DENDYS, Konrad, BIENIASZ, Jan, KAZZI, Marcel, PUŁA, Michał & WYCHOTA, Marta. Eosinophilic esophagitis – epidemiology, clinical manifestations and current therapy menagement. Journal of Education, Health and Sport. 2023;13(5):46-53. eISSN 2391-8306.
DOI http://dx.doi.org/10.12775/JEHS.2023.13.05.006
https://apcz.umk.pl/JEHS/article/view/42707
https://zenodo.org/record/7705545

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. L.p. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.02.2023. Revised: 22.02.2023. Accepted: 04.03.2023. Published: 07.03.2023.

Eosinophilic esophagitis – epidemiology, clinical manifestations and current therapy management

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Keywords: Esophagitis; Eosinophilic Esophagitis; Eosinophilia; Gastroenterology

Abstract:

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease, which in recent years has shown a clear upward trend of incidence and prevalence in the general population. The symptoms of EoE are very heterogeneous as well as therapy management of this entity which often causes problems in the clinical approach to the patient. Adults most often suffer from dysphagia, while children usually present non-specific symptoms such as food refusal, vomiting, nausea, etc.. Currently, we have many therapeutic paths that change the course of the disease, but high expectations are also placed on new biological drugs. This publication attempts to summarize the current state of knowledge about epidemiology, age-related clinical presentation, and therapeutic strategy of eosinophilic esophagitis.

Introduction:

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease associated with inflammatory infiltration of the esophageal mucosa with the dominance of eosinophils leading to esophageal dysfunction.[1] This disease entity was first described in 1978 by Landres RT[2], but it was listed as a separate disease syndrome and gained more interest several years later, in the early 90s [1]. Originally, the idea that the presence of eosinophils in the esophagus was a hallmark of esophageal reflux was considered[3], but it soon became clear that the esophagus is an immunologically active organ and a variety of stimuli can lead to the recruitment of eosinophils[4]. The exact pathogenesis is unknown, but it is known that genetic, environmental, and immunological factors play an important role[1]. In recent years, the number of diagnoses of this disease in both children and adults has increased significantly, which has contributed to

even greater interest[5]. Currently, eosinophilic esophagitis is one of the most common diseases of the esophagus and the leading cause of dysphagia and retention of solid food in the esophagus[1].

Epidemiology:

Over the last 20 years, eosinophilic esophagitis has transformed from a rare textbook entity to a disease that is commonly found in gastroenterology wards or even in general practitioners' offices[6]. Many clinical studies have investigated the prevalence and incidence of EoE in several heterogeneous populations, and although the results have not been identical, there is a clear upward trend over time[6]. These studies are summarized in two meta-analyses that have attempted to determine the prevalence and incidence of EoE in the general population. The first one published in 2016, conducted by Arias A., Perez-Martinez I., and Tenias J.M., included 13 population-based studies from North America, Europe, and Australia, with the results showing high heterogeneity. The pooled EoE incidence rate was 3.7/100,000 persons/year [95% confidence interval (CI): 1.7-6.5]. The pooled prevalence of EoE was 22.7 cases/100,000 inhabitants (95% CI: 12.4-36)[7]. The second was published in 2019 by Pilar Navarro and colleagues and concerned a total of 2,386 documents; 29 studies reported on the prevalence and incidence of EoE in the general population. The results revealed the pooled prevalence of EoE was 34.4 cases per 100 000 inhabitants (95% CI, 23.1-47.5), and was higher for adults (42.2; 95% CI, 31.1-55) than for children (34; 95% CI, 22.3-4e9.2). The pooled EoE incidence rates were 6.6/100 000 person/year (95% CI, 3-11.7) in children and 7.7/100 000 (95% CI, 1.8-17.8) in adults[8]. That study also showed no differences between European and North American studies using different sources of data[8].

Clinical manifestation:

EoE is a very heterogeneous disease, moreover, the symptoms vary depending on the age of the patient[9].
According to European guidelines among older children and adults with EoE solid food dysphagia, food impaction, and non-swallowing associated chest pain are the most commonly reported symptoms. In younger children and infants, the most common symptoms are reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive[10].
Adults usually complain of dysphagia to solid food, up to 70-80% of patients present with this symptom, it's often followed by food impaction (up to 54 percent of patients)[10–13]. The impaction of a food bolus is a typical and usually recurring symptom, which in some cases requires upper endoscopy for unblocking[14,15]. One study was conducted with a single, adult, community-based group and as many as 17 people presenting with food impaction from the group of 31 were later diagnosed with EoE[13]. Eosinophilic esophagitis can mimic gastroesophageal reflux disease (GERD) in its presentation with heartburn and regurgitation, prospective studies showed that EoE has been noted in 25% percent of patients with refractory reflux[14,16]. Exercise-induced chest pain is also common among adults[14].
Infants and small children in general present non-specific symptoms such as food refusal, vomiting, nausea, reflux-like symptoms, abdominal pain, and failure to thrive[17]. It has been widely described that symptoms in children vary depending in part upon their age: failure to thrive in the youngest children (median age 2 years), vomiting in older children (median age 8 years), abdominal pain in young adolescents (median age 12 years), dysphagia (mean age 13.5 years) and food impaction (median age 17 years) in older adolescents[18].
According to some studies, eosinophilic esophagitis is also associated with feeding disorders; in one study in a group of 200 children with eosinophilic gastrointestinal disease, 16.5% had significant feeding disorders[19]. A variety of learned maladaptive feeding behaviors were reported for example failure to develop normal eating patterns (not advancing past liquids or soft foods) and adopting coping strategies (refusing to eat solids after previously eating them, eating slowly, chewing excessively, drinking excessive liquids with meals)[9,19].

The possibility of disease progression was tested in a case-control study of patients with retrospectively identified histologic eosinophilic esophagitis; results showed that increased esophageal eosinophil counts increase the rate of dysphagia and food impaction in 15 years period and also esophageal eosinophilia is associated with reduced quality of life and persistent symptoms 15 years after presentation[20].

Treatment:

Untreated EoE is most commonly associated with persistent inflammation causing symptoms and leading to esophageal remodeling resulting in stricture formation and functional abnormalities[10]. Eosinophilic esophagitis also significantly impacts the health-related quality of life of patients, impairing their social and psychological

functioning[10]. Some evidences show that effective anti-inflammatory treatment limits progression of EoE therefore, several treatment strategies have been considered[10].
In the treatment of eosinophilic esophagitis, both in children and adults, dietary and pharmacological treatment are being used, sometimes in the case of esophageal stenosis also endoscopic procedures[1]. The choice of therapy should be discussed individually with the patient. Treatment may be changed over time depending on the outcome of treatment[10].

- Dietary treatment:

Evidence showed that some food allergens are involved in the pathogenesis of EoE[21] and prolonged avoidance of irritating foods may lead to drug-free sustained clinical and histological remission of EoE[10]. Many studies have been conducted testing different dietary approaches to EoE treatment, including an elemental diet, an empiric elimination diet, and a food allergy testing-guided elimination diet[22,23] and in 2014 a team led by A. Arias published a meta-analysis summarizing the results so far[23]. The team analyzed data on a total of 1317 patients with EoE (1128 children and 189 adults) who received different dietary treatments. Diets that were tested:

- Elemental diet - exclusive feeding with carbohydrates, single amino acids, and medium-chain fatty acids. The overall efficiency of the elemental diet in achieving histologic remission of EoE was 90.8% (95% CI, 84.7%–95.5%). The response rate was very high in children and adults (90.4% vs 94.4%, respectively), although data for adults are limited because of the small number of patients studied. Nevertheless, elemental diets have significant flaws that strongly limit clinical use: poor palatability and price of elemental formulas[24], risk of delayed onset of oral motor-skills in children[25], social and psychological distress associated with food-behavior dysregulation in adults[22].

- Target elimination diet - the approach of eliminating foods that gave a positive result in skin allergy tests (skin prick test and atopy patch test)[23]. Overall efficacy was 45.5% (95% CI, 35.4%–55.7%). However, the studies have mostly focused on children, only 2 studies were carried out on adult patients and showed a significantly lower response rate of 26.6%[26] and 35%[27]. The results are disappointing and these days the accuracy of skin allergy tests is considered insufficient to target food elimination from the diet, although this point is still debatable for children[10]. The main reason for these doubts is a conspicuous that atopy patch test (APT) has not been validated in food allergies[10] and skin prick test (SPT) results have low accordance with EoE food triggers when histology (count of eosinophils) is monitored after food reintroduction[28].

- Six-Food Elimination Diet (6-FED) - It is an elimination diet, patients are disallowed to eat the most common allergens: milk, wheat, egg, soy, nuts, and fish/seafood. The combined efficacy was 72.1% (95% CI, 65.8%–78.1%), which means that by eliminating the above allergens, almost 3 out of 4 patients have achieved clinical and histological remission, both in children and adults[23].

Other dietary modifications (Four-food elimination, two-food elimination, gluten-free, etc.) were also assessed in the above meta-analysis, however, due to the too limited amount of data and large discrepancies in individual studies, the authors point out the limited reliability of the results[23]. European guidelines notice that an empiric four-food elimination diet may still be effective in 40% of patients but the strength of recommendation is weakly in favor[10].

- Proton pump inhibitors (PPIs)

The indication that PPIs induce disease remission in patients with EoE was initially reported by one case series and three retrospective studies published between 2005 and 2009[29–31]. The first large prospective study was published in 2011; researchers showed in an adult group with clinical and histological features of EoE, that 8 week therapy with PPI led to complete response in 50% of cases[32]. The effectiveness and favorable safety profile of PPIs cause that these days accoring to European guidelines PPI are usually recommended as first line therapy in inducing clinical and histological remission of pediatric and adult patients with EoE and in PPI responders group, long-term therapy is adequate in maintaining remission[10]. The interplay between PPIs and EoE is likely to associate with few co-adhering mechanisms, two main effects are described by: reduced level of eotaxin-3, which is a cytokine released by Th-2 lymphocytes and involved in eosinophil-mediated inflammation[33] and promoted regeneration of the mucosal barrier by reduced acid production in stomach which leads to limitation of exposure to environmental allergens[34].

Typical therapy with PPI starts with omeprazole, doses of 20–40 mg (or equivalent PPI) twice a day for adults, children should receive 1–2 mg/kg daily, to assess the response[10]. Histological response to treatment is usually seen after 8 weeks therapy[35]. When treatment is stopped, EoE relapses over a 3–6-month period[10].

- Corticosteroids

Eosinophilic esophagitis is a chronic inflammatory disease associated with inflammatory infiltration of the esophageal mucosa[1] so steroidal anti-inflammatory activity is the backbone of the therapy. Numerous studies have shown that both systemically and topically administered corticosteroids are suitable for inducing EoE remissions in both adults and children[10,36]. Corticosteroids also reduce esophageal fibrosis and remodeling, but systemic therapy is connected with serious sides effects (hyperphagia, weight gain, cushingoid features, growth retardation in children, osteoporosis, glucose intolerance, cataract formation, etc.), therefore due to the European guidelines systemic steroids are not recommended in EoE[10,36]. In contrast, topical therapy is safe, does not involve frequent side effects, and is recommended[10]. Several meta-analyses have shown that topical corticosteroids reduce esophageal inflammatory infiltration with eosinophils, however, a serious difficulty in drawing conclusions is the high variability of individual studies regarding: dosages, duration of therapy, administered steroids, and methods of administration[10,37–40]. European guidelines describe fluticasone and budesonide in induction and maintenance remission for both children and adults delivered by: swallowed puffs from inhalers, suspension, viscous slurry, or effervescent tablets[10]. Suggested dosages are presented in table number 1.

Drug	Population	Induction dosage	Maintenance dosage
Fluticasone propionate	Children	880-1760 mcg/day	440-880 mcg/day
	Adults	1760 mcg/day	880-1760 mcg/day
Budesonide	Children	1-2 mg/day	1 mg/day
	Adults	2-4 mg/day	2 mg/day

Table 1. Swallowed topical steroid initial dosing for eosinophilic esophagitis treatment[10]. Specific doses in children will be determined by age, height, or weight.

- Endoscopic dilation

Fibrostenotic complications in patients with EoE are much more common in adults (event 30-80%[41]), they occur as a: narrowed esophageal diameter, rings, strictures, furrows and leads to difficulty swallowing[10]. In patients with dysphagia and food blockage in the esophagus that does not respond to conservative treatment, endoscopic esophageal balloon dilation should be performed (however in a case of food impairment or severe narrowing endoscopic procedures are first-line therapy in clinical practice). It is a safe procedure with a risk of esophageal perforation less than 1%[10]. Endoscopic esophageal dilation reduces dysphagia in more than ¾ of adult patients with esophageal obstruction, but has no effect on esophagitis[10].

- Immunosuppressants - azathioprine and 6-mercaptopurine

European guidelines say that azathioprine and 6-mercaptopurine might play a role in both inducing and maintaining remission in EoE[10] but only one case series did show promising results in three patients with steroid-dependent EoE who received remission after the addition of azathioprine or 6-mercaptopurine, although evidence of recommendation is weakly in favor[10,42]. Hoewer remission was maintained at follow-up 3-8 years later, stopping immunosuppression therapy resulted in a relapse of histological presentation or symptoms[42].

- Biological agents

- Mepolizumab (humanized anti-IL-5 monoclonal antibody) was the first estimated antibody in an open-label study of adults with symptomatic EoE but the poor clinical and histological improvement were observed[43]. Similar results were obtained in a phase 2 trail in the pediatric population tested with reslizumab (another anti-interleukin 5 monoclonal antibodys)[44]. Although according to European guidelines the anti-IL5 antibodies have no effect on symptoms and moderate effect on histological presentation so they are not recommended[10].

-An anti-tumor necrosis factor alpha antibody, like Infliximab has no proven effect on symptoms of esophageal eosinophilia[10]. There was a suspicion that using biological drugs, used in the management of inflammatory bowel diseases (IBD) may have an encouraging impact on the symptoms and histological profile of patients with EoE[45]. However, a prospective clinical study showed that infliximab, in a standard induction dosage schedule, is not able to induce a reduction of the eosinophilic tissue infiltration and alleviate the resulting symptoms[46]. Taking into account current knowledge of the mechanism of disease in EoE, TNF-α blockade is unlikely to have any clinical impact on EoE, because it not correlate with eotaxin-3 expression[5].

-Omalizumab (humanized monoclonal anti-IgE antibody) was tested in the management of EoE treatment, it decreased mast cells activation in a prospective, randomized, double-blind, placebo-controlled trial of adults with EoE but also has no effect on symptoms of esophageal eosinophilia although is not recommended[10,47].

Biological agents used in allergic conditions (such as benralizumab, dupilumab, cendakimab, etc.) proved promising for the treatment of EoE[5]. IL-4, IL-13 pathways, and antibodies against it have been considered as a potential management in a therapy of patients with EoE, because they are related to the currently considered pathomechanism of the disease[5].
-Dupilumab (anti-interleukin 4 receptor monoclonal antibodys) was tested and in a phase two trial of patients with active EoE, it reduced the percentage of dysphagia, histologic presentation of disease (including eosinophilic infiltration), and abnormal endoscopic features compared with placebo[48], but further studies are required to resolve the long-term outcome and safety of dupilumab in the therapy of EoE[48].
-Cendakimab (anti-interleukin 13 monoclonal antibodys) also has shown promising results in phase 2 trials in patients with EoE, it has reduced histologic and endoscopic features compared with placebo and was well tolerated by patients[49].
-Benralizumab (anti-interleukin 5 monoclonal antibody) is also taken into consideration as a candidate in the management of patients with EoE. In the phase 2 trial benralizumab has showed in a group of patient with increased level of eosinophils significant reduction compared to placebo[50], there was published case-report of patients with eosinophilic asthma and EoE in whom benralizumab was prescribed for asthma but also resulted in complete demission of dysphagia symptoms and histological remission[51].
Currently, due to the lack of big randomized controlled trial data in EoE (which are ongoing), the guidelines do not recommend the use of biological drugs in the standard scheme, however, these drugs show great potential[5,10].

Conclusions:

-EoE is an emerging disorder, the number of diagnoses of this disease in both children and adults has increased significantly in recent years and there is no indication that this is about to change.
-EoE is a very heterogeneous disease, and its manifestations depend mainly on age, but nevertheless, each patient suffers differently.
-When the patient presents very non-specific symptoms from the gastrointestinal tract that do not respond to standard treatment, EoE should be considered.
-Currently, we have many therapeutic agents that significantly change the natural course of the disease and improve the quality of life of patients. However, in many cases there are no data on long-term treatment effects, effective doses, and safety. This areas will likely become a promising research direction in the future.

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