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AN ALLERGIST'S APPROACH TO EOSINOPHILIC ESOPHAGITIS

Background

Eosinophilic esophagitis (EoE) is a chronic, inflammatory disease of the esophagus that produces a range of symptoms in both adults and children, from acid reflux to food bolus impaction. The diagnosis is confirmed by endoscopic biopsies showing 15 or more eosinophils per high-power field.[1] The pathophysiology of EoE is believed to be either immune-mediated or antigen-mediated, ultimately resulting in a T helper 2 (TH2) immune response, eosinophilic inflammation, barrier dysfunction, and tissue remodelling.[2,3]

Since its recognition, EoE has been fundamentally linked to atopy, with early case reports drawing attention to this relationship.[4] Patients with EoE tend to be highly atopic, demonstrating a higher incidence of allergic rhinitis, asthma and atopic dermatitis compared to healthy controls.[5] There is also a high prevalence of IgE-mediated food allergies among these patients. A U.S.-based cross-sectional study reported that 32.4% of children and 37.3% of adults with EoE had an IgE-mediated food allergy to at least one food.[6] More recent research has shown that 87% of a cohort of 92 EoE patients had comorbid atopic conditions.[7] A review of 1,218 patients with EoE found that these patients have a 67-fold increased risk of anaphylaxis compared to that of the general population.[8] With this in mind, allergists play a key role in controlling esophageal inflammation and addressing atopic comorbidities.

Allergy testing for foods to identify triggers for EoE has gradually fallen out of favour in the literature. For the 2020 AGA (American Gastroenterological Association) and Joint Task Force (AAAAI/ACAAI) EoE management guidelines, the weakest recommendation ("conditional") and lowest quality of evidence ("very low quality") was assigned to the role of allergy-based testing for identification of specific food triggers when compared to no treatment (i.e. testing was similar to not doing anything), due to limited accuracy.[9] More recently, the 2022 British EoE guidelines explicitly recommending against all forms of food allergy testing (skin prick, specific IgE, specific IgG4, and atopy patch testing) to guide dietary elimination.[1] This evolution is due to multiple revelations in the pathophysiology of EoE and clinical experience. The failure of omalizumab to effectively treat EoE suggests a non-IgE-mediated pathophysiology.[10] Moreover, elimination diets guided by allergy testing have been shown to be no more effective than empiric dietary elimination.[11,12] However, allergy testing for aeroallergens is a key part of EoE management to maintain control of comorbid atopic disorders.[13] While IgE-based testing methods for food allergies cannot reliably predict triggering foods for EoE, such testing can guide the reintroduction of previously avoided foods to which patients may have developed new IgE sensitization, when used in conjunction with oral food challenges. Allergists have special training and expertise in the proper selection and interpretation of skin and serum-specific IgE tests, conducting oral food challenges, and guiding immunotherapy such as aeroallergen or food immunotherapy.

In our first case, we will describe a pediatric patient with EoE and multiple IgE-mediated food allergies, and the potential role of oral immunotherapy (OIT). Our second case will focus on the management of a young adult with EoE and severe allergic rhinitis with consideration for sublingual immunotherapy (SLIT). Our third case, a woman with severe EoE and multiple atopic comorbidities, will allow us to discuss the potential role of dupilumab. All three cases require the unique skill set of an allergist.

Case 1

A 2-year-old female has a known history of EoE and IgE-mediated food allergies to hen's egg, peanut, cashew, and sesame. While she had a clear history of anaphylaxis to egg, cashew and sesame, there was an unclear history for peanut and skin testing was intermediate in size (5 mm wheal) with peanut sIgE of 2.05 kU/L, therefore the diagnosis of peanut allergy was confirmed by an oral challenge. Her EoE is well-controlled with the elimination of cow's milk. However, the family has found food allergen avoidance burdensome and has expressed interest in OIT for the foods of concern. On further review, the patient had an immediate-onset urticaria after accidentally ingesting milk, which had been avoided for approximately six months. Prior to initiating OIT, allergen skin prick testing to cow's milk was performed and was positive. Similar to this patient's history, previous reports have shown EoE patients developing IgE-mediated food allergies after a period of avoidance.[14]

The overall prevalence of EoE after OIT is estimated to be 2.7%, with EoE often resolving after discontinuation of therapy.[15,16] Our centre participated in a real-world Canadian preschool peanut OIT safety analysis, which

showed similar results: three of 270 patients reported symptoms of possible EoE, with one having biopsy-proven EoE (0.37%).[17] Based on the available literature, it is apparent that EoE or esophageal eosinophilia may be a transient feature seen in a subset of long-term OIT patients. This issue is further complicated by a Brazilian study showing that at baseline, cow's milk-allergic patients may have asymptomatic esophageal eosinophilia, suggesting that OIT may "unmask" rather than cause EoE in some patients.[18] The relationship between EoE and OIT remains complex, and the question of whether this represents causation, unmasking or coincidence remains unanswered.

Current OIT guidelines from the Canadian Society of Allergy and Clinical Immunology (CSACI) permit the use of grocery store based OIT products outside of the research setting, due to the absence of Health Canada licensed OIT products. The guidelines list EoE as a relative contraindication (not absolute) for initiating therapy. In fact, EoE patients are typically excluded from OIT trials, given the possible relationship between the two that we have described. The available literature sheds new possibilities on whether OIT causes, unmasks or is coincidental with EoE. Furthermore, esophageal eosinophilia tends to resolve once OIT therapy is discontinued.[14,19] In a longitudinal peanut OIT study of 21 patients, at baseline 3 patients (14%) had asymptomatic eosinophil counts of > 15 eosinophils per high-power field, with most patients showing only transient esophageal eosinophilia during OIT (one patient in this study developed symptomatic EoE).[20] In contrast, other reports have shown that EoE diagnosed in the context of OIT may persist, suggesting that the disease may have been unmasked.[21,22] Regardless, EoE diagnosed during the course of OIT can be effectively treated with the use of swallowed steroids or proton pump inhibitors without stopping OIT.[23,24] For patients in the real world who are diagnosed with EoE in the context OIT, a recent publication has suggested adopting a shared decision-making approach with patient families instead of declaring absolute contraindications.[25] In light of the current understanding of EoE pathogenesis, it is the author's personal opinion and proposal that OIT may be carefully started in patients with EoE who desire it, with the understanding that adjustments to OIT or EoE management can be considered should concern for disease worsening arise.

In cases where a patient suffers from EoE and IgE-mediated food allergies, there is a need for shared decision-making between the family and gastroenterology colleagues. When patients experience gastrointestinal (GI) symptoms during OIT, it is recommended to categorize the symptoms based on whether they are immediate or delayed relative to the OIT dose (**Figure 1**).[19] Immediate IgE-mediated symptoms usually improve with ongoing treatment as desensitization occurs. Delayed reactions of more than two hours raise concern for EoE-related symptoms. It is also important to recognize GI symptoms that are unrelated to OIT: common causes include infectious gastroenteritis, functional abdominal pain, constipation, gastroesophageal reflux disease, and celiac disease.

If a patient with EoE on OIT experiences delayed symptoms, it is important to assess the patient with endoscopy and biopsies if a gastroenterologist is readily available. If there is worsening, there are several possible management approaches involving modifications to OIT dosing or addition of EoE medications, as detailed in **Figure 1**. If these approaches are not successful, the risks and benefits of OIT should be reweighed and therapy may be discontinued. Collaborating with gastroenterology colleagues to optimize pharmacotherapy is the best approach.

Case 2

A 21-year-old male has a known history of EoE, as well as allergic rhinoconjunctivitis. His EoE is currently well-managed with swallowed viscous budesonide. However, his allergy symptoms have been increasingly severe during the spring, affecting his daily activities such as sports and school. Skin testing revealed positive results for alder, birch and grass mix. The patient is unable to undergo subcutaneous immunotherapy due to his busy schedule and would prefer SLIT for tree pollen.

The product monographs for SLIT tablets commonly state that EoE is a contraindication to therapy.[26,27,28] Worsening or causation of EoE on SLIT is generally felt to be rare given how many patients are on SLIT, with case reports having documented some patients developing biopsy-confirmed EoE while receiving SLIT,[29] with endoscopic findings returning to normal between four weeks and 16 months following discontinuation of therapy. The possibility that SLIT can induce EoE suggests that aeroallergens may trigger EoE, potentially through a T cell mediated response.[30] Growing evidence supports the role of aeroallergens in influencing EoE disease activity. Retrospective data has revealed a correlation between EoE diagnoses and seasonal patterns, possibly related to pollen counts.[31] Direct esophageal deposition of aeroallergens is also believed to play a role in EoE inflammation.[32,33] Aeroallergen allergy testing can help identify allergens to avoid, which may improve EoE control, and may also help guide the timing of esophageal biopsies

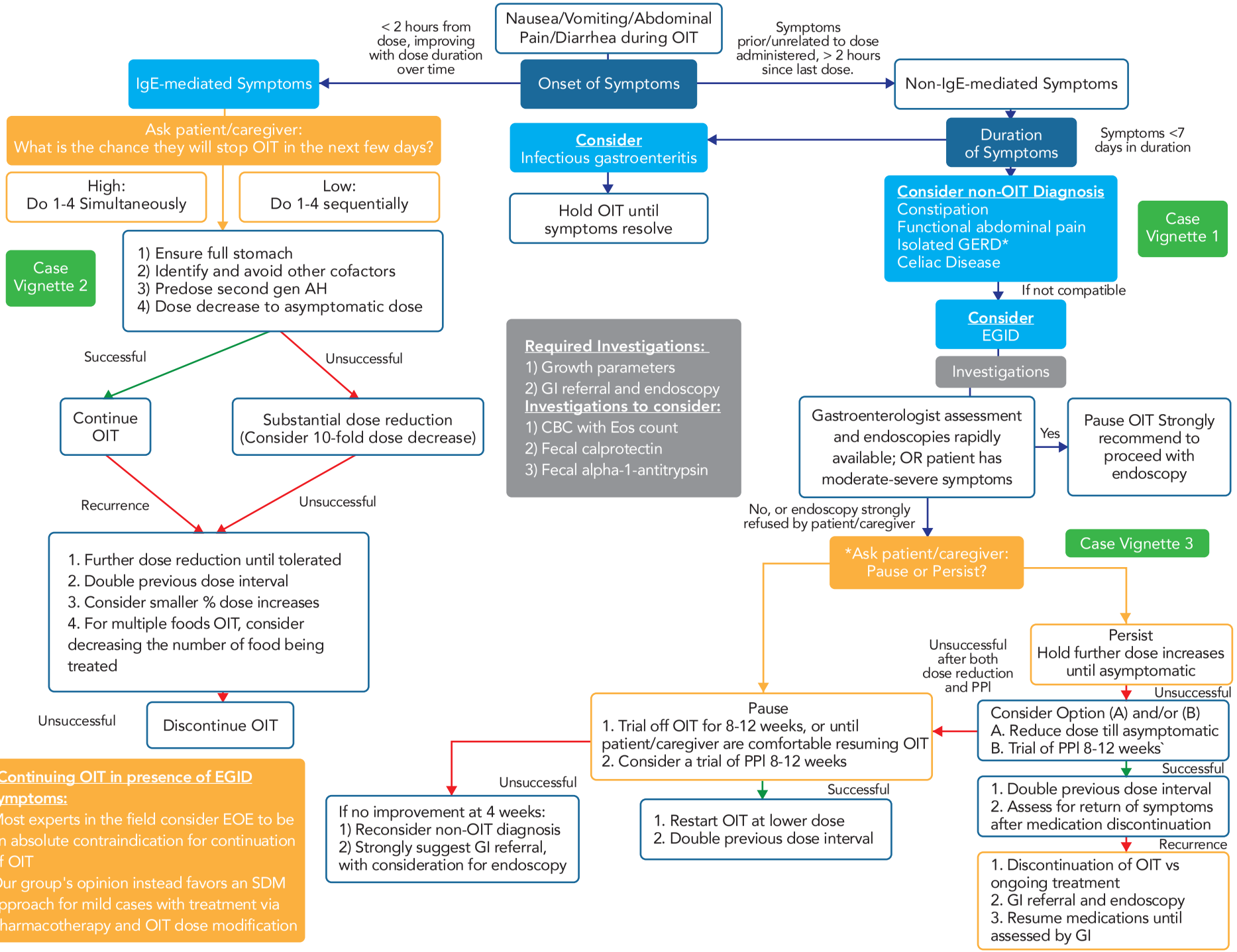

Figure 1: *Flow diagram of diagnosis of gastrointestinal symptoms during oral immunotherapy. CBC, Complete blood count; EoE, eosinophilic esophagitis; EoS, eosinophilic colitis. Reproduced with permission from Chua et al.*[19]

OIT: Oral immunotherapy, Second gen AH: Second generation anti-histamine, PPI: Proton pump inhibitor, GERD: Gastroesophageal reflux disease, EGID: Eosinophilic gastrointestinal disease, GI: Gastroenterology specialist, SDM: Shared decision making

to avoid confounding the interpretation of disease control during periods of seasonal worsening.[13]

While evidence suggests a relationship between local esophageal aeroallergen exposure and esophageal inflammation, SLIT may still have a role in managing underlying atopic disorders in select patients with EoE. In this particular case, SLIT may improve control of the patient's severe allergic rhinoconjunctivitis. Furthermore, clinical studies have linked control of allergic rhinitis to reduced esophageal eosinophilia.[34] Given the literature suggesting that pollen exacerbates EoE, it is possible that immunotherapy could conversely improve seasonal EoE.

After discussing the risks and benefits of aeroallergen SLIT with a patient with EoE, it may be reasonable to initiate this therapy in select patients for whom the benefits of immunotherapy outweigh the risk of exacerbating EoE. It is important to inform the patient's gastroenterologist that this therapy has been initiated, and it may be preferable to document a baseline endoscopy to confirm adequate control of EoE prior to SLIT. These patients should also be instructed to closely monitor for EoE-related symptoms.

Extrapolating from the approach outlined by Chua et al for managing GI symptoms in patients receiving OIT,[19] for a patient who has an established diagnosis of EoE and experiences worsening EoE symptoms while on SLIT, a number of approaches can be considered. If a gastroenterologist is available for assessment, endoscopy with biopsies should be considered. If evidence of worsening EoE is found, several approaches can be taken, such as initiating or adjusting topical swallowed corticosteroid therapy. If the wait time for repeat endoscopy is considered unacceptable, it would be reasonable to proceed with initiating therapy such as a trial of a proton pump inhibitor (PPI). After discontinuation of the medication, the patient should be monitored for symptom recurrence. If these approaches are unsuccessful, the risks and benefits of SLIT should be re-evaluated, and discontinuation of therapy or collaboration with gastroenterology colleagues to optimize pharmacotherapy should be considered.

Case 3

A 35-year-old woman with EoE is seen in follow up in clinic. She is currently managed with swallowed budesonide orodispersible tablets. She reports daily dysphagia. She has a history of emergency department visits for bolus impaction, and her endoscopy shows widespread exudates and edema. Biopsy results showed 65 eosinophils per high-power field and indicate Barrett's esophagus. Additionally, her esophagus was severely narrowed and strictured, precluding passage of a standard endoscope. Her medical history includes severe asthma managed with an inhaled corticosteroid/long-acting beta-agonist inhaler, severe atopic dermatitis managed with betamethasone valerate 0.1% ointment, anaphylactic food allergy to peanut, tree nuts, and fish, and allergic rhinoconjunctivitis.

Dupilumab received Health Canada approval in May 2023 as a primary treatment for eosinophilic esophagitis in patients 12 years and older, weighing at least 40 kg.[35] It is a fully human monoclonal antibody targeting the IL-4Rα chain, which antagonizes both IL-4 and IL-13 signaling. In EoE patients, IL-13 is highly upregulated and plays a key role in promoting an eosinophilic inflammatory response and inducing histologic changes. Meanwhile, IL-4 promotes differentiation of TH2 cells and regulates eosinophil migration.[3]

Specialists caring for EoE patients have raised questions about where this medication fits into the treatment algorithm.[36] It has not been shown to be more effective than swallowed topical corticosteroids. In a phase 3 international, multi-centre, placebo-controlled trial, approximately 60% of patients showed histologic remission after 24 weeks of dupilumab treatment.[37] However, swallowed topical corticosteroids can induce histologic remission in up to 90% of patients, depending on the formulation.[38] Additionally, dupilumab is a costly therapy compared to other available options, and its cost-effectiveness over conventional EoE therapies has not been demonstrated.

Several scenarios have been proposed where dupilumab could be considered as a first-line agent.[39] The drug may be considered for patients with multiple comorbid atopic conditions, including moderate, persistent, or difficult-to-control asthma, atopic dermatitis, and chronic sinusitis with nasal polyps. Patient preference to avoid swallowed topical steroids or dietary restrictions may also be considered. As a step-up therapy, dupilumab can be considered for difficult-to-treat EoE, failure to thrive, poor growth, significant weight loss due to EoE, and frequent use of rescue therapies such as oral systemic corticosteroids or esophageal dilations. Additionally, it may be used for patients with severe diet restriction or those requiring amino acid formulas, clinically significant esophageal strictures or narrow caliber esophagus, and those refractory to current therapies due to continued symptoms, persistent abnormal esophageal inflammation, adverse effects, intolerance, or inability to adhere to existing treatments.

Besides dupilumab, several other biologics have been studied for treatment of EoE and eosinophilic gastrointestinal disorders.[40] Results from clinical trials

of anti-IL-5 agents (reslizumab, mepolizumab, and benralizumab) and the anti-Siglec-8 agent lirentelimab have shown improvement on biopsy but persistence of symptoms, suggesting that eosinophils are only one component of EoE pathology. Omalizumab has not shown efficacy. Clinical trials are ongoing for the S1P receptor modulator etrasimod, anti-IL-13 agents, and anti-IL-15. Additional targets studied in asthma that may have benefit for EoE include anti-IL-33 (itepekimab) and anti-TSLP (tezepelumab).

Identifying severe EoE patients who may benefit from biologic therapy is challenging because there is currently no standardized measure for grading EoE severity. The control of EoE can be assessed by histology and patient symptoms, which may not always align with each other. An "Index of Severity for Eosinophilic Esophagitis" (I-SEE) has been proposed to gauge disease severity in both the research and clinical setting, with a score of ≥ 15 suggesting severe EoE.[41] This index considers symptoms and complications, inflammatory features, and fibrostenotic features and can be easily completed during patient visits.

In this case, our patient has severe EoE (I-SEE score of 25) and is refractory to current therapy with a swallowed topical steroid. Furthermore, she has multiple severe atopic comorbidities, and a history of significant esophageal strictures and narrow caliber esophagus. Given these factors, she may benefit from dupilumab as step-up therapy. Besides controlling her EoE, asthma, and atopic dermatitis, dupilumab could additionally allow her to undergo oral immunotherapy safely to treat her anaphylactic food allergy.[42]

Conclusion

As allergists, we can offer our EoE patients a comprehensive evidence-based approach to controlling esophageal inflammation and addressing atopic comorbidities via our unique skills in proper selection and interpretation of skin or serum-specific IgE tests, oral food challenges, and conducting immunotherapy. Aeroallergen skin testing remains an important facet of EoE management for identifying environmental allergens that may be triggering disease activity. While the role of food allergy testing to identify EoE triggers and guide dietary elimination has fallen out of favour, it plays a role in guiding the reintroduction of previously avoided foods in conjunction with oral food challenges in case of development of potentially anaphylactic IgE-mediated food allergy. The cases we have described illustrate these points, and further touch upon the potential role of immunotherapy in these patients. OIT may be considered for patients with EoE and food allergies, with careful symptom monitoring and a plan for managing GI symptoms. SLIT may also be a consideration for patients with EoE and severe atopic comorbidities. Although approved by Health Canada, the role of dupilumab in the real world needs to be more clearly defined based on its high cost, but it may be most beneficial and cost-effective in treating patients with concurrent severe EoE and multiple atopic comorbidities. Overall, a collaborative approach with our gastroenterology colleagues, and a focus on individualized patient management is essential for the successful management of EoE.

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References

1. *Dhar A, Haboubi HN, Attwood SE, Auth MK, Dunn JM, Sweis R, Morris D, Epstein J, Novelli MR, Hunter H, Cordell A. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. Gut. 2022 Aug 1;71(8):1459-87.*
2. *Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, Spechler SJ, Attwood SE, Straumann A, Aceves SS, Alexander JA. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018 Oct 1;155(4):1022-33.*
3. *Underwood, B., Troutman, T. D., & Schwartz, J. T. (2022). Breaking down the complex pathophysiology of eosinophilic esophagitis. Annals of Allergy, Asthma & Immunology.2023 Jan;130(1):28-39.*
4. *Dobbins JW, Sheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. Gastroenterology. 1977 Jun 1;72(6):1312-6.*
5. *González-Cervera, J., Arias, Á., Redondo-González, O., Cano-Mollinedo, M. M., Terreehorst, I., & Lucendo, A. J. (2017). Association between atopic manifestations and eosinophilic esophagitis: a systematic review and meta-analysis. Annals of Allergy, Asthma & Immunology, 118(5), 582-590.*
6. *Cianferoni A, Warren CM, Brown-Whitehorn T, Schultz-Matney F, Nowak-Wegrzyn A, Gupta RS. Eosinophilic esophagitis and allergic comorbidities in a US-population-based study. Allergy. 2020 Jun;75(6):1466.*
7. *Caldeira, L. E., Limão, R., Brás, R., Pedro, E., & Costa, C. (2023). A real-world characterization of a cohort with eosinophilic esophagitis: looking for severity biomarkers. European Annals of Allergy and Clinical Immunology. Mar 28. doi: 10.23822/EurAnnACI.1764-1489.292.*
8. *Leigh LY, Spergel JM. An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis. Annals of Allergy, Asthma & Immunology. 2019 Jan 1;122(1):65-72.*
9. *Hirano I, Chan ES, Rank MA, Sharaf RN, Stollman NH, Stukus DR, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. Annals of Allergy, Asthma & Immunology. 2020 May 1;124(5):416–23.*
10. *Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, Lowichik A, Chen X, Emerson L, Cox K, O'Gorman MA. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 2014 Sep 1;147(3):602-9.*
11. *Rank MA, Sharaf RN, Furuta GT, Aceves SS, Greenhawt M, Spergel JM, Falck-Ytter YT, Dellon ES, Chachu KA, Day L, Lebwohl B. Technical review on the management of eosinophilic esophagitis: a report from the AGA institute and the joint task force on allergy-immunology practice parameters. Annals of Allergy, Asthma & Immunology. 2020 May 1;124(5):424-40.*
12. *Arias Á, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology. 2014 Jun 1;146(7):1639-48.*
13. *Woo W, Aceves SS. The role of the allergist in the management of eosinophilic esophagitis. Current Opinion in Gastroenterology. 2021 Jul 7;37(4):390.*
14. *Erdle SC, Soller L, Avinashi V, Roberts H, Hsu E, Chan ES. Multiple shifting phenotypes with cow's milk: From eosinophilic esophagitis to immediate hypersensitivity and back again. The Journal of Allergy and Clinical Immunology: In Practice. 2020 Mar 1;8(3):1117-8.*
15. *Lucendo AJ, Arias Á, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Annals of Allergy, Asthma & Immunology. 2014 Dec 1;113(6):624-9.*
16. *Vickery BP, Hourihane JO, Adelman DC. Oral Immunotherapy for Peanut Allergy. The New England Journal of Medicine. 2019 Feb 1;380(7):691-2.*
17. *Soller L, Abrams EM, Carr S, Kapur S, Rex GA, Leo S, et al. First real-world safety analysis of preschool peanut oral immunotherapy. J Allergy Clin Immunol Pract. 2019;7(8):2759-2767.e5.*
18. *Barbosa AC, Castro FM, Meireles PR, Arruda LK, Cardoso SR, Kalil J, Yang AC. Eosinophilic esophagitis: latent disease in patients with anaphylactic reaction to cow's milk. The Journal of Allergy and Clinical Immunology: In Practice. 2018 Mar 1;6(2):451-6.*
19. *Chua GT, Chan ES, Invik R, Soller L, Avinashi V, Erdle SC, Wong T, Cook VE, Mak R, Cameron SB. How We Manage Gastrointestinal Symptoms During Oral Immunotherapy Through a Shared Decision-Making Process—A Practical Guide for the Community Practitioner. The Journal of Allergy and Clinical Immunology: In Practice. 2023 Apr 1;11(4):1049-55.*
20. *Wright BL, Fernandez-Becker NQ, Kambham N, Purington N, Cao S, Tupa D, et al. Gastrointestinal Eosinophil Responses in a Longitudinal, Randomized Trial of Peanut Oral Immunotherapy. Clin Gastroenterol Hepatol. 2021 Jun;19(6):1151-1159.e14.*
21. *Avinashi V, Al Yarubi Z, Soller L, Lam G, Chan ES. Oral peanut immunotherapy acutely unmasking eosinophilic esophagitis with an esophageal stricture. Annals of Allergy, Asthma & Immunology. 2021 Dec 1;127(6):691–2.*
22. *Hamant L, Freeman C, Garg S, Wright BL, Schroeder S. Eosinophilic Esophagitis May Persist after Discontinuation of Oral Immunotherapy. Ann Allergy Asthma Immunol. 2021 Mar;126(3):299–302.*
23. *García Vega M, Fernández-Fernández S, Echeverría Zudaire L, Bracamonte Bermejo T, Cano del Águila B, Vega Hernández P, et al. Long-term medical treatment efficacy in patients with eosinophilic oesophagitis and oral food immunotherapy. Clinical & Experimental Allergy. 2022;52(12):1440–3.*
24. *Epstein-Rigbi N, Elizur A, Levy MB, Nachshon L, Koren Y, Shalem Z, et al. Treatment of oral immunotherapy–associated eosinophilic esophagitis. The Journal of Allergy and Clinical Immunology: In Practice. 2023 Apr 1;11(4):1303-1305.e2.*
25. *Wilson BE, Meltzer EC, Wright BL. Ethical implications of continuing oral immunotherapy after the development of eosinophilic esophagitis. The Journal of Allergy and Clinical Immunology: In Practice [Internet]. 2023 Aug 10 [cited 2023 Aug 15]*
26. *Oralair® Sublingual Tablets [product monograph]. Oakville (ON): Stallergenes Greer Ltd.; 2016 Nov 18 [cited 2023 Mar 14]. Available from: https://pdf.hres.ca/dpd_pm/00037241.PDF*
27. *Grastek® Sublingual Tablets [product monograph]. Hørsholm (DK): ALK-Abelló A/S; 2017 May 17 [cited 2023 Mar 14]. Available from: https://pdf.hres.ca/dpd_pm/00039371.PDF*
28. *Ragwitek® Sublingual Tablets [product monograph]. Mississauga (ON): ALK-Abelló A/S; 2014 Apr 10 [updated 2020 Dec 18, cited 2023 Mar 14]. Available from: https://pdf.hres.ca/dpd_pm/00059607.PDF*
29. *Fujiwara Y, Tanaka F, Sawada A, Nadatani Y, Nagami Y, Taira K, et al. A case series of sublingual immunotherapy-induced eosinophilic esophagitis: stop or spit. Clin J Gastroenterol. 2021 Dec 1;14(6):1607-11.*
30. *Miehlke S, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. Case Reports in Gastroenterology. 2013;7(3):363-8.*
31. *Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, DeVault KR, Wolfsen H, Raimondo M, Guarderas JC, Achem SR. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Official journal of the American College of Gastroenterology| ACG. 2009 Apr 1;104(4):828-33.*
32. *Ravi A, Marietta EV, Geno DM, Alexander JA, Murray JA, Katzka DA. Penetration of the esophageal epithelium by dust mite antigen in patients with eosinophilic esophagitis. Gastroenterology. 2019 Jul 1;157(1):255-6.*
33. *Aceves SS. Local antigen deposition in eosinophilic esophagitis: implications for immune activation. Gastroenterology. 2019 Jul 1;157(1):17-20.*
34. *Ram G, Lee J, Ott M, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, Liacouras CA, Spergel JM. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. Annals of Allergy, Asthma & Immunology. 2015 Sep 1;115(3):224-8.*
35. *Dupixent® Dupilumab Injection. Product Monograph. Laval (QC): Sanofi-aventis Canada Inc; 2023 [cited 2023 Aug 5]. Available from: https://pdf.hres.ca/dpd_pm/00070465.PDF*
36. *Straumann A. Biologics in Eosinophilic Esophagitis — Ready for Prime Time? New England Journal of Medicine. 2022 Dec 22;387(25):2379–80.*
37. *Dellon ES, Rothenberg ME, Collins MH, Hirano I, Chehade M, Bredenoord AJ, et al. Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis. N Engl J Med. 2022 Dec 22;387(25):2317–30.*
38. *Lucendo AJ, Miehlke S, Schlag C, Vieth M, Arnim U von, Molina-Infante J, et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial. Gastroenterology. 2019 Jul 1;157(1):74-86.e15.*
39. *Aceves SS, Dellon ES, Greenhawt M, Hirano I, Liacouras CA, Spergel JM. Clinical guidance for the use of dupilumab in eosinophilic esophagitis: A yardstick. Annals of Allergy, Asthma & Immunology. 2023 Mar 1;130(3):371–8.*
40. *Sindher SB, Barshow S, Tirumalasetty J, Arasi S, Atkins D, Bauer M, et al. The role of biologics in pediatric food allergy and eosinophilic gastrointestinal disorders. J Allergy Clin Immunol. 2023 Mar;151(3):595–606.*
41. *Dellon ES, Khoury P, Muir AB, Liacouras CA, Safroneeva E, Atkins D, et al. A Clinical Severity Index for Eosinophilic Esophagitis: Development, Consensus, and Future Directions. Gastroenterology. 2022 Jul;163(1):59–76.*
42. *Sindher SB, Hillier C, Anderson B, Long A, Chinthrajah RS. Treatment of food allergy: Oral immunotherapy, biologics, and beyond. Ann Allergy Asthma Immunol. 2023 Jul;131(1):29–36.*