Meeting Summary

A Clinical Severity Index for Eosinophilic Esophagitis: Development, Consensus, and Future Directions

Evan S. Dellon,[a] Paneez Khoury,[b] Amanda B. Muir,[c,d] Chris A. Liacouras,[c,d,e] Ekaterina Safroneeva,[f] Dan Atkins,[g,h] Margaret H. Collins,[i,j] Nirmala Gonsalves,[k] Gary W. Falk,[d,l] Jonathan M. Spergel,[d,m] Ikuo Hirano,[k] Mirna Chehade,[n] Alain M. Schoepfer,[o] Calies Menard-Katcher,[p,q] David A. Katzka,[r] Peter A. Bonis,[s] Albert J. Bredenoord,[t] Bob Geng,[u,v] Elizabeth T. Jensen,[w] Robert D. Pesek,[x,y] Paul Feuerstadt,[z,aa] Sandeep K. Gupta,[bb,cc,dd] Alfredo J. Lucendo,[ee,ff,gg] Robert M. Genta,[hh] Girish Hiremath,[ii] Emily C. McGowan,[jj] Fouad J. Moawad,[kk] Kathryn A. Peterson,[ll] Marc E. Rothenberg,[mm,nn] Alex Straumann,[oo] Glenn T. Furuta,[q,pp]* and Seema S. Aceves,[v,qq]*

Chapel Hill and Winston-Salem, NC; Bethesda, Md; Philadelphia, Pa; Bern, Lausanne, and Zurich, Switzerland; Aurora, Colo; Cincinnati, Ohio; Chicago, Ill; New York, NY; Rochester, Minn; Boston, Mass; Amsterdam, The Netherlands; San Diego and La Jolla, Calif; Little Rock, Ark; New Haven and Hamden, Conn; Indianapolis, Ind; Ciudad Real and Madrid, Spain; Houston, Tex; Nashville, Tenn; Charlottesville, Va; and Salt Lake City, Utah

Background & Aims: Disease activity and severity of eosinophilic esophagitis (EoE) dictate therapeutic options and management, but the decision-making process for determining severity varies among practitioners. To reduce variability in practice patterns and help clinicians monitor the clinical course of the disease in an office setting, we aimed to create

From [a]the Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill; [b]the Human Eosinophil Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda; [c]the Division of Gastroenterology, Hepatology, and Nutrition, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [d]the The Children's Hospital of Philadelphia, Philadelphia; [e]the Center for Pediatric Eosinophilic Disorders, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [f]the Institute of Social and Preventive Medicine, University of Bern, Bern; [g]the Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Aurora; [h]the Children's Hospital Colorado, Aurora; [i]the Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Cincinnati; [j]the Cincinnati Children's Hospital Medical Center, Cincinnati; [k]the Gastroenterology and Hepatology, Feinberg School of Medicine, Northwestern University, Chicago; [l]the Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [m]the Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [n]the Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York; [o]the Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne; [p]the Department of Pediatrics, University of Colorado School of Medicine, Aurora; [q]the Digestive Health Institute, Children's Hospital Colorado, Aurora; [r]the Mayo Clinic, Rochester; [s]the Tufts Medical Center, Boston; [t]the Department of Gastroenterology, Amsterdam University Medical Center, Amsterdam; [u]the University of California San Diego, San Diego; [v]the Rady Children's Hospital, San Diego; [w]the Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem; [x]the Division of Allergy/Immunology, University of Arkansas for Medicine Sciences, Little Rock; [y]the Arkansas Children's Hospital, Little Rock; [z]the Division of Gastroenterology, Yale-New Haven Hospital, New Haven; [aa]the Physicians Alliance of Connecticut, Gastroenterology Center, Hamden; [bb]the Section of Pediatric Gastroenterology/Hepatology/Nutrition, Indiana University School of Medicine, Indianapolis; [cc]the Riley Hospital for Children, Indianapolis; [dd]the Community Health Network, Indianapolis; [ee]the Department of Gastroenterology, Hospital General de Tomelloso, Ciudad Real; [ff]the Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid; [gg]the Instituto de Investigación Sanitaria La Princesa, Madrid; [hh]the Baylor College of Medicine, Houston; [ii]the Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville; [jj]the Allergy and Clinical Immunology, University of Virginia, Charlottesville; [kk]the Division of Gastroenterology, Scripps Clinic, La Jolla; [ll]the Division of Gastroenterology, University of Utah Health, Salt Lake City; [mm]the Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati; [nn]the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati; [oo]the University Hospital Zurich, Zurich; [pp]the Department of Pediatrics, Gastrointestinal Eosinophilic Diseases Program and Mucosal Inflammation Program, University of Colorado School of Medicine, Aurora; and [qq]the Division of Allergy, Immunology, University of California-San Diego, San Diego.

*Authors share co-senior authorship.

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an international consensus severity scoring index for EoE.
Methods: A multidisciplinary international group of adult and pediatric EoE researchers and clinicians, as well as non-EoE allergy immunology and gastroenterology experts, formed 3 teams to review the existing literature on histology, endoscopy, and symptoms of EoE in the context of progression and severity. A steering committee convened a 1-day virtual meeting to reach consensus on each team's opinion on salient features of severity across key clinicopathologic domains and distill features that would allow providers to categorize disease severity.
Results: Symptom features and complications and inflammatory and fibrostenotic features on both endoscopic and histologic examination were collated into a simplified scoring system—the Index of Severity for Eosinophilic Esophagitis (I-SEE)—that can be completed at routine clinic visits to assess disease severity using a point scale of 0-6 for mild, 7-14 for moderate, and ≥15 for severe EoE.
Conclusions: A multidisciplinary team of experts iteratively created a clinically usable EoE severity scoring system denominated "I-SEE" to guide practitioners in EoE management by standardizing disease components reflecting disease severity beyond eosinophil counts. I-SEE should be validated and refined using data from future clinical trials and routine clinical practice to increase its utilization and functionality. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *Eosinophilic esophagitis, severity, complications, symptoms, endoscopy, histology*

Abbreviations used

BZH:	Basal zone hyperplasia
DEC:	Dyskeratotic epithelial cell
EoE:	Eosinophilic esophagitis
EoEHSS:	Eosinophilic Esophagitis Histologic Scoring System
Eos/hpf:	Eosinophils per high-power field
EREFS:	Eosinophilic Esophagitis Endoscopic Reference Score
I-SEE:	Index of Severity for Eosinophilic Esophagitis
LPF:	Lamina propria fibrosis
SEA:	Surface epithelial alteration

Over the past 3 decades, the knowledge base related to eosinophilic esophagitis (EoE) has grown dramatically. EoE has been transformed from a little-known, case-reportable condition to a well-characterized, chronic, clinicopathologic disease often encountered in clinical practice.[1-3] The descriptive epidemiology has been reported, with an increasing incidence and prevalence documented.[4-6] Diagnostic guidelines have been published and updated,[7-11] and evidence-based management recommendations have been released.[12,13] Pathogenesis, as well as predisposing genetic, molecular, and environmental features, are being decoded.[14-16] These developments have spurred a host of treatments, including dietary elimination and swallowed/topical corticosteroids, as well as novel agents still in development.[17-20]

Despite these advances, important knowledge gaps about EoE remain. One area of note relates to variability in practice patterns[21-24] and how to monitor the clinical course or natural history of a patient during follow-up in the office setting. Previously, this deficit was driven by a lack of knowledge regarding the chronicity of EoE, lack of metrics to determine disease severity, and limited number of therapeutic approaches. Over the course of the last 20 years, clinical experiences and research studies have identified key features needed to begin to prospectively assess EoE clinical severity. Development of patient-reported outcomes,[25-27] endoscopic assessment platforms,[28] and histologic metrics of disease activity,[20,29-34] and even a clinical outcomes set,[35] provided robust metrics to measure patients' responses to treatments and assess disease activity. However, no published guidance has combined all elements of disease activity into a single score that could be applied in a practitioner's office to follow and risk stratify patients with EoE.

To address this need, the American Gastroenterological Association facilitated a process to identify key features of EoE disease activity meaningful to clinicians and patients that may also be linked to outcomes. This resulted in a consensus conference ("EoE Disease Severity Index Consensus Conference"), held virtually on August 13, 2021, with the following 4 goals: 1) determine key elements of disease severity in patients with EoE; 2) assess how to measure disease severity components using a clinically actionable methodology; 3) align stakeholders on an EoE severity index; and 4) discuss future research needs on the

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Corresponding author: Evan S. Dellon, MD, MPH, Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, CB#7080, Bioinformatics Building, 130 Mason Farm Road, Chapel Hill, NC 27516. E-mail: edellon@med.unc.edu.
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impact of severity on EoE treatment and outcomes. The conference involved a web-based meeting of 32 faculty (composed of a steering committee, session chairs, presenters, and a working group) and 9 additional key stakeholder discussants or observers, including patient advocates (see Appendix for details). The faculty was an international multidisciplinary group spanning adult and pediatric specialties of gastroenterology, allergy/immunology, pathology, epidemiology, and basic/translational research. After a series of premeeting teleconferences in which faculty reviewed pertinent literature and clinical experiences and synthesized them into presentations, the conference began with an introductory session discussing the need for a severity index. This was followed by sessions reviewing evidence associated with increased severity using symptoms and clinical features, endoscopy, and histology. A final session aimed to define overall EoE clinical severity, design a tool to measure severity, and identify future research directions. At the end of this session, we had achieved a verbal consensus on concepts and specific features to be included in the index from all participants. After the conference, presenters, steering committee members, and session chairs drafted sections relevant to their areas of expertise and worked with other meeting participants to achieve consensus on the disease severity index. The steering committee members then worked iteratively with the rest of the faculty to integrate these contributions into a final manuscript. During the critical revision phase of the manuscript preparation, each coauthor was able to comment, all comments were circulated to the entire author group, and all authors provided final approval for content of the severity index, thus confirming consensus was achieved. This report summarizes the proceedings from the conference and presents an initial Index of Severity for Eosinophilic Esophagitis (I-SEE), to be implemented in clinical care and ultimately updated and validated as it is tested and refined.

EoE LANDSCAPE: WHY SHOULD EoE SEVERITY BE DETERMINED?

Since the publication of the first diagnostic guidelines for EoE in 2007,[7] at least 3 transformations have paved the path for developing a clinical activity/severity scale. First, adoption of the initial and subsequent guidelines permitted clinicians to establish diagnosis and apply diagnostic criteria to set a benchmark for entry criteria into clinical trials.[7,8,10,11] Second, dialogues between patient-facing providers and pathologists led to a more standard practice of quantifying eosinophil counts and a subsequent further characterization of the associated histologic findings of EoE in the esophageal squamous mucosa.[36-39] During this process, it became evident that levels of esophageal eosinophils, initially assumed to be a marker of disease severity, were not a comprehensive biomarker of severity, as mild presentations and fibrostenotic phenotypes could present with similar levels of esophageal eosinophils.[15,40-42] Finally, the ability to recognize disease features other than histology and the development of methods to assess these features has enhanced tracking of EoE across a variety of domains, including symptoms, quality of life, endoscopic appearance, and molecular patterns.[25-28,42-45]

Although all of these events permitted advancements in patient care and treatment as well as research studies, they did not address the increasing challenges clinicians face in day-to-day patient care, including assessing disease activity, response to therapy, risk for progression, and the thresholds at which a change in therapy is needed. Many providers today categorize disease severity in EoE on an intuitive or subjective level; for gastroenterologists, data suggest that symptoms and endoscopic features tend to drive assessment of disease activity.[46] Patients also frequently ask "how bad" their EoE is, and providers do not have a standard way to answer this question. As the number of children and adults with EoE increases worldwide, a simple system to assess and track disease activity in a meaningful way in a clinical setting is needed.

Several indices developed previously for other gastrointestinal conditions, including the Pediatric Ulcerative Colitis Activity Index and the Mayo Score for ulcerative colitis, offer potential roadmaps for an EoE severity score.[47] Severity metrics are also used in autoimmune disorders, such as psoriatic arthritis and Sjögren's syndrome,[48,49] and in allergic diseases, such as atopic dermatitis (SCORAD [Scoring Atopic Dermatitis] or EASI [Eczema Area and Severity Index]).[50] The most widely recognized severity indexes are for asthma and include the GINA (Global Initiative for Asthma)[51] and National Heart, Lung, and Blood Institute guidelines.[52] These asthma guidelines use components of severity, including lung function, symptoms, and disease exacerbation, not only to classify patients but also to link the classification to recommended treatment algorithms.[53] This type of system can be valuable but remains aspirational for EoE.

For EoE, changes in symptom scores and mucosal eosinophilia have served as primary end points for research studies, but for several reasons may not be appropriate for providers in clinical practice. For example, symptom scores were often cumbersome, time-consuming, not readily available, or impractical for use in electronic medical records systems or in routine practice. In addition, levels of mucosal eosinophilia may not always be quantified, and associated histologic features that may independently reflect disease severity often go unreported. Endoscopic features of EoE are increasingly recognized but not all reporting platforms have adopted the EoE Endoscopic Reference Score (EREFS) and not all providers are aware of this. These realities can make it challenging for providers to convey meaningful and consistent information to patients and to track disease activity during therapeutic interventions in the office.

In developing an EoE severity index, the goal was not to change or deconstruct previously validated instruments, but to focus on the critical elements of clinical severity across all domains (ie, symptoms, complications, endoscopy, and histology) and distill features that would allow providers to categorize patients with EoE as having inactive, mild, moderate, or severe disease. The immediate results of this effort should help providers understand that there are key indicators that should be considered when caring for patients with EoE and that these indicators can change over time. Importantly, it should also allow for a common language for communicating with patients and other providers. Longer-term aims include helping standardize practice for treatments and monitoring based on disease severity similar to the asthma model, with the recognition that additional data will be required for full realization and to assess the index's reliability and reproducibility.

EoE symptoms

Symptoms in EoE are often attributable to esophageal dysfunction (eg, dysphagia, food impaction, heartburn, and feeding

refusal), but can also be nonspecific (eg, abdominal pain, vomiting, and problems with eating). Severity of symptoms can be challenging to discern, as patients may employ compensatory feeding mechanisms, such as avoiding certain foods, taking smaller bites and chewing foods more thoroughly, adding additional lubricants to ease food bolus transit, and food or texture avoidance.[54] Decreased quality of life from missed school and social withdrawal present additional challenges.[55] Consequently, evaluating symptom magnitude, frequency, and behavioral modifications requires measuring additional features of disease activity. Symptoms also vary with age, with the youngest children presenting primarily with feeding issues, older children with heartburn, vomiting, or abdominal pain, and adolescents or adults with dysphagia or food impaction.[6] Given these differences, the 4 validated outcome measures for EoE incorporate key symptoms by age. The Eosinophilic Esophagitis Activity Index,[40] Dysphagia Symptom Questionnaire,[56] and Straumann Dysphagia Index[57] used in adults primarily ask about dysphagia symptom frequency and severity; whereas the Pediatric Eosinophilic Esophagitis Symptom Score[58] incorporates symptoms such as nausea and abdominal pain in a multisymptom instrument.

Although evaluating disease has traditionally required repeated endoscopy, the symptom committee was tasked with exploring validated measures and incorporating key symptoms or complications that could be used in a routine office visit to assess severity, recognizing that symptoms alone are an incomplete measure of disease activity.[40] Although social disruptions, such as missing school and avoiding public eating, may impact the quality of life of patients with EoE, they are often variable and do not necessarily correlate with objective measures of disease activity (eg, inflammation, fibrostenosis, and esophageal dysfunction) or the visual appearance of the esophagus.[40] One unifying feature of the outcome measures, however, is the frequency with which either symptoms and/or coping mechanisms occur, allowing medical providers to assess frequency of key symptoms in routine clinical practice.

Some patients with EoE can experience debilitating symptoms and require higher levels of care as they develop complications indicative of more severe disease. The most common complication is esophageal food impaction. Although impactions are less common and are less frequent in children, impactions may represent early-onset fibrostenosis. We therefore deemed children with food impactions to have higher disease severity than their adult counterparts. Most providers would also consider the need for an EoE-related hospitalization to represent moderately severe disease as well. Finally, 3 additional complications were deemed indicative of the most severe disease presentations. The first is esophageal perforation, a rare but serious complication often requiring intensive care and surgical intervention.[59] The second is malnutrition in children when weight loss and poor growth may impact development. Lastly, disease refractory to standard treatments (eg, proton pump inhibitors, topical swallowed corticosteroids, and diet elimination) is considered severe due to the difficulty with controlling disease activity. In addition, therapy-recalcitrant EoE may be associated with uncontrolled inflammation for longer periods of time and, therefore, a more severe or advanced molecular pathogenesis.[60]

EoE endoscopy

Endoscopy with biopsy is a critical diagnostic and management tool for EoE in children and adults. Endoscopic features, especially those that are considered inflammatory, correlate with esophageal eosinophilia and can be followed post treatment.[61] Specific endoscopic features, including severe rings, strictures, and white plaques, have been associated with symptom severity.[32] Esophageal rings have also been associated with a greater likelihood of an esophageal food impaction that is either self-limited or requires endoscopic removal,[62] and esophageal rings and the degree of narrowing are proportional to specific esophageal transcripts, especially *TSPAN12*.[63] Together these findings suggest that several endoscopic features are important to assess for disease severity.

A validated method for reporting and quantifying endoscopic involvement in children and adults with EoE,[28] EREFS measures endoscopic features reflecting esophageal inflammation (eg, edema, exudates, and furrows), as well as those reflecting fibrostenosis (rings and strictures). Among its advantages, EREFS provide uniform language that: 1) is a validated grading and classification system[28,64]; 2) is accurate in predicting EoE diagnosis and histologic remission in both children and adults[65,66]; 3) has been reliably used for both observational and randomized controlled clinical studies of adult patients[67,68]; and 4) is a major determinant of gastroenterologists' assessment of disease activity.[46] Disadvantages include 1) not being commonly reported in studies of pediatric EoE patients; 2) lack of agreement among many endoscopists, until recently, on EREFS scoring; 3) difficulty of use in daily clinical practice in centers not specializing in EoE[35]; and 4) lack of incorporation into all endoscopy reporting platforms. Simplified versions of EREFS that collapse scoring of individual features to "absent" or "present" have comparable inter- and intrarater intraclass correlation coefficients, but are likely less reflective of response to therapy.[69] Although EREFS has helped standardize the endoscopic activity assessment in studies, it does not appear to be uniformly applied and is therefore underused in clinical practice.

When considering using features of EREFS as a part of an "EoE index," we discussed both inflammatory and fibrostenotic features. For the latter category, the discussion focused on remodeling consequences of disease and considered ranges for luminal diameter: normal (≥20 mm), mildly decreased (15-19 mm), moderate (10-14 mm), severe (5-9 mm, failed passage of an adult upper endoscope), and critical (<5 mm, failed passage of pediatric upper endoscope).[70] However, these definitions would require changes to daily clinical practice to include esophageal diameter assessment without evidence of narrowing. A barium esophagram can provide more quantitative evidence of narrowing that may be missed during endoscopy,[70,71] but lacks adequate sensitivity for features of EoE and is thus a poor indicator of disease activity.

These considerations regarding fibrostenosis led panelists to simplify elements related to esophageal narrowing or stricturing as 1) present, but a standard upper endoscope (8-10 mm) passes easily; 2) present but requires dilation; or appreciating a "snug fit" (such as mild resistance) when passing a standard endoscope; and 3) cannot pass standard upper endoscope. Although this proposed grading of esophageal narrowing is easy to use, it still requires validation, given that there is variability in dilation practices among physicians, this simplification does not account for the longitudinal extent or the presence of multiple strictures, and these elements may not be present in pediatric patients because most endoscopic features in pediatric patients are inflammatory.[72] To account for this, any requirement for dilation

in children and adolescents was interpreted to reflect severe disease, and only repeated dilations in an adult met this criterion.

Ultimately, the knowledge gap regarding EREFS among both adult and pediatric endoscopists outside tertiary centers, and the overlap between endoscopic and histologic assessment of inflammation, led panelists to conclude that endoscopic assessment of esophageal narrowing should be a discrete component of the EoE severity index. In addition, it became clear that proposing or developing any grading scale in adults and/or pediatric patients would require more engagement of the clinical community and further education of practitioners who would be using it.[72]

EoE histology

Because EoE is a disease defined by both pathologic and clinical features, assessment of severity should include both inflammatory and fibrotic histologic changes. Metrics to evaluate histologic severity in gastrointestinal diseases other than EoE already exist for ulcerative colitis and gastroesophageal reflux disease.[73] The histologic severity index for gastroesophageal reflux disease, for example, evaluates intraepithelial eosinophils, basal zone hyperplasia (BZH), papillary elongation, and dilated intercellular spaces.[74]

A unique study of resected esophageal strictures in children (1 of whom had EoE, but most of whom had prior caustic ingestion), showed significant muscularis propria hyperplasia, and subepithelial myofibroblast proliferation.[75] Both eosinophils and mast cells were increased in the thickened muscularis propria, suggesting that inflammation in deep as well as superficial layers is important for esophageal stricture formation. Consistent with the concept that inflammation may contribute to esophageal narrowing/stricture are reports that anti-inflammatory therapy may reduce food impactions,[76] histologic fibrosis,[77] and luminal narrowing in EoE patients presenting with severe strictures,[78] and decrease the number of esophageal dilations required.[79,80] The validated Eosinophilic Esophagitis Histologic Scoring System (EoEHSS)[36] evaluates 7 pathologic features in addition to peak eosinophil count for both severity and extent of pathology. Aggregate scores[81] and individual feature scores[82] generally correlate with symptoms more strongly than the peak esophageal eosinophil count, and biopsies showing remission by the EoEHSS score correlate with significantly reduced symptom scores.[82] The EoEHSS has also been shown to be responsive to treatment and provide a more complete picture of overall histologic severity.[83,84] BZH, a feature evaluated in the EoEHSS, may persist in children and adult EoE patients who have persistent symptoms but fewer than 15 eosinophils per high-power field (eos/hpf) in esophageal biopsies.[38,85] Both BZH and lamina propria fibrosis (LPF), another feature evaluated in the EoEHSS, may contribute to long-term remodeling of esophageal biopsies in children who have EoE.[86] Although many esophageal biopsies do not contain evaluable LP, the presence of surface epithelial alteration (SEA) and dyskeratotic epithelial cells (DECs) may predict the presence, but not severity, of fibrosis in these biopsies.[39,87]

Peak eosinophil count, BZH, and LPF (or SEA and DECs if LP is absent or unevaluable) are important features to evaluate and grade to better understand disease severity for patients with EoE. To mitigate the risk of EoE-related complications, presence or increase of these histologic features should prompt closer follow-up as these findings may identify a patient who requires more intensive therapy.

THE INDEX OF SEVERITY FOR EoE (I-SEE)

Overview

After conference participants reached initial consensus, defined as agreement on key elements of severity in EoE, an extended discussion followed to refine these elements and position them within a table that would form the basis of the severity index. We began with a discussion of a table that had mild, moderate, and severe features represented across 3 domains (ie, symptoms, endoscopy, and histology),[88] which was developed during the preparatory phase of the conference. Based on discussion and feedback, this initial table transitioned to one with a more expansive definition of severity. The newer table included symptoms and quality of life, clinical complications, inflammatory features for both endoscopy and histology, fibrotic features for both endoscopy and histology, and treatment responsiveness. The focus on inflammatory and fibrotic features as overall categories represents a shift both in how EoE is conceptualized and in how treatment of EoE may be approached. Using this framework, we incorporated mild, moderate, and severe disease activity components for each category. We then pared down the index to the most essential aspects with a goal of clinical applicability and simplicity, and instituted a point system.

The final version of the severity index—which we named the Index of Severity for Eosinophilic Esophagitis (I-SEE)—has the following 3 domains: symptoms and complications, inflammatory features, and fibrostenotic features (Table I). The 3 domains reflect EoE's key clinicopathologic features: symptoms, endoscopy, and histology. Each feature is assigned points (1-15), which are then summed to determine severity (1-6 points = mild; 7-14 points = moderate; ≥15 points = severe). Notably, some features were deemed impactful enough to automatically categorize a patient as severe, and thus they automatically garner 15 points, as indicated in the last column of Table I.

Importantly, assessing the severity of EoE depends on an accurate diagnosis as per current guidelines, which currently include symptoms of esophageal dysfunction, an isolated esophageal eosinophilia with ≥15 eos/hpf, and the exclusion of other etiologies.[11] I-SEE can be used at initial diagnosis and then at each subsequent visit, with the recall being only between visits so that the severity can be assessed over time and ultimately (when data support this step) treatment and monitoring adjusted based on severity. If an endoscopy and biopsy have not been performed between visits, prior information can be carried forward, but assessing severity can be a prompt to determine whether a monitoring endoscopy is needed.

Symptoms and complications

In the I-SEE, symptom severity is to be judged primarily by symptom frequency and the specific symptoms are not specified but should be assessed by the provider. In children, these symptoms can include abdominal pain, vomiting, heartburn/reflux, chest pain, unintentional weight loss, feeding difficulty (eg, refusal, failure to progress, and trouble swallowing), transient food impaction (spontaneous clearance), failure to thrive, and others, and in adolescents and adults, potential symptoms can include dysphagia, transient food impaction (spontaneous clearance), heartburn, and chest pain.[54,89] It is important to note that after esophageal dilation, symptoms of dysphagia and food impaction can no longer be reliably assessed as a determinant of disease activity.[90-93] The index also recognizes that symptoms

TABLE I. Eosinophilic Esophagitis Severity Index

To be assessed at initial diagnosis and then at each visit (with the recall being only between visits). The severity of EoE depends on an accurate diagnosis which includes an isolated esophageal eosinophilia with ≥15 eos/hpf and with other etiologies excluded. Select the box the patient fits for each row, and then calculate the number of points. For boxes with more than one element, each selected feature gets points.

Total Score: <1: Inactive EoE; 1-6: Mild Active EoE; 7-14: Moderate Active EoE; ≥15: Severe Active EoE

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy (*patient ≥18 years*)	● Food impaction with ER visit or endoscopy (*patient <18 years*) ● Hospitalization due to EoE	● Esophageal perforation ● Malnutrition with body mass <5th percentile or decreased growth trajectory ● Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15-60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations (*in an adult ≥18 years*); or any dilation (*in a child <18 years*)
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

Additional notes on the table:

- The table can be used at diagnosis, and then updated at each subsequent visit (with the recall being only between visits). If an endoscopy and biopsy have not been performed between visits, prior information can be carried forward, but assessing severity can be a prompt to determine whether a monitoring endoscopy is needed.
- Symptoms in adults can include dysphagia, transient food impaction (spontaneous clearance), heartburn, chest pain, etc.
- Symptoms in children can include abdominal pain, vomiting, heartburn/reflux, chest pain, unintentional weight loss, feeding difficulty (refusal, failure to progress, trouble swallowing, etc), failure to thrive, etc.
- After esophageal dilation in any patient, symptoms of dysphagia and food impaction cannot be reliably assessed.
- Examples of impact on or disruption of social function could include EoE-related missed work or school, fear of eating in a public setting, social isolation, etc.
- Endoscopic features are best assessed clinically with EREFS and can be divided into inflammatory (edema, exudates, furrows) and fibrostenotic (rings, stricture). The worst overall finding for the esophagus should be assessed; if a stricture is identified, the diameter should be estimated.
- The peak eosinophil count should be quantified in all cases for both diagnosis and to allow monitoring of eosinophil counts; additional histologic features should be assessed, particularly BZH, LPF, DEC, and SEA; if LP is not present, DEC/SEA can be used to predict LPF.

[a]See additional notes for guidance about symptoms and complications.
[b]Immunomodulatory medications can include biologics, azathioprine/6MP, or other immune-targeted treatments.
[c]The peak eosinophil count should be specifically quantitated both for diagnosis and to allow monitoring; however, this table uses thresholds and ranges.
[d]Seen with a 10-14 mm esophagus; esophageal diameter can be measured by balloon-sizing, dilation effect, barium esophagram, etc.

in both children and adults can disrupt social function in a variety of ways, including EoE-related missed work or school, fear of eating in a public setting, social isolation, and others.

As the index shows, complications of EoE were deemed to drive EoE severity assessment in many cases as well. These include food impaction prompting an emergency department visit or urgent/emergent endoscopy (with a higher point value assigned to impactions occurring in children), hospitalization due to EoE, esophageal perforation, and malnutrition (ie, <5th percentile body mass or decreasing growth trajectory in children). In addition, patients with EoE that is difficult to treat—defined as persistent symptoms and inflammation requiring an elemental diet, systemic corticosteroids, or immunomodulatory treatments (eg, biologics, azathioprine/6 mercaptopurine, or other immune-targeted modalities)—would be assigned the highest point total.

Inflammatory features

The use of the inflammatory features category that encompasses both endoscopic and histologic components is a conceptual change from assessing endoscopy and histology separately. The rationale for this approach is that it allows prompt and simultaneous analysis of disease features that reflect inflammation and those that represent disease complications of fibrostenosis when selecting treatments and assessing outcomes.[4,42,54]

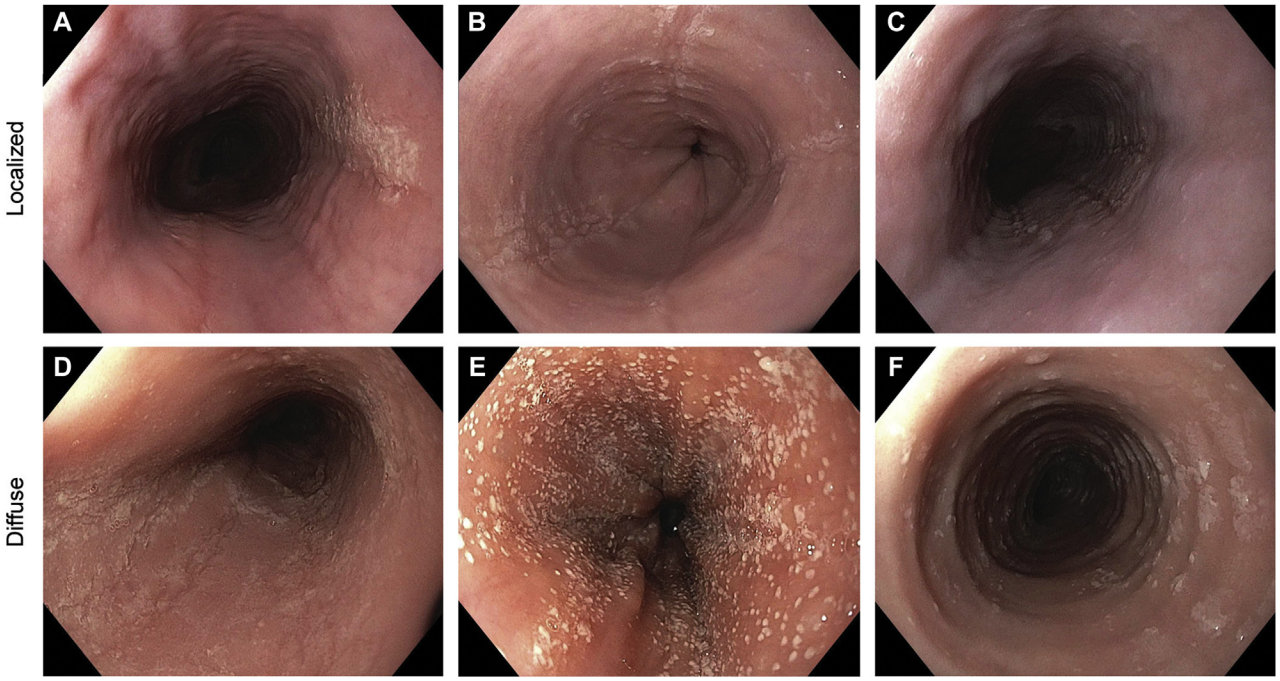

FIG 1. Inflammatory endoscopic findings. Examples of localized findings include (**A**) focal exudates in the proximal esophagus; (**B**) exudates, furrows, and edema in the distal esophagus; and (**C**) exudates, furrows, and edema in the mid esophagus. Examples of diffuse findings throughout the esophagus include (**D**) exudates, furrows, and edema; (**E**) marked exudates and edema; and (**F**) exudates and edema (also with the presence of rings).

When assessing endoscopic features in EoE, meeting participants agreed that these are best assessed with EREFS as the recommended standard of care. However, despite its value for standardizing reporting of endoscopic severity in both practice and clinical trials,[20,28-30,65,66,94,95] current data do not support using prespecified scores to determine severity.[96] Therefore, a somewhat abbreviated version of the EREFS should be used clinically to assess the endoscopic inflammatory features, defined as edema, furrows, and exudates. In addition, a determination of "localized" vs "diffuse" should be reported. Fig 1 provides examples of both localized and diffuse findings.

For the histologic features of inflammation, the *sine qua non* remains esophageal eosinophilia. Meeting participants strongly emphasized that the peak eosinophil count must be specifically quantified for diagnosis and at each follow-up biopsy. However, data consistently show that eosinophil counts alone only modestly correlate with symptoms, and may not strongly relate to other disease features.[31,40,97] For purposes of this index, it was important to show that esophageal eosinophilia ≥15 eos/hpf was required to define the presence of active EoE, although eosinophil counts alone were not felt to be a uniform driver of disease severity. This approach—for example, a patient with 100 eos/hpf may not be considered as having more severe disease than a patient with 20 eos/hpf on biopsy—may require a conceptual change for many patients and providers. Nevertheless, based on the traditional focus on eosinophil numbers, and that an eosinophil count of >60/hpf garners a maximum score in the EoEHSS, inflammatory eosinophilic activity was divided between 15-60 eos/hpf and >60 eos/hpf for this first iteration of the index.

For histologic findings of EoE, the EoEHSS has been developed, validated, and shown to be highly responsive in clinical trials, and may be a more robust indicator of treatment response than eosinophil count alone.[31,33,36,37] However, as a starting point for a clinical severity tool, it was felt that the best histologic reflection of remodeling and fibrosis was the presence of either BZH or LPF. Assessment of LPF can be hampered, however, because LP itself may not be obtained in a standard biopsy sample.[98] In the absence of LP, the presence of DECs and SEA should be used to predict LPF.[39,87] It is important to note that points given for DECs or SEA predict the presence, but not the severity, of fibrosis. In the future, both severity and persistence of fibrosis may turn out to have important prognostic and treatment implications, but additional data are required before these features are added to the index. Similar to the way in which EREFS should be used for all patients to assess endoscopy, a more routine reporting of BZH, LPF, and (when present) DECs and SEA will not only highlight the importance of searching for histologic findings beyond the eosinophil count, but will help to prompt use of the EoEHSS. A simple approach to assessing these findings, with example histology images, is shown in Fig 2.

Fibrostenotic features

The severity index separates out fibrostenotic features into a separate category for several reasons. First, these features often drive gross esophageal changes that can lead to symptoms of dysphagia and food impaction, particularly in adolescents and adults.[62,99] Second, EoE appears to progress to fibrostenosis in many, although not all, patients with EoE, as evidenced by increasing stricture rates with longer symptom duration before diagnosis in adults, longer durations without therapeutic response after diagnosis, and modification of the esophageal transcriptome from inflammatory to epithelial

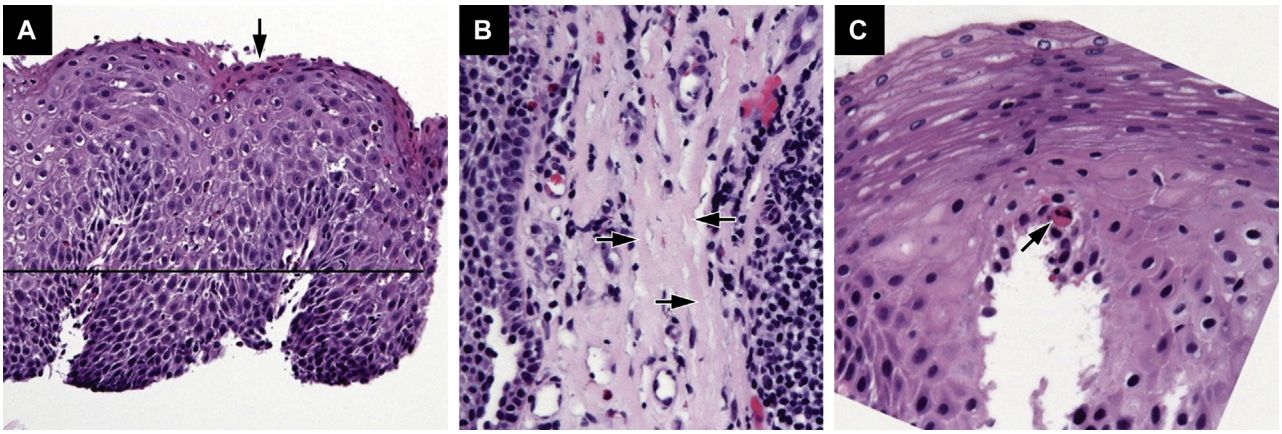

FIG 2. Representative pathologic findings of EoE pertinent for the severity index. The findings in *panels* **A, B,** and **C** can best be interpreted for use in the I-SEE histology sections by answering the following series of questions:
Question 1: Is basal zone hyperplasia exceeding one-third of total epithelial thickness (*bar* in *panel A*) present? __Yes __No.
Question 2: Is lamina propria present and not crushed (*arrows* in *panel B*)?
__Yes, go to question 3 and do not complete questions 4 and 5.
__No, do not complete question 3 and go to questions 4 and 5.
Question 3: Is any lamina propria fibrosis (*arrows* in *panel B*) present? __Yes __No.
Question 4: Is surface epithelial alteration (*arrow* in *panel A*), with or without admixed eosinophils, attached or partially/completely detached, present? __Yes __No.
Question 5: Are dyskeratotic epithelial cells (*arrow* in *panel C*) present? __Yes __No.

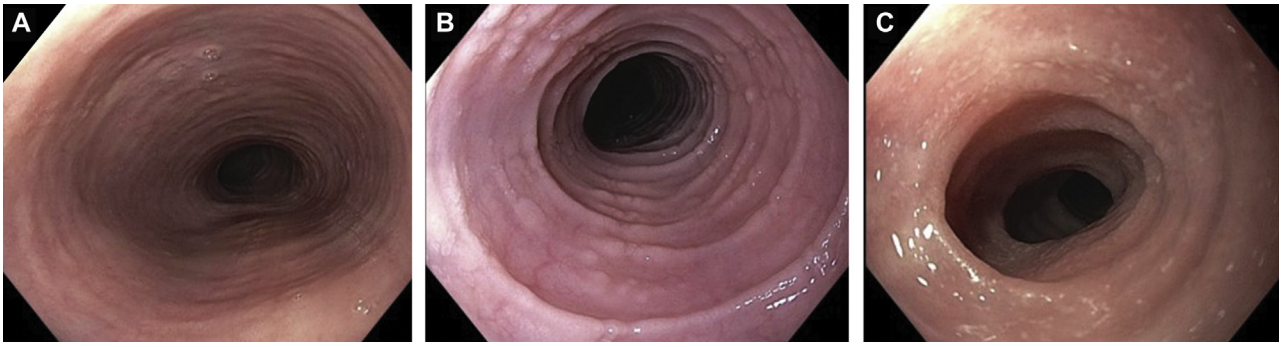

FIG 3. Fibrotic endoscopic findings. Examples include (**A**) mild rings where the endoscope passes easily, (**B**) prominent rings with some narrowing where dilation is required and the endoscope passes with a "snug fit," and (**C**) severe rings with a focal stricture that precludes passage of a standard upper endoscope.

differentiation pathways.[60,86,100-105] Third, because treating the inflammatory component of the disease alone may not adequately alleviate symptoms, it is important to recognize fibrostenosis and consider performing esophageal dilation in symptomatic patients.[106,107] Finally, an ultimate goal should be to diagnose and treat EoE early enough, such that patients neither develop nor progress to fibrostenosis.

On endoscopy, it was recommended to assess esophageal rings and strictures but not to include specific EREFS thresholds due to a lack of data regarding thresholds for severity and the reality that endoscopists do not frequently detect strictures or esophageal narrowing on endoscopy.[70,71] Therefore, the elements of severity were chosen to be objective and easy to recognize clinically. These elements should be based on the definitions presented related to endoscopic assessment and ability to pass an adult or pediatric endoscope. It was further noted that given the limitations of endoscopic measurement of esophageal stricture diameter, balloon-sizing, notation of the diameter where dilation effect is achieved, barium esophagram, or a functional lumen imaging probe measurement could be used for complementary information.[70,106,108,109] The most severe fibrostenosis would be denoted by inability to pass a standard upper endoscope (8-10 mm), repeated dilation in adults, or any dilation in a child. Fig 3 shows examples of fibrostenotic features.

Using the severity index: Examples

Several patient examples illustrate how the index could be applied (Table II). The first is a 12-year-old child with daily symptoms of abdominal pain, no listed complications, localized

TABLE II. Examples of Using the Severity Index

(A) A 12-year-old child with daily symptoms of abdominal pain, no listed complications, localized inflammatory endoscopic features, 45 eos/hpf, and no fibrostenotic features. The score is calculated by adding 2 points for symptoms, 1 point for inflammatory endoscopy features, and 1 point for inflammatory histology features, for a total of 4 points, which would be in the mild active range.

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy *(patient ≥18 years)*	● Food impaction with ER visit or endoscopy *(patient <18 years)* ● Hospitalization due to EoE	● Esophageal perforation ● Malnutrition with body mass <5th percentile or decreased growth trajectory ● Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15-60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations *(in an adult ≥18 years)*; or any dilation *(in a child <18 years)*
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

(B) A 32-year-old man with daily symptoms of dysphagia, two prior emergency department visits for food bolus impaction, diffuse exudates and edema on endoscopy, 35 eos/hpf and BZH on biopsy, and a severely narrowed/strictured esophagus that precluded passage of a standard endoscope. The score is calculated to be 2 + 2 + 2 + 1 + 15 + 2, for a total of 24, in the severe active range.

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy *(patient ≥18 years)*	● Food impaction with ER visit or endoscopy *(patient <18 years)* ● Hospitalization due to EoE	● Esophageal perforation ● Malnutrition with body mass <5th percentile or decreased growth trajectory ● Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15-60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations *(in an adult ≥18 years)*; or any dilation *(in a child <18 years)*
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

(Continued)

TABLE II. *(Continued)*

(C) A 17-year-old with symptoms of chest pain, heartburn, and dysphagia multiple times per day that have led to eating-related anxiety and social isolation, no listed complications, diffuse exudates, edema, and furrows on endoscopy, 100 eos/hpf, rings but the scope passes easily, and BZH and LPF on biopsy. The score is calculated to be 4 + 2 + 2 + 1+ 2 = 11, categorizing the patient as having moderately active EoE.

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy *(patient ≥18 years)*	● Food impaction with ER visit or endoscopy *(patient <18 years)* ● Hospitalization due to EoE	● Esophageal perforation ● Malnutrition with body mass <5th percentile or decreased growth trajectory ● Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15-60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations *(in an adult ≥18 years)*; or any dilation *(in a child <18 years)*
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

NOTE. The red highlighted boxes indicate the choice in each row that should be selected based on this patient's presentation and history, so that the severity score can be calculated correctly.
[a,b,c,d]See Table I for corresponding footnotes to the table.

inflammatory endoscopic features, 45 eos/hpf, and no fibrostenotic endoscopic features. Here the severity index score would be calculated by adding 2 points for symptoms, 1 point for inflammatory endoscopy features, and 1 point for inflammatory histology features, for a total score of 4 points, which would be in the mild active range.

The second example is a 32-year-old man with daily symptoms of dysphagia, 2 prior emergency department visits for food bolus impaction, diffuse exudates and edema on endoscopy, 35 eos/hpf and BZH on biopsy, and a severely narrowed/strictured esophagus that precluded passage of a standard endoscope. The assigned points here would be 2, 2, 2, 1, 15, and 2, for a total of 24, placing this patient in the severe active range.

The third example is a 17-year-old with symptoms of chest pain, heartburn, and dysphagia multiple times per day that have led to eating-related anxiety and social isolation, no listed complications, diffuse exudates, edema, and furrows on endoscopy, 100 eos/hpf, rings but the endoscope passes easily, and BZH and LPF on biopsy. The assigned points are 4, 2, 2, 1, and 2, for a total score of 11, categorizing the patient as having moderately active EoE.

FUTURE RESEARCH NEEDS AND RECOMMENDATIONS

It is important to note that this first version of the I-SEE will be refined in coming years. In the short term, the tool will require validation, endorsement, use, and real-world and clinical research data to determine how to best refine it (Table III). One aspect of this will be to ensure usability, with a goal of straightforward application at the point of care. It is important not to create confusion with a tool such as this, and we acknowledge that this initial iteration of the tool has inherent limitations that will be addressed going forward. Therefore, further refinements in the realm of symptoms will require clearer and more objective definitions of unintentional weight loss, a simplified symptom metric with a documented recall time, and means of differentiating activity from severity. Other objective tools may also be useful, for example, a video "feeding test" to grade the potential difficulty and adjustment with which patients with EoE consume foods and use of molecular profiling, such as a panel of esophageal transcripts with the EoE Diagnostic Panel.[45,110]

In addition, endoscopic refinement to the most salient findings of the EREFS and the use of a dichotomous tool for findings such as narrowing to simplify scoring should be studied in a prospective fashion as well. In the context of histology, activity vs severity and the notion of persistence of inflammatory and remodeling features also require further investigation, as does the potential simplification of the EoEHSS and examination of composite metrics, such as a physician global assessment. The longitudinal sensitivity of the severity index will need to be studied as well, along with

TABLE III. Future Research Directions

Category	Research questions
Symptoms	Consideration of the number of meals and consistencies of foods (eg, solid, liquid, and puree) eaten
	Recall time that is most accurate
	Acute vs chronic symptoms
	Severity of symptoms over time (days, weeks, months)
	Weight loss considerations and impact of therapy (eg, elimination diets)
	Impact of comorbid atopic conditions or peripheral blood eosinophilia
Endoscopy	Use of composite score for the whole esophagus rather than by segment
	Use of score (eg, narrowing "absent" or "present")
	Terminology: "narrowing" vs "fibrostenotic"
Histology	Relationship of subepithelial findings to endoscopic features
	Limiting to the simplest and most practical features reported on pathology reports
	Assessing the role of LPF, DECs, and SEA as diffuse or localized, as well as the longitudinal trajectory of these findings in the context of disease course
Global	Confirm usability at the point of care[a]
	Distill to the most salient symptom, endoscopic, and histologic features[a]
	Use of a physician global assessment tool for comparisons and validation purposes[a]
	Mixing of categories especially mild and moderate or moderate and severe
	Use of separate indexes for children and adults[a]
	Uses of the same or separate indexes for initial diagnosis vs follow-up[a]
	Addition of a component of response to therapy when considering severity[a]
	Relationship to endotypes and molecular features
	Relationship to functional assessments (EndoFLIP)
	Validation of the index in existing databases (clinical trials, prospective cohorts, retrospective cohorts)[a]
	Validation of the index in prospective studies (eg, real-world use and pragmatic trials)[a]
	Assessment of whether index use leads to changes in treatment or practice patterns[a]
	Assessment of whether severity classification affects long-term outcomes[a]
	Linking of the index to future quality metrics or increased uptake or EREFS or HSS[a]

FLIP, Functional luminal imaging probe; *HSS*, histologic severity score.
[a]Areas where further optimization and validation of the severity index are required.

the relationships between the subcomponents of endoscopy, histology, and symptoms. This may also yield information on weighting specific measures of these scoring systems. Lastly, launching the severity tool in a pragmatic, practical, and prospective manner that includes both academic and nonacademic clinical practices will be essential to determine how to link specific treatment and monitoring recommendations to disease severity. It is important to re-emphasize, however, that because the I-SEE has yet to be validated, extensive additional study will be needed to assess longitudinal use for monitoring and the relation to treatments, and to associate the categories of severity with treatment and monitoring. Ultimately, learning how this severity index correlates with patient outcomes, both more immediate and long-term outcomes will be critical.

SUMMARY AND CONCLUSIONS

Standardized metrics to assess disease severity are used routinely to guide management choices for diseases such as asthma, eczema, and pediatric inflammatory bowel disease. As EoE—a clinicopathologic diagnosis with a pathogenesis akin to other atopic diseases, including T2 immunity, antigens, and barrier disruption—becomes increasingly prevalent, the need for similarly simple, accessible indices for EoE severity is pressing. Although diagnostic criteria for EoE are generally agreed upon and used relatively uniformly, clinical practice parameters vary, and clinicians managing this disease still lack guidance regarding decisions to add or remove therapy based on systematic, standardized, and objective measures of severity.

With the I-SEE, a new severity index for use in adult and pediatric patients with EoE created by an international team of more than 30 experts in allergy, gastroenterology, and pathology, it is now possible to grade the severity of EoE using an array of clinicopathologic criteria (symptoms/complications, and inflammatory and fibrostenotic features on endoscopy and histology). Although all practitioners may not have access to each of the histologic parameters it assesses, the I-SEE metric can already guide conversations between clinicians and pathologists regarding features most salient for assessing EoE severity based on the current state of the literature. Future clinical trials and data from patients undergoing routine clinical care should also be used to assess this index's performance, including responsiveness to change as disease progresses, and to refine and update the index, with the goal of validating the index to increase its utilization and functionality. Ultimately, assessing, tracking, and managing disease activity based on severity could provide meaningful improvements in patient management, as well as align research and regulatory end points.

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Drs Khoury, Liacouras, and Atkins, contributed to manuscript drafting, critical revision, and final approval. Drs Bonis, Bredenoord, Feuerstadt, Geng, Genta, Hiremath, Jensen, Lucendo, McGowan, Moawad, Pesek, Peterson, Rothenberg, Schoepfer, and Straumann participated as conference faculty and provided critical revisions and final approval to the manuscript.

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Author names in bold designate shared co-first authorship.

APPENDIX

Meeting Co-Chairs

Evan S. Dellon, MD, MPH, Professor (Chair), University of North Carolina School of Medicine

Seema S. Aceves, MD, PhD, Professor, University of California San Diego, Rady Children's Hospital

Glenn T. Furuta, MD, Professor, University of Colorado School of Medicine, Children's Hospital Colorado

Session Chairs

EoE Symptom Severity: Paneez Khoury, MD, National Institute of Allergy and Infectious Diseases (NIAID) and Amanda B. Muir, MD, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia

EoE Endoscopic Severity: Chris A. Liacouras, MD, University of Pennsylvania Perelman School of Medicine, Children's Hospital of Philadelphia and Ekaterina Safroneeva, PhD, PD, University of Bern

EoE Histologic Severity: Dan Atkins, MD, University of Colorado School of Medicine, Children's Hospital Colorado and Margaret H. Collins, MD, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center

Presenters

Seema S. Aceves, MD, PhD, University of California San Diego, Rady Children's Hospital

Margaret H. Collins, MD, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center

Gary W. Falk, MD, MS, University of Pennsylvania Perelman School of Medicine

Nirmala P. Gonsalves, MD, Northwestern University-Feinberg School of Medicine

Ikuo Hirano, MD, Northwestern University-Feinberg School of Medicine

Mirna Chehade, MD, MPH, Icahn School of Medicine at Mount Sinai

Calies Menard-Katcher, MD, MSCs, University of Colorado School of Medicine, Children's Hospital Colorado

Dave A. Katzka, MD, Mayo Clinic

Jonathan M. Spergel, MD, PhD, University of Pennsylvania Perelman School of Medicine, Children's Hospital of Philadelphia

Working Group

Peter A. Bonis, MD, Tufts Medical Center

Albert J. Bredenoord, MD, PhD, Amsterdam University Medical Center

Paul Feuerstadt, MD, Physicians Alliance of Connecticut, Gastroenterology Center

Bob Geng, MD, University of California San Diego, Rady Children's Hospital

Robert M. Genta, MD, Baylor College of Medicine

Sandeep K. Gupta, MD, Indiana University School of Medicine/Community Health Network

Girish Hiremath, MD, MPH, Monroe Carell Jr. Children's Hospital at Vanderbilt

Elizabeth T. Jensen, PhD, Wake Forest School of Medicine

Alfredo J. Lucendo, MD, PhD, Hospital General de Tomelloso

Emily C. McGowan, MD, PhD, University of Virginia

Fouad J. Moawad, MD, Division of Gastroenterology, Scripps Clinic, La Jolla, CA

Robert D. Pesek, MD, Arkansas Children's Hospital, University of Arkansas for Medicine Sciences

Kathryn A. Peterson, MD, University of Utah Health

Marc E. Rothenberg, MD, PhD, Cincinnati Children's Hospital Medical Center, University of Cincinnati

Alain M. Schoepfer, MD, Centre Hospitalier Universitaire Vaudois and University of Lausanne

Alex Straumann, MD, University Hospital Zurich

Discussants

Wendy Book, MD, American Partnership for Eosinophilic Disorders

Patricia C. Fulkerson, MD, PhD, National Institute of Allergy and Infectious Diseases

Michael D. Kappelman, MD, MPH, University of North Carolina at Chapel Hill

Ellyn Kodroff, Campaign Urging Research for Eosinophilic Disease

Ryan Piansky, American Partnership for Eosinophilic Disorders

Lisa Wheatley, National Institute of Allergy and Infectious Diseases

Amy Zicarelli, Eosinophilic Family Coalition

Observers

Jessica Lee, US Food and Drug Administration

Erica Lyons, US Food and Drug Administration