A New Tool to Assess Disease Severity in Eosinophilic Esophagitis

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Abstract: The presentation of eosinophilic esophagitis (EoE) is heterogeneous with varied clinical, endoscopic, and histologic features impacting the severity of the condition. Until recently, however, and in contrast with many other conditions, there has been no standardized way to measure disease severity in EoE. A clinically applicable method for assessing severity in routine practice has been recognized as necessary to standardize assessment and management of EoE. Therefore, the American Gastroenterological Association has sponsored a consensus conference to determine elements of severity in EoE and develop the first tool to measure severity. This article presents details of this severity metric, which is known as the Index of Severity in EoE (I-SEE), and outlines the elements within I-SEE and how to categorize EoE as mild, moderate, severe, or inactive. The domains of I-SEE include symptoms and complications, inflammatory features (both endoscopic and histologic), and fibrostenotic features (both endoscopic and histologic). The article also provides an update on emerging data related to I-SEE and discusses the future studies necessary to implement I-SEE as part of a treatment framework in EoE.

Keywords
Eosinophilic esophagitis, severity, outcomes, treatment, monitoring, clinical tool

Although defined as a clinicopathologic disease with symptoms of esophageal dysfunction and an esophageal eosinophilic infiltration, eosinophilic esophagitis (EoE) is a heterogeneous condition.[1] Symptoms, endoscopic features, and distribution of histologic findings vary from patient to patient.[2] Duration of disease prior to diagnosis, as well as control of disease after diagnosis, impacts clinical phenotype.[3-7] Treatment responses vary in certain populations, and a subset of patients are treatment refractory.[8-12] Taken together, all of these features can impact the overall severity of EoE in practice. Until recently, however, there has been no standardized way to measure disease severity in EoE. In many other conditions, but particularly of note for asthma,[13] measuring clinical severity is standardized, linked to treatment and monitoring recommendations, and associated with outcomes. Because a clinically applicable method for assessing severity in routine practice was needed to begin standardization of management of EoE, the American Gastroenterological Association (AGA) sponsored a consensus

conference to bring experts and stakeholders together to discuss elements of severity in EoE and develop the first tool to measure severity (https://eoe.gastro.org/). This article presents details from the development of this severity metric, which is known as the Index of Severity in EoE (I-SEE)[14]; outlines the elements in I-SEE and how to categorize EoE severity as mild, moderate, severe, or inactive; provides an update on the applications of I-SEE to date in existing databases; and discusses what future studies will be needed to implement I-SEE as part of a treatment framework in EoE.

Development of the Index of Severity in Eosinophilic Esophagitis

Thirty-two faculty members across several disciplines (gastroenterology, allergy/immunology, pathology, epidemiology), with both adult and pediatric providers represented, participated in the development process and ultimate consensus conference, along with 9 stakeholders (patient advocacy group representatives, National Institutes of Health representatives, US Food and Drug Administration representatives [with the last group present as observers only]). As outlined in the resulting publication summarizing the meeting,[14] there were 4 major goals of the endeavor: (1) determine key elements of disease severity in EoE; (2) assess how to measure disease severity in the clinical setting; (3) align stakeholders; and (4) determine a future research agenda. To accomplish these goals, severity metrics in other atopic and gastroenterology diseases were reviewed, and elements of severity in EoE were discussed and divided into topics of symptoms, endoscopy, and histology. Ultimately, a framework for severity was adopted with 3 major domains: symptoms and complications, inflammatory features, and fibrostenotic features. Specific endoscopic and histologic findings were divided among the inflammatory and fibrostenotic domains in order to emphasize that these were 2 critical aspects of the disease that need to be considered clinically. In addition, although there are validated tools to quantify symptoms,[15-17] endoscopic severity,[18-21] and histologic severity in EoE,[22,23] many of these were developed for registration clinical trials[24] and were not thought to be feasible for implementation in a practice setting. Therefore, elements of severity that were either readily available or thought to be important enough to be determined on a routine clinical basis were included.

The elements of I-SEE, as well as the scoring paradigm, are presented in the Table. Use of I-SEE is predicated on an accurate diagnosis of EoE, as per consensus guidelines,[1] and requires collaboration among gastroenterologists (for carefully assessing the extent of endoscopic features, ideally with the EoE Endoscopic Reference Score [EREFS]), pathologists (for quantifying peak eosinophil counts and assessing for associated histologic epithelial changes, including basal zone hyperplasia and lamina propria fibrosis), and other clinical providers (for accurately assessing symptom frequency and complications). The initial goal was to have one metric for patients of all ages, recognizing that the elements of severity could differ between children and adults. In addition, some features on their own were thought to be so prominent (ie, an esophageal perforation or malnutrition) that having that single feature present would be enough to merit a severe categorization.

Symptoms are assessed by frequency, either none, weekly, daily, multiple times per day, or symptoms severe enough to disrupt social functioning. Notably, the types of symptoms experienced are not specified, and because the provider completes the assessment, the symptom component is not a patient-reported outcome metric. Complications in I-SEE include food impaction requiring an emergency department visit or urgent endoscopy, hospitalization owing to EoE, esophageal perforation, malnutrition, or disease refractory to first-line treatments (proton pump inhibitors, topical corticosteroids, empiric diet elimination) that requires elemental formulation, systemic corticosteroids, or immunomodulatory (including biologic) treatments.

The inflammatory features are divided into endoscopic and histologic components. On endoscopy, the inflammatory EREFS features,[18] edema, exudates, and furrows, should be assessed and whether these features are localized or diffuse should be recorded in the tool. On histology, the peak esophageal eosinophil count is the metric of interest. However, this count was not thought to correlate with overall severity. For example, a patient with 300 eosinophils per high-power field (eos/hpf) is not 6 times more severe than a patient with 50 eos/hpf. Therefore, the peak counts are categorized as fewer than 15, 15 to 60, or greater than 60 eos/hpf, with the highest category echoing the worst inflammatory ranking in the EoE Histologic Scoring System.[22]

The fibrostenotic features are also divided into endoscopic and histologic components. The endoscopic features are esophageal rings and strictures and also incorporate a subjective determination of esophageal caliber. Rings and strictures can be present but the endoscope passes easily; there can be a snug fit as the endoscope passes (indicating narrowing) or dilation is required; or the endoscope cannot pass or repeated dilations are needed. Of note, dilations in children younger than 18 years of age are deemed more severe (and receive more points) than dilations in adults. On histology, basal zone hyperplasia and lamina propria fibrosis are assessed. Recently, a Web-based prediction tool was developed for

Table. Components and Scoring for I-SEE

Clinical features of severity	Points assigned
Symptoms and complications	
Symptoms	
None	0
Weekly	1
Daily	2
Multiple times per day or disrupting social functioning	4
Complications	
None	0
Food impaction with emergency department visit or endoscopy (patient ≥18 years)	2
Food impaction with emergency department visit or endoscopy (patient <18 years)	4
Hospitalization due to EoE	4
Esophageal perforation	15
Malnutrition with body mass index <5th percentile or decreased growth trajectory	15
Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory treatments	15
Inflammatory features	
Endoscopy (edema, furrows, and/or exudates)	
None	0
Localized	1
Diffuse	2
Histology	
<15 eos/hpf	0
15-60 eos/hpf	1
>60 eos/hpf	2
Fibrostenotic features	
Endoscopy (rings, strictures)	
None	0
Present, but endoscope passes easily	1
Present, but requires dilation or a snug fit when passing a standard endoscope	2
Cannot pass standard upper endoscope, repeated dilations in an adult ≥18 years, or any dilation in a child <18 years	15
Histology	
None	0
Basal zone hyperplasia or lamina propria fibrosis (or dyskeratotic epithelial cells/ surface epithelial alterations if no lamina propria)	2
Category	**Total score**
Inactive	<1
Mild	1-6
Moderate	7-14
Severe	≥15

EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; I-SEE, Index of Severity in EoE.

lamina propria fibrosis when lamina propria tissue is not obtained in biopsies (which often occurs in the majority of samples).[25] In these cases, the findings of surface epithelial alterations and dyskeratotic epithelial cells can predict the presence of lamina propria fibrosis with a high degree of accuracy.[25,26]

Scores are calculated by finding the point value assigned to each element selected in the severity index and adding each (noting that patients may have multiple complications with each one scored). Scores of less than 1, 1 to 6, 7 to 14, and 15 or greater are assigned to the categories of inactive, mild, moderate, and severe disease activity, respectively. In the following example, a 23-year-old woman who experiences dysphagia on a weekly basis presents to the emergency department with a food bolus impaction requiring an urgent endoscopy. She is found to have exudates, edema, and furrows diffusely through the esophagus; a peak eosinophil count of 55 eos/hpf; a snug fit with passage of the upper endoscope but no dilation required as of yet; and other histologic findings of basal zone hyperplasia and lamina propria fibrosis. She would receive I-SEE values of 1, 2, 2, 1, 2, and 2, respectively, for a total score of 10 and a severity category of moderate at the time of her diagnosis.

Applications of the Index of Severity in Eosinophilic Esophagitis

The first application of I-SEE was as a secondary analysis of a randomized clinical trial conducted at the University of North Carolina comparing the efficacy of budesonide vs fluticasone after 8 weeks of treatment in a primarily adult EoE population.[27] Data elements from the trial, supplemented by chart review, were used to calculate I-SEE.[28] There were several notable findings in the 111 patients analyzed. First, I-SEE was readily calculated, and once data were available, it took less than 1 minute to calculate a score for each patient. Second, several baseline (pretreatment) clinical features correlated with EoE severity as measured by I-SEE, even though these features were not explicitly included in the index. For example, an increasing severity category was associated with lower body mass index, longer symptom duration prior to diagnosis, more frequent food allergies, higher EREFS, smaller esophageal caliber, and more lamina propria fibrosis. Interestingly, peak eosinophil count was not associated with severity. Third, severity improved with EoE treatment. At baseline, 18%, 68%, and 14% of patients were mild, moderate, and severe, respectively, and this improved posttreatment to 14% being inactive, 71% mild, 8% moderate, and 7% severe. The changes were more pronounced in histologic responders (<15 eos/hpf) compared with nonresponders. Although baseline severity did not predict treatment outcome, more severe patients were more likely to need dilation (or repeat dilation) on their follow-up endoscopy. These data showed that I-SEE was feasible, that the elements included from the expert consensus tracked with elements of clinical severity, and that the score and severity category were responsive to successful treatment, indicating that I-SEE could potentially be used over time to measure treatment effect.

The second application of I-SEE was a retrospective cohort study of children followed at the University of California San Diego Rady Children's Hospital.[29] In this study, 67 children were followed for a median of 6.6 years, and I-SEE was calculated at their first clinical instance (eg, at diagnosis), their next instance (after their initial treatment), and their last instance in the system; some children had more than 10 instances of care assessment recorded over the study time frame. There were notable findings in this study as well. First, I-SEE could again be calculated from the database and medical record elements available, although symptom frequency was difficult to determine in some cases. Second, severity category improved over time as children were treated. For example, at the first instance, 43% of patients were mild, 36% moderate, and 21% severe, but this had improved by the last instance to 22% inactive, 66% mild, 6% moderate, and 6% severe. Third, the average severity scores in the children in this study tended to be similar to the scores calculated in the prior adult study (9.7 ± 7.2 in children vs 10.9 ± 7.4 in adults), but the drivers of severity were different. Severity in children was driven by malnutrition, whereas severity in adults was driven by fibrostenotic complications and need for esophageal dilation. In addition, it was interesting to note the time frame of improvement of different elements of severity in children, with inflammatory endoscopic and histologic features improving by the first follow-up, but the complication of malnutrition and associated normalization of body mass index not improving until later in the treatment time course. These data confirmed the utility of I-SEE in a pediatric population and replicated the response to therapy data seen in the adult study, again lending credence to the consensus process during which the tool was developed.

Eosinophilic Esophagitis Severity in the Future

Although the development and initial use of I-SEE is an exciting milestone for the field, there are additional steps that are required and areas of research that must be conducted (some of which are underway) before I-SEE can be used to the same clinical effect as asthma severity and management guidelines.[14] First, I-SEE must continue to be tested in existing data sources, including prospective

cohort studies and completed clinical trials. Second, the AGA is leading an effort to develop an I-SEE app that will ultimately be rolled out to adult and pediatric providers across allergy and gastroenterology practices for field testing. This will give the first sense of usability in real time with routinely collected clinical data and will provide information about which of the data elements are expected to be found easily and where practice needs to change to report these data elements. Indeed, some specific elements in I-SEE were included (eg, quantification of eosinophil counts, reporting of EREFS findings, reporting of select histologic findings in addition to eosinophil counts) to purposefully try to push the field forward,[14] as these elements have been linked to important clinical outcomes and optimal clinical practice.[30-35] Subsequently, prospective studies of I-SEE must be conducted to link severity to clinical outcomes in order to achieve the ultimate goal of linking severity to treatment and monitoring recommendations to standardize and improve treatment algorithms and patient follow-up.[35-37]

Other issues may also need to be addressed in future I-SEE refinements. For example, the best recall time between uses is not known, so currently the recall is recommended for between visits. In addition, there is a subtle distinction between severity and activity that is not currently recognized by I-SEE. Severity is often intrinsic to the disease (ie, unchanging), whereas activity may change with disease control. For example, a patient who presents with an esophageal perforation complicating a food bolus impaction in the setting of a stricture has severe EoE, but he or she may be able to be successfully treated and have no current disease activity. A related point is that depending on the frequency of I-SEE assessments in a given patient, there may not be enough time for complications to develop. This was generally the case in the 8-week treatment study where I-SEE was first applied.[28] Therefore, that study had a subanalysis of an activity score (essentially the I-SEE minus the complication domain) that performed similarly well to the overall score. Finally, additional studies in children will be needed to confirm that the same tool and same scoring system can be used in all patients regardless of age, although the first pediatric study suggests this will be possible.[29]

Conclusion

The I-SEE has been developed and is now available for use in clinical practice at the point of care to assess severity in patients with EoE. It can provide an answer to patients asking their doctor how bad their EoE is compared with other patients, and also help the practitioner quantify what might be a previously vague concept of severity in this disease. Moreover, I-SEE will hopefully push practice patterns forward according to guideline recommendations, including for quantifying peak eosinophil counts in esophageal biopsies, using EREFS during a careful and purposeful examination to assess endoscopic features, and considering histologic features of disease activity apart from simply the eosinophil count. In the long term, I-SEE implementation will hopefully help to achieve the goal of standardizing patient assessment, treatments, and monitoring paradigms, and ultimately improve outcomes for patients with EoE.

Disclosures

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