An update on Eosinophilic Esophagitis

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Abstract

Eosinophilic Esophagitis (EoE) is a chronic condition characterized by eosinophilic infiltration of the esophageal mucosa and symptoms resulting from esophageal dysfunction. The most important symptom is dysphagia, which causes an impaired quality of life and significant healthcare costs. Food allergies have a key role in the development of EoE: the removal of specific foods from the diet is sufficient to reduce esophageal inflammation and improve symptoms. The diagnosis of EoE is based on a combination of symptoms, eosinophilic infiltration and the absence of other conditions which can explain esophageal eosinophilia (mainly gastro-esophageal reflux disease). Diagnostic delay should be avoided because if left untreated, a fibrostenotic phenotype can develop with strictures. Current therapeutic approaches are based on the "3 D's" concept: Dietary management, Drug therapy and esophageal Dilation. Dietary management can be based on an elemental diet (amino acid-based), which is rarely used in adults because of the poor palatability; an empiric elimination diet (2-4-6 food elimination diet). Medical treatment is still the most commonly used approach in EoE. In particular, swallowed topic corticosteroids such as topical budesonide or fluticasone have been shown to be very effective in reducing esophageal inflammation. More recently, biological treatments have been evaluated as novel treatment options for EoE, targeting different cytokines or receptors in the Th2 immune reaction. Finally, in case of esophageal stricture, dilation is warranted. (Acta gastroenterol. belg., **2023,** 86, **533-542**).

Keywords: eosinophilic esophagitis, dysphagia, food allergy, corticosteroids, elimination diet.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, local immune-mediated disorder characterized by clinical symptoms of esophageal dysfunction and histological findings of eosinophils infiltrating the esophageal epithelium (1). The first case was most likely described by Landres in 1978, but it was only recognized as a separate entity by Straumann *et al.* and Attwood *et al.* in the early 90s (2-4). Since then the incidence has increased at a rhythm that surpasses the increased awareness and recognition (5). The main symptoms depend on the age of the patient, but dysphagia is the most common presentation. In the current narrative review, we present the current status of knowledge about EoE: we provide an overview of the clinical presentation and diagnosis, the most recent theories underlying differences in global prevalence and underlying risk factors and, finally, an evidence-based overview of the potential treatments.

Epidemiology

The incidence of EoE is currently estimated to be around 10 cases/100.000 persons annually, whereas its prevalence varies between 10 and 57 cases/100.000 persons (5-7). Furthermore, the incidence rates are similar with 6.6/100.000 (95% confidence interval (CI) 3-11.7) in children and 7.7/100 000 (95% CI 1.8-17.8) per year in adults. In North American and European studies a prevalence of 34.4 cases per 100.000 inhabitants (95% CI 23.1-47.5) was reported, which was higher for adults (42.2; 95% CI 31.1-55) than for children (34; 95% CI 22.3-49.2), reflecting the chronic nature of the condition (8). EoE can start at every age, also in young children under the age of 5 years (9). EoE prevalence rises with age until peaking around 35-45 years and then starts to decrease, which probably reflects the increased incidence and awareness in the last two decades, especially in young individuals (10). EoE is significantly more prevalent in males than in females (OR 2.48; 95% CI 2.32-2.65) (11).

Initially considered a Western disease, EoE is currently found all around the globe, but with some remarkable differences in geographical distribution. The majority of cases are reported in the Western World: North America, Western Europe and Australia have the highest prevalence of the disease but also the majority of studies (5,12,13). The prevalence in the US is estimated between 25.9 and 55/100.000 (14-18), whereas in Western Europe a prevalence between 13.8 and 111.9 per 100.000 inhabitants was found (35.1/100.000 in Switzerland, 44.6-111.9/100.000 in Spain, 13.8/100.000 in Denmark) (19-23). In Australia a prevalence of 8.91/100.000 was already found in childhood (24). However, disease awareness is likely to be higher in Western in contrast to Asian countries, where EoE is still considered as a rare condition and its epidemiology has not been fully characterized yet (25). In China, a prevalence of 0.34% was reported in patients undergoing endoscopy with esophageal biopsies, compared to a rate of 1.2% in a US cohort (26,27). The condition is also diagnosed in Latin America, in the Middle East and in India. Even if the exact prevalence and the incidence trends of the condition in developmental areas need to be further characterized, evidence of a lower incidence in tropical areas is emerging (28-35).

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Submission date: 21/05/2023
Acceptance date: 23/08/2023

Some studies reported a higher prevalence of EoE among Caucasians compared to other ethnicities, although more data are needed and a selection bias in the available studies may be present (36,37). The variation in prevalence between geographical areas suggested the possibility of antigens specific for some regions or climates, which can be of relevance for dietary treatment. A study from the US found an important divergence in incidence between climate zones: using the temperate zone as the reference, and after performing multivariate analysis, EoE prevalence was highest in the colder region (odds ratio (OR) = 1.39, 95% CI: 1.34-1.47), compared to the tropical (OR = 0.87; 95% CI: 0.71-10.8) and the arid region (OR = 1.27; 95% CI: 1.19-1.36) (38). Additionally, EoE seems to be more prevalent in rural compared to urban areas, in contrast to what is traditionally hypothesized for an allergy-driven condition. In particular, population density appears to be inversely correlated to the prevalence of EoE. This specific finding opens various possibilities to better understand the impact of environmental factors present in rural areas on the development of the disease (39,40).

The incidence of EoE is increasing throughout the world at a rate which cannot only be attributed to increased awareness (7). In Denmark a steep increase in the incidence of new diagnoses of EoE was reported over a 15-year period from 0.13/100.000 to 2.6/100.000 (23). In the Netherlands a similar increase was seen from 0.01/100.000 in 1995 to 3.16/100.000 in 2019 (11). A similar trend was reported in the US, where data from Minnesota reported an incidence increase from 0.35/100.000 between 1991 and 1995 to 9.45/100.000 between 2001 and 2005 (18). Even though a stable incidence was reported in New Zealand, the increasing incidence appears as a general trend, at least in the Western World (41).

Together with the increasing incidence, the healthcare costs associated with EoE are rising as well, and today these represent a significant expense for the healthcare system: EoE-associated costs have been estimated at $1.36 billion per year in the U.S. (42).

Risk factors and etiology

Many risk factors have been reported as possible triggers in developing EoE: food allergies, pollen, early life exposures, infections, alterations in the gut microbiota, immunotherapy, proton pump inhibitor (PPI) treatment, low or borderline levels of vitamin D, celiac disease, connective tissue disorders, autoimmune conditions, Loeys-Dietz syndrome and genetic factors (5).

EoE is a condition that is clearly linked to food allergy. This is suggested by the fact that 50-80% of EoE patients present with allergic or atopic comorbidities such as asthma, rhinitis, conjunctivitis, eczema (43,44). EoE is often described as a form of food allergy, although clarification is needed why some foods that seem to have always been tolerated by the patients could become the cause of EoE (45). An international consensus in 2012 defined a food allergy as a health effect arising from a specific immune response that occurs reproducibly upon exposure to a given food (46,47). A significant proportion of EoE patients successfully respond to an elemental diet or to an empirical elimination diet, leading to disease remission, which again underlines the important role of food antigens (48,49). At the same time, reintroduction of specific foods could lead to recurrence of the symptoms (47). Interestingly, Clayton *et al.* demonstrated that IgE depletion using omalizumab, a humanized monoclonal anti-IgE antibody, did not change the number of eosinophils in the esophagus or impacts symptoms, suggesting that EoE is not a classical IgE-mediated allergy. Instead, they demonstrated the presence of IgG4 granular deposits, abundant IgG4-containing plasma cells, and elevated serum levels of IgG4 reactive to specific foods, potentially suggesting an IgG4-associated process although confirmatory evidence is lacking (50). The presence of elevated serum IgE levels is a rather frequent finding in about 60-80% of patients, despite most likely being not strictly related to EoE pathogenesis, although its presence does suggest the loss of food-specific immunotolerance (51,52). Erwin et al. stated how the predicted probability of having ≥15 eosinophils/high power field (hpf) ranged from 12% (95% CI, 4.8-26) for females without detectable serum IgE antibodies to any food to 86% (95% CI, 71-94) for males with four or five serum IgE positive foods (51). Milk was the most common food sensitization with elevated IgE levels in 78% of patients with EoE followed by wheat (69%), egg (64%), peanut (54%), and soy (53%) (51). Nevertheless, food-specific IgE tests lack the specificity to identify the food triggers responsible of EoE in an individual patient (47). The incidence of both food allergies and EoE is increasing in the majority of developed countries which could be explained by overlapping etiology of the two conditions (47). In general, evidence supports the role of food and inhaled allergens as important factors contributing to EoE pathogenesis.

Aeroallergens can also be considered as potential contributing factors in the pathophysiology of EoE. Mishra *et al.* reported that intranasal allergen exposure in mice induces marked eosinophil infiltration, eosinophil degranulation and epithelial hyperplasia in the esophageal mucosa (53). As oral or intragastric allergen exposure promoted EoE development, this suggests a link between the development of allergic hypersensitivity in the respiratory tract and in the esophagus in EoE (53,54). Several studies have observed seasonality of EoE diagnosis, strongly related with the pollen season, which supports the link between EoE and pollen allergens (5,55,56). Indeed, a study of 11 different pollen taxa in New York City where an increase in symptoms in patients during summer, and an increased number of diagnoses reported in the following season, reflecting a delay between the onset of symptoms and

the diagnosis (57, 58). Moreover, Fogg et al. reported a patient with EoE with negative skin prick tests for food allergy, whose symptoms and eosinophils counts in the esophageal mucosa increased during pollen season and improved after the end of the pollen season (59). However, it is important to note that some studies were not able to reproduce this finding. For instance, Molina-Infante *et al.* reported that no seasonal variation was observed in the incidence of EoE in mid-western Spain during the period between 2007 and 2016 (53% during pollen season vs. 47%, outside the pollen season p = 0.4) (60). A retrospective study from the Mayo Clinic found no differences in the number of diagnoses neither an increase in symptom exacerbations during summer (61). Until the role of seasonal aeroallergen exposure in EoE is better elucidated, it is suggested to try and identify each patient's allergen sensitivities and exposures and aiming to reduce these exposures while treating comorbid allergic disease (62).

Another potential trigger for the development of EoE is early life exposure to different factors (63,64). Jensen *et al.* were able to demonstrate that specific early life exposures could indeed increase the odds of developing a pediatric-onset EoE compared to gastro-esophageal reflux disease (GERD) controls. In particular, antibiotic therapy during the first year of life was associated with a sixfold increased likelihood to develop EoE (95% CI, 1.7-20.8). In the same study cesarean delivery, preterm birth, formula-only or mixed feeding, and infants of mothers positive for group B Streptococcus were linked to a higher risk of developing EoE (64).

More recently, an inverse association was found between *Helicobacter pylori* infection and EoE. In particular, an infection with *H. pylori* was reported to be protective against EoE, possibly related to its immunomodulatory effect (65,66). In a large systematic review and meta-analysis including data from 377,795 individuals worldwide Shailja *et al.* demonstrated that *H. pylori* exposure reduced the odds of developing EoE by 37% (OR = 0.63, 95% CI: 0.51-0.78) (66). Mechanisms behind this association are still not clarified and controversy on this possible link remains (67,68).

Other infectious diseases have been hypothesized to be related to EoE: *Mycoplasma pneumoniae*, *Herpes simplex virus* and the parasitic infection anisakiasis. However, further evidence is needed and a plausible pathophysiological link between the two different pathological conditions is also missing (5,69-73).

Lastly, the possible role played by the microbiota in many conditions, including EoE, is a topic of intense research (74). The significantly higher prevalence in developed countries compared to developing countries supports the "hygiene hypothesis" (75). This theory assumes that a lack of exposure to microbial pathogens during the early life might cause a defect in immune tolerance, which therefore leads to an increase in susceptibility to allergic diseases, including EoE (76,77). Studies evaluating the fecal microbiota discovered a significant difference in structure, richness and evenness in patients with active EoE compared to healthy volunteers, together with a decrease in taxa within *Clostridia* (78). Notable differences in the esophageal and oral microbiome in EoE patients also emerged (79,80). Moreover, the environment may have effects on the host-microbiome balance, necessary for the correct development of the immune system (57). The commensal microflora of the gut may direct the immune system toward a T helper-2 cell (Th2) phenotype as a consequence of early life events such as: cesarian section, antibiotic exposure, lack of breastfeeding and long period spent in a neonatal intensive care unit (77,81,82). These circumstances have already been considered separately as potential triggers for the development of EoE (63,64).

Likewise, a higher incidence of EoE in patients undergoing oral (OIT) or sublingual immunotherapy (SLIT) as a treatment for food or environmental allergies has also been reported. However, further studies are needed to confirm the potential immunological mechanisms and to uncover the long-term effects of OIT and SLIT on patients with an active EoE. A better knowledge on the risks of developing EoE during dose escalation or maintenance therapy is also needed (83).

Clinical presentation

The clinical presentation is different in children versus adults. Generally, the prevalence of symptoms changes importantly throughout the course of the disease with a role of age and ethnicity: for instance, dysphagia and food impaction become more frequent with age, and are more common among Caucasians than other ethnicities (84).

Infants present with more non-specific symptoms such as food rejection, vomiting and less commonly growth retardation; school-aged children and adolescents can present with dysphagia, food impaction and more rarely with chest pain, abdominal pain, vomiting and regurgitation (85). In adults dysphagia is the main symptom together with refractory chest pain (85). Food bolus impaction necessitating endoscopy for bolus extraction can actually be the first presentation in patients with EoE. However, symptoms correlate poorly with histological severity and eosinophil counts (86,87).

Diagnosis

Chronic symptoms of esophageal dysfunction are very suggestive of EoE, especially in young patients and they should raise clinical suspicion. Nevertheless, symptoms alone are not sufficient to confirm the diagnosis, which also holds true for evaluation of treatment during follow-up. Therefore, the diagnosis should be based on 3 pillars (12):

1. symptoms of esophageal dysfunction
2. histologic criteria
3. exclusion of alternative etiologies of esophageal eosinophilia.

The definition of the histological criteria has been a difficult and controversial topic for a long time. A variability in the assessment of diagnostic criteria for EoE is widely present in the scientific literature and this lack of a common disease definition hampers reporting cumulative data from EoE studies (88). In normal conditions the esophagus is devoid of eosinophils in contrast to other regions of the gastrointestinal tract. Dellon *et al.* found 10 different histologic criteria to diagnose EoE: in the examined studies the number of eosinophils per hpf used to confirm EoE varied from 5 to 30, with also 35% of the analyzed articles which did not even state the utilized diagnostic criteria. Moreover, a substantial variation in esophageal biopsy protocols was also reported (88). During the AGREE (A working Group on PPI-REE (PPI responsive esophageal eosinophilia)) conference, researchers defined EoE diagnostic criteria as the presence of esophageal dysfunction symptoms together with the finding of at least 15 eosinophils/hpf on esophageal biopsy after a full evaluation of possible non-EoE disorders that might cause or potentially contribute to esophageal eosinophilia, including mainly GERD and achalasia (89). The same criterium was also included in the core outcome set for therapeutic studies (COREOS) (90). The European guidelines advise a total of 6 esophageal biopsies divided in the proximal and distal esophagus (91).

Endoscopic findings are another key factor in the diagnosis of EoE. Patients can present with an inflammatory pattern, identified by the presence of exudates, furrows (longitudinal grooves), and edema; a fibrotic phenotype, characterized by the presence of rings and stenosis; or a combination of these two phenotypes (92). Narrow-caliber esophagus, Schatzki rings, superficial tears of the mucosa and a slight resistance while taking the biopsy ('pull sign') are also described (85). To standardize the endoscopic evaluation, Hirano *et al.* developed the Endoscopic Reference Score (EREFS), which also corresponds to the endoscopic signs: Edema, Rings, Furrows and Strictures (Figure 1) (93). A meta-analysis assessed the frequency of endoscopic findings: esophageal rings were present in 44% of patients; strictures in 21%; narrow-caliber esophagus in 9%; linear furrows in 48%; white plaques in 27%; and pallor or decreased vasculature in 41%. The endoscopy was reported to be completely normal in 17% of patients, but this number decreased to 7% in case the analysis was limited to prospective studies only, indicating that awareness and training is crucial. They also confirmed a wide variety of results and data among the different studies (94). Moreover, it is clear that awareness campaigns can dramatically improve the detection rate of the disease (95).

As mentioned before, esophageal eosinophilia can also be explained by conditions other than EoE. Consequently, alternative etiologies need to be excluded before diagnosing EoE. The most frequent overlapping condition is GERD with typical symptoms of heartburn and regurgitation, but also other diseases should be considered on a case-by-case basis, such as achalasia, infections, connective tissue diseases, Crohn's disease, Pill esophagitis, hypereosinophilic syndrome or drug hypersensitivity (12). Failure to respond to PPI treatment should not be used as a criterium to exclude GERD (cf. infra).

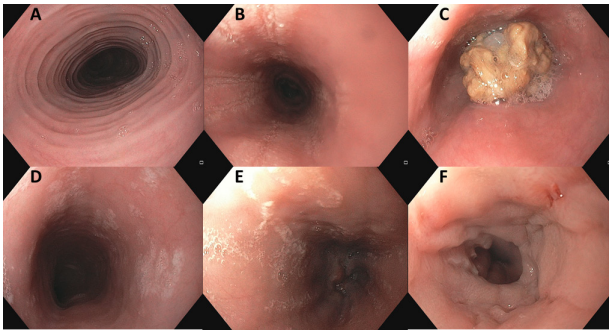

Figure 1. — Endoscopic signs of eosinophilic esophagitis. A: rings; B: Furrows and Exsudates; C: Food bolus impaction; D and E: Exsudates; F: Stricture at the level of the esophago-gastric junction.

Etiology and phenotypes

If left untreated, strictures can develop with the prevalence of strictures correlating to the duration of untreated disease. Therefore, the diagnostic delay should be minimized and suspicion is warranted in patients with esophageal dysfunction (92). However, not all cases of EoE have the same pattern of presentation at the moment of diagnosis. In a retrospective study, Dellon *et al.* divided the patients in different groups according to their phenotype: fibrostenotic in case of esophageal rings, narrowing or strictures, but without the evidence of linear furrows or white plaques; inflammatory in case of furrows, exudates or in case of a normal esophagus without the evidence of fibrostenotic changes; and mixed in case of a combined presence of elements from both patterns. Patients with an inflammatory phenotype appeared to have a better outcome compared to those with mixed or fibrostenotic phenotype and less likely to have dysphagia, food impaction and esophageal dilation during follow-up (86). Colizzo *et al.* reported that patients with the fibrostenotic phenotype presented with an intrabolus pressure that was significantly higher on high-resolution manometry than that of the inflammatory phenotype group suggesting more resistance to bolus passage in the esophagus which may be related to the occurrence of dysphagia (96). The two main phenotypes also appear to be related with the age of the patient. In particular, the chance of developing fibrostenotic disease increases with age: this suggests that the development of EoE is characterized by a progression from an inflammatory phenotype to a mixed or fibrostenotic phenotype (86). To investigate this hypothesis, Koutlas *et al.* in 2017 presented a retrospective study with 6

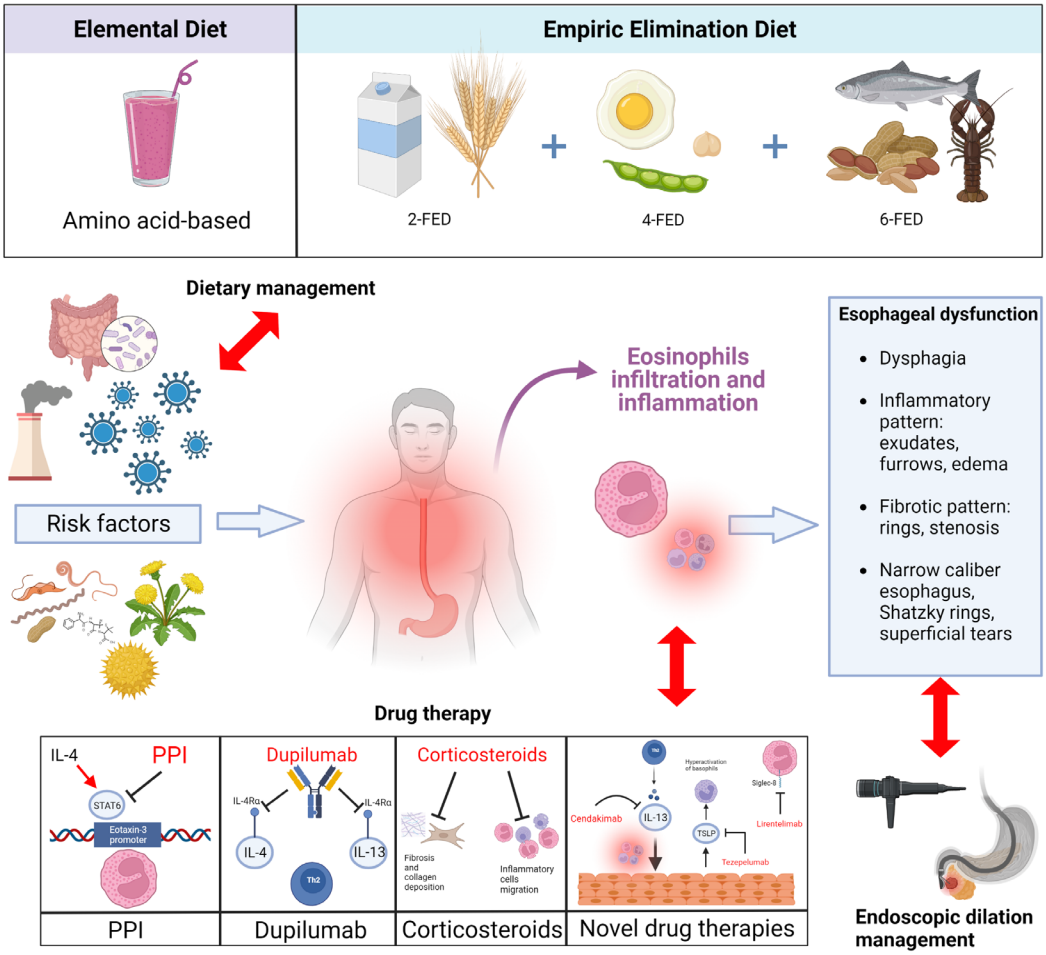

Figure 2. — Overview of the current treatment options for eosinophilic esophagitis. Current available therapies include elimination diets, drug treatments and dilation. Novel drug therapies that are still undergoing clinical trials to better understand if they could be introduced into clinical practice could result in superior symptom control. Created with biorender.com.

patients in which they followed the disease phenotype in the absence of treatment. None of those patients presented with fibrostenosis at the time of diagnosis and after a period of time (on average 7.8 ± 2.0 years) without follow-up and without treatment, the majority of patients developed strictures (n = 5; 83%) or small-caliber esophagus (n = 4; 67%) and most of them required an esophageal dilation in the following period (97). On the other hand, a multicenter study by Singla and colleagues demonstrated that the majority of patients under proper treatment maintained their phenotype over a period of 1.7-year follow-up and these patients did not show any sign of progression to fibrosis or even demonstrated regression. Therefore, they were able to establish that an early therapeutic strategy with the aim of controlling EoE inflammation may prevent progression to fibrostenosis in patients with an inflammatory phenotype, even if caution is needed because of the relatively short follow up period in this study (98).

Treatment

The first aim in treating EoE is to control esophageal inflammation, responsible for the development of symptoms and the fibrotic process. The basis of the EoE treatment can be summarized by the so-called '3 Ds' of treatment: "Diet", "Drugs" and "Dilation". The "Diet" approach is based on controlling the environmental triggers of the condition, i.e. food. A medicinal approach i.e. "Drug", aims to reduce the inflammatory Th2 response in the esophageal mucosa. Endoscopic "Dilation" is used for patients with significant remodeling which led to esophageal stenosis (85). The available treatment options are summarized in Figure 2.

Dietary Management

Currently, three different approaches in dietary management can theoretically be used as a treatment:

1) Elemental diet (amino acid-based)
2) Empiric elimination diet
3) Allergy testing-guided food elimination diet (48).

Elemental diet is exclusively based on amino acid-based products with exclusion of immunogenic peptides. An elemental diet has been shown to lead to a complete histological response in 72% of the cases (48). These

results underline the importance of food allergens in the development of EoE in adults. Moreover, the recurrence of symptoms after the reintroduction of trigger foods and the reduced expression of inflammatory cytokines, with a subsequent reduction of esophageal inflammation, further support this hypothesis. However, an elemental diet has important limitations in clinical practice including the poor palatability, the psychological impact due to the lack of food variety and the high costs which lead to a low adherence in patients and preclude its use in adult patients. However, more recent formulas with an improved palatability may increase treatment compliance, possibly also in highly selected adult patients. Warners *et al.* reported a complete histological response in 71% of patients, with 81% of adult patients able to complete the dietary trial. Nevertheless, European Guidelines also state that elemental diet should only be considered after failure of drug treatment and/or a standard elimination diet, which is rare (48,85,91,99).

The most commonly utilized dietary treatment is an empiric elimination diet which is based on the elimination of the foods most commonly associated with food allergy. It was first studied in 2006 in a pediatric population in Chicago and consisted of the elimination of 6 food groups (6 food elimination diet (6-FED)): cow's milk protein, wheat, egg, soy, peanut/tree nuts, fish and shellfish (49,100-102). After 6 weeks, patients with histologic improvement underwent a stepwise food reintroduction to identify the culprit food item(s). This is only possible through single food item reintroduction, followed by endoscopies and histological follow up, which leads to a long trial-and-error period of consecutively eliminating and reintroducing different food items and can take up to a year with up to 7 endoscopies (49). However, in the large majority of patients, only 1 or 2 foods were found to be responsible for EoE development, of which milk and wheat were the two most common ones. Therefore, in an important study by Molina-Infante, the 2-4-6 dietary approach was developed. A 2-FED (cow's milk and gluten-containing grains) already achieved a remission in 43% of patients, enabling a reduction in the overall number of endoscopies required. Non-responders were escalated to a 4-FED (additional elimination of egg and soy/legumes), with a response rate of 60%. Finally, the remaining 40% could continue to the original 6-FED with a final cumulative response rate in all patients combined of 79% (102). Other studies also explored the possibility of eliminating only cow's milk from the diet in children, with an efficacy from 25% to 65% (103). The step-up reintroduction strategy starting with a 2-FED has several advantages compared to a highly restrictive step-down strategy with in general less endoscopies, a shorter dietary optimization phase and a lower risk of a restrictive and avoidant eating behavior. Nevertheless a knowledgeable dietitian and a highly-motivated patient are crucial to the success of this treatment (100,102,104). The results and feasibility of a long-term elimination remain to be evaluated (102).

The allergy testing-guided food elimination diet is based on the exclusion of food items to which specific antibodies are present or which led to a positive skin-prick test. Milk and egg are the most frequently found positive allergens (105). However, studies show a notably lower response rate for every allergy testing-guided diet protocol, ranging from an overall 32.2% of efficacy in adults to 47.9% in children, compared to an empiric elimination diet. Several allergy tests were used across trials, e.g. SPT (skin-prick test), APT (atopy-patch test) and blood specific IgE levels. Nevertheless, none of these techniques could accurately predict food triggers (91,106). Hence, no allergy testing is recommended in the absence of extra-esophageal symptoms.

Drug therapy

PPI have now been included as a possible treatment for EoE. Initially, PPI responsive esophageal eosinophilia (PPI-REE) patients were considered as a separate entity akin to GERD. However, it has been demonstrated that EoE and PPI-REE are identical in terms of clinical presentation, histology, endoscopy and gene expression and the term PPI-REE has been abandoned (107). Zhang et al. showed how patients could respond to PPI therapy independently from the acid suppressive effects. In particular, it was demonstrated that PPI can inhibit IL-4-stimulated eotaxin-3 expression in esophageal cells of EoE patients and therefore block STAT6 binding to its promoter. Eotaxin-3 is an eosinophil chemoattractant which contributes significantly in the pathophysiology of the Th2-driven esophageal eosinophilia (108). In general, about 50% of EoE patients will respond to high-dose PPI therapy (109). However, dosing in maintenance therapy and long-term outcome with PPI is still unclear. Since PPI therapy is relatively cheap and safe, it is in most cases still the first line treatment.

In patients not responding to PPI, corticosteroids still represent the core of the treatment of EoE. Swallowed topical corticosteroids solutions containing budesonide or fluticasone suppress eosinophilic inflammation with limited central effects. Budesonide orodispersible tablets have been approved in 2018 in Europe as the first marketed drug for the treatment of EoE (110). In a landmark randomized placebo-controlled trial, Lucendo *et al.* demonstrated the superiority of budesonide oro-dispersible tablets compared to placebo, inducing clinical and histological remission in up to 85% of patients (111). Moreover, Straumann *et al.* reported the superiority of budesonide over placebo also in maintaining remission over a longer period, up to 48 weeks of treatment, with the administration of 0.5mg or 1.0mg twice daily (112). However, this formulation is not available worldwide (or not reimbursed), and hence physicians still often rely on solutions prepared by the pharmacists (e.g. xanthane gum or sucralose-based viscous solutions) or off-label use of inhalers used to treat asthma. Dellon *et al.* compared oral viscous budesonide therapy (OVB)

with swallowed fluticasone therapy administered through a multi-dose inhaler (MDI). Interestingly, results showed OVB was not superior to MDI and, therefore, both can be considered as valid therapeutic alternatives for the treatment of EoE (113). Nevertheless, Dellon *et al.* reported in another important study how OVB was superior to swallowed nebulized budesonide (NEB) in reducing the number of esophageal eosinophils in patients with EoE. This is probably related to the higher deposition of the therapeutic agent in the esophageal mucosa with OVB compared to NEB. By using a nuclear scintigraphy esophageal emptying scan it was seen how in NEB a significant proportion of the medication still ends up in the airways and in the lungs, therefore not reaching the esophageal mucosa (114).

The recommended budesonide dosing for induction is 2x1mg. Fluticasone 880-1760μg/daily in adults and 88-440μg/daily in children is considered as a valid alternative to budesonide administration. The result of the induction treatment should be evaluated endoscopically and histologically after 8-12 weeks. Symptoms alone cannot be used to evaluate treatment success (110,113). The overall response rate after swallowed-corticosteroid therapy is high, up to 85%. Longer-terms adverse events include esophageal candidiasis in 7.4% of patients, which is not always symptomatic. A suppression of the hypothalamic-pituitary-adrenal-axis can be seen with decreased cortisol endogenous secretion, but this is a rare event, since budesonide has a high hepatic first pass metabolism limiting corticosteroid exposure. Indeed, in clinical trials, no signs of adrenal cortisol suppression were found, except for children being treated with a dose of fluticasone >440μg/daily, which is not recommended (110). As already mentioned above, it was demonstrated how 0.5mg twice daily of budesonide could efficiently maintain EoE in clinicohistologic remission in three-quarters of patients also over a long-term period. Administration of a budesonide orodispersible tablet was proven to be a safe and effective for long-term maintenance therapy and the adverse effects that emerged during trials were mild and did not raise safety concerns (112). A follow-up of the long-term therapeutic efficacy is generally suggested, with patients undergoing clinical visits, endoscopy and biopsies once a year for monitoring the disease activity (115). In clinical practice it is advised to continue swallowed topical corticosteroids long term with 2x0.5mg of budesonide as the suggested maintenance dose. In case of relapse of symptoms or re-appearance of esophageal eosinophilia, dose escalation to 2x1mg is recommended.

Novel biologic treatments are recently emerging as novel therapeutic options to treat EoE. Dupilumab is an entirely human antibody directed against the IL-4 receptor-α component of the type 2 receptor capable to inhibit signaling of both IL-4 and IL-13, both key cytokines of the Th2 immune response. In a phase 2 study, Dupilumab was administered subcutaneously once a week for 12 weeks and tested vs. placebo. Dupilumab was generally well tolerated and reduced the frequency and severity of dysphagia symptoms besides lowering the esophageal eosinophil counts. Moreover, also macroscopic features were assessed through the EREFS score with an increased distensibility and an improved overall esophageal function being reported (116). These results have recently been confirmed in a phase 3 study in 321 patients. The primary endpoint of achieving a peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf in all three 3 esophageal biopsies (proximal, mid and distal) was met in 60% of patients treated once a week with dupilumab vs. 5% in the placebo group ($p<0.0001$) (117). These favorable results led to market approval in the US by the FDA in May 2022 and in Europe by the EMA in January 2023.

Cendakimab is an antibody directed against IL-13, preventing its binding with the receptor subunits α1 and α2, with the final effect of reducing Th2 inflammation and eosinophil counts (118). Preliminary results from a phase 2 study reported reduced eosinophil counts and improved histologic and endoscopic outcomes, but dysphagia symptoms did not seem to improve. A phase 3 trial is currently ongoing (119). Other potential molecular therapeutic targets have recently been identified, such as IL15, TSLP, Siglec-8, S1P receptor, TGF-β1 and L-type calcium channels (118,120). IL15 is overexpressed in EoE epithelium and submucosa of EoE patients (121). TSLP is an epithelium-derived cytokine which is released upon interaction of food antigens with the epithelium in EoE and supports a Th2-mediated inflammation and activation of basophiles. Anti-TSLP treatment has already shown to reduce esophageal eosinophilia in murine models (118,120,122). Furthermore, Siglec-8 has been hypothesized as one of the promising new molecular targets, leading to eosinophil cell death and inhibition of mast cells. However, preliminary results showed that even if eosinophils were significantly reduced, the effect on symptoms was disappointing, suggesting that other inflammatory cells and pathways besides eosinophils are relevant in EoE pathophysiology and providing the rationale to evaluate more upstream targets such as TSLP and IL-15 (123,124). More trials are needed to confirm the efficacy of these new molecules.

Endoscopic dilation

In patients with significant strictures, dilation can be performed with through-the-scope balloons or with Savary-Guillard bougies, providing an immediate symptomatic benefit in 95% of patients. Nevertheless, endoscopic procedures do not have an impact on the eosinophilic inflammation and, therefore, repeated procedures over time might be necessary and should always be combined by medical or dietary treatment if there is ongoing inflammation (125). There has been a concern that dilations in EoE patients had a high rate of complications. However, more recent studies show a perforation risk of less than 1% and mucosal tears after

the procedure should not be considered as a complication. The only frequently reported side effect is mild to moderate chest pain after the procedure (125,126).

Conclusion

EoE is a chronic allergic disease with increasing incidence and symptoms of esophageal dysfunction. Timely diagnosis through a high index of suspicion of the gastroenterologist with a low threshold for biopsies and also awareness by the pathologist should avoid long-term complications such as strictures and lead to early treatment. Empiric elimination diets and anti-inflammatory treatment with PPI or swallowed topical corticosteroids are the first line treatments. With the increasing insight in the complex pathophysiology of EoE, novel biologic treatments are currently under evaluation to further improve the long-term outcome, especially in patients refractory to corticosteroid treatment.

Conflicts of interest

TV has received speaker and consultancy fees from Dr. Falk Pharma.

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