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Screening children for eosinophilic esophagitis: allergic and other risk factors

Melanie A. Ruffner,^{1,2} Peter Capucilli,¹ David A. Hill,^{1,2} Jonathan M. Spergel,^{1,2}

¹ Children's Hospital of Philadelphia, Division of Allergy & Immunology, Philadelphia, PA, USA

² University of Pennsylvania Perelman School of Medicine, Department of Pediatrics, Philadelphia, PA, USA

*Correspondence: Jonathan Spergel MD, PhD

The Children's Hospital of Philadelphia

Division of Allergy and Immunology

3401 Civic Center Boulevard

Wood Building, 3rd floor

Philadelphia, PA 19104

spergel@email.chop.edu

215-590-2549

ORCID ID INFO:

Jonathan M Spergel: 0000-0002-4658-5353

Melanie A Ruffner: 0000-0002-2943-9944

David A Hill: 0000-0001-9286-4268

Peter Capucilli: 0000-0002-3460-7594

Abbreviations: EoE, eosinophilic esophagitis, AR, allergic rhinitis, AD atopic dermatitis, IgE, immunoglobulin E; HR, hazard ratio; ASD Autism Spectrum Disorder; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia

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Eosinophilic esophagitis (EoE) is a chronic allergic inflammatory disease of the esophagus that is triggered by specific foods. EoE presents across the lifespan, with symptoms of failure to thrive, poor weight gain, feeding intolerance, food refusal, vomiting, dysphagia and food impaction [1,2]. Any patient may present with symptoms of EoE, regardless of preexisting risk factors. All patients with symptoms of esophageal dysfunction suggestive of EoE should receive screening via esophagastroduodenoscopy (EGD) with esophageal biopsies [3,4]. However, many patients with EoE develop symptoms slowly over time, and the frequency of compensatory eating behaviors is high in this population [5–7]. Therefore, it is important to consider which patient populations may be at increased risk for the development of EoE and ask targeted screening questions in order to pinpoint esophageal symptoms. Here we review epidemiologic and clinical features that may increase suspicion for EoE.

A family or personal history of preexisting allergic disease should increase the suspicion for EoE, as it has been reproducibly demonstrated in multiple cohorts that individuals with EoE have a high prevalence of allergic comorbidity [8,9]. As atopic disorders are prevalent, screening for EoE is an important consideration for general pediatricians in addition to allergists. A recent meta-analysis by González-Cervera et al examined 21 observational case-control studies of 53,542 individual EoE patients, demonstrating that EoE patients have higher rates of allergic comorbidity than the background population [10]. The odds of a personal history of atopy in EoE patients was increased, including reported rates of eczema (odds ratio [OR] 2.85, 95% confidence interval [CI] 1.87-4.34), allergic rhinitis (AR; OR 5.09, 95% CI 2.91-8.90), and asthma (OR 3.01, 95% CI 1.96-4.62). Using a large pediatric virtual birth cohort, we have measured these risk relationships in individuals revealed that history of AD (hazard ratio [HR] 3.2, 95% confidence interval [CI] 2.2-4.6), IgE-mediated food allergy (IgE-FA; HR 9.1, 95% CI 6.5-12.6), and asthma (HR 1.9, 95% CI 1.3-2.7) are independently and cumulatively associated with subsequent EoE diagnosis (Table 1) [11].

The relationship between IgE-FA and EoE is particularly strong—children with IgE-FA develop EoE at 9 times the rate of children without IgE-FA [12]. IgE-FA and EoE has been reported to co-occur at rates between 9.8-44% in EoE cohorts, up to as high as 68% [10,13]. Specifically, IgE-FA to milk, egg or shellfish has been associated with development of EoE [13]. Barbosa et al. studied esophageal eosinophilia in a pediatric cohort with persistent milk IgE-FA, and found that 38% had esophageal eosinophilia on biopsy with 23.5% of patients exhibiting symptoms [14]. In a cohort of adult patients with IgE-FA undergoing screening prior to oral

immunotherapy (OIT), Wright et al. found 14% of patients had >15 eosinophils per high-power field (eos/hpf) [15]. These studies illustrate a growing recognition of the unique risk association between IgE-FA and EoE

An additional concern is the risk for EoE development in IgE-FA patients on oral immunotherapy for food allergy. The risk of developing EoE has been quantitated in recent reviews as between 2.7%-5.3%, however this is likely an underestimate. Gastrointestinal side effects like abdominal pain and vomiting are common in OIT, with approximately 30% of patients reporting these symptoms which can be presenting symptoms of EoE. However, biopsies to assess for EoE were performed in a minority of studies [16,17]. This suggests that the rate of EoE is increased in OIT patients and if symptoms are persistent they should be screened with biopsy to assess for EoE.

Multiple reports have shown EoE to be associated with several non-allergic disorders including gastrointestinal, autoimmune disorders, and connective tissue diseases (Table 2) [18–20]. The association of EoE with celiac disease has been reported but is somewhat uncertain. We have recently seen an association between EoE and celiac disease in our pediatric referral population, with 3-5.6% of celiac disease patients with concurrent esophageal eosinophilia on biopsy [9,26,27]. While some investigators have seen similar associations, some studies have not observed this association [28,29]. Esophageal eosinophilia has been also noted to precede or coexist with development of inflammatory bowel disease, and the incidence of IBD in patients diagnosed with EoE in our cohort of pediatric patients is increased [9,30,31]. However, the precise clinical or mechanistic relationship of tissue eosinophilia to IBD has not been established. It is debated whether the increased association of some GI disorders with EoE results from potential bias associated with increased endoscopic screening or points to commonly dysregulated immune mechanisms.

Within some pediatric cohorts, patients with connective tissue disorders have been identified to be at significantly increased risk for EoE. The risk of EoE was found to be increased 8-fold in patients with connective tissue disorders including Marfan's, Ehlers-Danlos, and Loeys-Dietz syndromes within one US pediatric cohort [20]. Patients within this population had typical syndromic features including characteristic facies, hypermobility, and lower BMI compared to EoE-only controls. Extra-esophageal eosinophilic gastrointestinal disease was found in 24% (10/24) in this population, making this complication unusually common in the cohort with

connective tissue disorders [20]. Heart defects characteristic of connective tissue disorders were also common. Within our distinct pediatric cohort, we have seen an increase in the risk 11.0 (OR, 95% CI 4.9-24.8) of connective tissue disease in our EoE cohort once data was adjusted for age and gender. However, when some population of connective tissue disorder disease patients are retrospectively reviewed, EoE does not emerge as a major comorbidity in these patients [32]. It can be hypothesized that this is due to the studies' focus on children and adults and that more evidence will emerge about this link will emerge as familiarity with these diagnoses increases among providers.

Of particular importance for the practicing immunologist is the association of EoE with hyper-IgE syndrome caused by *STAT3* mutations (AD-HIES) [25]. 60% of 70 patients in a large American cohort of AD-HIES syndrome had chronic GI complaints. Of these, 23 patients underwent esophagogastroduodenoscopy, demonstrating eosinophilic inflammation in 65% of these patients. This suggests that secondary eosinophilic esophagitis is a significant consideration in these patients. EoE has additionally been described in case reports of Common Variable Immunodeficiency [33,34].

In addition, we observed a higher prevalence of Autism Spectrum Disorder (ASD) within our cohort of EoE patients; the rate of ASD in children with EoE is 7.5%, compared to 1.9% in those without EoE (OR 4.2, 95% CI 2.9-6.0, $P < 0.0001$) [9]. While the etiology of this relationship remains unknown, the often-severe adverse feeding behaviors that can be characteristic of ASD may in part be due to underlying and potentially undiagnosed esophageal disease. These findings support a recommendation screen for EoE in patients with ASD and unexplained feeding dysfunction and highlights a potential role for nutritionists and occupational therapists in screening for EoE. These specialists can play a pivotal role in recognizing when abnormal feeding behaviors may be indicative of esophageal or other GI dysfunction. Future research efforts are needed to verify the extent of this association on a population scale. Delineating specific symptoms indicative of EoE as opposed to a behavioral feeding disorder in ASD will be paramount to providing more specific evidence-based clinical recommendations.

Regardless of preexisting risk factors, EoE should be suspected in any patient with a consistent clinical presentation. Characteristic symptoms that suggest a diagnosis of EoE are those of chronic esophageal dysfunction. Symptoms vary with patient age. Failure to thrive and feeding problems are seen more commonly in younger children whereas older adolescents present more

frequently with dysphagia, odynophagia and food impaction. Patient-reported outcome tools have been developed for EoE, but their utility for diagnostic purposes is limited. This is because it has been observed in randomized control trials that esophageal eosinophilia may be present without esophageal symptoms and vice versa [35]. As a consequence, diagnostic application of patient-reported outcome tools has had limited sensitivity and specificity, but have had some success in following patients longitudinally for clinical trials. The PEESS v2.0 is a pediatric-specific, validated questionnaire to assess patient symptoms [36]. The survey has been validated for use in children (ages 8-18) and for completion by a parent-proxy (ages 2-18). Scoring for dysphagia in PEESS is highly correlated to increased EoE disease activity on biopsy. In adult populations, the Straumann dysphagia instrument [5], the Dysphagia Symptom Questionnaire [37], and the EESAI PRO instrument [38] have been validated and incorporate slightly different aspects of EoE presentation into their symptom questionnaires. There is interest in refining these scales to improve their ability to be used to follow EoE patients longitudinally over time.

Finally, it is important for all physicians to be aware of recent updates in the diagnostic criteria for eosinophilic esophagitis [3,4]. Previously, response of esophageal eosinophilia to proton pump inhibitor (PPI) therapy was considered diagnostic for gastroesophageal reflux disease (GERD), a distinct disease entity. As such, the 2007 diagnostic guidelines required a diagnostic trial of high-dose proton pump inhibitor (PPI) to rule out GERD [39]. There is a growing recognition that approximately 50% of patients with EoE have decreased mucosal inflammation with PPI therapy, indicating that PPI is more correctly considered a therapy for EoE. Updated diagnostic criteria from 2017 indicate that PPI trial prior to endoscopy is not required to make a diagnosis of EoE [3]. All patients with greater than 15 eos/hpf on esophageal biopsy meet criteria for EoE diagnosis, provided that there are symptoms of esophageal dysfunction and non-EoE etiologies of esophageal eosinophilia have been excluded (Table 3). The decision to initiate or continue PPI therapy, therefore, should be guided by patient symptoms.

In our experience, in pediatric patients under the age of 12, GERD symptoms can overlap with symptoms of EoE. Therefore, many younger pediatric patients benefit from a trial of PPI both to determine the extent to which GERD may affect their EoE and also to determine if this improves symptoms. Some children may experience quick improvement without symptom recurrence, wean off of PPI successfully and require no further intervention. However, if patients cannot stop taking PPI without recurrent symptoms, then esophagastroduodenoscopy can still be performed when the patient is on high-dose PPI. However, if the eosinophil count is under 15

eosinophils/hpf while on high-dose PPI in a symptomatic patient, it does not rule out a diagnosis of EoE which has been treated by PPI.

In summary, EoE should be suspected in any patient with chronic symptoms of esophageal dysfunction. In addition, screening for a personal history of atopy, with particular emphasis on current or prior IgE-mediated food allergy, can aid in identification of at-risk individuals. Esophageal eosinophilia has been associated with a number of syndromes (Table 2). In these patients, evidence suggests that the pretest probability for EoE may be higher and when esophageal symptoms are present, and referral for EoE screening by EGD with biopsy may help to curtail diagnostic odyssey and promote use of correct therapy for patients.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References:

1. Ruffner MA, Spergel JM: **Pediatric eosinophilic esophagitis**. *Curr Opin Pediatr* 2018, doi:10.1097/MOP.0000000000000698.
2. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, Liacouras CA: **14 years of eosinophilic esophagitis: Clinical features and prognosis**. *J Pediatr Gastroenterol Nutr* 2009, **48**:30–36.
3. Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, Bussmann C, Amil Dias J, Bove M, González-Cervera J, Larsson H, et al.: **Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults**. *United Eur Gastroenterol J* 2017, doi:10.1177/2050640616689525.
4. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, Spechler SJ, Attwood SE, Straumann A, Aceves SS, et al.: **Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference**. *Gastroenterology* 2018, doi:10.1053/j.gastro.2018.07.009.
5. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, Haas NA, Romero Y, Hirano I, Alexander JA, et al.: **Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis**. *Gastroenterology* 2014, **147**:1255–1266.e21.
6. Mehta P, Furuta GT, Brennan T, Henry ML, Maune NC, Sundaram SS, Menard-Katcher C, Atkins D, Takurukura F, Giffen S, et al.: **Nutritional State and Feeding Behaviors of Children with Eosinophilic Esophagitis and Gastroesophageal Reflux Disease**. *J Pediatr Gastroenterol Nutr* 2018, **66**:603–608.
7. Menard-Katcher C, Henry M, Furuta GT, Atkins D, Maune NC, Haas AM: **Significance of feeding dysfunction in eosinophilic esophagitis**. *World J Gastroenterol* 2014, **20**:11019–11022.
8. Mohammad AA, Wu SZ, Ibrahim O, Bena J, Rizk M, Piliang M, Bergfeld WF: **Prevalence of atopic comorbidities in eosinophilic esophagitis: A case-control study of 449 patients**. *J Am Acad Dermatol* 2017, **76**:559–560.
9. Capucilli P, Cianferoni A, Grundmeier RW, Spergel JM: **Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population**. *Ann Allergy, Asthma Immunol* 2018, **121**:711–716.
10. González-Cervera J, Arias Á, Redondo-González O, Cano-Mollinedo MM, Terreehorst I,

- Lucendo AJ: **Association between atopic manifestations and eosinophilic esophagitis: A systematic review and meta-analysis.** *Ann Allergy, Asthma Immunol* 2017, **118**:582–590.e2.
11. Hill DA, Grundmeier RW, Ramos M, Spergel JM: **Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March.** *J Allergy Clin Immunol Pract* 2018, **6**:1528–1533.
 12. Hill DA, Dudley JW, Spergel JM: **The Prevalence of Eosinophilic Esophagitis in Pediatric Patients with IgE-Mediated Food Allergy.** *J Allergy Clin Immunol Pract* 2017, **5**:369–375.
 13. Hill DA, Shuker M, Cianferoni A, Wong T, Ruchelli E, Spergel JM, Brown-Whitehorn TF: **The development of IgE-mediated immediate hypersensitivity after the diagnosis of eosinophilic esophagitis to the same food.** *J Allergy Clin Immunol Pract* 2015, **3**:123–124.
 14. 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.** *J Allergy Clin Immunol Pract* 2018, **6**:451–456.e1.
 15. Wright BL, Fernandez-Becker NQ, Kambham N, Purington N, Tupa D, Zhang W, Rank MA, Kita H, Shim KP, Bunning BJ, et al.: **Baseline Gastrointestinal Eosinophilia Is Common in Oral Immunotherapy Subjects With IgE-Mediated Peanut Allergy.** *Front Immunol* 2018, **9**:2624.
 16. Lucendo AJ, Arias Á, Tenias JM: **Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: A systematic review with meta-analysis.** *Ann Allergy, Asthma Immunol* 2014, **113**:624–629.
 17. Petroni D, Spergel JM: **Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy.** *Ann Allergy, Asthma Immunol* 2017, **120**:237–240.e4.
 18. Peterson K, Firszt R, Fang J, Wong J, Smith KR, Brady KA: **Risk of Autoimmunity in EoE and Families: A Population-Based Cohort Study.** *Am J Gastroenterol* 2016, **111**:926–932.
 19. Leigh LY, Spergel JM: **An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis.** *Ann Allergy, Asthma Immunol* 2018, doi:10.1016/j.anai.2018.09.452.
 20. Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, Collins MH, Putnam PE, Franciosi JP, Von Tiehl KF, et al.: **High prevalence of eosinophilic esophagitis**

- in patients with inherited connective tissue disorders.** *J Allergy Clin Immunol* 2013, **132**:378–386.
21. Leung DYM, Ledford DK, Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, et al.: **Eosinophilic esophagitis: updated consensus recommendations for children and adults.** *J Allergy Clin Immunol* 2011, **128**:3-20.e6; quiz 21–2.
 22. Paluel-Marmont C, Bellon N, Barbet P, Leclerc-Mercier S, Hadj-Rabia S, Dupont C, Bodemer C: **Eosinophilic esophagitis and colonic mucosal eosinophilia in Netherton syndrome.** *J Allergy Clin Immunol* 2017, **139**:2003–2005.e1.
 23. Henderson CJ, Ngeow J, Collins MH, Martin LJ, Putnam PE, Abonia JP, Marsolo K, Eng C, Rothenberg ME: **Increased prevalence of eosinophilic gastrointestinal disorders in pediatric PTEN hamartoma tumor syndromes.** *J Pediatr Gastroenterol Nutr* 2014, **58**:553–560.
 24. McAleer MA, Pohler E, Smith FJD, Wilson NJ, Cole C, MacGowan S, Koetsier JL, Godsel LM, Harmon RM, Gruber R, et al.: **Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plak domain of desmoplakin.** *J Allergy Clin Immunol* 2015, **136**:1268–1276.
 25. Arora M, Bagi P, Strongin A, Heimall J, Zhao X, Lawrence MG, Trivedi A, Henderson C, Hsu A, Quezado M, et al.: **Gastrointestinal Manifestations of STAT3-Deficient Hyper-IgE Syndrome.** *J Clin Immunol* 2017, **37**:695–700.
 26. Ooi CY, Day AS, Jackson R, Bohane TD, Tobias V, Lemberg DA: **Eosinophilic esophagitis in children with celiac disease.** *J Gastroenterol Hepatol* 2008, **23**:1144–8.
 27. Ari A, Morgenstern S, Chodick G, Matar M, Silbermintz A, Assa A, Mozer-Glassberg Y, Rinawi F, Nachmias-Friedler V, Shamir R, et al.: **Oesophageal eosinophilia in children with coeliac disease.** *Arch Dis Child* 2017, **102**:825–829.
 28. Omar I, Ahmed SAQJAAANSIDH: **Esophageal Eosinophilia in Pediatric Patients With Celiac Disease: Is It a Causal or an Incidental Association?** *J Pediatr Gastroenterol Nutr* 2015, **60**:493–497.
 29. Hommeida S, Alsawas M, Murad MH, Katzka DA, Grothe RM, Absah I: **The Association Between Celiac Disease and Eosinophilic Esophagitis.** *J Pediatr Gastroenterol Nutr* 2017, **65**:58–63.
 30. Justinich CJ, Mulder DJ, Hookey LC, Hurlbut DJ: **Impact of Crohn Disease on Eosinophilic Esophagitis: Evidence for an Altered T(H)1-T(H)2 Immune**

- Response.** *J Pediatr Gastroenterol Nutr* 2011, **53**:213–215.
31. Suttor VP, Chow C, Turner I: **Eosinophilic esophagitis with Crohn's disease: A new association or overlapping immune-mediated enteropathy?** *Am J Gastroenterol* 2009, **104**:794–795.
 32. Nelson AD, Mouchli MA, Valentin N, Deyle D, Pichurin P, Acosta A, Camilleri M: **Ehlers Danlos syndrome and gastrointestinal manifestations: A 20-year experience at Mayo Clinic.** *Neurogastroenterol Motil* 2015, **27**:1657–1666.
 33. Hannouch KJ, McGoeys BA, Hauk MJ, Michelis MAE: **Common Variable Immunodeficiency and Eosinophilic Esophagitis Complicated by Atypical Burkitt's Lymphoma: A Case Report.** *J Allergy Clin Immunol* 2017, **139**:AB114.
 34. Chen M, Ko HM, Riffle ME, Andrae DA, Cunningham-Rundles C, Chehade M, Maglione PJ: **Eosinophilic esophagitis diagnosed in a patient with common variable immunodeficiency.** *J Allergy Clin Immunol Pract* 2016, **4**:995–997.
 35. Safroneeva E, Schoepfer AM: **Symptom-based patient-reported outcomes in adults with eosinophilic esophagitis: value for treatment monitoring and randomized controlled trial design.** *Curr Opin Allergy Clin Immunol* 2019, doi:10.1097/ACI.0000000000000514.
 36. Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, Varni JW, Grotjan JT, Eby M, He H, et al.: **Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease.** *J Allergy Clin Immunol* 2015, **135**:1519–1528e8.
 37. Dellon ES, Irani AM, Hill MR, Hirano I: **Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis.** *Aliment Pharmacol Ther* 2013, **38**:634–642.
 38. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, Haas NA, Romero Y, Hirano I, Alexander JA, et al.: **Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis.** *Gastroenterology* 2014, **147**:1255–1266.e21.
 39. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME: **Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment.** *Gastroenterology* 2007, **133**:1342–1363.

1° Diagnosis	EoE HR [95% CI]
AD	3.2 [2.2-4.6]
IgE-FA	9.1 [6.5-12.6]
Asthma	1.9 [1.3-2.7]
AR	2.8 [2.0-3.9]
Any 1	2.5 [1.6-3.9]
Any 2	5.6 [3.5-8.9]
Any 3	9.1 [5.2-16.0]

Table 1. Effect of primary atopic diagnosis (1° Diagnosis) on likelihood of developing EoE as single diagnosis or in combination. Case-control analysis was performed on a primary care birth cohort of 130,435 children in a United States health system to determine the extent that existing allergic conditions influence the rate of subsequent EoE diagnosis. Data shown as Cox hazard ratios (HR) with 95% confidence interval (95% CI) indicating likelihood of developing EoE. From Hill DA, et al., *J Allergy Clin Immunol Pract* 2018, **6**:1528–1533.

Causes of non-EoE esophageal eosinophilia:	
• Gastroesophageal reflux disease	[21]
• Infection(s): fungal, viral	
• Drug Hypersensitivity	
• Vasculitis	
• Graft versus host disease	
• Achalasia	
• Pemphigus vegetans	
Conditions associated with increased risk of eosinophilic esophagitis:	
• Atopy: eczema, asthma, food allergy	[10,12]
• Inflammatory bowel disease	[16,17]
• Monogenic conditions:	
○ Connective tissue disease Marfans II, Loeys-Dietz, Ehlers-Dhanlos)	[20]
○ Netherton Syndrome (<i>SPINK5</i> deficiency)	[22]
○ <i>PTEN</i> hamartoma syndrome: 200x risk of EoE/EGID	[23]
○ Severe dermatitis, multiple allergies, and metabolic wasting (SAM), <i>DSG1</i> deficiency	[24]
○ Hyper-IgE syndrome	[25]

Table 2: Additional diagnostic considerations during the evaluation of esophageal eosinophilia. Top Pane: a number of diseases can affect the esophagus resulting in a secondary eosinophilic infiltrate and should be ruled out prior to diagnosing EoE. Bottom Pane: disorders reported to have association with a diagnosis of EoE.

1. Symptoms of esophageal dysfunction
 - Concomitant atopic conditions should increase suspicion for EoE
 - Endoscopic findings characteristic of EoE should increase suspicion
2. Biopsy findings of 15 eosinophils per high-power field (approximately 60 eosinophils/mm²), with tissue eosinophilia isolated to the esophagus
3. Other causes of esophageal eosinophilia have been ruled out, for example: eosinophilic gastrointestinal disease with esophageal involvement; achalasia and other disorders of esophageal dysmotility; Hypereosinophilic syndrome; Crohn disease with esophageal involvement; infections (fungal, viral); connective tissue disorders; dermatologic conditions with esophageal involvement (ie: pemphigus); drug hypersensitivity reactions; pill esophagitis; graft vs host disease; Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, PTEN hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

Table 3. Summary of updated EoE diagnostic criteria [3,4]