Recognition and Assessment of Eosinophilic Esophagitis: The Development of New Clinical Outcome Metrics

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Abstract: Eosinophilic esophagitis (EoE) is a chronic, food-allergic disease manifest by symptoms of esophageal dysfunction and dense esophageal eosinophilia in which other causes have been excluded. Treatments include dietary restriction of the offending allergens, topical corticosteroids, and dilation of strictures. EoE has become increasingly prevalent over the past decade and has been increasingly recognized as a major health concern. Advancements in research and clinical needs have led to the development of novel pediatric- and adult-specific clinical outcome metrics (COMs). These COMs provide ways to measure clinically relevant features in EoE and set the stage for measuring outcomes in future therapeutic trials. In this article, we review novel symptom measurement assessments, the use of radiographic imaging to serve as a metric for therapeutic interventions, recently developed standardized methods for endoscopic assessment, novel techniques to evaluate esophageal mucosal inflammation, and methods for functional assessment of the esophagus. These advancements, in conjunction with current consensus recommendations, will improve the clinical assessment of patients with EoE.

Keywords
Eosinophil, eosinophilic esophagitis, eosinophilic gastrointestinal disease, clinical outcome metrics

Although the original case series involving eosinophilic esophagitis (EoE) were published in the early 1990s featuring adult patients,[1,2] the following wave of publications focused on the identification and treatment of EoE in children. Subsequently, in 1995, a study of 10 pediatric patients with esophageal eosinophilia who were unresponsive to standard anti–gastroesophageal reflux disease therapies experienced symptomatic and histologic improvement after the use of elemental formulas, indicating a possible immunologic mechanism to the intake of intact dietary proteins.[3] As clinical experiences increased with the recognition of EoE as more than a pediatric concern, the second generation of interest spawned the publication of consensus recommendations in 2007, with subsequent revisions and reports in 2011, 2013, and 2014.[4-7] Each of these publications has

been built on research and clinical experiences of adult and pediatric investigators from a number of subspecialties and locations from across the world.

Currently, EoE is defined as a chronic, food-allergic disease that is manifest by symptoms referable to esophageal dysfunction and dense esophageal eosinophilia that are persistent after a proton pump inhibitor (PPI) trial in which other causes have been excluded. Treatments include diet restriction of the offending allergens, topical corticosteroids, and dilation of strictures.[6] The role of PPIs in the diagnosis of EoE is beyond the scope of this article and has been reviewed recently elsewhere.[8,9] Current consensus recommendations provide guidelines for diagnosis and management of EoE.[6]

Together, the tide of research and clinical recognition of EoE in children and adults has led to not only the identification of EoE as a major health concern, but also to a new era of developing novel clinical outcome metrics (COMs) to support prospective therapeutic trials. The development of each of these new COMs has been based on the clinical impact that EoE has imparted on children and adults. These COMs are being used to support patient-oriented research in EoE. This article will review recently developed COMs for the assessment of EoE patients and relate how these metrics measure clinically relevant aspects of EoE-related inflammation.

Symptom Measurement

Measuring symptoms experienced by children and adults poses challenges because of compensatory behaviors that develop around long-standing symptoms related to swallowing. For instance, swallowing itself may not be reported as a problematic issue because patients learn to chew for prolonged periods of time, use water or other lubricants to aid in the passage of foods, or avoid problematic foods that may be highly textured (eg, meats, breads, rice).[10] This observation may have led to the inability to capture symptom differences in some clinical trials.

To address this issue, pediatric- and adult-specific EoE COMs have been developed that identify not only whether dysphagia is present, but also whether compensatory behaviors are being used. A European research team has led a multidisciplinary team of pediatric and adult investigators from across the world to develop the Eosinophilic Esophagitis Symptom Activity Index (EESAI). The adult version of the EESAI was recently published, and the pediatric index is near completion.[11] This index provides a visual analogue of foods for subjects to examine and rate for difficulty in swallowing. In addition, the Dysphagia Symptom Questionnaire (DSQ) has been developed as a daily 3-question method to assess dysphagia severity in adults with EoE (Table 1).[12] This COM was shown to have

Table 1. The Dysphagia Symptom Questionnaire

Since you woke up this morning, did you eat solid food? Yes (go to the next question) No (go to the next question)
Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest? Yes (go to the next question) No (stop)
For the most difficult time you had swallowing food today (during the past 24 hr), did you have to do anything to make the food go down or to get relief? No, it got better or cleared up on its own Yes, I had to drink liquid to get relief Yes, I had to cough and/or gag to get relief Yes, I had to vomit to get relief Yes, I had to seek medical attention to get relief

Adapted from Dellon ES et al.[12]

content validity and measure dysphagia frequency and intensity. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) uses both child and parent proxy scores to assess dysphagia in pediatric subjects (Table 2).[13] Recently, the PEESS reported a significant association with histologic evidence of inflammation as well as some EoE-related genes, in particular those related to mast cells.[14]

Symptoms of gastroesophageal reflux, heartburn, and regurgitation are very common in children with EoE and can be present in adults. Both the EESAI and PEESS assess for esophageal symptoms other than dysphagia and feeding difficulties. COMs that evaluate beyond dysphagia and feeding difficulties are important so as not to miss signs of symptom activity and so that clinicians may more completely identify how therapeutic interventions improve global symptoms.

These assessments set the stage for future development of therapeutic trials that will provide the first US Food and Drug Administration–approved treatment for EoE.[15] In addition, they help raise awareness to clinicians about the detailed history-taking necessary to identify patients with EoE.

Radiographic Imaging

Early case reports of EoE, emanating from the radiographic literature, described some of the well-known imaging patterns of the condition, including proximal focal strictures and long segment narrowing.[16-18] More recently, esophagrams have also served as a metric for therapeutic intervention in adults[19,20] and possibly as a more sensitive marker for esophageal narrowing than endoscopy in children.[21] In a study of 11 adults with EoE, maximal and minimal esophageal diameters were measured before and after 6 weeks of topical corticosteroid treatment. Of

Table 2. Questions From the Pediatric Eosinophilic Esophagitis Symptom Score for Children and Teenagers

How often do you have chest pain, ache, or hurt?
How bad is the chest pain, ache, or hurt?
How often do you have heartburn (burning in your chest, mouth, or throat)?
How bad is your heartburn (burning in your chest, mouth, or throat)?
How often do you have stomach aches or belly aches?
How bad are the stomach aches or belly aches?
How often do you have trouble swallowing?
How bad is the trouble swallowing?
How often do you feel like food gets stuck in your throat or chest?
How bad is it when food gets stuck in your throat or chest?
How often do you need to drink a lot to help swallow your food?
How bad is it if you don't drink a lot to help swallow your food?
How often do you vomit (throw up)?
How bad is the vomiting (throwing up)?
How often do you feel nauseous (feel like you're going to throw up, but don't)?
How bad is the nausea (feeling like you're going to throw up, but don't)?
How often does food come back up your throat when eating?
How bad is the food coming back up your throat when eating?
How often do you eat less food than others?
How often do you need more time to eat than others?

Adapted from Franciosi JP et al.[13]

the total group, neither maximal nor minimal esophageal diameters were shown to increase significantly following treatment; upon subgroup analysis, subjects with an abnormal pretreatment esophageal diameter were found to have a significant increase following treatment.[19]

In a study of 22 children who underwent both esophagram and endoscopy within 3 months of each other, 55% had an esophageal narrowing identified by esophagram but not endoscopy. This discrepancy highlights that there is no current single and specific clinical assessment of clinically relevant stricture in EoE. Radiographic imaging likely complements endoscopy in identifying problematic strictures.[21]

More research is needed to determine the specificity and sensitivity of esophagrams if they are to be used in future therapeutic studies and pre-endoscopic assessments. Regardless, if an esophageal narrowing, whether it is isolated or a long segment, is identified in a radiographic image, the diagnosis of EoE should be strongly considered if it has not already been made.

Endoscopic Analysis

Along with defining novel methods of assessing clinical symptoms of EoE, at least 1 new strategy toward scoring endoscopic appearances associated with inflammation has been developed in Chicago. The Endoscopic Reference Score (EREFS) grades the severity of endoscopic features, including edema, rings, exudate, furrows, and strictures, with a numerical score.[22] The EREFS has been validated externally by a center in Europe.[23] A meta-analysis of 100 articles and abstracts with over 4500 patients with EoE has shown that the prevalence of individual endoscopic findings in EoE can vary significantly and is not universal. In this meta-analysis, the prevalence of esophageal rings was 44%, strictures was 21%, linear furrows was 48%, white plaques was 27%, and decreased vasculature was 41%.[24] Therefore, this scoring system provides endoscopists with a relatively straightforward and efficient method to assess the mucosa.[22]

Although no pathognomonic feature has yet been identified for EoE, the longitudinal tear or crepe paper esophagus[25] and esophageal pull or "tug sign"[26] may provide the closest approximation. The longitudinal tear of the squamous epithelia and underlying tissue occurs following passage of an endoscope; the tear likely represents a fibrotic change of the mucosa that renders the underlying tissue susceptible to shearing. The tug sign occurs in some patients with EoE undergoing an endoscopic mucosal biopsy; a rubbery tension is felt and requires extra exertion on the forceps in order to retract the tool into the endoscope. The tug sign is also thought to occur following extensive remodeling of the mucosal surface.

Finally, new imaging techniques, including confocal and other endomicroscopy procedures, offer added benefit by providing cross-sectional images of the gastrointestinal mucosa, which may allow for tissue diagnosis during endoscopy without biopsy.[27] In this regard, these minimally invasive tests offer a new level of assessing enumeration of eosinophils and mucosal architecture.

The EREFS provides a much-needed standard method to assess the endoscopic appearance of EoE as part of clinical care and for future studies. If encountered as a part of clinical practice, the longitudinal tear and tug sign should alert clinicians to the possibility of EoE.

Inflammatory Mediators and Assessment of Disease Activity

To date, the gold standard for diagnosing EoE and monitoring disease activity has been the large number of eosinophils in the squamous epithelia from endoscopically obtained mucosal biopsy samples.[6] Although enumeration of eosinophils from biopsy samples has proven

clinically useful and has provided rigor for studies by setting a benchmark for maintaining entry homogeneity and establishing diagnoses, it still has a number of problems. First, obtaining biopsies requires repeat endoscopic procedures with associated risks and costs. Second, with increasing knowledge as to the pathophysiology of EoE, eosinophils likely are not the only responsible inflammatory cell and may not be the best available biomarker. Other concerns include variability of eosinophil numbers within a single mucosal sample and among specimen location, observer variability in counting eosinophils, and limited sampling of the mucosal surface.

To address the last issue, a number of new methods to assess the mucosal surface and inflammation of the esophagus have been developed, including the Esophageal String Test (EnteroTrack), Cytosponge (University of Cambridge), and esophageal brushings.[28-30] To date, each technique is based on harvesting luminal effluents and cells for eosinophil- or eosinophil-protein–based analysis. One limitation to these methods is that biopsies can provide insight on submucosal fibrosis; therefore, these procedures may be best used in conjunction with other modalities for ongoing management of EoE.

To expand the scope of assessment beyond eosinophils, the Eosinophilic Esophagitis Diagnostic Panel (EDP) uses genechip assessments of mucosal samples to determine a score based on the number of EoE genes that are up- or downregulated.[31] Investigators using the EDP have been able to develop a scoring platform to define diagnostic clarity and, potentially, therapeutic efficacy. In the future, the EDP may be a modality to improve EoE diagnosis and treatment.

Functional Measurements

Despite the fact that numerous methods exist to assess symptoms and inflammation characteristic of EoE, functional assessment of the esophagus was limited to esophageal manometry until the development of EndoFLIP (Endolumenal Functional Lumen Imaging Probe; Crospon). This catheter-based technology is used during endoscopy, and can determine esophageal distensibility as a measure of compliance (ie, the less distensible, the less compliant).[32] Use of this technology in adults has created a plateau measurement that identifies subjects who are more likely to develop food impactions. Interestingly, no correlation was found between mucosal eosinophil density and food impaction, need for dilation, or distensibility plateau, suggesting that eosinophil enumeration may not fully identify clinically relevant outcomes that are a result of fibrostenosis, such as dysphagia.[33] This device will likely serve as a necessary metric for therapeutic trials as well as for improving clinical care.

Summary

Clinical needs have sparked interest in the development of pediatric- and adult-specific COMs. This has led to the development of symptom assessment guides, including EESAI, DSQ, PEESS, and EREFS. These COMs provide methods to measure clinically relevant features in EoE and set the stage for measuring outcomes in future therapeutic trials. The EREFS score, a standardized and validated method for endoscopic evaluation, provides an efficient method for assessment in clinical practice. In addition, the longitudinal tear and tug sign should alert clinicians to the possibility of EoE. Although histologic evaluation with enumeration of eosinophils remains the gold standard for the diagnosis of EoE, a number of new methods, including the Esophageal String Test, Cytosponge, esophageal brushings, and the EDP, have been developed to assess the mucosal surface. To evaluate the function of the esophagus, EndoFLIP has been shown to determine esophageal distensibility as a measure of compliance and, in adults, to identify subjects with reduced distensibility as more likely to have food impaction. These new developments, in conjunction with current consensus recommendations, will help to improve the clinical assessment of patients with EoE and improve the quality of COMs in clinical trials.

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References

1. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci*. 1993;38(1):109-116.
2. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings [in German]. *Schweiz Med Wochenschr*. 1994;124(33):1419-1429.
3. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503-1512.
4. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol*. 2013;108(5):679-692.
5. Furuta GT, Liacouras CA, Collins MH, et al; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommen-

dations for diagnosis and treatment. *Gastroenterology*. 2007;133(4):1342-1363.
6. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6; quiz 21-22.
7. Papadopoulou A, Koletzko S, Heuschkel R, et al; ESPGHAN Eosinophilic Esophagitis Working Group and the Gastroenterology Committee. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr*. 2014;58(1):107-118.
8. Asher Wolf W, Dellon ES. Eosinophilic esophagitis and proton pump inhibitors: controversies and implications for clinical practice. *Gastroenterol Hepatol (N Y)*. 2014;10(7):427-432.
9. Katzka DA. Eosinophilic esophagitis and proton pump-responsive esophageal eosinophilia: what is in a name? *Clin Gastroenterol Hepatol*. 2014;12(12):2023-2025.
10. Straumann A, Aceves SS, Blanchard C, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy*. 2012;67(4):477-490.
11. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014;147(6):1255-1266.e21.
12. 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(6):634-642.
13. Franciosi JP, Hommel KA, DeBrosse CW, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. *BMC Gastroenterol*. 2011;11:126.
14. Martin LJ, Franciosi JP, Collins MH, 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(6):1519-1528.e8.
15. Fiorentino R, Liu G, Pariser AR, Mulberg AE. Cross-sector sponsorship of research in eosinophilic esophagitis: a collaborative model for rational drug development in rare diseases. *J Allergy Clin Immunol*. 2012;130(3):613-616.
16. Feczko PJ, Halpert RD, Zonca M. Radiographic abnormalities in eosinophilic esophagitis. *Gastrointest Radiol*. 1985;10(4):321-324.
17. Vitellas KM, Bennett WF, Bova JG, Johnston JC, Caldwell JH, Mayle JE. Idiopathic eosinophilic esophagitis. *Radiology*. 1993;186(3):789-793.
18. White SB, Levine MS, Rubesin SE, Spencer GS, Katzka DA, Laufer I. The small-caliber esophagus: radiographic sign of idiopathic eosinophilic esophagitis. *Radiology*. 2010;256(1):127-134.
19. Lee J, Huprich J, Kujath C, 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):481-486.
20. Gentile N, Katzka D, Ravi K, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. *Aliment Pharmacol Ther*. 2014;40(11-12):1333-1340.
21. Menard-Katcher C, Swerdlow MP, Mehta P, Furuta GT, Fenton LZ. Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis [published online May 20, 2015]. *J Pediatr Gastroenterol Nutr*. doi: 10.1097/MPG.0000000000000849.
22. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013;62(4):489-495.
23. van Rhijn BD, Warners MJ, Curvers WL, et al. Evaluating the endoscopic reference score for eosinophilic esophagitis: moderate to substantial intra- and interobserver reliability. *Endoscopy*. 2014;46(12):1049-1055.
24. Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(9):988-996.e5.
25. Straumann A, Rossi L, Simon HU, Heer P, Spichtin HP, Beglinger C. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? *Gastrointest Endosc*. 2003;57(3):407-412.
26. Dellon ES, Gebhart JH, Higgins LL, Hathorn KE, Woosley JT, Shaheen NJ. The esophageal biopsy "pull" sign: a highly specific and treatment-responsive endoscopic finding in eosinophilic esophagitis (with video). *Gastrointest Endosc*. 2015;S0016-5107(15)02500-6.
27. Neumann H, Vieth M, Atreya R, Mudter J, Neurath MF. First description of eosinophilic esophagitis using confocal laser endomicroscopy (with video). *Endoscopy*. 2011;43(Suppl 2 UCTN):E66.
28. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut*. 2013;62(10):1395-1405.
29. Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2015;13(1):77-83.e2.
30. Kern E, Lin D, Larson A, et al. Prospective assessment of the diagnostic utility of esophageal brushings in adults with eosinophilic esophagitis. *Dis Esophagus*. 2014.
31. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology*. 2013;145(6):1289-1299.
32. 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.
33. Nicodeme F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2013;11(9):1101-1107.e1.