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Jakub Milczarek, Anita Kurlenda, Katarzyna Ziobro, Bartosz Ostrowski

Eosinophilic oesophagitis – symptoms, diagnosis and treatment

Eozynofilowe zapalenie przełyku – objawy, diagnostyka, leczenie

Department of Gastroenterology and Hepatology, K. Gibiński University Clinical Centre, Medical University of Silesia, Katowice, Poland
Correspondence: Bartosz Ostrowski, Department of Gastroenterology and Hepatology, K. Gibiński University Clinical Centre, Medical University of Silesia, Medyków 14, 40-752 Katowice, Poland, e-mail: bartoszostrowski8@gmail.com

ORCID iDs

1. Jakub Milczarek https://orcid.org/0000-0002-4099-0999
2. Anita Kurlenda https://orcid.org/0000-0002-9113-9539
3. Katarzyna Ziobro https://orcid.org/0000-0002-8156-9383
4. Bartosz Ostrowski https://orcid.org/0000-0003-2216-3276

Abstract

Eosinophilic oesophagitis is a complex multifactorial disorder and one of the leading causes of dysphagia in children and adults. An allergen-mediated inflammatory response is the underlying cause of this disease. Allergen-activated Th2 cells, eosinophils and interleukins 4, 5 and 13 play a major role in the pathogenesis of eosinophilic oesophagitis. Difficulties swallowing, especially dry food, and the related increase in chewing time, as well as episodes of oesophageal food impaction, often requiring endoscopic treatment, are the leading symptoms. Children develop nausea, vomiting, abdominal pain, irritability and reluctance to consume foods. The incidence of eosinophilic oesophagitis has increased dramatically in recent years and is now estimated at approximately 42.2/100,000 per year in adults. Endoscopy followed by histopathological examination of at least six biopsy specimens taken from two different sections of the oesophagus is the gold diagnostic standard. The eosinophilic oesophagitis endoscopic reference score (EREFS) is used for endoscopy and the eosinophilic oesophagitis histologic scoring system (EoE HSS) is used for histopathology to objectify the assessment. Pharmacological and dietary therapies are of primary importance in eosinophilic oesophagitis. Proton pump inhibitors and glucocorticoids are most commonly used. Allergen-free diets significantly contribute to the achievement of permanent histological and clinical remission. In the case of permanent oesophageal remodelling, endoscopic and/or surgical treatment should be considered.

Keywords: eosinophilic oesophagitis, diagnosis, treatment

Streszczenie

Eozynofilowe zapalenie przełyku to złożona i wieloczynnikowa choroba będąca jedną z głównych przyczyn dysfagii wśród dzieci i dorosłych. U podłoża tego schorzenia leżą proces zapalny oraz wpływ chorób alergicznych. W patogenezie eozynofilowego zapalenia przełyku główną rolę odgrywają aktywowane alergenem limfocyty Th_2, eozynofile oraz interleukiny 4, 5 i 13. Wiodącymi objawami są trudności z połykaniem, zwłaszcza suchych pokarmów, i związane z tym wydłużenie czasu przeżuwania oraz epizody uwięźnięcia kęsów w przełyku, często wymagające leczenia endoskopowego. U dzieci występują nudności, wymioty, bóle brzucha, drażliwość i odmowa przyjmowania pokarmów. Częstość występowania eozynofilowego zapalenia przełyku w ostatnich latach znacząco wzrasta i obecnie szacuje się, że u dorosłych wynosi około 42,2/100 000 rocznie. Złotym standardem diagnostycznym jest badanie endoskopowe i histopatologiczne nie mniej niż sześciu bioptatów pobranych z dwóch różnych odcinków przełyku. W celu obiektywizacji oceny w endoskopii wykorzystuje się punktację EREFS, natomiast w badaniu histopatologicznym skalę EoE HSS. W terapii eozynofilowego zapalenia przełyku podstawowe znaczenie ma leczenie farmakologiczne i dietetyczne. Najczęstsze zastosowanie mają inhibitory pompy protonowej oraz glikokortykosteroidy. Do uzyskania trwałej remisji histologicznej i klinicznej w istotny sposób przyczyniają się diety pozbawione wybranych alergenów pokarmowych. W przypadku wystąpienia trwałych zmian strukturalnych w obrębie przełyku należy rozważyć leczenie endoskopowe i/lub chirurgiczne.

Słowa kluczowe: eozynofilowe zapalenie przełyku, diagnostyka, leczenie

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic inflammation involving different layers of the oesophageal wall. EoE is considered to be one of the major causes of dysphagia and oesophageal food retention in adults, as well as feeding dysfunctions in children. The pathogenesis of EoE is complex and multifactorial, including genetic, immunological and environmental factors[1,2]. High levels of immunoglobulin E (IgE) and sensitisation to food (about 75%) and inhalant allergens (about 73%) play an important role in the pathogenesis. Atopic diseases are found in 2/3 of EoE patients[3–5].

As a result of exposure to allergen, Th_2 cell activation occurs, which causes eosinophils to migrate and infiltrate the mucosa. Interleukins (IL) 4 and 13 are mediators that play an important role in the initiation of the Th_2-mediated signalling pathway. IL-13, which may increase up to 16-fold in the oesophagus during active disease, is of particular importance. This interleukin stimulates the secretion of a chemokine (eotaxin-3) and a proteolytic enzyme (calpain-14) by eosinophils, which are responsible for remodelling and changing the epithelial architecture, which even involve the full-thickness of the oesophagus[6,7]. The contribution of IL-5, which stimulates eosinophilopoiesis, is also worth mentioning[8]. Chronic inflammation causes dysfunction of the involved oesophageal areas and contributes to the risk of complications in the form of fibrosis and, as a result, oesophageal stricture[1,9].

It seems an important clinical aspect to differentiate between EoE and gastroesophageal reflux disease (GERD) due to the similarity of symptoms[10]. It should be remembered that both disorders can also coexist. Furthermore, it has been hypothesised that gastroesophageal reflux is involved in the etiopathogenesis of EoE. The proposed mechanism involves loss of oesophageal mucosal integrity and prolonged re-exposure to allergens contained in regurgitated gastric contents[11]. In a small group of patients, EoE may develop secondary to inherited connective tissue disorders, such as Marfan syndrome, Loeys–Dietz syndrome or Ehlers–Danlos syndrome. Although only 1% of patients present with EoE overlapping with connective tissue disorders, it is estimated that the risk of EoE in individuals suffering from this type of disorder is up to 8-fold higher[12].

Environmental factors predisposing to EoE include preterm delivery, caesarean section, the need for neonatal intensive care, and early exposure to antibiotics and proton pump inhibitors[1]. It is also assumed that the risk of EoE may be increased by non-steroidal anti-inflammatory drugs (NSAIDs), smoking and alcohol consumption; however, there is no sufficient evidence to support these relationships[13].

The incidence of EoE has been increasing significantly in recent years, which may be associated with the growing rates of allergies on the one hand, and the use of more advanced diagnostic methods on the other hand[1]. It is assumed, however, that the rise in the incidence of EoE outpaces the diagnostic increases[14]. EoE affects both children, with the peak incidence between 5 and 10 years of age, and adults, especially 30–50 year olds. EoE is three times more common in Caucasian men than in women[1]. An analysis of 2008–2011 data on US population showed that the mean age of patients diagnosed with EoE was 33.5 years and 65% were men. Furthermore, dysphagia was the first symptom in 55.8% of patients, while at least one allergic condition was found in 52.8% of patients[15]. In 2014, two decades of experiences related to the epidemiology of EoE in different countries were summarised. The overall prevalence of the disease was estimated at 50–100/100,000, and the incidence of new cases at approximately 10/100,000 per year[16]. According to current population studies, the cumulative incidence of EoE in adults is 7.7/100,000 per year. In one of the latest studies, the prevalence of EoE was up to 42.2/100,000[17].

SYMPTOMS

The symptoms of EoE are non-specific, mainly in the form of oesophageal disfunction. Difficulties and discomfort associated with swallowing dry foods, which is often associated with prolonged chewing time and using high amounts of liquids to wash the food down, with some patients resigning from meals, are of particular importance. Approximately 30% of adult patients with EoE experience episodes of food bolus impaction requiring endoscopic intervention[18]. Furthermore, heartburn and chest pain may occur[9]. All these symptoms reduce the quality of social life of patients, who may avoid social food consumption[1].

Nausea, vomiting, refusal to eat, abdominal pain, heartburn, and poor height and weight are the main symptoms in children[1,9]. Irrespective of the patient's age, symptoms indicating the presence of atopic diseases are an important clue that should prompt the diagnosis of EoE in the presence of other typical symptoms of this disease[18].

DIAGNOSIS

The diagnostic process begins with a thorough medical history taking, aimed at identifying the presence of characteristic symptoms, which often depend on the patient's age[1,19]. The coexistence of atopic diseases, including family members, is also important. Additionally, patients with positive family history for EoE have an increased risk of the disorder[19]. The next step is to perform endoscopy and collect specimens from the oesophageal mucosa for histopathology. Endoscopy and biopsy are the gold diagnostic standard and the only reliable method of monitoring the therapeutic efficacy[1,19–21].

Exclusion of other potential causes of the presence of eosinophils in the oesophageal mucosa is an essential element of the differential diagnosis. The most important include GERD, eosinophilic gastroenteritis, hypereosinophilic

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syndrome, fungal or viral oesophageal infections, oesophageal Crohn's disease, cardia achalasia and graft vs. host disease (GvHD)[19,22]. A method of endoscopic assessment of EoE lesions (Endoscopic Reference Score, EREFS) was developed and validated in 2012. It is used to diagnose the disorder and assess its severity, as well as to qualify patients for appropriate treatment (e.g. the presence of strictures or trachealisation may require endoscopic dilation of the oesophagus). The tool is used to determine severity of five major endoscopic findings: white exudates, mucosal oedema, oesophageal rings, furrows, and strictures. It is also possible to assess minor findings, which include, among others, crepe paper oesophagus and tug sign. The first sign indicates a high fragility of the mucosa, which is damaged when the endoscope is moved around the strictures, and the second refers to the need to use greater force when collecting mucosal biopsy specimens with biopsy forceps, which results from subepithelial fibrosis. Both symptoms were excluded from EREFS due to their insufficient sensitivity and specificity[19,20].

Particular attention should be paid to the differences in the endoscopic picture of EoE depending on the patient's age. Children mostly present with exudates, longitudinal crack-like fissures and oedematous mucosa, while trachealisation and oesophageal strictures are much more common in adults. With age, the degree of stenosis increases, which correlates with the increased amount of collagen fibres in histopathology. Reduction in oesophageal luminal diameter to less than 10 mm occurs in approximately 38% of adult patients[19,20].

Although the abnormal findings included in the EREFS score are present in 90–95% of EoE patients[19], endoscopic image is unremarkable in a certain group of patients (25% of cases). Irrespective of the lack of pathological macroscopic findings, mucosal specimens should be taken when EoE is suspected[1,23]. Müller et al. found EoE in histopathology despite the lack of endoscopic findings typical of this disorder in 9% of patients with Schatzki ring. Radiography of the upper gastrointestinal (GI) tract using barium sulfate as a contrast agent or a more recent method, high-resolution impedance planimetry (EndoFLIP), can be used for oesophageal strictures that cannot be visualised by endoscopy[1,24].

For diagnostic purposes, at least six biopsies are taken from at least two different parts of the oesophagus, most often from its proximal and distal sections, with preference of macroscopically altered sites, if any. The described method of biopsy collection depends on the heterogeneity in the occurrence of mucosal inflammatory changes along the entire length of the oesophagus. Proximal and distal biopsies should be placed in separate containers with formaldehyde as a fixative[23].

Multiple changes typical of EoE are described in histopathology. However, the presence of eosinophilic infiltrates is the most important factor in establishing the diagnosis, therefore each microtome paraffin section stained with haematoxylin and eosin must be assessed for eosinophil density. Microscopic slide with the highest eosinophil count is used for quantitative assessment. EoE is diagnosed if there are at least 15 eosinophils/high-power field (×40). Due to the fact that various models of microscopes are used in pathology laboratories around the world, it is recommended to present the results in the form of units expressing eosinophil density (eos/mm^2)[19,23].

The Eosinophilic Esophagitis Histologic Scoring System (EoE HSS) was created to assess histological severity and therapeutic efficacy. In addition to eosinophil density, it assesses the following parameters: basement membrane hyperplasia, eosinophilic microabscesses (i.e. clusters of ≥4 granulocytes), eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, lamina propria fibrosis, and dyskeratotic epithelial cells, i.e. keratinisation of single cells below the stratum corneum, where no physiological keratinisation occurs. Each EoE HSS item is assessed on a scale from 0 to 3[19].

In addition to endoscopy and histopathology, a molecular test (EoE Diagnostic Panel, EDP) and a questionnaire to assess the patient's quality of life can be used to estimate disease activity. Two questionnaires have been developed for adults: The Adult Eosinophilic Esophagitis Activity Index PRO (EEsAI) and The Dysphagia Symptom Questionnaire (DSQ). The Pediatric Eosinophilic Esophagitis Symptom Score questionnaire is used for the paediatric population. However, it should be remembered that questionnaires are only of supportive nature in the diagnostic and therapeutic process, and their clinical value in assessing the severity of the disease is low[1,19,20].

Molecular testing (EDP) is currently used mainly as a research tool. It uses multiplex quantitative polymerase chain reaction (qPCR) to assess the expression of 96 genes involved in the pathomechanism of EoE[1,19]. According to the latest research, this method requires only one oesophageal specimen, which makes it less burdensome while maintaining comparable or even higher diagnostic value than traditional histopathology. Furthermore, molecular results are not affected by the biopsy site. The results of these analyses are extremely promising when it comes to a modern diagnostic approach not only to EoE, but also to other inflammatory GI diseases[25].

Intensive research is currently underway on new diagnostic methods that are minimally invasive and less burdensome for patients. Such methods include the Esophageal String Test (EST) and Cytosponge. In EST, the patient ingests a capsule attached to a string. Part of the string remains in the patient's oral cavity, and the rest travels to the oesophagus, where the capsule, after dissolution, releases the remaining piece of string (a brush is used instead of a string in Cytosponge). After an hour, the kit is removed from the oesophagus and analysed. During this test, various inflammatory mediators are absorbed[1,19,21,26]. The levels of eosinophil-associated proteins (EAPs), such as eotaxin-2 and -3 and major basic protein (MBP), were similar in

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EST and traditional biopsy specimens, and correlated with tissue eosinophil density (eos/mm^2). Patients clearly preferred the EST method as less burdensome. This technique could be used as a screening method in the paediatric population. EoE biomarkers are also sought in the blood and other body fluids[19,26].

TREATMENT

The primary goals of EoE treatment are to control the disorder and prevent its complications. Therefore, the aim is to achieve clinical and histological remission within the affected oesophageal segments. Literature points to the individualised nature of combination therapy, consisting of pharmacological, dietary, endoscopic and surgical treatment, referred to as 3Ds (Drugs, Diet, Dilation)[27–30].

Proton pump inhibitors

Several groups of drugs selected depending on the initial assessment of their efficacy are used in pharmacological management. Proton pump inhibitors (PPIs), which bring benefits on several levels, are the basic group of drugs. First, by increasing the pH of gastric acid, they reduce its destructive effects on the oesophageal mucosa. This reduces the exposure to food allergens as well as the pain associated with reflux[27,28,31]. Secondly, an anti-inflammatory effect of PPIs on EoE by inhibiting the Th_2- and eotaxin 3-mediated immune response has been demonstrated[31–33]. The available publications suggest the use of standard PPI doses given twice a day in adults and 1–2 mg/kg in children. In paediatric studies, clinical and histological improvement occurred within 8 weeks of treatment. The use of maintenance therapy at the lowest effective dose for the following 12 months still allowed for satisfactory outcomes[19,34]. A meta-analysis of studies conducted among children and adults has shown that 60.8% and 50.5% of PPI-treated patients achieve clinical and histological remission, respectively. Furthermore, the twice-daily PPI therapy proved slightly superior than the once-daily PPI regimen[35].

Glucocorticoids

Glucocorticoids (GCs) are another group of drugs with proven efficacy in the treatment of EoE. Usually, 1 mg of oral budesonide or 800 µg of oral or inhaled fluticasone twice daily is recommended[27,28]. Studies have shown that a budesonide/sucralose slurry (oral viscous budesonide, OVB) is more effective, as it has a higher viscosity, allowing for longer mucosal contact time[27,36]. The use of GCs allows for clinical improvement and histological remission, which means an increased elasticity of the oesophageal walls and easier food passage through the oesophagus. It is assumed that maintenance therapy should lead to a "deep remission" of ≥6 months, although studies indicate a high risk of relapse after treatment completion[19,34]. Adverse effects of GCs include oral and oesophageal candidiasis, herpes oesophagitis and adrenal insufficiency[28,37].

Dietary treatment

Food elimination diet

The treatment of EoE involves the use of specific forms of nutrition to achieve clinical improvement. A diet eliminating the most common food allergens is one of these methods. Typically, six food elimination diet (SFED), four food elimination diet (FFEDs), or two food elimination diet (TFEDs) are used. SFED excludes milk, eggs, soybeans, wheat, fish/shellfish, treenuts/peanuts from the patient's diet for 6–8 weeks. After this time, follow-up endoscopy with biopsy is performed to confirm remission. Then, individual allergens are reintroduced into the diet to determine which product is the triggering factor based on the recurrence of clinical and endoscopic symptoms. Studies indicate 72% efficacy of this diet. FFED excludes milk, eggs, wheat and soya/legumes based on the frequency of food allergies, while TFED eliminates milk and wheat, i.e. the two most common allergens. These diets are have lower therapeutic effectiveness, i.e. 60% and 43%, respectively. It is worth noting that milk and wheat trigger symptoms in 50% of adults and 74% of children[38–40]. The step-up 2-4-6 method, which is a reversal of the procedure, is another modification of the elimination diet. In this case, treatment of EoE is usually initiated with TFED and, if necessary, extended to FFED and SFED until improvement is achieved. It is estimated that such an approach may reduce the time of the diagnostic and therapeutic process by 20%[40,41].

Targeted elimination diet

The methodology behind the targeted elimination diet assumes the exclusion of potential allergens based on medical history and laboratory workup, e.g. prick or patch tests, serum IgEs or provocation tests[38,41]. The efficacy of targeted elimination diet in achieving histological remission is estimated at approximately 45%[39]. Other methods to increase the remission rate are also proposed, but require further research. These include IgG4 expression in the oesophageal biopsies together with the lymphocyte proliferation test or esophageal prick test (EPT), which delivers more clinically relevant information[41,42].

Elemental diet

In elemental diet, the elimination of potential allergens is achieved through the use of commercial amino acid-based formulations. The literature indicates high rates of histological EoE remission, reaching 75% in adults and 90% in children[27,38,39]. Unfortunately, elemental diets have multiple disadvantages, such as poor taste, high costs, inducing nutritional deficiencies and complete deprivation of conventional diet, which significantly limits their use[27,43]. For these reasons, such a diet is implemented in young children when it is necessary to achieve rapid remission,

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in the case of elimination diet failure or persistent chronic oesophageal inflammation[38].

Endoscopic and surgical approaches

Endoscopic and surgical methods are needed in patients with permanent oesophageal remodelling, i.e. fibrosis leading to loss of oesophageal elasticity and strictures, as well as increased mucosal viscosity or corrugation. These changes cause the characteristic, burdensome symptoms of EoE. The management consists in gradual dilatation of oesophageal strictures; however, it should be noted that despite improved dysphagia in about 80% of patients, this treatment does not eliminate inflammation and no histological remission is achieved[27,44]. Chest pain and oesophageal perforation are complications of endoscopic treatment[44]. Partial or total oesophagectomy is rarely performed, usually in cases of serious complications[43].

Other approaches

Research is currently underway to assess many pharmacological agents, including omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, QUAX576, RPC4046 and infliximab, i.e. prostaglandin D2 (CRTH2) receptor antagonists or antibodies directed against the key pathogenic immunoglobulins, interleukins or their receptors. Furthermore, reports on the use of substances such as montelukast, cromoglycate, 6-mercaptopurine and azathioprine may be found in literature, but currently these treatments are not recommended[41,45,46].

CONCLUSIONS

Eosinophilic oesophagitis is a relatively recently described clinical entity, the knowledge and awareness of which are still insufficient, despite the fact that it is one of the most common upper GI disorders. The upward trend in the incidence of EoE, observed for several years now, prompts constant search for better diagnostic and therapeutic modalities. The unexplained etiopathogenesis of this disorder makes it a particularly interesting topic for scientific research.

Currently, endoscopic biopsy remains the method of choice in the diagnosis of EoE. However, there are many gaps in the latest guidelines of the European Society Gastrointestinal Endoscopy (ESGE) on the management of EoE. For example, it has not been determined whether follow-up endoscopies with microscopic evaluation should be performed after elimination diet therapy. Recommendations point out that clinical improvement is an adequate parameter to assess therapeutic efficacy on the one hand, but they emphasise the role of endoscopy in choosing a further treatment strategy on the other hand. This way, the guidelines leave some room for manoeuvre in choosing the method to assess response to treatment to the physician based on his/her knowledge and experience. Due to the chronic nature of the disorder, and thus the long duration of the treatment process, intensive research on minimally invasive diagnostic methods is underway. This is particularly important as early diagnosis allows for optimal treatment outcomes.

The treatment of EoE is a major challenge, as the chronic nature of the disorder requires lifelong therapy. Currently, therapeutic strategies are individualised and based primarily on pharmacotherapy with PPIs and/or GCs and elimination diets. Oral viscous budesonide (OBV) represents an improved pharmacological treatment. Research on biological treatments is also underway, but no superiority over standard therapies has been demonstrated yet.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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