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REVIEW PAPER

Eosinophilic esophagitis in children – current state of the problem

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ABSTRACT

In recent years, eosinophilic esophagitis (EE) has become a general clinical problem for allergists and gastroenterologists. The prevalence of EE is two times more likely to occur in children than in adults. Despite the large number of studies, it is considered that the aetiology and pathogenesis of EE have not been completely determined. The peculiarity of EE is that inflammatory changes are focal and evenly cover the distal and proximal oesophagus. During the allergic inflammatory process of the epithelium the oesophagus acquires hyperplastic characteristics, which causes the accumulation of eosinophils within it. The clinical picture of EE is nonspecific and varies according to the child's age and the degree of progression of the disease. It is known that the onset of EE in children or adolescents subsequently leads to the need for endoscopic and surgical correction of dysphagia, strictures, narrowing of the oesophagus in a low number of these patients.

KEY WORDS:

children, eosinophils, oesophagus, eosinophilic oesophagitis.

In recent years, eosinophilic oesophagitis (EoE) has become a common clinical problem for allergists and gastroenterologists [1–3]. According to the American Gastroenterology Association, the prevalence of EoE is two times more common in children than in adults [4]. The increase in the frequency of this disease [5, 6] is due to the awareness of doctors, as well as the improvement of various diagnostic methods [4, 7].

Oesophageal eosinophilia was first reported in 1978 by Landers, who noted these features in a patient with achalasia [4]. In the early 1990s, Attwood and Straumann independently described the phenotypic and histological features of EoE, and subsequently EoE was isolated into a separate clinical and morphological syndromes [4, 8, 9]. In 1995, a justification was given for the allergic nature of EoE [10] in the form of an "antigenic" or "immune" reaction with consistent clinical and histological disorders [11]. The first EoE recommendations were described in 2007 [12], with subsequent updates in 2011 [13], 2013 [14], and 2017 [15, 16].

EoE is a chronic immunological antigen-mediated disease of the oesophagus, characterised by mucosal infiltration by eosinophils and clinical symptoms associated with oesophageal dysfunction [1, 13, 15]. Carr *et al.* call EoE the atopic state of the oesophagus [6].

According to the research of Liacouras *et al.*, who observed 381 children with EoE during 1994–2003, an increase in the incidence of cases from one in 1994 to more than 70 in 2003 was noted [17].

Taking into account the data of Iwanczak *et al.*, when conducting 35,631 endoscopic examinations in children from four months to 18 years of age, EoE was detected

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in 84 patients [18]. The frequency of diagnosis of EoE in these children was almost six times more frequent with the scientific characteristic of EoE clinical and endoscopic features [18].

The prevalence of EoE in North America and Europe ranges from one to six per 10,000 people [6, 19–22].

Today it is known that oesophageal eosinophilia also accompanies the course of eosinophilic gastrointestinal diseases, celiac disease, Crohn's disease, infectious oesophagitis, hypereosinophilic syndrome, achalasia, vasculitis, pemphigus, and connective tissue disease. It can be found in patients with hypersensitivity to medicines [3].

According to scientific research, since childhood, EoE is diagnosed three times more often in men than in women [15, 23, 24]. The prevalence of EoE in boys is associated with a mutation in the TSLP gene located in chromosome 5q22 and a mutation of another gene found in the sex chromosomes Xp22.3 and Yp11 [4].

EoE is found in all racial and ethnic groups, although many studies describe a higher prevalence of EoE in white people [25, 26].

Despite the large number of studies, it is considered that the aetiology and pathogenesis of EoE are not definitive [1]. However, the literature reports a genetic predisposition to the disease [1, 27, 28]. For example, D'Alessandro *et al.* tracked an increased incidence of EoE in patients with Marfan, Ehlers-Danlos, Lois-Dietz syndrome, and other hereditary pathologies of connective tissue [28].

According to the literature, the importance of air and food allergens is given in the development of EoE [1, 4]. Thus, Ram *et al.* found an increase in the severity of symptoms and a worsening of the histological picture in a group of patients with EoE during the season, which corresponded to their specific sensitisation to the aeroallergen. At the same time, no adjustment of diet and treatment for this period of time was performed in patients [7, 15].

Literature data indicate that EoE is more common in people with asthma, allergic rhinitis, eczema, food allergy associated with the IgE-dependent mechanism [29], and other allergic manifestations [12, 15] than in the general population [15, 29]. Interestingly, with the above listed diseases, mutations of such genes as in patients with EoE were observed, which leads to the development of an immune response by activation of type 2 helper cells [4]. Exacerbations of EoE are more common in patients with concomitant seasonal allergic rhinitis during peak pollen seasons [6, 30]. Due to the presence of similar clinical and pathophysiological characteristics with asthma, EoE is sometimes referred to as "oesophageal asthma" [6].

Some authors have suggested the development of EoE in the use of oral or sublingual immunotherapy (SLIT) [15] and describe the positive dynamics and recovery after completion of SLIT [31–33].

Normally, eosinophils and other leukocytes are absent in the multilayered flat epithelium of the oesophageal mucosa [1, 3, 4, 6]. Only the presence of lymphocytes, dendritic cells, and mastocytes (mast cells, basophils) is allowed [1, 4]. It is normal to find eosinophils in their own lining of the mucous membranes of the gastrointestinal tract covered with cylindrical epithelium [4]. It is there that they perform their basic protective function against multicellular parasites – helminths [4].

During the allergic inflammatory process, the oesophagus epithelium acquires hyperplastic features, which causes the accumulation of eosinophils in it [3, 34], unlike in a healthy body, when eosinophils from the blood migrate into the connective tissue of the organ to perform its function [35].

The clinical picture of EoE is nonspecific and varies depending on the age of the child [15] and the degree of disease progression [15, 36–38]. For example, parents of infants and young children express complaints of eating disorders [39, 40], refusal of food, vomiting, and abdominal pain [15, 41, 42]. Children who are able to describe their complaints in more detail complain of difficulty with swallowing food [24, 43], swallowing pain, heartburn, pain and discomfort in the sternum, and upper abdominal pain. They also, demonstrated food preferences [25, 33, 44–48]. When diagnosing EoE it is also important to consider physical development indicators of children according to age, body weight, and height, but they are not specific for EoE [3].

Given the new EoE diagnostic criteria developed by experts from 14 countries and published in October 2018, the following symptoms of oesophageal dysfunction should be noted: food clogging, heart failure, regurgitation, vomiting, chest pain, abdominal pain, swallowing pain, etc. [15, 49].

The gold standard for the diagnosis of EoE is endoscopic examination with biopsy from the proximal and distal oesophagus [3] with the detection of 15 or more eosinophils assessed in so-called HPF (high power field) i.e. magnification ×400 [6]. No pathognomonic features of the endoscopic picture of EoE have been identified so far because changes in the mucous membrane of EoE are found in other diseases of the oesophagus [3].

According to some studies, 10–25% of patients with EoE do not have visually pathological changes, i.e. from the outside, mucous looks like that of a healthy person, and only the biopsy results report a pathological process [22, 50, 51]. Some authors encounter a normal endoscopic picture in as much as 20–30% of cases [4]. Given the above, oesophageal biopsy should be performed for all patients with EoE in order to diagnose and monitor the effectiveness of the prescribed treatment [3, 4] because endoscopically unchanged mucosa does not exclude the presence of EoE [49, 52].

Pathologically altered mucosa has fixed oesophageal rings, white exudates or plaques, longitudinal furrow, swelling in the form of mucous membranes, diffused oesophageal constriction, and oesophageal ruptures caused by passage of the endoscope and which are the consequence of the collapse [13, 53–56].

Patients who have not previously been diagnosed with EoE, who have symptoms of gastric and intestinal abnormalities with endoscopic changes, should be biopsied from the antral compartment of the stomach and/or duodenum to exclude other causes of oesophageal eosinophilia [3]. Some researchers believe that 100% sensitivity of histological examination is obtained from five biopsies [4]. The peculiarity of EoE is that inflammatory changes are focal in nature and uniformly cover the distal and proximal divisions of the oesophagus [4].

The authors of the research recommend not to interpret separately clinical and endoscopic indicators of EoE with biopsy results [13].

Low controversy and many fundamental issues can be traced to this nosology, which is particularly evident in the difference between EoE and gastroesophageal reflux disease (GERD) [3]. GERD is considered a cofactor in the development of EoE, due to the deeper penetration of antigens into the damaged mucosa of the oesophagus due to the action of acid-peptic reflux [4].

According to the literature, translational diagnostic methods (using microarrays, identifying relevant genes, protein levels using immunochemistry capabilities, and immunofluorescence studies) are at the development stage and are not ready for implementation and use in clinical practice by a physician [3].

Not only diagnostics but also determining the therapeutic response of EoE is relevant [3]. The low number of publications indicates the positive dynamics of topical steroids [6, 15, 57–64], which prevents the growth of fibrous tissue [15, 65–70], excretion of food antigens [42, 59], and use of elimination diet [3, 6, 15, 23, 71–75].

Some authors have described the safe and long-lasting effect of treatment of strictures that complicate EoE with endoscopic dilatation [9, 55, 64, 76–80]. Most often, endoscopic dilation of the oesophagus is used in adults with established oesophageal strictures [6]. 75% of patients arfe at risk of pain while performing this procedure, and there is a likelihood of bleeding and oesophageal perforation [35, 59].

From the literature, it is known that the occurrence of EoE in childhood or adolescence subsequently leads to the need for endoscopic and surgical correction of dysphagia, strictures, and narrowing of the oesophagus [9].

Eliminating or reducing the severity of dysphagia symptoms is not considered to be a reliable parameter for evaluating disease activity and treatment efficacy because compensatory factors for diet and lifestyle can mask symptoms [3]. Therefore, it is believed that the result of histological evaluation in EoE is important [15]. Clinical and endoscopic improvement in eosinophil counts of less than 15 were observed, but a strong correlation was found between the disappearance of disease symptoms, positive endoscopic dynamics, and decreased eosinophil levels in the oesophageal mucosa to 5 and less [15, 81, 82].

Proton-pump inhibitors (PPI) should be considered as a potential early or initial treatment, because of their low cost, good safety profile, convenience, and a large body of literature describing PPI response in patients with oesophageal eosinophilia. PPI is recommended at dose between 1 and 2 mg/kg/d for eight weeks [83].

Some authors recommend as first-line pharmacological therapy for the treatment of EoE the use of topical steroids orally (fluticasone or budesonide) for eight weeks [3]. It should be stated that current algorithms of diagnosis and treatment of EoE advise trying high doses of proton pump inhibitors, even starting with it in many cases prior to topical steroids. It is also recommended to take into account an empirical elimination diet. The peculiarity of corticosteroid hormones to reduce the synthesis of eosinophil growth factors (interleukin-5, granulocyte-macrophage colony-stimulating factor) and chemoattractants (eotaxin-3), to induce eosinophil apoptosis, determines their therapeutic effect [4]. The required dose with a nebuliser of fluconazole is given by inhalation without inhalation, followed by ingestion of the drug to swallow [6]. Fluticasone is recommended at a dosage of 88–440 mcg 2–4 times up to 880 mcg per day [4, 15] and budesonide in the form of a thick suspension of 1 mg per day for children up to 10 years old, and 2 mg for children over 10 years old [4]. Steinbach reports this as twice as effective when using budesonide in the form of a thick suspension of 1 mg twice a day than when administering the same dose with a nebuliser [15]. Systemic corticosteroids are recommended for patients with weight loss and narrowing of the oesophagus in the form of prednisolone 1–2 mg/kg [4].

It was also found that using a thick budesonide suspension is more convenient and effective. When using fluconazole, the most common complication was oesophageal candidiasis [58, 60, 64, 84–86].

If diet or steroid therapy is used as a first-line therapy but is ineffective on follow-up endoscopy with biopsy, PPI therapy should be considered [83].

Steinbach emphasises the need to develop an individualised treatment plan for each patient, taking into account their values, lifestyle, financial component, and social environment [15].

In the absence of positive dynamics of the histological picture of EoE and the purchase of symptoms, the effectiveness of prescribing higher doses and prolonging the course of topical steroids has a low level of evidence [3].

According to the researchers, high doses of leukotriene receptor antagonists do not affect the degree of mucosal infiltration of eosinophils but contribute to the relief of symptoms [4]. Experimental studies on the use of mast cell stabilisers and leukotriene inhibitors are underway [3].

Given the literature, it is necessary to take into account the presence of atopic conditions that accompany EoE and apply appropriate therapy and an elimination

diet. Endoscopy with biopsy is only one method to evaluate the effectiveness of the diet and drug therapy [3]. Regarding the monitoring of the effectiveness of treatment, some recommendations have been described that consist of endoscopy with biopsy within 6-8 weeks of starting the treatment [15]. Once EoE control has been achieved, some clinicians conduct repeated examinations once a year, others less frequently, and some consider it necessary to refer to the clinical picture for the purpose of biopsy endoscopy. The final rules on the timing of EoE monitoring have not yet been approved [15].

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Budkina TN, Sadikov IS, Makarova SG, et al. Eosinophilic esophagitis in children. Review paper. Questions of modern pediatrics 2016; 15: 239-249.
2. Aceves SS. Food allergy testing in eosinophilic esophagitis: what the gastroenterologist needs to know. Clin Gastroenterol Hepatol 2014; 12: 1216-1223.
3. Dellon ES, Gonsalves N, Hirano I, et al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). The American Journal of Gastroenterology. Am J Gastroenterol 2013; 108: 679-692.
4. Ivashkin VT, Baranskaya EK, Trukhmanov AS, et al. Eosinophilic esophagitis. Study Guide for Doctors. M.: AISPI RAS 2013; 80.
5. Chen JW, Kao JY. Eosinophilic esophagitis: update on management and controversies. BMJ 2017; 359: j4482.
6. Carr S, Chan ES, Watson W. Eosinophilic esophagitis. Allergy Asthma Clin Immunol 2018; 14 (Suppl 2): 58.
7. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr 2014; 58: 107-118.
8. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993; 38: 109-116.
9. Straumann A, Spichtin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings [in German]. Schweiz Med Wochenschr 1994; 124: 1419-1429.
10. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995; 109: 1503-1512.
11. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. Gastroenterology 2009; 137: 1238-1249.
12. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007; 133: 1342-1363.
13. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011; 128: 3-20.e6; quiz 1-2.
14. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013; 108: 679-692; quiz 693.
15. Steinbach EC, Hernandez M, Dellon ES, et al. Eosinophilic Esophagitis and the Eosinophilic Gastrointestinal Diseases: Approach to Diagnosis and Management. J Allergy Clin Immunol Pract September/October 2018; 6: 1483-1495.
16. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017; 5: 335-358.
17. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol 2005; 3: 1198-1206.
18. Iwanczak B, Janczyk W, Ryzko J, et al. Eosinophilic esophagitis in children: frequency, clinical manifestations, endoscopic findings, and seasonal distribution. Adv Med Sci 2011; 56: 151-157.
19. Ally MR, Maydonovitch CL, Betteridge JD, et al. Prevalence of eosinophilic esophagitis in a United States military healthcare population. Dis Esophagus 2015; 28: 505-511.
20. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014; 12: 589-596.
21. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population based study in Olten County, Switzerland. J Allergy Clin Immunol 2011; 128: 1349-1350.
22. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009; 7: 1055-1061.
23. Kapel RC, Miller JK, Torres C, et al. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. Gastroenterology 2008; 134: 1316-1321.
24. Prasad GA, Talley NJ, Romero Y, et al. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. Am J Gastroenterol 2007; 102: 2627-2632.
25. Bohm M, Malik Z, Sebastiano C, et al. Mucosal eosinophilia: prevalence and racial/ethnic differences in symptoms and endoscopic findings in adults over 10 years in an urban hospital. J Clin Gastroenterol 2012; 46: 567-574.
26. Sperry SLW, Woosley JT, Shaheen NJ, et al. Influence of race and gender on the presentation of eosinophilic esophagitis. Am J Gastroenterol 2012; 107: 215-221.
27. Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol 2014; 134: 1084-1092.e1.
28. D'Alessandro A, Esposito D, Pesce M, et al. Eosinophilic esophagitis: From pathophysiology to treatment. World J Gastrointest Pathophysiol 2015; 6: 150-158.
29. Gonzalez-Cervera J, Arias A, Redondo-Gonzalez O, et al. Association between atopic manifestations and eosinophilic esophagitis: a systematic review and meta-analysis. Ann Allergy Asthma Immunol 2017; 118: 582-590.e2.
30. Ram G, Lee J, Ott M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. Ann Allergy Asthma Immunol 2015; 115: 224-228.
31. Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. J Allergy Clin Immunol 2014; 133: 1482-1484.
32. Miehlke S, Alpan O, Schroder S, et al. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. Case Rep Gastroenterol 2013; 7: 363-368.
33. Remedios M, Campbell C, Jones DM, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to

treatment with fluticasone propionate. Gastrointest Endosc 2006; 63: 3-12.
34. Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol 2009; 104: 485-490.
35. Lutsik OD, Ivanova AY, Kabak KS, et al. Human histology. Kiev 2003: 593.
36. Binkovitz LA, Lorenz EA, Di Lorenzo C, et al. Pediatric eosinophilic esophagitis: radiologic findings with pathologic correlation. Pediatr Radiol 2010; 40: 714-719.
37. Chehade M, Sampson HA, Morotti RA, et al. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2007; 45: 319-328.
38. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014; 79: 577-585.e4.
39. Aceves SS, Newbury RO, Dohil MA, et al. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. Ann Allergy Asthma Immunol 2009; 103: 401-406.
40. Mukkada VA, Haas A, Maune NC, et al. Feeding dysfunction in children with eosinophilic gastrointestinal diseases. Pediatrics 2010; 126: e672-677.
41. Aceves SS, Newbury RO, Dohil MA, et al. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. Ann Allergy Asthma Immunol 2009; 103: 401-406.
42. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009; 48: 30-36.
43. Mackenzie SH, Go M, Chadwick B, et al. Clinical trial: eosinophilic esophagitis in patients presenting with dysphagia: a prospective analysis. Aliment Pharmacol Ther 2008; 28: 1140-1146.
44. Fass R, Gasiorowska A. Refractory GERD: what is it? Curr Gastroenterol Rep 2008; 10: 252-257.
45. Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. Gastrointest Endosc 2003; 58: 516-522.
46. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009; 7: 1305-1313; quiz 261.
47. Kahn J, Bussmann C, Beglinger C, et al. Exercise-induced chest pain: an atypical manifestation of eosinophilic esophagitis. Am J Med 2015; 128: 196-199.
48. Rassbach W, Rubenstein JH, Elkins M, et al. Age-based differences in the diagnosis and management of esophageal eosinophilia. J Allergy Clin Immunol Pract 2015; 3: 81-87.e1.
49. Umanets TR, Kreposniak AA. Asthma combined with eosinophilic esophagitis in children: current condition of the problem. Review paper. Asthma and Allergy 2019; 1: 36-43.
50. Lucendo AJ, Pascual-Turrion JM, Navarro M, et al. Endoscopic, bioptic and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. Endoscopy 2007; 39: 765-771.
51. Muller S, Puhl S, Vieth M, et al. Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. Endoscopy 2007; 39: 339-344.
52. Abhishek Watts, Jeffrey A. Alexander, Sandeep K; Gupta Gastrointestinal endoscopy 2016; 83: 307-308. www.giejournal.org.
53. Gupta SK, Fitzgerald JF, Chong SK, et al. Vertical lines in distal esophageal mucosa (VLEM): a true endoscopic manifestation of esophagitis in children? Gastrointest Endosc 1997; 45: 485-489.
54. Kim HP, Vance RB, Shaheen NJ, et al. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clin Gastroenterol Hepatol 2012; 10: 988-996.e5.
55. Straumann A, Rossi L, Simon HU, et al. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? Gastrointest Endosc 2003; 57: 407-412.
56. Straumann A, Spichtin HP, Bucher KA, et al. Eosinophilic esophagitis: red on microscopy, white on endoscopy. Digestion 2004; 70: 109-116.
57. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic responses of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012; 10: 742-749.e1.
58. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010; 139: 418-429.
59. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142: 1451-1459.e1; quiz e14-e15.
60. Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. Am J Gastroenterol 2008; 103: 2194-2199.
61. Kagalwalla AF, Akhtar N, Woodruff SA, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. J Allergy Clin Immunol 2012; 129: 1387-1396.e7.
62. Lieberman JA, Morotti RA, Konstantinou GN, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. Allergy 2012; 67: 1299-1307.
63. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol 2008; 6: 165-173.
64. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010; 139: 1526-1537.
65. Abu-Sultaneh SM, Durst P, Maynard V, et al. Fluticasone and food allergen elimination reverse subepithelial fibrosis in children with eosinophilic esophagitis. Dig Dis Sci 2011; 56: 97-102.
66. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. Allergy 2010; 65: 109-116.
67. Carlson DA, Hirano I, Zalewski A, et al. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. Clin Transl Gastroenterol 2017; 8: e119.
68. Lucendo AJ, Arias A, de Rezende LC, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. J Allergy Clin Immunol 2011; 128: 1037-1046.
69. Rajan J, Newbury RO, Anilkumar A, et al. Longterm assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids. J Allergy Clin Immunol 2016; 137: 147-156.e8.
70. Wolf WA, Jerath MR, Sperry SL, et al. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014; 12: 1272-1279.
71. Gonsalves N. Eosinophilic esophagitis: history, nomenclature, and diagnostic guidelines. Gastrointest Endosc Clin N Am 2008; 18: 1-9; vii.
72. Liacouras CA. Eosinophilic esophagitis in children and adults. J Pediatr Gastroenterol Nutr 2003; 37 (Suppl 1): S23-28.

73. Rothenberg ME, Mishra A, Collins MH, et al. Pathogenesis and clinical features of eosinophilic esophagitis. J Allergy Clin Immunol 2001; 108: 891-894.
74. van Rhijn BD, Verheij J, van den Bergh Weerman MA, et al. Histological response to fluticasone propionate in patients with eosinophilic esophagitis is associated with improved functional esophageal mucosal integrity. Am J Gastroenterol 2015; 110: 1289-1297.
75. Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet. Am J Gastroenterol 2017; 112: 1061-1071.
76. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointest Endosc 2010; 71: 706-712.
77. Hirano I. Dilation in eosinophilic esophagitis: to do or not to do? Gastrointest Endosc 2010; 71: 713-714.
78. Jung KW, Gundersen N, Kopacova J, et al. Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis. Gastrointest Endosc 2011; 73: 15-21.
79. Straumann A. The natural history and complications of eosinophilic esophagitis. Gastrointest Endosc Clin N Am 2008; 18: 99-118; ix.
80. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011; 9: 400-409.
81. Reed CC, Wolf WA, Cotton CC, et al. Optimal histologic cutpoints for treatment response in patients with eosinophilic esophagitis: analysis of data from a prospective cohort study. Clin Gastroenterol Hepatol 2018; 16: 226-233.e2.
82. Wolf WA, Cotton CC, Green DJ, et al. Evaluation of histologic cutpoints for treatment response in eosinophilic esophagitis. J Gastroenterol Hepatol Res 2015; 4: 1780-1787.
83. Evan S. Dellon et al.; Clinical-Alimentary tract. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the Agree Conference. Gastroenterology 2018; 155: 1022-1033.
84. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology 2012; 143: 321-324.
85. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2015; 13: 66-76.
86. Kuchen T, Straumann A, Safroneeva E, et al. Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis. Allergy 2014; 69: 1248-1254.