Inflammatory Intestinal Diseases

Review Article

Inflamm Intest Dis 2024;9:296–303
DOI: 10.1159/000542435

Received: June 17, 2024
Accepted: August 9, 2024
Published online: November 12, 2024

The Role of Esophageal Physiologic Tests in Eosinophilic Esophagitis

Jeanine Wakim El-Khoury[a] Ekaterina Safroneeva[b] Alain M. Schoepfer[a]

[a]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland; [b]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Keywords
Eosinophilic esophagitis · Physiologic tests · High-resolution manometry · Functional lumen imaging probe · pH monitoring

Abstract
Background: In patients with eosinophilic esophagitis (EoE), the correlation between symptoms of esophageal dysfunction and endoscopic and histologic disease activity is generally poor and probably related to multiple causes such as esophageal remodeling processes that might go undetected using endoscopy and histology as well as esophageal hypervigilance and symptom-specific anxiety. Hence, there is a need for a holistic management of patients that goes beyond the control of eosinophilia and symptoms. ***Summary and Key Messages:*** Physiological esophageal testing using high-resolution manometry, functional lumen imaging probe, pH-impedance, wireless pH monitoring, and mucosal impedance may unveil the effects of chronic transmural fibro-inflammatory changes of the esophageal wall as well as esophageal hypervigilance, thereby assisting to phenotype patients, predict therapeutic response to therapy, and identify motility disorders that may need a specific targeted therapy to ameliorate patients' outcomes. This article discusses the role of functional esophageal examinations in the diagnosis and management of EoE.

Introduction

Since its first description by Straumann in Switzerland and Attwood in the USA, eosinophilic esophagitis (EoE) has become one of the most common causes of esophageal symptoms, mainly dysphagia and food impactions in adults. It has a negative impact on health-related quality of life and is a burden to health care systems [1]. Studies from Switzerland and the USA have shaped our understanding of EoE's natural history leading to the development of conceptual models for disease progression from an inflammatory phenotype to a combined inflammatory-fibrostenotic one [2, 3]. Its pathophysiology involves the interplay of genetic susceptibility, early-life exposures, and environmental factors, mainly food allergens leading to a T-helper 2-mediated immune response with eosinophil recruitment into the esophagus [4].

Uncontrolled inflammation and long diagnostic delay are associated with fibrotic remodeling of the esophageal wall [2, 5–7], epithelial mesenchymal transition, subepithelial fibrosis [8], angiogenesis, smooth muscle hypertrophy, and a marked inflammatory infiltration of the myenteric plexus [9, 10]. The full-thickness fibro-inflammatory cascade makes EoE a transmural esophageal disease, ultimately leading to strictures with food impactions [2, 5, 7, 11, 12] as well as dysmotility [10, 12, 13] with impaired bolus clearance and dysphagia.

karger@karger.com
www.karger.com/iid

Correspondence to:
Jeanine Wakim El-Khoury, jeanine.wakim@chuv.ch

Although dysmotility seems to be mainly secondary to the biomechanical remodeling-dependent muscular dysfunction with asynchrony of circular and longitudinal muscle contraction during swallows [14, 15], there is evidence that eosinophil degranulation products lead to smooth muscle hypertrophy promoting fibroblast to myofibroblast differentiation [8], activate the muscarinic acetylcholine receptors with subsequent smooth muscle reactivity [16, 17], alter smooth muscle contractility [4], cause myenteric axonal necrosis and impairment of neurotransmitters delivery to the esophagus [16, 18, 19]. Moreover, there is an increasing body of evidence for the role of mast cells in EoE [4, 16, 20, 21] which promote muscle cell differentiation in the muscularis propria into a more contractile phenotype. In addition, their degranulation products (tryptase, histamine, serotonin) activate smooth muscle contraction, decrease lower esophageal sphincter relaxation, and may participate in neuron damage in the myenteric plexus [22].

The correlation between EoE-related symptoms on one hand and endoscopic and histologic activity on the other hand is only modest [23] which indicates a major role for esophageal remodeling processes that are not fully captured by validated instruments to evaluate clinical, endoscopic, and histologic activity. Complementary esophageal physiological testing allows for a comprehensive understanding of the full-thickness structural and functional esophageal alterations of EoE, highlighting the key role of dysmotility, impaired bolus clearance, esophageal hypervigilance, and symptom-specific anxiety [24] in symptom generation. Physiological esophageal tests have the potential to fill this gap in EoE. In this review, we present the findings and the clinical utility of esophageal functional tests in EoE which are summarized in Table 1.

Table 1. Esophageal physiologic tests

Properties evaluated	HRM	FLIP	BE	pH-I	DMI
Primary peristalsis	X		X	–	–
Secondary peristalsis		X	X	–	–
Longitudinal muscle	X	X		–	–
EGJ opening	X	X	X	–	–
Bolus transit	X		X	–	–
Compliance	–	X	–	–	–
CSA/caliber	–	X	–	–	–
Distensibility	–	x	–	–	–
Reflux burden	–	-	–	X	–
MI	X	-	–	X	X
Esophageal clearance					
Strictures detection	–	X	X	–	–
Physiomechanical classification	–	X	–	–	–
Prediction of response to PPIs	–	X	–	X	–

Information derived from each esophageal physiologic test and clinical applicability in EoE. EoE, eosinophilic esophagitis; HRM, high-resolution manometry; LES, lower esophageal sphincter; FLIP, functional lumen imaging probe; EGJ, esophagogastric junction; CSA, cross-sectional area; PPIs, proton-pump inhibitors; BE, barium esophagram; pH-I, pH-(impedance) monitoring; GERD, gastroesophageal reflux disease; DMI, endoscope-guided direct mucosal impedance.

Functional Testing in EoE

High-Resolution Manometry

High-resolution manometry (HRM) is the gold standard for the evaluation of esophageal primary peristalsis and lower esophageal sphincter integrity and function through the representation of acquired data as pressure topography plots. The globally adopted Chicago Classification version 4.0© provides standardized interpretation parameters and diagnostic criteria for HRM. Although esophageal mechanical obstruction is key in the development of dysphagia in EoE, up to one-third of patients present symptoms of esophageal dysfunction despite a normal endoscopy, unveiling the importance of motor dysfunction secondary to the fibrotic esophageal wall remodeling [16, 23] with an added component of reactive contractile response encompassing spasms and hypercontractility secondary to strictures. The prevalence of motor dysfunction in EoE increases with longer disease duration [25, 26].

Although dysmotility in EoE spans the entire motility spectrum [27–30], normal motility is the most common finding, followed by ineffective motility in approximately one-third of patients [31]. Achalasia (subtypes I, II, III) and esophagogastric junction (EGJ) outflow obstruction may be present too and may need targeted management [32]. Even though HRM mainly evaluates the circular muscle function through primary peristalsis [15], it may also reflect longitudinal muscle contractions responsible for esophageal axial shortening. In normal esophageal physiology, there is a synchronization of circular and longitudinal muscle contraction during peristalsis to facilitate the propulsion of the bolus along the esophagus [33]. In EoE, there is a lack of coordination between these muscle layers [5] with a selective longitudinal layer impairment due to fibrosis precluding esophageal shortening along that

axis [15]. This phenomenon is followed by abnormal longitudinal muscle relaxation that may be reflected as stenosis on imaging [15] and endoscopy. An ensuing panesophageal pressurization (PEP) pattern is seen on HRM characterized by simultaneous esophageal pressurization exceeding 30 mm Hg, extending from the upper esophageal sphincter to the EGJ and impairing bolus transit. PEP is one of the most frequent abnormalities in EoE [27, 29, 31] and is seen in 36% of patients [27], reflecting the reduced wall compliance and dysregulated wall mechanical properties secondary to fibrosis. PEP has been shown to be associated with previous episodes of food impaction [29].

One other pressurization pattern that is important to bolus transit is intrabolus pressure (IBP) which normally increases with increasing bolus volume and viscosity. IBP is the compartmentalized pressure encountered by a bolus when transiting through the esophagus [34] and reflects the resistance to bolus flow which is increased in EoE [27, 35], especially in the fibrostenotic subtype compared to the inflammatory one [35]. Elevated IBP is linked to dysphagia [36], and an IBP above 16 mm Hg seems to predict a fibrostenotic phenotype with a 70–75% sensitivity and specificity but cannot predict the location of the stricture [35]. Abnormal pressurization patterns reflect impaired bolus transit secondary to the fibrotic transformation of the esophageal wall, impairing normal biomechanics. IBP as well as esophageal motor abnormalities parallels disease duration [25, 26, 35]. Motility abnormalities can resolve in up to 86% of patients after 8 weeks of topical steroids except for intrabolus pressurization [30], corroborating the hypothesis that eosinophils might cause reversible esophageal motility abnormalities [37].

For the time being, HRM does not predict EoE's phenotypes which may be either due to its scarce use or to the heterogeneity of protocols applied in research trials until now. However, it plays a central role in patients who remain symptomatic despite a well-controlled inflammation by unraveling esophageal motor abnormalities that may need specific therapies [31]. Moreover, HRM may raise the clinical suspicion of EoE in patients with previously negative endoscopy in whom a repeated endoscopy with esophageal biopsies is necessary to achieve a final diagnosis of EoE. Therefore, HRM may help to unmask a missed EoE diagnosis as well as esophageal strictures in established EoE patients in cases of high IBP.

Functional Lumen Imaging Probe

Functional lumen imaging probe (FLIP) is the new kid in the block for the evaluation of the esophagus and is already integrated in several guidelines and expert consensuses [38]. It uses high-resolution impedance planimetry technology during volume-controlled distension of an infinitely compliant bag filled with a conducting solution. The Northwestern group transformed high-resolution impedance planimetry into FLIP topography plots [13, 39] with a color-coded display of diameter, axial length, and time. Its advantage over HRM does not solely lie in its ability to objectively determine the biomechanical properties of the esophageal wall [40] and evaluate the contractile response to distension (secondary peristalsis), but it also reflects the function of the esophageal longitudinal muscle [15, 41]. The detailed assessment of the biomechanical properties of the esophageal wall and the EGJ provided by FLIP with a greater accuracy and objectivity than endoscopy, reflects the impact of inflammation and fibrotic remodeling on bolus transit and motility in EoE [35], and emphasizes the importance of FLIP in EoE [40, 42].

When compared to healthy esophagus subjects, EoE patients more frequently present with an abnormal secondary peristalsis (33% of patients) that is correlated with the fibrostenotic rather than the inflammatory features of the disease [26]. Moreover, EoE patients display reduced esophageal cross-sectional area (<225 mm^2, especially <125 mm^2) and compliance (<450 mm^3/mm Hg), defined as the change in volume as a function of intraluminal pressure as well as a reduced distensibility plateau (DP) (<17 mm, especially 12.5 mm) [41, 43–45], defined as the narrowest, fixed diameter that does not expand despite increasing pressure [26]. These parameters are more robust predictors of the risk for food impaction and the need for dilation than endoscopy [43] and eosinophilia [40]. Within EoE, DP is lower in patients with prior food impactions compared to those with dysphagia alone [40]. Reduced distensibility correlates with the endoscopic severity of rings, a marker of esophageal remodeling, but not with eosinophilia [40, 41], exudates, or furrows [43] which are markers of inflammation.

The application of FLIP has further consolidated the concept of EoE being a progressive fibrostenotic disease [2, 46] since the reduced distensibility and strictures formation are proportional to the duration of disease and to the diagnostic delay [47]. The Northwestern group went a step further and developed a physiomechanical classification of EoE based on FLIP panometry [44] with the ability to predict histologic response rates to proton pump inhibitors (PPIs). The application of this classification opens new horizons in guiding management, potentially leading to the upfront avoidance of therapies such as PPIs that would fail in patients with spastic-reactive fibrostenosis or

nonreactive fibrostenosis, probably due to the greater symptom duration (~20 years) and the more severe ring subscores (EREFS grade 2–3) compared to patients with a "normal" physiomechanical classification. Research focusing on the standardization of the FLIP protocol is ongoing and is the cornerstone of the future of this technology [48].

Esophageal distensibility measured by FLIP is modifiable with medical and dietary therapy, and DP improvement [49, 50] correlates with an improvement in endoscopic rings and is a better indicator of symptomatic improvement than eosinophilia, suggesting that symptom improvement in EoE is more related to the improvement in the biomechanical properties of the esophageal wall [50]. Hence, FLIP will likely be a key player in the field of EoE not only by an early prediction of therapeutic response, guiding management, and monitoring therapeutic response but also by filling the gap between inflammatory and symptom improvement.

Barium Esophagram

In a recent study, 40% of EoE patients showed a diffusely narrowed esophagus when using a standardized barium esophagram (BE) [51]. By using a standardized approach to calculation of the maximal esophageal diameter and the minimal diameter, 55% of EoE patients had abnormal esophageal caliber, reflecting the impact of remodeling on the esophageal wall [52]. Esophageal diameter evaluated by BE increases over time in EoE patients in remission, independent of dilation and medical therapy according to a recent study with a follow-up of 12 years [53]. Hence, BE is an objective test that fills the gap of the suboptimal detection of esophageal luminal dimensions on endoscopy which has poor sensitivity (14.7–25%) and only modest specificity (79.2%) for detection of a narrowed esophagus even at a cutoff diameter of maximal esophageal diameter ≤15 mm compared with BE [54]. Furthermore, BE is a cheap and readily available test with a greater accuracy for the detection of strictures and narrow-caliber esophagus as well as for the location of strictures than endoscopy [54]. Its sensitivity is further increased with the use of a 12.5-mm barium tablet [55, 56].

pH-(Impedance) Monitoring

The relationship between gastroesophageal reflux disease (GERD) and EoE is complex. They are not considered mutually exclusive disorders [57] and can coexist, but the directionality of the link between them remains unknown [58]. PPIs are a mainstay in the medical armamentarium of EoE [58]. They decrease esophageal eosinophilia by both, an anti-inflammatory effect [58–60] and by restoring the integrity of the epithelial barrier with the reduction of esophageal exposure to acid reflux, hence reducing transepithelial allergen influx to the mucosa and submucosa [61]. Reflux-like symptoms in EoE may be either due to concomitant GERD or to physiological reflux in a hypersensitive eosinophil-inflamed esophageal mucosa with the association of motility and clearance impairments.

The diagnosis of GERD is based on the updated Lyon 2.0 consensus [62] which defines specific and validated endoscopic, pH-impedance and wireless-pH criteria. In the field of EoE, pH testing may be used in patients in histologic remission who present reflux symptoms. It can be done either off or on PPI depending on the absence or the presence of endoscopic proof of GERD, respectively. pH-impedance monitoring allows for the assessment of flow of air and liquids as well as their directionality through the esophagus by measuring the changes in esophageal conductivity or impedance, expressed in Ohms. Low baseline impedance or mean nocturnal baseline impedance reflects an impairment in the esophageal mucosal barrier integrity and has now been integrated in the GERD diagnosis algorithm [62]. Physiologically, there is a caudal decrease of baseline impedance throughout the esophagus with a proximal to distal gradient but not in EoE [63]. In EoE, the dilation of the intercellular space and the reduction in the expression in intercellular junction proteins and adhesion molecules [64–66] increase the permeability of the mucosa, decreasing its transepithelial resistance and baseline impedance throughout the esophagus [63, 67]. Another novel pH-impedance metric is the post-reflux swallow-induced peristaltic wave (PSPW) index which reflects the physiological chemical clearance of reflux linked to a vagally mediated esophago-salivary reflex eliciting primary peristalsis and delivering bicarbonate and epidermal growth factor to the esophagus to increase the pH and heal the mucosa.

Although some previous studies have shown that pH monitoring is not helpful to accurately predict histologic and symptomatic response to therapy in EoE, recent studies using pH-impedance [68, 69] proved it as a predicting tool of therapeutic response to PPIs. EoE patients have an abnormal reflux burden with a higher number of reflux episodes compared to controls [68]. The low mean nocturnal baseline impedance gradient between the mid and distal esophagus off PPI and the low PSPW index on PPI are present in PPI-refractory

patients, suggesting a role for reflux in the pathogenesis of EoE in genetically susceptible patients, leading to the inflammatory eosinophilic cascade [61].

Endoscope-Guided Direct Mucosal Impedance

As previously mentioned, impedance measures the conductivity of the epithelium to low-intensity electrical current and reflects the dilation of the intercellular spaces between esophageal epithelial cells (spongiosis) secondary to chronic esophageal disorders such as GERD and EoE [70]. The endoscope-guided direct mucosal impedance (MI) test uses a through-the-scope probe formed of impedance electrodes mounted on a balloon allowing for direct sensor contact onto the epithelium [70]. This technology can distinguish normal esophageal mucosa from inflammatory disorders such as EoE and GERD [70]. In GERD, the typical MI pattern shows a gradual decrease in impedance from the proximal to the distal esophagus, while in active EoE, MI is consistently low all along the esophagus [70, 71]. MI may alleviate costs by reducing the need for esophageal biopsies since there is an inverse correlation between MI and both eosinophilia and dilation of the intercellular spaces [67, 72]. The typical EoE MI pattern is capable of predicting the diagnosis of EoE with a sensitivity of 100%, a specificity of 96%, a positive predictive value of 96%, and a negative predictive value of 100% [73, 74]. Improvement in MI values correlates well with successful EoE treatment (PPI, steroids, diet) [70, 72].

Conclusion

Since current diagnosis and follow-up in EoE require serial endoscopies with biopsies, there is a growing interest in less invasive tests for the upfront prediction of therapeutic response and follow-up. The exact place of esophageal functional testing in EoE is yet to be determined taking into account the mounting evidence of its utility in clinical practice and its ability to help streamline upfront effective therapy, reducing the interval to histologic remission as well as the need for repetitive endoscopies and biopsies. Esophageal physiological testing can segregate patients into different phenotypes characterized by various therapeutic responses. Physiological testing is indicated in symptomatic patients despite histologic remission and an esophageal caliber >16 mm [75], so the biomechanical properties of the esophageal wall as well as esophageal hypervigilance contributing to persistent symptoms can be unmasked [76]. Finally, the lack of correlation between esophageal distensibility and mucosal eosinophil density and the better correlation between the former and symptoms suggest the future need to target both of these variables to improve outcomes [40].

Conflict of Interest Statement

J.W.E. has no relevant financial, professional, or personal relationships to disclose. E.S. has received consulting fees and/or speaker fees and/or research funding from Dr. Falk Pharma, GSK, Celgene/Receptos/BMS, and Regeneron-Sanofi. She is an employee of Tillotts Pharma AG. A.M.S. has received consulting fees and/or speaker fees and/or research funding from Adare/Ellodi, AstraZeneca, Dr. Falk Pharma, Gossamer Bio, GSK, Celgene/Receptos/BMS, and Regeneron-Sanofi.

Funding Sources

Work supported by a grant from the Swiss National Science Foundation (32003B_204751/1 to A.M.S.) and the Swiss EoE foundation (to A.M.S.).

Author Contributions

Jeanine Wakim El-Khoury and Alain M. Schoepfer contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Ekaterina Safroneeva contributed to study concept and design, acquisition of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

References

1 Mukkada V, Falk GW, Eichinger CS, King D, Todorova L, Shaheen NJ. Health-related quality of life and costs associated with eosinophilic esophagitis: a systematic review. Clin Gastroenterol Hepatol. 2018;16(4):495–503.e8. https://doi.org/10.1016/j.cgh.2017.06.036

2 Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013;145(6):1230–6.e62. https://doi.org/10.1053/j.gastro.2013.08.015

3 Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology. 2003;125(6):1660–9. https://doi.org/10.1053/j.gastro.2003.09.024

4 O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of eosinophilic esophagitis. Gastroenterology. 2018;154(2):333–45. https://doi.org/10.1053/j.gastro.2017.06.065

5 Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterol Clin North Am. 2014;43(2):297–316. https://doi.org/10.1016/j.gtc.2014.02.015
6 Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology. 2018;154(2):319–32.e3. https://doi.org/10.1053/j.gastro.2017.06.067
7 Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol. 2016;50(2):134–40. https://doi.org/10.1097/MCG.0000000000000297
8 Rieder F, Nonevski I, Ma J, Ouyang Z, West G, Protheroe C, et al. T-helper 2 cytokines, transforming growth factor β1, and eosinophil products induce fibrogenesis and alter muscle motility in patients with eosinophilic esophagitis. Gastroenterology. 2014;146(5):1266–77.e779. https://doi.org/10.1053/j.gastro.2014.01.051
9 Davis BP, Rothenberg ME. Mechanisms of disease of eosinophilic esophagitis. Annu Rev Pathol. 2016;11:365–93. https://doi.org/10.1146/annurev-pathol-012615-044241
10 Spechler SJ. Eosinophilic esophagitis: novel concepts regarding pathogenesis and clinical manifestations. J Gastroenterol. 2019;54(10):837–44. https://doi.org/10.1007/s00535-019-01604-7
11 Dellon ES, Kim HP, Sperry SLW, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc. 2014;79(4):577–85.e4.
12 Schoepfer A, Safroneeva E, Straumann A. Eosinophilic esophagitis: impact of latest insights into pathophysiology on therapeutic strategies. Dig Dis. 2016;34(5):462–8. https://doi.org/10.1159/000445201
13 Lin Z, Kahrilas PJ, Xiao Y, Nicodème F, Gonsalves N, Hirano I, et al. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. Therap Adv Gastroenterol. 2013;6(2):97–107. https://doi.org/10.1177/1756283X12470017
14 Rothenberg ME. Eosinophilic esophagitis: biology to therapy. Gastroenterology. 2009;137(4):1238–49. https://doi.org/10.1053/j.gastro.2009.07.007
15 Korsapati H, Babaei A, Bhargava V, Dohil R, Quin A, Mittal RK. Dysfunction of the longitudinal muscles of the oesophagus in eosinophilic oesophagitis. Gut. 2009;58(8):1056–62. https://doi.org/10.1136/gut.2008.168146
16 Visaggi P, Ghisa M, Marabotto E, Venturini A, Stefani Donati D, Bellini M, et al. Esophageal dysmotility in patients with eosinophilic esophagitis: pathogenesis, assessment tools, manometric characteristics, and clinical implications. Esophagus. 2023;20(1):29–38. https://doi.org/10.1007/s10388-022-00964-z
17 Nurko S, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008;18(1):73–ix. https://doi.org/10.1016/j.giec.2007.09.006
18 Nurko S, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008;18(1):73–89; ix. https://doi.org/10.1016/j.giec.2007.09.006
19 Lucendo AJ, Castillo P, Martín-Chávarri S, Carrión G, Pajares R, Pascual JM, et al. Manometric findings in adult eosinophilic oesophagitis: a study of 12 cases. Eur J Gastroenterol Hepatol. 2007;19(5):417–24. https://doi.org/10.1097/MEG.0b013e328010bd69
20 Bolton SM, Kagalwalla AF, Arva NC, Wang MY, Amsden K, Melin-Aldana H, et al. Mast cell infiltration is associated with persistent symptoms and endoscopic abnormalities despite resolution of eosinophilia in pediatric eosinophilic esophagitis. Am J Gastroenterol. 2020;115(2):224–33. https://doi.org/10.14309/ajg.0000000000000474
21 Aceves SS, Chen D, Newbury RO, Dohil R, Bastian JF, Broide DH. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-β1, and increase esophageal smooth muscle contraction. J Allergy Clin Immunol. 2010;126(6):1198–204.e4. https://doi.org/10.1016/j.jaci.2010.08.050
22 Nelson M, Zhang X, Pan Z, Spechler SJ, Souza RF. Mast cell effects on esophageal smooth muscle and their potential role in eosinophilic esophagitis and achalasia. Am J Physiol Gastrointest Liver Physiol. 2021;320(3):G319–27. https://doi.org/10.1152/ajpgi.00290.2020
23 Safroneeva E, Straumann A, Coslovsky M, Zwahlen M, Kuehni CE, Panczak R, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology. 2016;150(3):581–90.e4. https://doi.org/10.1053/j.gastro.2015.11.004
24 Taft TH, Carlson DA, Simons M, Zavala S, Hirano I, Gonsalves N, et al. Esophageal hypervigilance and symptom-specific anxiety in patients with eosinophilic esophagitis. Gastroenterology. 2021;161(4):1133–44. https://doi.org/10.1053/j.gastro.2021.06.023
25 van Rhijn BD, Oors JM, Smout AJPM, Bredenoord AJ. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil. 2014;26(9):1349–55. https://doi.org/10.1111/nmo.12400
26 Carlson DA, Shehata C, Gonsalves N, Hirano I, Peterson S, Prescott J, et al. Esophageal dysmotility is associated with disease severity in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2022;20(8):1719–28.e3. https://doi.org/10.1016/j.cgh.2021.11.002
27 Roman S, Hirano I, Kwiatek MA, Gonsalves N, Chen J, Kahrilas PJ, et al. Manometric features of eosinophilic esophagitis in esophageal pressure topography. Neurogastroenterol Motil. 2011;23(3):208–e111. https://doi.org/10.1111/j.1365-2982.2010.01633.x
28 Bassett J, Maydonovitch C, Perry J, Sobin L, Osgard E, Wong R. Prevalence of esophageal dysmotility in a cohort of patients with esophageal biopsies consistent with eosinophilic esophagitis. Dis Esophagus. 2009;22(6):543–8. https://doi.org/10.1111/j.1442-2050.2009.00949.x
29 Martín Martín L, Santander C, Lopez Martín MC, Espinoza-Ríos J, Chavarría-Herbozo C, Gisbert JP, et al. Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. J Gastroenterol Hepatol. 2011;26(9):1447–50. https://doi.org/10.1111/j.1440-1746.2011.06770.x
30 Nennstiel S, Bajbouj M, Becker V, Slotta-Huspenina J, Wagenpfeil S, Schmid RM, et al. High-resolution manometry in patients with eosinophilic esophagitis under topical steroid therapy: a prospective observational study (HIMEOS-study). Neurogastroenterol Motil. 2016;28(4):599–607. https://doi.org/10.1111/nmo.12753
31 Visaggi P, Ghisa M, Barberio B, Marabotto E, de Bortoli N, Savarino E. Systematic Review: esophageal motility patterns in patients with eosinophilic esophagitis. Dig Liver Dis. 2022;54(9):1143–52. https://doi.org/10.1016/j.dld.2022.01.003
32 Ghisa M, Laserra G, Marabotto E, Ziola S, Tolone S, de Bortoli N, et al. Achalasia and obstructive motor disorders are not uncommon in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2021;19(8):1554–63. https://doi.org/10.1016/j.cgh.2020.07.056
33 Mittal RK, Padda B, Bhalla V, Bhargava V, Liu J. Synchrony between circular and longitudinal muscle contractions during peristalsis in normal subjects. Am J Physiol Gastrointest Liver Physiol. 2006;290(3):G431–8. https://doi.org/10.1152/ajpgi.00237.2005
34 Lin Z, Yim B, Gawron A, Imam H, Kahrilas PJ, Pandolfino JE. The four phases of esophageal bolus transit defined by high-resolution impedance manometry and fluoroscopy. Am J Physiol Gastrointest Liver Physiol. 2014;307(4):G437–444. https://doi.org/10.1152/ajpgi.00148.2014
35 Colizzo JM, Clayton SB, Richter JE. Intrabolus pressure on high-resolution manometry distinguishes fibrostenotic and inflammatory phenotypes of eosinophilic esophagitis. Dis Esophagus. 2016;29(6):551–7. https://doi.org/10.1111/dote.12360
36 Myers JC, Jamieson GG, Sullivan T, Dent J. Dysphagia and gastroesophageal junction resistance to flow following partial and total fundoplication. J Gastrointest Surg. 2012;16(3):475–85. https://doi.org/10.1007/s11605-011-1675-7

37 Patel DA, Yadlapati R, Vaezi MF. Esophageal motility disorders: current approach to diagnostics and therapeutics. Gastroenterology. 2022;162(6):1617–34. https://doi.org/10.1053/j.gastro.2021.12.289
38 UK guidelines on oesophageal dilatation in clinical practice: PMC [Internet]. [cited 2023 Sep 30]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969363/
39 Carlson D, Lin Z, Rogers M, Lin C, Kahrilas P, Pandolfino J. Utilizing functional lumen imaging probe topography to evaluate esophageal contractility during volumetric distention: a pilot study. Neurogastroenterol Motil. 2015;27(7):981–9. https://doi.org/10.1111/nmo.12572
40 Nicodème F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2013;11(9):1101–7.e1. https://doi.org/10.1016/j.cgh.2013.03.020
41 Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology. 2011;140(1):82–90. https://doi.org/10.1053/j.gastro.2010.09.037
42 Hirano I, Pandolfino J, Boeckxstaens G. Functional lumen imaging probe for the management of esophageal disorders: expert review from the clinical practice updates committee of the AGA institute. Clin Gastroenterol Hepatol. 2017;15(3):325–34. https://doi.org/10.1016/j.cgh.2016.10.022
43 Chen JW, Pandolfino JE, Lin Z, Ciolino JD, Gonsalves N, Kahrilas PJ, et al. Severity of endoscopically identified esophageal rings correlates with reduced esophageal distensibility in eosinophilic esophagitis. Endoscopy. 2016;48(9):794–801. https://doi.org/10.1055/s-0042-107340
44 Carlson DA, Hirano I, Gonsalves N, Kahrilas PJ, Araujo IK, Yang M, et al. A PhysioMechanical model of esophageal function in eosinophilic esophagitis. Gastroenterology. 2023;165(3):552–63.e4. https://doi.org/10.1053/j.gastro.2023.05.031
45 Moosavi S, Shehata C, Kou W, Hirano I, Gonsalves N, Peterson S, et al. Measuring esophageal compliance using functional lumen imaging probe to assess remodeling in eosinophilic esophagitis. Neurogastroenterol Motil. 2023;35(4):e14525. https://doi.org/10.1111/nmo.14525
46 Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, Smout AJPM, Bredenoord AJ. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol. 2018;113(6):836–44. https://doi.org/10.1038/s41395-018-0052-5
47 Araujo IK, Shehata C, Hirano I, Gonsalves N, Kahrilas PJ, Tetreault MP, et al. The severity of reduced esophageal distensibility parallels eosinophilic esophagitis disease duration. Clin Gastroenterol Hepatol. 2024;22(3):513–22.e1. https://doi.org/10.1016/j.cgh.2023.04.027
48 Wakim El-Khoury J, Pandolfino JE, Kahrilas PJ, Godo B, Farina DA, Kou W, et al. Relaxation of the lower esophageal sphincter in response to reduced volume distension during FLIP Panometry. Neurogastroenterol Motil. 2023;35(11):e14663. https://doi.org/10.1016/j.cgh.2023.04.027
49 Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Gastroenterology. 2020;158(1):111–22.e10. https://doi.org/10.1053/j.gastro.2019.09.042
50 Carlson DA, Hirano I, Zalewski A, Gonsalves N, Lin Z, Pandolfino JE. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. Clin Transl Gastroenterol. 2017;8(10):e119. https://doi.org/10.1038/ctg.2017.47
51 Muinuddin A, O'Brien PG, Hurlbut DJ, Paterson WG. Diffuse esophageal narrowing in eosinophilic esophagitis: a barium contrast study. J Can Assoc Gastroenterol. 2019;2(1):1–5. https://doi.org/10.1093/jcag/gwy022
52 Lee J, Huprich J, Kujath C, Ravi K, Enders F, Smyrk TC, et al. Esophageal diameter is decreased in some patients with eosinophilic esophagitis and might increase with topical corticosteroid therapy. Clin Gastroenterol Hepatol. 2012;10(5):481–6. https://doi.org/10.1016/j.cgh.2011.12.042
53 Snyder DL, Alexander JA, Ravi K, Fidler JL, Katzka DA. Course of esophageal strictures in eosinophilic esophagitis using structured esophagram protocol. Gastro Hep Adv. 2024;3(4):448–53. https://doi.org/10.1016/j.gastha.2024.01.010
54 Gentile N, Katzka D, Ravi K, Trenkner S, Enders F, Killian J, et al. Oesophageal narrowing is common and frequently underappreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther. 2014;40(11–12):1333–40. https://doi.org/10.1111/apt.12977
55 Richter JE. Esophageal dilation in eosinophilic esophagitis. Best Pract Res Clin Gastroenterol. 2015;29(5):815–28. https://doi.org/10.1016/j.bpg.2015.06.015
56 Ghahremani GG, Weingardt JP, Curtin KR, Yaghmai V. Detection of occult esophageal narrowing with a barium tablet during chest radiography. Clin Imaging. 1996;20(3):184–90. https://doi.org/10.1016/0899-7071(95)00015-1
57 Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated International consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. Gastroenterology. 2018;155(4):1022–33.e10. https://doi.org/10.1053/j.gastro.2018.07.009
58 Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United Eur Gastroenterol J. 2017;5(3):335–58. https://doi.org/10.1177/2050640616689525
59 Cheng E, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013;62(6):824–32. https://doi.org/10.1136/gutjnl-2012-302250
60 Laserna-Mendieta EJ, Casabona S, Savarino E, Perelló A, Pérez-Martínez I, Guagnozzi D, et al. Efficacy of therapy for eosinophilic esophagitis in real-world practice. Clin Gastroenterol Hepatol. 2020;18(13):2903–11.e4. https://doi.org/10.1016/j.cgh.2020.01.024
61 Frazzoni M, Frazzoni L, De Bortoli N, Russo S, Tolone S, Arsiè E, et al. Response of eosinophilic oesophagitis to proton pump inhibitors is associated with impedance-pH parameters implying anti-reflux mechanism of action. Aliment Pharmacol Ther. 2021;53(11):1183–9. https://doi.org/10.1111/apt.16371
62 Gyawali CP, Yadlapati R, Fass R, Katzka D, Pandolfino J, Savarino E, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. Gut. 2024;73(2):361–71. https://doi.org/10.1136/gutjnl-2023-330616
63 van Rhijn BD, Kessing BF, Smout AJ, Bredenoord AJ. Oesophageal baseline impedance values are decreased in patients with eosinophilic oesophagitis. United Eur Gastroenterol J. 2013;1(4):242–8. https://doi.org/10.1177/2050640613496411
64 Simon D, Page B, Vogel M, Bussmann C, Blanchard C, Straumann A, et al. Evidence of an abnormal epithelial barrier in active, untreated and corticosteroid-treated eosinophilic esophagitis. Allergy. 2018;73(1):239–47. https://doi.org/10.1111/all.13244
65 Katzka DA, Tadi R, Smyrk TC, Katarya E, Sharma A, Geno DM, et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2014;12(11):1824–9.e1. https://doi.org/10.1016/j.cgh.2014.02.039
66 Approaches and challenges to management of pediatric and adult patients with eosinophilic esophagitis: PMC [Internet]. [cited 2023 Sep 22]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8063595/
67 Warners MJ, van Rhijn BD, Verheij J, Smout AJPM, Bredenoord AJ. Disease activity in eosinophilic esophagitis is associated with impaired esophageal barrier integrity. Am J Physiol Gastrointest Liver Physiol. 2017;313(3):G230–8. https://doi.org/10.1152/ajpgi.00058.2017
68 Frazzoni M, Penagini R, Frazzoni L, de Bortoli N, Mauro A, Tolone S, et al. Role of reflux in the pathogenesis of eosinophilic esophagitis: comprehensive appraisal with off- and on PPI impedance-pH monitoring. Am J Gastroenterol. 2019;114(10):1606–13. https://doi.org/10.14309/ajg.0000000000000379

69 Ilia S, Monica V, Daniel S. Mean nocturnal baseline impedance and endoscopic mucosal impedance measurements in patients with eosinophilic esophagitis: a new tool for follow up and management? Updates Surg. 2023; 75(2):389–93. https://doi.org/10.1007/s13304-022-01331-4
70 Vaezi MF, Choksi Y. Mucosal impedance: a new way to diagnose reflux disease and how it could change your practice. Am J Gastroenterol. 2017; 112(1):4–7. https://doi.org/10.1038/ajg.2016.513
71 Ates F, Yuksel ES, Higginbotham T, Slaughter JC, Mabary J, Kavitt RT, et al. Mucosal impedance discriminates GERD from non-GERD conditions. Gastroenterology. 2015; 148(2):334–43. https://doi.org/10.1053/j.gastro.2014.10.010
72 Katzka DA, Ravi K, Geno DM, Smyrk TC, Iyer PG, Alexander JA, et al. Endoscopic mucosal impedance measurements correlate with eosinophilia and dilation of intercellular spaces in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2015; 13(7):1242–8.e1. https://doi.org/10.1016/j.cgh.2014.12.032
73 Choksi Y, Lal P, Slaughter JC, Sharda R, Parnell J, Higginbotham T, et al. Esophageal mucosal impedance patterns discriminate patients with eosinophilic esophagitis from patients with GERD. Clin Gastroenterol Hepatol. 2018;16(5):664–71.e1. https://doi.org/10.1016/j.cgh.2017.12.020
74 Barrett C, Choksi Y, Vaezi MF. Mucosal impedance: a new approach to diagnosing gastroesophageal reflux disease and eosinophilic esophagitis. Curr Gastroenterol Rep. 2018;20(7):33. https://doi.org/10.1007/s11894-018-0639-4
75 Aceves SS, Alexander JA, Baron TH, Bredenoord AJ, Day L, Dellon ES, et al. Endoscopic approach to eosinophilic esophagitis: American society for gastrointestinal endoscopy consensus conference. Gastrointest Endosc. 2022;96(4):576–92.e1. https://doi.org/10.1016/j.gie.2022.05.013
76 Strauss AL, Falk GW. Refractory eosinophilic esophagitis: what to do when the patient has not responded to proton pump inhibitors, steroids and diet. Curr Opin Gastroenterol. 2022;38(4):395–401. https://doi.org/10.1097/MOG.0000000000000842