Mechanisms and clinical management of eosinophilic oesophagitis: an overview

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Abstract | Since the first description of eosinophilic oesophagitis (EoE) less than three decades ago, we have observed a striking increase in the number of patients diagnosed with EoE and the understanding of its clinical and immunopathogenic background. Nonetheless, a plethora of open questions await elucidation. In this Review, we discuss the current state of knowledge regarding the underlying mechanisms, particularly environmental factors and their interaction with genetic susceptibility. Subsequently, we discuss how to translate these factors into the diagnostic and therapeutic management of this chronic, immune-mediated disorder. Finally, we dissect the still long list of unmet needs, such as reasons for and handling refractory EoE and atypical clinical presentations. These open questions can guide us through future research steps and potentially foster reconsideration of the diagnostic guidelines of EoE.

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated inflammatory disease of the oesophagus[1]. The first case of EoE was reported in 1978 and was misinterpreted as a motility disorder[2]. A few years later, in 1982, the clinical relevance of oesophageal eosinophilia was perceived but again misinterpreted as the diagnostic hallmark of gastroesophageal reflux disease (GERD)[3]. It took over a decade before EoE was independently described in two case series and recognized as a distinct disease entity characterized by symptoms of oesophageal dysfunction and a predominant eosinophilic infiltration of the oesophageal tissue[4,5]. Nevertheless, the clinicopathological characterization of EoE is still valid, and accordingly, both publications showed that EoE was prevalent in young male patients with atopic conditions, and those endoscopic findings were rather discrete but particularly different from those in GERD.

Epidemiology

EoE was initially regarded as a rare disease. However, it soon became evident that its incidence and prevalence were rapidly increasing[1], as it was observed in children and adults in North and South America, Europe, Asia and Australia[6]. Several population-based studies from the USA[7,8] and Europe[9,10] indicated that this increase was, at least partially, a true increase and not an artificial effect due to raised awareness. Based on a comprehensive meta-analysis, the prevalence of EoE in adults is currently 32.5, and in children, 30.9 patients per 100,000 population. Thus, in westernized areas, EoE currently affects 1 in 3,000 inhabitants[11]. Although EoE mainly affects individuals 20 to 40 years of age, all age groups can be affected[12]. Currently, the incidence and prevalence of EoE are steadily approaching those of Crohn's disease (prevalence around 40 up to above 300 per 100,000 population in South and North America, respectively)[13,14].

The confrontation with a presumably new disease raises the question of whether EoE is indeed a novel condition or simply a newly recognized condition. The diagnosis of EoE is established in more than one-third of patients only during an emergency endoscopy performed for removal of an impacted food bolus[15]. Impactions due to ingestion of foreign bodies or fish bones are well-known gastrointestinal emergencies. By contrast, impactions caused by 'ordinary' food appeared no longer than around five decades ago. Long-lasting food impactions force patients to visit the emergency unit, and these events are universally documented in medical records[16]. Thus, it is unlikely that the increased occurrence of impactions caused by ordinary food is a result of such impactions previously being missed but is in accordance with the marked increase in histological diagnosis of oesophageal eosinophilia that has clearly outpaced the numbers of upper gastrointestinal endoscopy procedures and oesophageal biopsy samples[16,17]. Thus, this observation is a strong argument that EoE is a truly novel disorder and not simply a newly recognized one.

A further relevant epidemiological question is whether the increased occurrence of EoE is due to increased allergenicity of food (environmental factor) or

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Key points

- Eosinophilic oesophagitis (EoE) is a T helper 2 (T_H2)-mediated inflammation of the oesophagus with a genetic component which, usually, is neither necessary nor sufficient to promote EoE.
- EoE represents a T cell-mediated food allergy.
- A diagnosis of EoE is based on a combination of clinical, endoscopic and histological findings.
- The detection of relevant eosinophilia in the oesophageal tissue is a cornerstone in diagnosing classic EoE, but at least three EoE variants with identical clinical manifestations without marked eosinophilia exist.
- Anti-inflammatory treatment modalities include swallowed topically acting corticosteroids, proton pump inhibitors, biologics and food elimination diets, whereas dilation only has an effect on symptoms.
- Based on our current understanding, EoE is a chronic and incurable disease requiring long-term anti-inflammatory treatment.

increased susceptibility of individuals (internal factor). A dramatic increase in the global prevalence of allergies has been observed during the past few decades[18]. Thus, an allergy epidemic is not an EoE-specific phenomenon and might be partially explained by the so-called hygiene hypothesis[19]. However, whether the hygiene hypothesis can explain the increase in EoE remains questionable for several reasons, most importantly, the de novo onset of EoE, its non-IgE-mediated pathogenesis[20] and its strong dependency on food proteins[21] that render this entity a unique form of allergy.

Moreover, in parallel with the increase in EoE, dramatic changes in production and food processing have occurred. Considering that cow's milk is the leading trigger of EoE[22], researchers were eager to explore in a small pilot study the tolerability of so-called A2 milk in patients with proven milk-sensitive EoE. β-Casein A is a 209 amino acid protein and is one of the most abundant cow's milk proteins. In wild-type β-casein A, referred to as A2, position 67 is covered by the amino acid proline[23], whereas in a dominant point mutation, proline is replaced by histidine[23,24]. This so-called A1 milk is currently the commercially available milk in most westernized areas. It is speculated that β-casein A1 might be a main culprit for cow's milk intolerance and allergy[25]. Under persistent vigorous elimination of A1 milk, three patients were exposed to A2 milk with a daily intake of at least 0.3 l. After more than 1 year of A2 milk exposure, two patients were still in clinical remission with a histologically confirmed response, whereas the third patient experienced a relapse a few weeks after exposure to A2 milk (unpublished data from our research team). This preliminary observation indicates that, at least in a subset of patients, EoE might be due to a modification of the food production and that in some patients, the mutated β-casein A1 might be the key protein triggering eosinophilic inflammation. Extended analyses of other food proteins are mandatory to confirm this observation.

Genetics

The risk of EoE in relatives of patients is increased between tenfold and 64-fold compared with the risk in the general population. This increased risk illustrates that genetics are important in EoE. Moreover, the increase in risk was shown to be associated with the proximity of the relationship with a markedly higher rate (roughly double) in monozygotic versus dizygotic twins[26]. However, in the latter, the rate was also distinctly higher (41%; 22% in dizygotic twins) than in siblings (2.4%; compared with 5.5 per 10,000 in the general population), strongly pointing to the crucial role of shared environmental factors (including the in utero environment, which is shared between dizygotic twins with a similar genetic relationship to siblings). Overall, the relative contribution of genetic heritability is relatively small compared with the more substantial effect of common environmental factors[26].

Thus, the effect of genetics seems to unfold in conjunction with other factors, including early environmental exposure in childhood and later on throughout adult life, and allergic sensitization. Such a gene–environment interrelationship can be seen, for instance, for *CAPN14* — a gene encoding a cysteine protease — which is overexpressed in patients with EoE. This overexpression was pronounced particularly in individuals with a high disease activity score upon exposure to IL-13 in conjunction with several genetic loci associated with allergic sensitization (for example, *CLEC16A*, *LRRC32*, *LPP* and *TSLP–WDR36*)[27].

In addition, early childhood environmental events, such as breastfeeding or staying in a neonatal intensive care unit, modulate the risk of acquiring EoE in the future according to prevalent distinctive risk genes (*CAPN14* and *KLF13*)[28]. Taken together, genetic risk factors are neither necessary nor sufficient to promote future EoE, although they clearly modulate the individual lifetime risk in a given carrier. However, EoE is a polygenic disease with various layering single nucleotide polymorphisms involved in modulating disease risk.

Interestingly, the risk increase in family members applies to not only EoE but also oesophageal eosinophilia, with a high prevalence identified in first-degree relatives of patients with EoE[29]. Potential shared genetic aetiologies are present in EoE and other autoimmune diseases, including ulcerative colitis, systemic sclerosis and multiple sclerosis[30], as indicated by an atopic and autoimmune comorbidity for these disease states in patients with EoE.

A meta-analysis including more than 600 patients with EoE and more than 300 individuals as controls identified a total of 13 genes[31] (including *CAPN14*, *TLSP*, *LRRC32*, *CLEC16A* and *GATA3*), confirming earlier genome-wide expression analysis[32]. These genes are expressed in epithelial cells (in which the expression of some of these genes is modulated by EoE disease activity), in fibroblasts and in immune cells[31]. Some of these genes are implicated in epithelial barrier homeostasis, regulated by IL-13, while others are important in the differentiation of immune cells[33].

Epithelial barrier

Epithelial cells, with tight junctions effectively sealing the paracellular space and mucosal immune cells, interact continuously with environmental factors and have a pivotal role in forming a physical and functional barrier against external antigens and infectious agents[34]. Impairment of epithelial barrier integrity and function

with increased permeability to antigens was identified in both mice and humans as a crucial factor fuelling inflammation in T helper 2 (T_H2)-type diseases, such as atopic dermatitis and allergic asthma[35–39], as well as chronic immune-mediated inflammatory diseases of the luminal gastrointestinal tract, including Crohn's disease, ulcerative colitis and microscopic colitis[40,41]. Indeed, direct deposition of penetrating antigens in the human oesophageal epithelium has been shown[42], and this local deposition, including subsequent immune response, seems to be an important factor in the pathogenesis of EoE[43]. There seems to be a delicate balance between factors promoting epithelial dysfunction and fuelling oesophageal inflammation, such as kallikrein 5 (a serine protease)[44], and counteracting forces, including protease inhibitors or the oxygen-sensing transcription factor HIF-1α in epithelial cell cultures and biopsy samples from patients with EoE[45].

In the skin, for instance, loss-of-function mutations in filaggrin, an essential protein for the differentiation of the squamous epithelium and the skin barrier, are strongly associated with a predisposition to atopic dermatitis in humans[46]. Interestingly, IL-13 modulates the expression of filaggrin that is also dysregulated in EoE, with an even higher overlap in the dysregulated gene expression profile between EoE and atopic dermatitis than between EoE and allergic asthma[47]. An IL-13-driven altered expression pattern of filaggrin (as indicated by aberrant immunofluorescent staining) was found in oesophageal biopsy samples from patients with EoE, resulting in increased permeability to small molecules[48]. This IL-13-driven alteration of tight junction proteins and decrease in oesophageal epithelial barrier integrity might be of potential use in predicting response to novel targeted therapies blocking IL-13 or proton pump inhibitors (PPIs)[49]. Genetic variants in other key proteins of the oesophageal barrier, including desmoplakin and periplakin, might further affect barrier function in patients with familial and sporadic EoE through an acquired loss of function of these proteins[50].

The following chicken-and-egg question arises: Are these gene expression patterns of integrity and barrier proteins a consequence of the inflammation and, therefore, potentially reversible under successful treatment, or are they a disease-inherent factor promoting eosinophilic inflammation? Evidence pointing to the latter (that is, a primary event) is an impaired expression of key barrier proteins, including E-cadherin, claudin, occludin, desmoglein-1 and filaggrin, in patients with treated and untreated EoE irrespective of therapy, as shown in a study in 60 patients with EoE and 20 individuals as controls[51]. By contrast, initiating PPI therapy was shown to partially restore the integrity and function of the epithelial barrier in a subset of patients with EoE (16 patients and 11 individuals as controls)[52]. Therefore, this crucial question on cause and effect currently awaits clarification.

A better understanding of these mechanisms might foster the modulation and restoration of barrier function in EoE as a therapeutic target. For instance, supplementation with butyrate and propionate might restore the expression of barrier proteins, such as filaggrin or desmoglein-1 (REF.[51]), as might inhibiting TGFB1, which is a driver of oesophageal remodelling and altered epithelial barrier function[53,54].

Box 1 | **Factors involved in the pathogenesis of eosinophilic oesophagitis**

Simplified overview of factors currently considered to be involved in the immunopathogenesis of eosinophilic oesophagitis.

Environment
- Caesarean birth
- Antibiotics and PPI use in childhood
- Formula feeding
- Cold, arid climate
- *Heliobacter pylori* (negative association)
- EoE is presumably more common in rural regions (twin studies have also demonstrated the importance of the environment)

Atopy
- Seasonal variation
- Oral immunotherapy-induced (potentially also for subcutaneous infusion therapy?)
- High rate of food allergy, atopic dermatitis and asthma
- High rates of food pollen allergy syndrome and food-induced immediate response of the oesophagus

Heritability
- Mainly of individuals of European descent (however, EoE is also on the rise in non-white individuals)
- High relative risk among family members, familial cases including several generations

Genetic variants
- GWAS or candidate-gene studies (currently 13 genes established, including *TSLP*, *STAT6* and *CAPN14*)
- Associated Mendelian disorders

Gender
- Male preponderance
- Higher family association amongst male patients

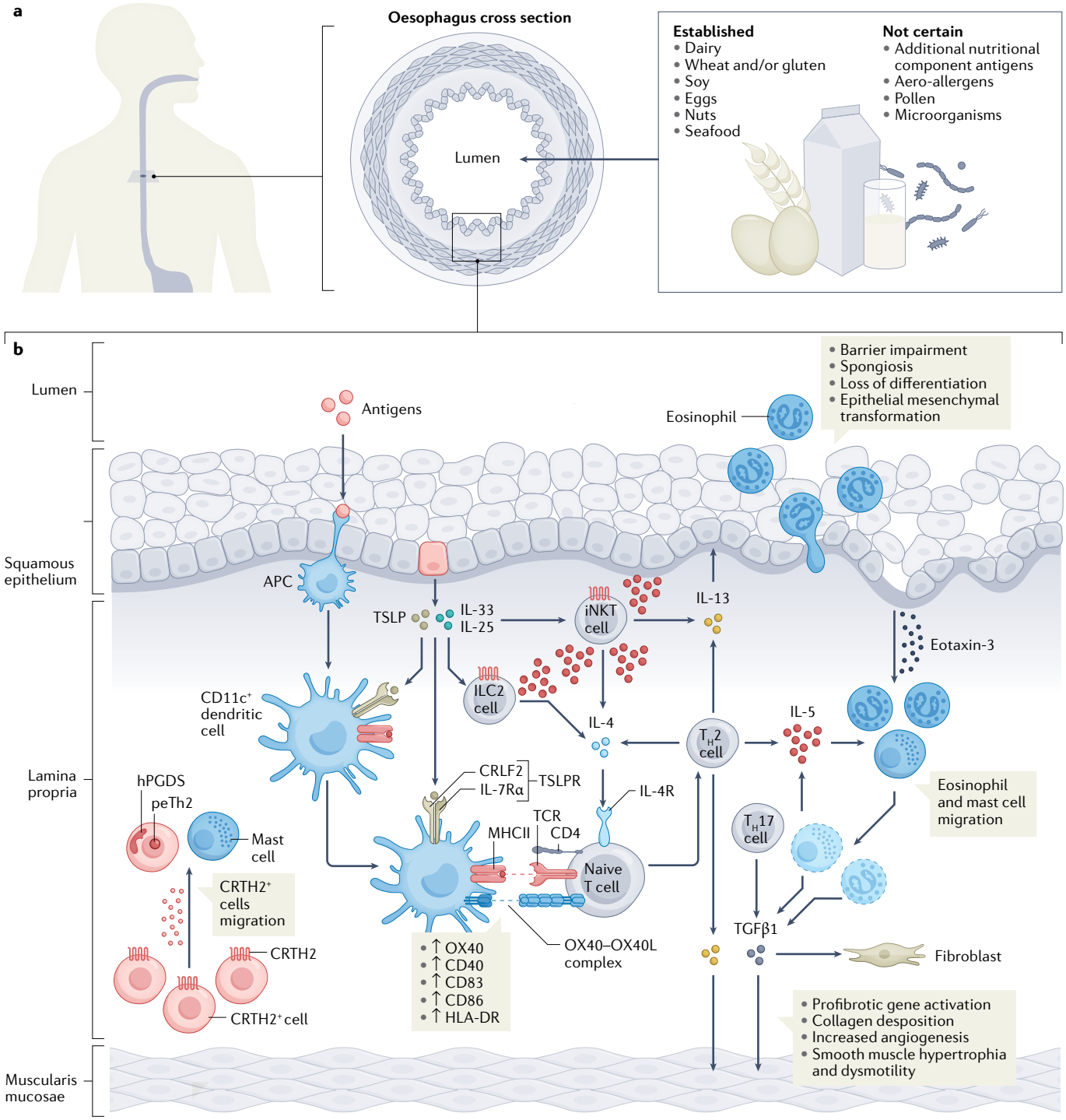
Cellular pathology
- Activated eosinophils
- Activated mast cells
- Also T cells involved in T_H2 immune response
- Impairment in epithelial barrier function and integrity

EoE, eosinophilic oesophagitis; GWAS, genome-wide association studies; PPI, proton pump inhibitor. Adapted with permission from REF.[55], Elsevier.

Immunopathogenesis

Exposure to distinct environmental factors in childhood and adulthood, along with an increasingly more detailed understanding of genetic susceptibility, indicate that chronic immune-mediated inflammation of the oesophageal wall is crucial in the pathogenesis of EoE. Activated eosinophils and other cells and mediators of the innate and adaptive immune system, such as mast cells, T cells, immunoglobulins and cytokines, including IL-5 and IL-13, are involved in this T_H2-type inflammatory[55,56] immunopathogenesis (BOX 1, FIG. 1).

The healthy oesophagus is completely devoid of eosinophils (in striking contrast to other areas of the luminal gastrointestinal tract, where a small number of eosinophils are present physiologically), and this is an indicator of a genuine pathogenetic role of eosinophils including their progenitor cells in EoE[57]. Eosinophil



migration is fuelled via the strongly upregulated *CCL26*, that encodes eotaxin-3, whose expression is induced by IL-13. Increased gene expression levels of eotaxin-3 correlate with the increased counts of eosinophils and mast cells in the oesophageal tissue[32] and might activate dendritic cells and ultimately enhance T_H2 immune activation, as shown in mice[58].

The presence of readily detectable eosinophils does not necessarily imply that these cells have a primary role in the immunopathogenesis of EoE. Amongst others, B cell-derived immunoglobulins such as IgE (pivotal in several atopic diseases) have been investigated overall in humans, suggesting a limited role of IgE in EoE[20,59–62]. By contrast, IgG4 levels have been consistently shown to be increased in the oesophageal tissue of patients with EoE[62] and equivalently in eosinophilic gastroenteritis[63], with systemic IgG4 levels significantly ($P=0.038$) higher (yet decreasing under topical steroid treatment)[64] in EoE.

The oesophageal microbiota appears to have a rather distinct composition. Modulating the oesophageal microbial composition affects not only morphological features of oesophageal tissue (specifically promoting epithelial development, with less-defined tissue architecture including mucosal layers and keratinization in

◀ Fig. 1 | **Overview of the pathogenesis of eosinophilic oesophagitis. a** | Via the oesophageal lumen, food-derived antigens (aero-allergens, such as pollen and microorganisms might also be implicated) penetrate the oesophageal epithelium, leading to activation of the mucosal immune system. **b** | The impaired epithelial barrier function represents a crucial element in the pathogenesis promoted by the activated immuno-inflammatory cascade (with a presumable reciprocal amplification), genetic susceptibility and luminal factors, including acid reflux. The contact between antigens and antigen-presenting cells (APCs) induces a transformation into dendritic cells. Subsequently, a complex interplay between dendritic cells and naive T cells results in a polarization of the T cells to a T helper 2 (T_H2) cell pattern. Activated immune response promotes fibrosis and stricture formation in the long term, at least in a fraction of susceptible patients. Antigens induce the secretion of cytokines, such as TSLP and IL-33, by the epithelial cells in the lamina propria, which leads to stimulation of immune cells, such as ILC2, iNKT, mast cells and dendritic cells. Mast cells produce PGD2, an important chemoattractant after binding to CRTH2 receptors, which are expressed on T_H2 cells, eosinophils and basophils. Secreted IL-4 induces the differentiation of T_H2 cells, which secrete IL-13 inducing eotaxin-3 release and subsequently IL-5. Subsequently, mast cells, eosinophils and T_H17 cells secrete TGFβ1, which stimulates fibroblasts. IL-13 secreted by T_H2 cells along with TGFβ1 and activated fibroblasts contributes to tissue damage and impaired barrier function. CRLF2, cytokine receptor-like factor 2; CRTH2, chemoattractant receptor expressed on T_H2 cells; hPGDS, human prostaglandin D synthase; ILC2, type 2 innate lymphoid cells; iNKT, invariant natural killer T cells; MHCII, major histocompatibility complex class II; OX40L, ligand for OX40; peTh2, pathogenic effector T_H2 cells; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor. Part of part **a** adapted with permission from REF.[55], Elsevier. Part **b** adapted from REF.[209], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

germ-free mice) but also gene expression (including genes involved in barrier function and associated with EoE, such as *POSTN*, *KLK5* and *HIF1A*)[65–69], pointing to a continuous host–microbiota interaction driving mucosal immune response, similar to that in inflammatory bowel disease[70].

Several other interactions within the oesophageal epithelium might be important for immune activation, such as, for instance, the crosstalk between endothelial cells and fibroblasts. In 311 patients with EoE and a fibrostenotic phenotype, reduced expression levels of TSPAN12 — a membrane protein from the tetraspanin family — in endothelial cells was associated with chronic T_H2-mediated inflammation and increased IL-13 protein levels in endothelial cells. This deficiency in TSPAN12 induced the production of profibrotic mediators in fibroblasts[71].

Finally, the importance of environmental factors (dramatic changes in which might be associated with an impressive epidemiological increase in the risk of EoE[26,72,73]) in the pathogenesis of EoE has increasingly been recognized. However, knowledge in this area remains limited compared to the extensive research in other domains[28,74].

Clinical guidelines

During the past years, several important guidelines and consensus papers concerning the diagnosis and treatment of EoE have been published[6,75,76]. The guideline initiatives mentioned represent a valuable resource for any practising clinician involved in the diagnosis, treatment and follow-up of patients with EoE.

The AGREE group (a working group on PPI-responsive oesophageal eosinophilia) provided an international consensus (global authorship contribution) on the diagnostic definitions and procedures in EoE in general and, more specifically, on the use and position of PPIs in the diagnostic process[77]. The American Gastroenterology Association and the Joint Task Force on Allergy-Immunology Practice Parameters provided comprehensive North American guidelines on the clinical management of patients with EoE[78]. In addition, diagnostic and therapeutic guidelines were created by a joint European group, comprising the United European Gastroenterology organization, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, the European Academy of Allergy and Clinical Immunology, and the European Society of Eosinophilic Oesophagitis[79]. Finally, the British Society of Gastroenterology, the British Society of Paediatric Gastroenterology, Hepatology and Nutrition published, in 2022, comprehensive consensus guidelines on the diagnosis and management of EoE in children and adults[76].

The differences between these guidelines are minor, mostly relating to nuances regarding weighting of available diagnostic procedures and thresholds or therapeutic options. However, what remains true for all these guidelines is that, with such a rapidly evolving field, updates are required, including novel clinical trial data on swallowed topical steroids and pivotal trials on biologic agents, specifically regarding the approval of the biologic agent dupilumab by the FDA.

Diagnosis

In a consensus conference in 2006, an international panel of paediatric and adult gastroenterologists, allergists, immunologists and pathologists confirmed the concept of the first description of the disease. EoE was defined as a disease restricted to the oesophagus characterized clinically by symptoms of oesophageal dysfunction and histologically by an eosinophil-predominant inflammation[1]. Other causes of oesophageal eosinophilia have to be ruled out, particularly reflux disease, eosinophilic gastroenteritis, coeliac disease, Crohn's disease, achalasia and drug hypersensitivity. The diagnostic instruments, which form the two diagnostic pillars in EoE, are a thorough anamnesis (medical history) and a careful histological examination.

Moreover, during the past decade, it has become evident that EoE also evokes characteristic endoscopic alterations[6]. Thus, endoscopic abnormalities, systematically assessed using the endoscopic reference score (EREFS)[80], can be regarded today as a third diagnostic pillar. Laboratory analyses, imaging studies and functional examinations have a subsidiary role and are indicated in complex diagnostic situations or for research purposes[81]. As the diagnosis of EoE is complex, clinicians should diagnose EoE based on a combination of symptoms, and histological and endoscopic findings, as no single feature is sufficient to establish a definitive diagnosis. In the following, we discuss the value, limitations and challenges of each diagnostic instrument.

Symptoms in children and adults

The symptoms of eosinophilic oesophagitis follow a hierarchal pattern from early childhood to adulthood[7,82]. In early childhood, symptoms are non-specific, and include food refusal, failure to thrive, nausea, vomiting,

regurgitation, abdominal pain and even diarrhoea. In older children, symptoms are more related to the oesophagus with heartburn, chest pain and early manifestations of dysphagia such as slow and picky eating. Symptoms mainly reflect oesophageal dysfunction with dysphagia for solid food and food impaction in adolescents and adults. Notably, heartburn mimicking reflux disease, in addition, is present in more than 50% of adults[12].

As dysphagia is a hidden symptom and challenging to quantify, several symptom scoring systems have been developed; amongst these, the Eosinophilic Oesophagitis Activity Index (EEsAI)[83] and the Dysphagia Symptom Questionnaire (DSQ)[84] are the leading ones for use adult patients. A fraction of patients (more frequently those with concomitant atopic conditions) also report immediate symptoms (discomfort, itching, burning, pressure sensation) after the ingestion of certain trigger foods or beverages (for example, fruits, nuts or wine) either in the oral cavity (referred to as food pollen allergy syndrome, or oral allergy syndrome[85]) or in the oesophagus or retrosternal region (referred to as food-induced immediate response of the oesophagus[86]).

Endoscopic abnormalities

Upper endoscopy is the first step in the diagnostic work-up of solid food dysphagia, the chief complaint in EoE. In addition, endoscopy is important in EoE to obtain biopsy samples[1]. Initially, endoscopic alterations in EoE were considered absent[4] or, if present at all, only subtle[5]. However, increasingly characteristic endoscopic findings have been recognized within the past years, and today completely normal-appearing oesophageal mucosa is found in less than 5% of patients with EoE[80].

To standardize endoscopic findings to monitor disease activity and clinical trials, a graded endoscopic grading tool has been developed[80]. The EREFS is a summation and scoring of the five most prominent EoE signs, in particular, oedema (E), rings (R), exudates (E), furrows (F) and strictures (S) (FIG. 2). One of the key questions is whether the EREFS corresponds to histologically defined disease activity. Several studies have addressed this question with conflicting results[87–89]. One explanation could be that the EREFS consists of inflammatory components (oedema, exudates and furrows) and fibrotic components (rings and strictures). The mounting opinion is that endoscopic findings can represent an important end point of disease activity. At the very least, using the EREFS provides clinicians and researchers with a common endoscopic language in the diagnosis and follow-up of patients with EoE. In contrast to the magnitude of other available clinical scores in different disease states, we feel that EREFS is also very useful, aside from clinical trials and research, in everyday clinical practice. Indeed, due to its simplicity and the acronymic coding of the key findings to investigate during upper endoscopy, it can also be a valuable tool for clinicians with little experience in EoE.

Histological findings

Six to eight endoscopically gathered biopsy samples separately obtained from the distal and proximal oesophagus are needed to ensure high sensitivity for

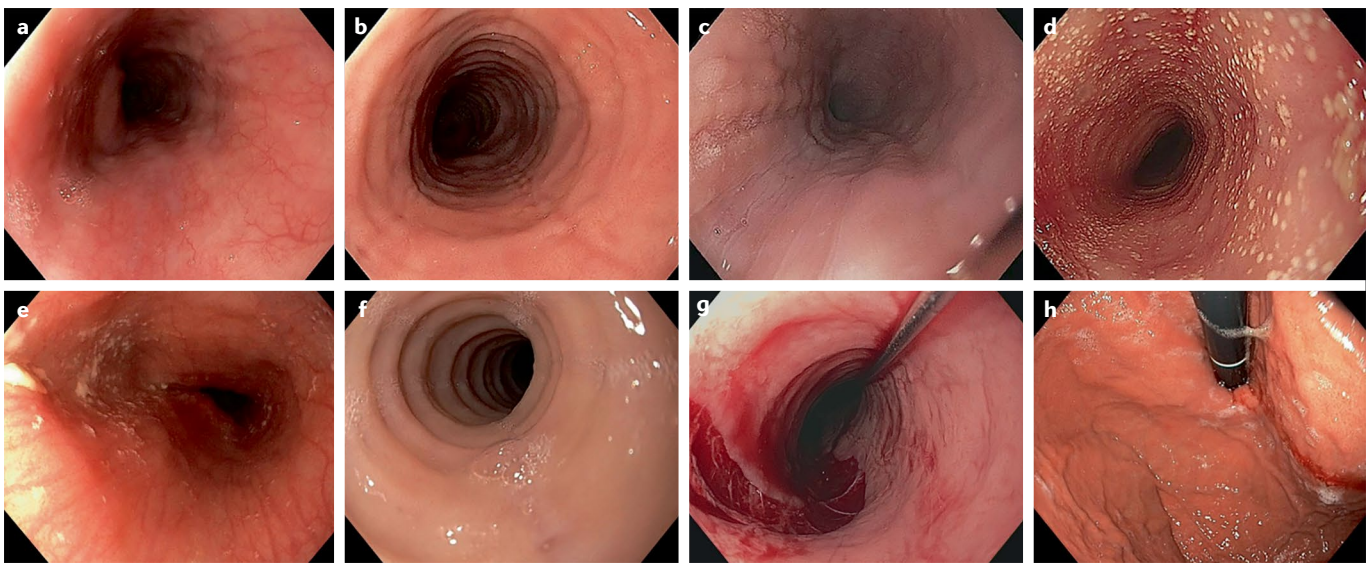


Fig. 2 | **Endoscopic features of eosinophilic oesophagitis. a** | Normal oesophageal mucosa in the distal oesophagus with no oedema or signs of active inflammation. A mild but distinctive formation of rings and discrete reflux lesion can be seen at the gastro-oesophageal junction. **b** | Whitish exudates. In contrast to the normal oesophagus, submucosal vessels cannot be identified, indicative of oedema of the mucosa. **c** | Formation of rings (moderate severity, passage with endoscope possible). **d** | Marked longitudinal furrows in conjunction with exudates within and adjacent to the furrows (oedema and mild ring formation are also present). **e** | *Candida* infection (thrush). Superficial whitish covering with normal underlying oesophageal mucosa without oedema (in contrast to the inflamed mucosa with active EoE and exudates). **f** | Stricture formation. The diameter of the oesophageal lumen is profoundly reduced with notable resistance during the passage of a standard gastroscope. **g** | Mucosal tear after endoscopic bougie dilation (the guide wire for endoscopic dilation is still in place). **h** | Inversion (that is, retrograde) view within the stomach towards the cardia and lower oesophageal sphincter. Closure of the cardia (insufficient closure can be indicative of an increased risk of concomitant gastroesophageal reflux). In this patient, a dilation with mucosal tear at the gastroesophageal junction was performed immediately prior to retroversion; therefore, some mild bleeding from this region can be observed. EoE, eosinophilic oesophagitis.

the histological diagnosis of EoE[90]. Within these biopsy samples, an eosinophil count (eos) greater than 15 in one high-power field (HPF) is the necessary condition for defining eosinophilic oesophagitis[6]. The arbitrary fixed threshold of 15 eos per HPF has proven valid as a criterion for diagnosis and disease activity follow-up[78,79]. Interestingly, data separating 20 patients with active and inactive EoE based on mucosal impedance measurements have shown that the histological threshold of 15 eos per HPF correlates with oesophageal mucosal integrity[91].

In addition to oesophageal eosinophilia, other histological changes, such as spongiosis (dilation of intercellular spaces), increased mast cell numbers (albeit special staining techniques are required[92]) and lymphocyte numbers, basal zone hyperplasia and papillary elongation occur in eosinophilic oesophagitis[93]. As the precise mechanisms leading to these changes are still unknown, the relationship between these parameters and disease activity is unclear. However, preliminary data in patients with EoE suggest that basal zone hyperplasia and spongiosis can persist despite the resolution of oesophageal eosinophilia[94]. Whether these persistent alterations represent an incomplete or slowly resolving inflammatory change or a baseline histological finding with EoE remains unclear. As a result, the authors of this Review question whether the normalization of all histological features should be introduced as a further and more rigorous definition of EoE in remission.

Similar to the assessment of symptoms and endoscopy, a replicable histological scoring system has been devised[93]. The eosinophilic oesophagitis histological scoring system (EoE-HSS) evaluates eight features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis[93]. The score discriminated well when applied to 201 biopsies from 104 patients who received or did not receive treatment, particularly for spongiosis, eosinophil surface layering and eosinophil abscesses. Importantly, it provides pathologists with a global common language for assessing the activity of EoE and conducting therapeutic trials[93]. However, until now, EoE-HSS is neither required nor routinely used in standard clinical practice due to its relatively high complexity.

Less-invasive methods for diagnosis

Although EoE is best diagnosed by endoscopy and oesophageal biopsy, the costs and risks of this procedure are burdensome. As a result, either less-expensive and/or less-invasive alternatives are currently being developed. However, these methods are not available for routine clinical practice and are not even used in most current EoE therapeutic trials (except for transnasal endoscopy in the paediatric population).

Transnasal endoscopy is a valuable alternative to standard endoscopy as it does not require sedation and directly visualizes the oesophageal mucosa. In addition, biopsy specimens from 190 children and young adults were adequate without a difference in surface area compared to standard endoscopy. Transnasal endoscopy is mainly used in paediatric patients, but further studies will demonstrate if this method will generally be applied in adult patients[95].

Cytosponge is a device that consists of a gelatin capsule containing a compressed mesh attached to a string. The capsule is swallowed, and in the stomach, the gelatin dissolves within a few minutes with the release of a spherical mesh. The attached string is used to withdraw the mesh, and a tissue specimen is collected from the sponge[96]. A robust specimen for cytology analysis can then be analysed through cellular markers or even as histology in a paraffin block. Cytosponge is an ideal technique to monitor EoE, potentially reducing the need for endoscopy.

The oesophageal string test consists of a capsule filled with a string. Upon swallowing, the capsule dissolves in the stomach or duodenum, and after 1–12 h (overnight), the string is withdrawn, and the secretions are scraped from the string and stained for eosinophil-derived protein markers[97]. A study evaluating the value of the oesophageal string test in children with reflux disease ($n = 8$), EoE (14 patients with active disease and 8 in remission) and controls (15 individuals) showed that the string test reliably distinguishes between active EoE, EoE in remission, GERD and normal oesophagus[97]. The oesophageal string test is, therefore, an additional less-invasive method to monitor EoE.

Examinations of oesophageal function

As symptoms of oesophageal dysfunction are part of the definition of EoE, examinations assessing the functional state of the oesophagus have been developed. A functional luminal imaging probe (FLIP) measures the oesophageal distensibility obtained through an orally passed catheter with an inflatable balloon. Oesophageal remodelling with damage to the organ structure and function is a well-known sequela of untreated EoE[98]. However, endoscopic, radiological and histological assessment of the degree of fibrosis and strictures is difficult. FLIP measures pressure–volume characteristics by stepwise inflation of the balloon and converts the data into a three-dimensional colour plot reflecting the degree of oesophageal fibrosis[99]. This technique gives an accurate and easily demonstrated assessment of oesophageal distensibility and can become an important tool for monitoring progression in eosinophilic oesophagitis[99].

Oesophageal impedance is a measure of the combined effect of electrical resistance and reactance in a circuit. As dilation of epithelial intercellular spaces increases paracellular fluid and electrolyte flow, the epithelium becomes a better conductor of electricity. As a result, the measurement of mucosal impedance becomes a potential tool to measure EoE histological activity[91]. In a study in 20 patients with EoE using an endoscopic impedance probe, point mucosal measurements demonstrated a 90% sensitivity and 91% specificity compared with the degree of spongiosis measured in terms of eosinophil count per HPF[91]. However, whether this method could replace the current endoscopic and histological determination of the inflammatory activity of EoE remains to be determined.

Challenges in diagnosis

A first debate relating to the diagnosis of EoE centred around the importance of eosinophilia in the oesophageal epithelium, which is currently the established cornerstone for diagnosing and monitoring this chronic inflammation[6]. However, despite the prominent appearance of late-phase inflammatory cells, that is, eosinophils, their role in the immunopathogenesis of EoE is still poorly understood. This lack of understanding is illustrated by therapeutic studies using monoclonal antibodies against IL-5 to block eosinophil recruitment. Although mepolizumab[100] and reslizumab[101] successfully reduced blood and tissue eosinophilia by approximately 90% and 55%, respectively, symptoms persisted, and other inflammatory cells, such as T cells and mast cells, remained almost completely unchanged. In addition, a multicentre study published in 2022 investigated EoE variants, that represent syndromes clinically presenting with oesophageal dysfunction resembling EoE but lacking relevant eosinophilia in the oesophageal tissue[102]. Interestingly, an infiltration with T cells and mast cells and a gene expression pattern resembling that of EoE could be demonstrated utilizing immunohistochemistry and molecular analyses[102]. These findings illustrate that the role of eosinophils is unclear, and other inflammatory markers must be considered in the diagnosis and pathogenesis of EoE.

A second challenge in the diagnostic procedure in EoE remains the identification of culprit food(s). It is well-established that EoE is caused in most patients by allergies to specific foods[1]. Thus, identifying culprit foods is an essential component of diagnostic procedures, potentially paving the way to non-medical and, ideally, treatment options to treat the cause. Unfortunately, almost all established diagnostic tools are based on the detection of IgE sensitizations and have only minimal value in the search for causative food allergens[20]. The only way to identify causative food allergens is to start an empirical elimination diet and confirm histological remission with each food addition or subtraction[103]. Therefore, developing reliable diagnostic tests to identify causative foods is another unmet diagnostic need in EoE. In addition, there seems to be a substantial diagnostic delay of around 10 years across patients with EoE, according to a longstanding cohort study from Denmark comprising 308 patients[104]. This delay, which does not appear to be decreasing currently[105], is of crucial importance and is associated with insufficient consistency concerning the initiation of adequate EoE-directed medical therapy[104] and an increase in the risk of a fibrostenotic phenotype[98,106].

Moreover, in contrast to other chronic immune-mediated diseases, there has been a lack of an established index on the clinical severity of disease in EoE, a potentially necessary prerequisite for decision-making regarding monitoring and treatment of EoE. In 2022, an international expert consensus initiative introduced a simple index developed for use in routine clinical practice (and not only therapeutic trials) based on symptoms, endoscopic and histological features, and complications: the Index of Severity for Eosinophilic Esophagitis (I-SEE)[107].

Monitoring of eosinophilic oesophagitis

So far, no medical or dietary measure can cure EoE. EoE must, therefore, still be regarded as a chronic disease[108] with the necessity for diagnostic and long-term therapeutic management. Despite this obvious need, to date neither guidelines nor consensus recommendations on the long-term management of EoE have been published. Nevertheless, EoE centres have been forced to implement empirically developed follow-up strategies in their clinical practice. In a twin-centre study, researchers from a US and Swiss EoE centre compared their diagnostic and therapeutic long-term regimes[109]. Based on their experience and a complementary literature search, the following monitoring strategy can be recommended.

In patients with EoE, a diagnostic work-up includes a structured assessment of symptoms (EEsAI, DSQ), endoscopic alterations (EREFS) and histological abnormalities (EoE-HSS score). Less-invasive methods potentially replacing endoscopy are on the horizon but not yet implemented in clinical routine[109]. A diagnostic work-up must be performed at the time point of the initial diagnosis and around 3 months after initiation of a novel treatment or after each relevant change of the therapy[109]. Under stable conditions and solid adherence to treatment, a diagnostic work-up once per year is adequate for most patients. However, a closer follow-up can be mandatory in more difficult-to-treat patients, such as those with a fibrostenotic disease, who often require more frequent dilation at the beginning. By contrast, this interval can be extended in the long-term perspective in selected patients with a stable course of disease under established therapy[109].

The presented concept seems to be a reasonable strategy with proven clinical practicability and is currently being used in many EoE centres. Nevertheless, we must acknowledge that it still has a poor evidence base, highlighting the need for future research on the ideal long-term management of EoE.

Therapy

Rationale

The treatment in EoE has two goals: control of symptoms and control of inflammation leading finally to the prevention of complications. The therapeutic armamentarium to achieve these goals can be subsumed under the initialism DDD, representing the following three categories: drugs (pharmacological therapy), diet (elimination of culprit food categories) and dilation (mechanical therapy). Notably, because of the current understanding of the pathogenesis of EoE as a food allergy, only an elimination diet can be considered a treatment of the cause. By contrast, drugs and dilation are administered with the intention of alleviating symptoms. However, there is increasing evidence that effective long-term medical control has disease-modifying potential and reduces long-term complications such as stricture formation and food impaction[79,98,106,110,111]. By contrast, although dilation can have a beneficial effect on symptoms, it appears to have no effect on the underlying oesophageal inflammation and, therefore, on the course of the disease[112].

There is consensus that — contrary to other immune-mediated diseases of the gastrointestinal tract such as

Crohn's disease — in EoE, a 'watch-and-wait' strategy cannot be recommended. With awareness of the progressive nature of EoE, therapy is required in all patients fulfilling the diagnostic criteria[78,79]. Moreover, most patients need to maintain this treatment in the long term as recurrent disease activity upon withdrawal of therapy is the rule, and sustained remission without therapy is the exception[110,113,114].

The therapeutic landscape is currently evolving dramatically and rapidly. At the time of writing, the only currently approved treatment options for EoE are budesonide effervescent tablets in most European territories (first approved agent for the indication of EoE by EMA in 2018 (REF.[115])). In May 2022, dupilumab received FDA approval as the first treatment option in the USA for the indication of EoE[116]. There can be a considerable discrepancy between the frequency of routine use in clinical practice and approval for the given indication of EoE, most prominently evident regarding PPIs, which are not approved for use in EoE. On the other hand, available clinical trial data for a given emerging treatment option or even approval by regulatory agencies in a territory might stimulate more frequent off-label use in other regions of the world (as expected, for example, with dupilumab outside the USA). An overview of topical steroids, PPIs and miscellaneous established and evolving medical therapies for EoE is provided in TABLES 1 and 2.

Drugs

Swallowed topical corticosteroids. The first study investigating the therapeutic potential of steroids was published in 1998 (REF.[117]). In this study, 20 paediatric patients with reflux symptoms and oesophageal eosinophilia refractory to aggressive anti-reflux therapy were treated with systemic oral steroids (1.5 mg methylprednisolone per kilogram body weight); there was a dramatic improvement in all but one patient. In the same year, a small case series was published[118]. In this series, four children were treated with topically administered steroid-using inhalers without a spacer chamber was published. Two important aspects of this pioneering work fuelled further development of swallowed topical corticosteroids (STCs): first, multiple courses of steroids are typically needed, and second, drug delivery to the oesophagus is critical, realizing that the current adoption of a vehicle being developed for optimal drug delivery to the airways is only a makeshift solution at best. Subsequently, various local-acting steroid preparations with budesonide, fluticasone, ciclesonide and mometasone in powder, syrup and slurry were investigated[119–127].

Three major clinical trial programmes have been initiated during the past few years, aiming to achieve an approved STC preparation. Amongst these, the use of budesonide as an effervescent tablet (budesonide oral dispersible tablet) is the most advanced[110,128], having received approval by the EMA in 2018 as the first medical treatment in the world for the indication of EoE. During development, the oral dispersible formulation was directly compared with a viscous slurry, and revealed similar efficacy but higher satisfaction in the 74 participating patients for the former[122]. In parallel, phase II and III studies (including 93 and 318 patients, respectively) for budesonide oral suspension in a large clinical trial programme including 25 US centres were successfully conducted[129–131], but the FDA has not so far approved this preparation, recommending a further clinical trial.

Phase IIa and IIb studies (including 24 and 106 patients, respectively) with participating centres in North America and Europe of an orally disintegrating fluticasone propionate tablet were successfully conducted[132,133], with a currently ongoing phase III study (NCT04281108, having enrolled 143 patients) using the higher dose of 3 mg at bedtime.

In summary, in these trials, all STC compounds and all formulations have convincingly demonstrated effectiveness in controlling symptoms and inflammation in EoE, both as induction and as maintenance treatment. Fortunately, neither loss of response nor relevant adverse effects have been observed so far. Furthermore, because of the more consistent and higher reported rates of remission with STCs than with PPIs, STCs can currently be regarded as the first-line medical treatment for EoE[78].

Proton pump inhibitors. There are several reasons why PPIs are used to treat patients with EoE. Given the high prevalence of GERD and EoE, both conditions can coexist and reciprocally promote each other[1]. These patients can be given PPIs as an adjunct therapy[78]. Oesophageal exposure to acid causes more pain in patients with EoE than in healthy individuals[134]. Acid blockade can therefore reduce symptoms of EoE. Some patients with typical features of EoE and pH-metric excluded GERD have symptoms and inflammation that respond to PPI monotherapy[135]. In 2016, a panel of experts agreed that PPI-responsive oesophageal eosinophilia — based on its clinical, endoscopic, histological and molecular similarities with conventional EoE — should be regarded as a clinical sub-phenotype of EoE and not as a distinct entity[136]. Several modes of action explaining the efficacy of PPIs in EoE are considered, including acid-related[137] and acid-independent ones, such as modulation of the transcriptome of oesophageal epithelial cells[138]. However, the mode of action of PPIs in EoE is not entirely clarified.

Antiallergic agents and immune modulators. Leukotriene inhibitors (such as montelukast), which represent a standard therapeutic measure in other atopic conditions such as allergic asthma, did not demonstrate effectiveness in controlling symptoms and inflammation in controlled trials despite an evident rationale for their use and promising preliminary data[139–141].

Immunosuppressants, particularly azathioprine and 6-mercaptopurine, have been investigated in a small study including three adult patients with steroid-dependent EoE[142]. Unfortunately, no further investigations are available despite the rather promising results in this uncontrolled setting.

Biologic agents. Biologic agents, mainly IL-13 and IL-4/IL-13 blockers, are currently almost exclusively available under study conditions and are considered a second-line medical treatment for patients with severe or refractory EoE[78,79].

Table 1 | **Clinical trials evaluating topical and systemic steroids for the treatment of eosinophilic oesophagitis**

Drug[a]	Dosing	Primary outcome	Other outcomes (selection[b])	Comments	Refs.
Fluticasone	880 µg per day for 12 weeks	≤1 eos per HPF: 50%	Decreased vomiting (symptom response), decreased furrows distally (endoscopic response)	Children (n = 36)	Konikoff et al. (2006)[197]
Fluticasone	880 or 1,760 µg per day for 4 weeks	≤1 eos per HPF: 56%	Improvement of presenting symptom	Children (n = 80); control group: prednisone (2 mg per kg per day); only open label (unblinded)	Schaefer et al. (2208)[198]
Budesonide	1,000 µg BID for 2 weeks	Significantly reduced mean eos (P < 0.0001)	Dysphagia improved significantly (P < 0.001 in the verum group; not in the PBO group)	Adults, RCT (n = 36)	Straumann et al. (2010)[120]
Budesonide	1,000 or 2,000 µg per day for 12 weeks	≤6 eos per HPF: 87%	Improvement in SDI (symptoms); improvement in furrows/exudates (endoscopy; no improvement in rings)	Children (n = 24); dose adjustment (subjects <5 feet tall received 1 mg; ≥5 feet tall 2 mg)	Dohil et al. (2010)[119]
Fluticasone	1,760 µg per day for 12 weeks	≤1 eos per HPF: 65% (<15 eos per HPF: 77%)	Improvement in heartburn	Adolescents and adults (n = 42); weaning schedule	Butz et al. (2014)[123]
Fluticasone	1,760 µg per day for 6 weeks	>90% decrease in eos	No symptom improvement in terms of MDQ; endoscopic resolution of initial EoE signs in 30%	Adults (n = 42)	Alexander et al. (2012)[199]
Budesonide (OVB)	2,000 µg per day for 8 weeks	<1 eos per HPF: 64% (<15 eos per HPF: 73%)	No difference in MDQ, Improvement in endoscopic findings (but not strictures)	Adults (n = 25)	Dellon et al. (2012)[200]
Fluticasone	880 µg per day for 8 weeks	Histological response (<7 eos per HPF), no significant difference between PPIs and STCs	No symptom improvement (according to MDQ), decrease in exudates (endoscopy)	Adults (n = 42); control group: PPI	Moawad et al. (2013)[191]
Budesonide (BOS)	2,800–4,000 µg per day for 12 weeks	≤1 eos per HPF: 77%	No difference in symptoms (clinical score)	Children (n = 71)	Gupta et al. (2015)[201]
Budesonide (BET versus BVS)	2,000 and 4,000 µg per day for 2 weeks	<16 eos per HPF: 94%	No difference in symptoms (Straumann Dysphagia Instrument) against PBO	BET (tablets) versus suspension in adults (n = 76)	Miehlke et al. (2016)[122]
Budesonide (BOS)	4,000 µg per day for 12 weeks	≤1 eos per HPF: 31% (<15 eos per HPF: 47%)	Improvement in Dysphagia Symptom Questionnaire; Improvement in EREFS	Adolescents and adults (n = 93)	Dellon et al. (2017)[129]
Budesonide (BET)	1,000 µg BID for 6 weeks	≤5 eos per HPF: 93%; primary EP was clinical/histological remission (58% versus 0% PBO)	Endoscopic remission in 61% (0% PBO)	Adults (n = 78); phase III induction study	Lucendo et al. (2019)[128]
Budesonide (BET)	1,000–2,000 µg BID for 48 weeks, after induction therapy versus withdrawal (PBO)	<1 eos per HPF: 79.4% versus 76.5% versus 1.5% for 2 mg/day, 1 mg/day and PBO; primary EP maintenance of clinical/histological remission (75% versus 73.5% versus 0% for 2 mg/day, 1 mg/day and PBO)	(Deep) endoscopic remission defined as EREFS 0 in 73.5% versus 67.5% versus 7.4% for 2 mg/day, 1 mg/day and PBO	Adults (n = 204; phase III; maintenance study; median time to relapse in the PBO arm was 87 days)	Straumann et al. (2020)[110]
Fluticasone (FODT)	1.5 mg or 3 mg FODT BID	Safety and tolerability as primary EP (drug was safe and well-tolerated)	Histological and endoscopic parameters revealing improvement	Adolescents and adults (n = 24), RCT, phase Ib/IIa	Hirano et al. (2020)[132]
Budesonide (BOS)	2,000 µg BID for 12 weeks open induction, followed by 36 weeks, after induction therapy versus withdrawal (PBO)	Primary EP histological and dysphagia symptom relapse (full analysis 24% versus 43.5% in BOS–BOS versus BOS–PBO)	13.2% of induction partial responders and non-responders fully responded at week 36	Adolescents and adults (n = 202 induction; n = 48 extension; phase III; long-term withdrawal)	Dellon et al. (2021)[131]
Budesonide (BOS)	2,000 µg BID for 12 weeks	Co-primary EP ≤6 eos per HPF: 53.1% (versus 1% PBO) or dysphagia symptom response (≥30% reduction in DSQ): 52.6% (versus 39.1% PBO)	Also greater endoscopic response than PBO	Adolescents and adults (n = 318; phase III, induction)	Hirano et al. (2022)[130]

Table 1 (cont.) | **Clinical trials evaluating topical and systemic steroids for the treatment of eosinophilic oesophagitis**

Drug[a]	Dosing	Primary outcome	Other outcomes (selection[b])	Comments	Refs.
Fluticasone (FODT)	Four doses: 3 mg BID and BT, 1.5 mg BID and BT for 12-week induction and 40 weeks of maintenance	≤6 eos per HPF: 80%, 67% (3 mg BID and BT), 86%, 48% (1.5 mg BID and BT); significant reduction for all dosages (PBO 0%; $P < 0.001$)	EREFS reduction and dysphagia frequency superior to PBO	Adults (phase IIb, dose finding), $n = 106$	Dellon et al. (2022)[133]

BET, budesonide effervescent tablet; BID, twice per day; BOS, budesonide oral suspension; BT, bedtime; BVS, budesonide viscous suspension; EoE, eosinophilic oesophagitis; eos, eosinophil count; EP, end point; EREFS, endoscopic reference score; FODT, fluticasone propionate orally disintegrating tablet; HPF, high-power field; MDQ, Mayo Dysphagia Questionnaire; OVB, oral viscous budesonide slurry; PBO, placebo; PPIs, proton pump inhibitors; RCT, randomized controlled trial; SDI, Straumann Dysphagia Instrument; STCs, swallowed topical corticosteroids. [a]Swallowed topical steroids for the treatment. [b]Selection focusing on available controlled trials.

Three controlled trials in which mepolizumab and reslizumab (humanized antibodies against IL-5) were used to treat children and adults with active EoE demonstrated a reduction in the number of peripheral blood eosinophils by more than 90% and of tissue eosinophilia by 55%, and both had a favourable safety profile. Unfortunately, clinical improvement was minimal, and non-eosinophil inflammatory cells persisted in oesophageal tissue[100,101,143]. Currently, a phase III trial using a monoclonal antibody against the IL-5 receptor[144] is active[145]. In a phase II study enrolling 99 patients, a monoclonal antibody against IL-13 was found to improve endoscopic and histological disease activity in the short term[146] and long term[147] (16 and 52 weeks, respectively), but its symptom-modifying potential remains to be proven.

Dupilumab represents the most advanced biologic therapy in the treatment of EoE. It constitutes a human monoclonal antibody specifically targeting the α-chain subunit of the IL-4 receptor, which is shared between IL-4 and IL-13, and therefore simultaneously inhibits signalling of both interleukins[148]. It was shown that a reduction in the hallmark T_H2-inflammatory response was associated with reduced expression levels of biomarkers, including thymus and activation-regulated chemokine, plasma eotaxin-3 and serum total IgE[149], and dupilumab is currently used to treat uncontrolled asthma[150] and atopic dermatitis[151]. In a phase II study in 47 patients with change in symptoms (Straumann Dysphagia Instrument patient-reported outcome scores) as the primary end point, weekly subcutaneous administration of dupilumab significantly improved dysphagia ($P = 0.03$) at week 12 and histological ($P < 0.0001$) and endoscopic ($P < 0.0001$) disease activity (secondary end points)[152]. Notably, the drug was well tolerated, no serious adverse events related to the drug occurred, and no increased conjunctivitis was observed. A phase III study of dupilumab has completed, and current abstract data confirm significant ($P < 0.001$) beneficial treatment effects on clinical symptoms and eosinophil counts[153]. However, the crucial question arises as to whether it is justified to tackle a disease localized to the oesophagus with a systemic intervention affecting the immune system. The answer depends first on the preceding course of the disease, particularly the severity and refractoriness of the EoE to conventional treatment options and, second, whether it is necessary to simultaneously treat one or more concomitant atopic diseases[154,155].

Sphingosine-1-phosphate (S1P) is a membrane-derived signalling molecule[156]. The five isoforms of the S1P receptor exert various functions in the adaptive and innate immune responses, including regulation of endothelial barrier function, fibrogenesis and trafficking of immune cells[156]. S1P receptor modulators have been approved or investigated for the treatment of numerous immune-mediated diseases, including multiple sclerosis and ulcerative colitis[157]. A phase II clinical trial in 108 patients is currently investigating the use of etrasimod, a selective $S1P_{1,4,5}$ receptor modulator, for the treatment of EoE[158].

Dietary treatment

EoE seems to be primarily driven by the exposure of the oesophageal epithelium to food proteins. Thus, contrary to any other available therapeutic option, an elimination diet is the only treatment that directly and causally targets the root cause of the disease[159]. In addition, an elimination diet offers the potential to achieve long-term remission and control of symptoms without the necessity for continuous drug intake[160]. Seminal work to reinforce the concept of food allergens mediating EoE dates back to a case series in ten children in 1995, in which an exclusive amino acid-based formula successfully controlled refractory oesophageal eosinophilia attributed to refractory GERD[21].

Despite these favourable factors, implementation and successful maintenance of dietary therapy, for various reasons, is still a challenge[157]. Most importantly, no tests are available to identify reliably which trigger food needs to be avoided in a given patient to achieve a therapeutic response[79,161]. As a result, most dietary regimens are currently selected empirically based on the known allergenic risk potential of food categories and upon the preference of the patient. Furthermore, almost all food categories include staple foods because strict adherence is a challenge for the patients and substantially impairs their quality of life[162].

Little is known about the efficacy of a combination of medical and dietary therapy. Considering the marked restrictions associated with an elimination diet, a truly effective elimination diet, even as monotherapy, should lead not only to control of symptoms but also to reductions in endoscopic and histological activity. In any case, dietary therapy should eliminate the lowest possible number of triggering foods to ensure proper nutrition and to minimize the negative effect on quality of life[157,162].

Table 2 | **Clinical trials evaluating proton pump inhibitors and miscellaneous non-steroidal drugs for the treatment of eosinophilic oesophagitis**

Drug name[a]	Mechanism of action	Dosing	Primary outcome	Other outcomes (selection[b])	Comments	Refs.
Esomeprazole	PPI	40 mg, OD, PO for 8 weeks; randomized versus aerosolized swallowed fluticasone (440 µg BID)	Dysphagia improvement 25% in PPI and 50% in fluticasone (NS); no significant differences between the two treatments regarding decrease in eosinophils per HPF (including in subgroup with abnormal pH study)	No differences in eosinophils per HPF decrease regarding partial (≤15 eos per HPF) or complete (≤5 eos per HPF) resolution	Adults (n = 25; 56% had acid reflux according to pH study); unblinded randomized	Peterson et al. (2010)[202]
Esomeprazole	PPI	40 mg, OD, PO for 8 weeks, versus fluticasone 440 µg BID	Histological response <7 eos per HPF: 19% fluticasone versus 33% PPI; 0 of 4 and 4 of 4 in fluticasone group and PPI group with concomitant GERD	Significant decrease in symptoms (MDQ) for PPI (P < 0.001) but not fluticasone; similar improvement in endoscopic findings in both groups	Adults (n = 42; 50% PPI) newly diagnosed; single-blind RCT; 19% coexisting GERD	Moawad et al. (2013)[191]
Omalizumab	Anti-IgE	SC, every 2–4 weeks (based on body weight and serum level of IgE) for 16 weeks	Reduction of eosinophils per HPF (no difference from placebo)	No reduction in symptoms	Adults, RCT (n = 30)	Clayton et al. (2014)[62]
OC000459	Anti-CRTH2	PO (tablet), 100 BID	Significant decrease in eosinophils in verum group (from 114 to 73 eos per HPF; P = 0.0256) but not in PBO group	PGA, improvement in verum group (not PBO group)	Adults, RCT (n = 26)	Straumann et al. (2013)[203]
Dupilumab	Anti-IL-4 receptor-α	SC, weekly, 300 mg for 12 weeks	Significant change from baseline dysphagia score (SDI) of −3 at week 10 versus 1.3 (PBO; P = 0.0304)	Greater reduction in peak eosinophils per HPF versus PBO	Adults, RCT (n = 47)	Hirano et al. (2020)[152]
Dupilumab	Anti-IL-4 receptor-α	SC; part A DB (300 mg weekly, 24 weeks); thereafter potential extension to 28 weeks (part C) with two dosages; part B additional 24-week induction arm (after end of part A) with weekly or EOW dupilumab versus PBO	Co-primary EP: ≤6 eos per HPF and mean absolute change in symptoms DSQ (both at week 24)	Variety of additional histological, symptomatic and endoscopic EPs	Adults and adolescents (n = 321), children (n = 102), separate trials; DB and OLE PBO-controlled, RCT, phase III	[153,204]
Mepolizumab	Anti-IL-5	IV, three infusions every 4 weeks (0.55, 2.5 or 10 mg per kg)	Reduction of eosinophils per HPF (no difference across dosages)	Some decrease in symptoms	Children, RCT (n = 59), no PBO control	Assa'ad et al. (2011)[143]
Reslizumab	Anti-IL-5	IV, 1, 2 or 3 mg per kg (or PBO), weeks 0, 4, 8 and 12	Significant reduction in peak eosinophil count of 59%, 67%, 64% versus 24% placebo (P < 001); symptom improvement (co-primary EP) in all groups including PBO (NS)	NA	Children, n = 226, RCT	Spergel et al. (2012)[101]
Benralizumab	Anti-IL-5	SC	Co-primary EP: ≤6 eos per HPF and change from baseline DSQ	Endoscopy (EREFS), other clinical and histological parameters	Adolescents and adults, phase III, PBO, DB (24 weeks), OL (28 weeks), PBO-controlled RCT (n = 203)	[145]

Table 2 (cont.) | **Clinical trials evaluating proton pump inhibitors and miscellaneous non-steroidal drugs for the treatment of eosinophilic oesophagitis**

Drug name[a]	Mechanism of action	Dosing	Primary outcome	Other outcomes (selection[b])	Comments	Refs.
QAX576	Anti-IL-13	IV, 6 mg per kg (three infusions every 4 weeks)	>75% decrease in eosinophils per HPF 40% (versus 12.5% PBO)	Trend for symptom improvement, improved expression of variable transcripts relevant in EoE	Adults, *n* = 23, phase II	Rothenberg et al (2015)[205]
Cendakimab	Anti-IL-13	SC, 180 or 360 mg per week for 16 weeks	Change in mean eosinophil count per HPF: −94.8, −99.9 and −4.4 in 180-mg, 360-mg and PBO groups, respectively	Significant reduction in EREFS in both verum groups, more pronounced improvement in dysphagia with higher dose	Adults, DB RCT, phase II (*n* = 99)	Hirano et al. (2019)[146]
Cendakimab	Anti-IL-13	SC, OLE, 360 mg per week for 52 weeks	Continues improvement and/or maintenance of histological, endoscopic and clinical activity	No considerable difference at week 12 of OLE between patients receiving verum or PBO in induction; sustained improvement in symptoms with 360-mg dose	OLE, phase II, (*n* = 86)	Dellon et al. (2021)[147]
Cendakimab	Anti-IL-13	SC, weekly 360 mg induction (24 weeks), EOW in maintenance (24 weeks) or 360 mg weekly in induction and maintenance or PBO (three arms)	Co-primary EP: changes in symptoms (dysphagia days over a 14-day period) or ≤6 eos per HPF; incidence of AE over a minimum of 28 months (NCT0499193)	Variety of endoscopic, histological, clinical and exploratory	Adolescents and adults (*n* = 399); phase III, DB, PBO-controlled RCT, OLE; *n* = 259 in NCT04991935	[206,207]
AK002	Sialic acid-binding immunoglobulin-type lectin 8 (Siglec-8)	IV (infusion), monoclonal antibody, 1 or 3 mg per kg	≤6 eos per HPF and mean absolute change in symptoms on DSQ	Histological improvement, clinical symptoms and endoscopy	Adolescents and adults, DB and OLE PBO-controlled RCT, phases II and III (300 patients planned)	[208]
Etrasimod	Sphingosine-1-phosphate receptor 1 modulator (S1PR1)	PO (tablet), 1 and 2 mg for 24 weeks	Percentage change from baseline peak eosinophil count	Clinical symptoms, other histological outcomes, safety	Adults (*n* = 96), DB (24 weeks) and OLE (28 weeks), PBO-controlled RCT, phase II	[158]

AE, adverse events; BID, twice per day; DB, double blind; DSQ, dysphagia symptom questionnaire; EoE, eosinophilic oesophagitis; eos, eosinophil count; EOW, every other week; EP, end point; EREFS, endoscopic reference score; GERD, gastroesophageal reflux disease; HPF, high-power field; IV, intravenous (infusion); MDQ, Mayo Dysphagia Questionnaire; NA, not applicable; NS, not significant; PBO placebo; PPI proton pump inhibitor; OD, once daily; OL, open label; OLE, open label extension; PGA, physician's global assessment; PO, oral; RCT, randomized controlled trial; SC, subcutaneous (injection); SDI, Straumann Dysphagia Instrument; STC, swallowed topical corticosteroid. [a]PPI and advanced (non-STC) therapeutic options. [b]Selection focusing on controlled trials and those trials with either positive or promising results. With regard to PPI, there are no randomized placebo-controlled trials available; however, there are two controlled trials against fluticasone as STC. As advanced treatment options in EoE represents a dramatically rapidly evolving field, we included also the most promising emerging therapies, currently under investigation in clinical trials (without available published efficacy data).

There are a few studies that have investigated a combined medical and dietary treatment approach. Initial response and adherence rates are promising.

Nevertheless, after withdrawal of topical steroids and continuous dietary elimination, relapse of endoscopic and histological activity might occur despite potentially sustained control of symptoms[163]. Despite these limitations, a combined treatment approach might benefit patients failing prior medical monotherapy[164]. In the following sections we discuss the three leading modalities of elimination diets.

Elemental diet. The complete elimination of food proteins by administering an amino acid-based formula was notably the first treatment to show that dietary elimination truly works in EoE[21]. This extensively rigorous

restrictive diet is also to date the most effective therapeutic option for achieving histological remission in adults and children[156], with success rates of more than 90%[103]. This option might resemble the situation in paediatric Crohn's disease, in which an elemental diet was shown to achieve comparable or even better success rates than systemic steroid treatment[165]. Unfortunately, these formulations are expensive and unpalatable, hampering adherence, and reintroducing food after remission is an additional challenge. As the therapeutic goals are often achieved with less-restrictive dietary regimens that are burdened with a less-negative effect on quality of life[166], elemental diets should be reserved for patients with severe disease.

Targeted elimination diet. It is beyond doubt that a targeted therapeutic approach based on either an in vivo or in vitro test strategy to identify the essential culprit foods would be a major therapeutic breakthrough, boosting the acceptance of dietary restriction as a therapeutic strategy in EoE. Unfortunately, the accuracy and the positive and negative predictive values of the currently available testing strategies — skin prick test, atopy patch, microarrays, specific serum IgE analysis — are inadequately low[22,167–169]. It is not surprising that the effectiveness of test-based elimination diets is limited and even slightly lower than that of empirical two-food or four-food elimination diets[103,156]. The latter terms refer to the number of food categories to be completely eliminated relating to the more comprehensive elimination of the six most common food allergens (cow's milk protein, soy, wheat, egg, peanut and seafood), that is, the Six-Food Elimination Diet (6-FED)[170]. However, failure of conventional tests does not equal general futility, and emerging diagnostic options, such as direct oesophageal mucosal 'prick' testing[171] or determination of food-specific IgG4 in the oesophageal tissue[172], might advance this field in the future. Nevertheless, the current version of the European guidelines advocates against using allergy tests to identify food triggers in EoE[79,156].

Empiric elimination diet. The empirical elimination of six food categories with known high allergenic risks (6-FED) was the first regimen of this approach applied in children and adults with EoE[22,170]. Both studies demonstrated success rates of more than 70% with significant ($P < 0.001$ in both studies) improvement in oesophageal inflammation (≤10 eos per HPF). The researchers involved in these seminal reports aimed to overcome the drawbacks of the elemental diet by eliminating several but not all food proteins, in particular: cow's milk, wheat, soy, egg, peanut and tree nuts, and seafood[170,173,174]. However, despite the undoubted advances in palatability and adherence compared to the elemental diet, additional attempts were undertaken to optimize the 6-FED because a consequent elimination of several staple foods limited its use in selected patients, and the controlled reintroduction was time-consuming and costly because repeated endoscopies with biopsy sampling were required[175]. Notably, these studies also showed that the allergenic risks of the six food categories are not evenly distributed, with milk and gluten being more likely to be crucial than seafood and nuts[156,176]. This information opened the door to the evaluation of less-restrictive regimens, such as a four-food elimination diet (milk, gluten, eggs and legumes) which achieved remission rates above 50%[176,177] or even a one-food elimination diet with the elimination of cow's milk with a histological remission rate of 51% in a paediatric trial including 41 children[178].

Taken together, we recommend an elemental diet currently as a rescue measure in patients with severe disease, and an empirical elimination diet, preferably a step-up strategy beginning with elimination of one food or two foods, as a valuable alternative to pharmacological treatment in motivated patients.

Dilation therapy

It is well-established that EoE is a chronic and progressive disease[179]. It is, therefore, not surprising that longstanding untreated disease is associated with the risk of remodelling with the rigidity of the oesophageal wall and stricture formation[98]. Mechanical dilation has therefore been, since the early recognition of EoE, a frequently performed therapy. Initially, there were major concerns that this procedure could be harmful due to an increased risk of perforation. However, several studies have shown that even in severely altered oesophageal tissue, dilation therapy is not only highly effective[112,180] in reducing symptoms but also safe[112,181] with no increased risk of complications compared to other indications. However, this mechanical procedure does not influence the underlying inflammation. The two most frequently used devices are oesophageal balloon dilation or bouginage (that is, the dilation of the oesophagus) with Savary dilators, with no established differences in safety or efficacy between the two modalities[112,182]. In 2021, a study in 50 patients found that the use of the BougieCap, a novel single-use over-the-scope device comprising a conic transparent plastic cap (allowing dilation under direct endoscopic visual control of the narrowed oesophagus), is potentially feasible, safe and effective in this indication[183].

Most experts, including ourselves, recommend not providing dilation as the sole therapeutic measure in active EoE[184]. It is generally advisable first to control active inflammation and perform dilation only in patients with persistent symptoms or relevant strictures[185,186]. However, if absolutely required, dilation can also be performed in severely active disease or as a bridge to emerging medical treatment options in patients with refractory disease[187] and even in the event of food impaction[188]. The persistence of perceived symptomatic effects is highly variable, lasting only about 2 months up to 2 years, and even beyond. Post-procedural pain for several hours up to 3 days is quite common and can be more frequent in patients with EoE[112,189] compared to patients in whom dilation was performed for other indications. This observation potentially reflects an increased hypersensitivity and/or hypervigilance in patients with EoE[190].

Practical treatment options – algorithm

STCs and PPIs are considered first-line medical treatments for EoE, whereas biologic agents are positioned as a second-line alternative in patients with severe or

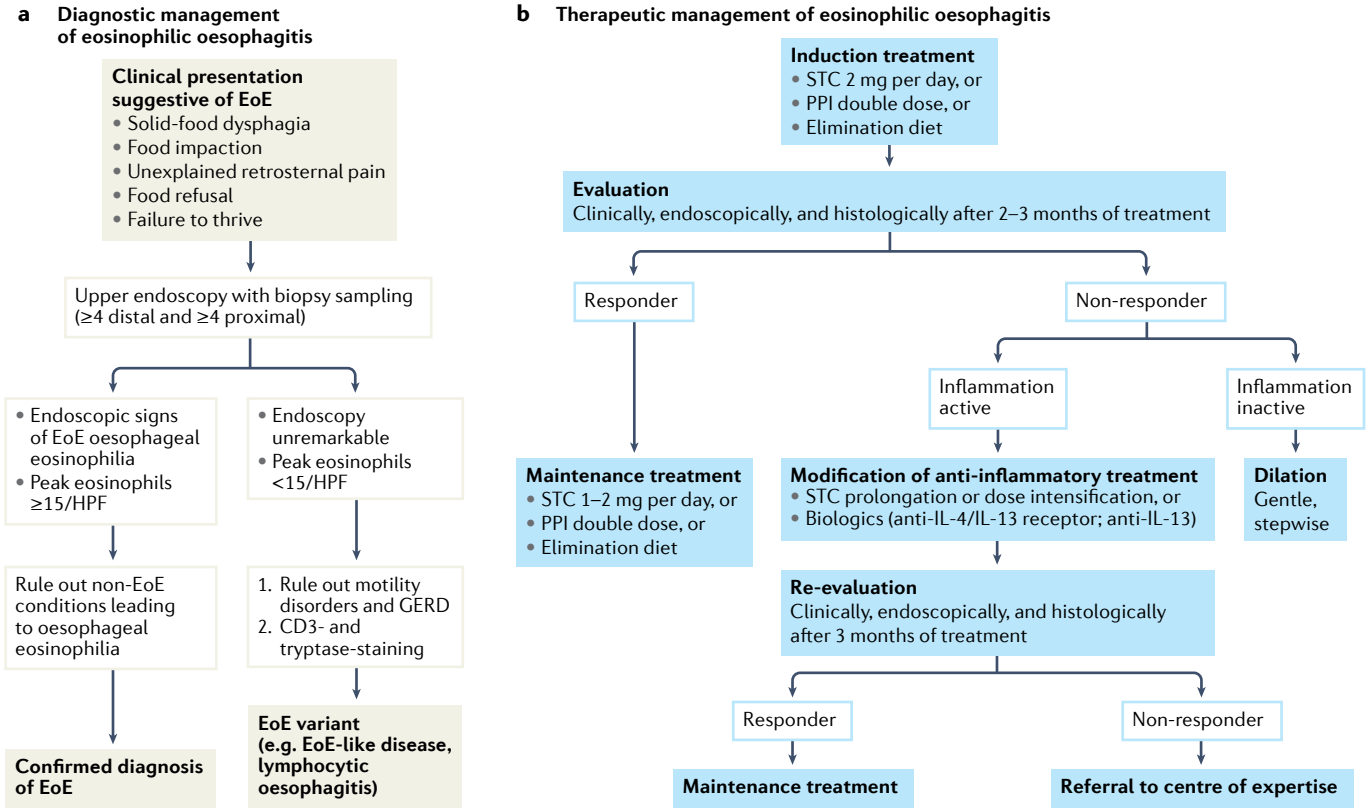


Fig. 3 | **Diagnostic and therapeutic algorithm.** Diagnostic (part **a**) and therapeutic (part **b**) algorithm for the management of EoE. Clinical symptoms suggestive of EoE (particularly if they are unexplained) should trigger diagnostic evaluation with endoscopy and histology representing the core diagnostic tests. After induction therapy, evaluation of therapeutic success is generally recommended, particularly as the isolated symptomatic response can be unreliable. In patients in whom successful control of endoscopic and histological inflammation is achieved but with persistence of symptoms, dilation therapy is often required. EoE, eosinophilic oesophagitis; GERD, gastroesophageal reflux disease; HPF, high-power field; PPI, proton pump inhibitor; STC, swallowed topical corticosteroid. Adapted with permission from REF.[210], Wiley.

refractory disease or with a relevant concomitant atopic condition (FIG. 3). The positioning of PPIs versus STCs has not been clarified as currently no well-powered head-to-head trial comparing PPIs and novel STC preparations is available. However, an older study including 42 patients comparing an off-label formulation of aerosolized swallowed fluticasone against a PPI identified no statistically significant difference between the two agents in achieving histological response[191]. By contrast, in real-life indirect comparison of therapeutic trials, STCs appear to be markedly more effective than PPIs in achieving histological response and remission[192]. In addition, the effectiveness of PPIs was found to be considerably lower in fibrostenotic phenotypes as opposed to inflammatory phenotypes in a Spanish cross-sectional study in 630 patients, including 76 children, in which 95% of included patients received a PPI as primary therapy[193], which is equally applicable to STCs. Nevertheless, it is reassuring that the emerging body of evidence regarding long-term safety for both agents is increasing, suggesting that there are virtually no relevant long-term safety concerns for either of the two classes of drugs[110,194–196].

In summary, the choice between STCs and the probably less effective PPIs as primary pharmacological therapy for EoE depends on several factors, including the experience of the physician, local habits and the preferences of the patient. Dietary treatment is a valuable alternative to medical treatment for motivated patients but requires educated staff. Dilation is indicated in patients with persistent symptoms despite successful treatment of inflammation.

Conclusions

During the three decades since the first recognition of EoE as a novel and distinct entity, extensive advances have been made in understanding the immunology and pathophysiology, in developing diagnostic criteria and in advancing therapeutic management of this chronic disorder. The complexity of the immunopathogenesis of EoE is substantial, with an interplay between external factors (for instance, alterations in the production and processing of food potentially increasing allergenicity) and internal factors (for example, impaired barrier function of the oesophageal surface). Aside from the established clinical and histological diagnostic criteria, endoscopy has increasingly gained importance in diagnosing and monitoring EoE in clinical practice and clinical trials. However, the current description of EoE variants with EoE-typical clinical manifestations without remarkable eosinophilia in the oesophageal tissue presents a therapeutic challenge and is a potential diagnostic pitfall. Despite the still limited understanding of the pathogenesis of EoE, therapeutic strategies

have been developed and evaluated, and have demonstrated the necessity for a medical or dietary long-term anti-inflammatory treatment in the vast majority of patients. It was shown that STCs maintain their high effectiveness with a favourable safety profile even in long-term use. These agents, therefore, can be regarded as the first-line medical treatment for children and adults with active EoE. PPIs appear to be somewhat less effective but are also well tolerated. New therapeutic options such as anti-IL-4/IL-13 receptor and anti-IL-13 are currently reserved for use in patients with refractory disease.

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