities for further research.[114]

Future work

Extensive research has aimed to establish genetic banking and define the phenotypes of eosinophilic oesophagitis.[115] The interplay between eosinophilic oesophagitis, PPI-responsive eosinophilic oesophagitis and gastroesophageal reflux disease, and the role of PPI treatment in these phenotypes remain contentious.

Future otolaryngology research could focus on comparisons of topical steroids and oesophageal dilatation, techniques for dilatation, the role of maintenance versus on-demand topical steroid therapies, biological agents, and biomarkers of disease progression.[41,42] Significantly, a collaborative venture, funded by United European Gastroenterology, hopes to establish a European-wide clinical network, registry and learning platform for eosinophilic oesophagitis. Involving both physicians and otolaryngologists, it is termed 'Harmonizing diagnosis and therapy of Eosinophilic Oesophagitis (EoE) across Europe (HaEoE-EU)'.[125]

Conclusion

Eosinophilic oesophagitis is a chronic, immune/antigen-mediated oesophageal disease that has recently become an increasingly recognised cause of upper gastrointestinal morbidity in adults and children. Characterised by eosinophilic infiltration, its typical clinical presentation includes dysphagia and food impaction due to fibrostenosis, associated with inflammatory changes and the alteration of biomechanical properties. It can only be recognised if the diagnosis is considered, and this necessary awareness may be lacking in our specialty, to which such patients frequently present. Despite characteristic endoscopic features, biopsy is mandatory. A PPI trial rules out the one-third of patients with PPI-responsive eosinophilic oesophagitis. Treatment comprises diet therapy, topical corticosteroids and/or endoscopic dilation. Further basic and clinical research data are needed to understand the pathophysiology and clinical course (including biomarkers), to update the diagnostic algorithm and develop novel treatments. The care of patients with eosinophilic oesophagitis and the study of the disease are multidisciplinary, involving gastroenterologists, otolaryngologists, allergists and dieticians. The role of the otolaryngologist may be to consider the diagnosis primarily, to obtain biopsy confirmation, and to treat complications such as bolus obstruction or stenosis.

Acknowledgement

We thank Professor Stephen Attwood (Department of Health Services Research, Durham University, UK), for his expert advice in the preparation of this manuscript, for reviewing the final draft and for providing the illustrations.

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Mr L Flood takes responsibility for the integrity of the content of the paper
Competing interests: None declared