

Clinical Communications

Integration of a clinical scoring system in the management of eosinophilic esophagitis

Punita Ponda, MD^{a,*}, Charmi Patel, MD^{a,*},
Seungjun Ahn, MS^b, Tung Ming Leung, PhD^b, and
Toni Webster, DO, MSc^c

Clinical Implications

- A simple tool to help distinguish eosinophilic esophagitis (EoE) likely to respond, from EoE unlikely to respond to proton pump inhibitors (PPIs), is potentially very useful. This article proposes consideration of a score (Mulder Adapted Scoring System) using demographic, clinical, and endoscopic findings, when determining PPI treatment recommendations.

TO THE EDITOR:

Eosinophilic esophagitis (EoE) is defined to be a chronic disease presenting with esophageal dysfunction and pathognomonic histologic findings of eosinophil predominant inflammation while excluding other causes of esophageal eosinophilia.¹ Although a proton pump inhibitor (PPI) trial is no longer required for diagnosis, a large subgroup (33% to 61%) responds to PPI treatment.^{2,3} All patients with EoE should be considered for treatment with PPIs because of their possible anti-inflammatory effects, separate from their acid-blocking properties, and demonstration of clinical improvement in specific subgroups of patients.¹⁻³ However, the exact mechanism, choice of PPI, dosing, and differences in pediatric and adult populations have to be elucidated.²

Although various scoring systems are described, most have used individual clinical, endoscopic, or histologic criteria, with variable success.^{4,5} Mulder et al⁶ described a scoring system incorporating 6 differentially weighted characteristics (gender, dysphagia, pain/heartburn, history of food impaction, furrowing, and white papules) that discriminated EoE from gastroesophageal reflux disease in an age-matched cohort including a small pediatric population. We hypothesized that a Mulder Adapted Scoring System (MASS) (Table I), applied after the first diagnostic esophagogastroduodenoscopy (EGD) showing 15 or more eosinophils, could be used to differentiate PPI nonresponsive EoE from PPI responsive EoE in pediatric patients.

We conducted a retrospective chart review using the International Classification of Diseases (ICD) 9 and ICD10 codes for EoE (530.13 and K20.0, respectively) that identified 298 patients seen in the Divisions of Pediatric Gastroenterology and Allergy and Immunology from 2013 to 2018 in a large academic center (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). A total of 118 patients met the inclusion criteria for EoE, defined by demonstrating 15 or more eosinophils per high-power field (HPF) on initial endoscopy,

TABLE I. Scoring system adapted from Mulder et al⁶ (MASS)

Variable	Score
Sex	
Male	+26
Clinical symptoms	
Dysphagia	+31
Absence of pain/heartburn	+41
History of food impaction	+74
Endoscopy findings	
Furrowing	+93
White papules/exudates	+100
Maximum total score	365

Weighted demographic, clinical, and endoscopic scoring system originally presented by Mulder et al.

MASS, Mulder Adapted Scoring System.

without other causes of esophageal eosinophilia, who were evaluated with a repeat EGD after high-dose PPI treatment (see footnote on Figure 1 for criteria of high dose). The primary objective was to identify pediatric subjects, using the MASS score, who failed a high-dose PPI trial. Predictor and baseline variables at the time of initial EGD included age, gender, history of dysphagia, pain/heartburn, or food impaction and endoscopy findings of furrowing or white papules/plaques. PPI response was defined as histology showing less than 15 eosinophils/HPF on repeat biopsy after high-dose PPI treatment for a minimum of 6 weeks. Type of PPI used was also noted.

A crude comparison of each predictor variable of PPI response was performed using univariable logistic regression (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Subsequently, a multivariable logistic regression model with a backward selection procedure was carried out, with the variable entry criterion of $P < .25$ and the variable retention criterion of $P < .10$ (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic discrimination (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Youden's index was used to determine a cutoff total score predicting lack of response to PPIs. Results were considered statistically significant if $P < .05$. Analysis was conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

The patient ages ranged from 6 months to 17 years, 76% were male, and 45.8% responded to high-dose PPIs (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Most patients were treated with omeprazole (52%) or lansoprazole (40%) at high dose. The PPI response rate (45.8%) is consistent with findings in the literature.

The main effect of total score ($P < .0001$) was significantly associated with lack of response to PPIs (odds ratio [OR]: 1.018, 95% confidence interval [CI]: 1.011, 1.025). The maximum possible total score of MASS is 365. Based on Youden's index value of 0.509, a cutoff value for total score predicting a lack of

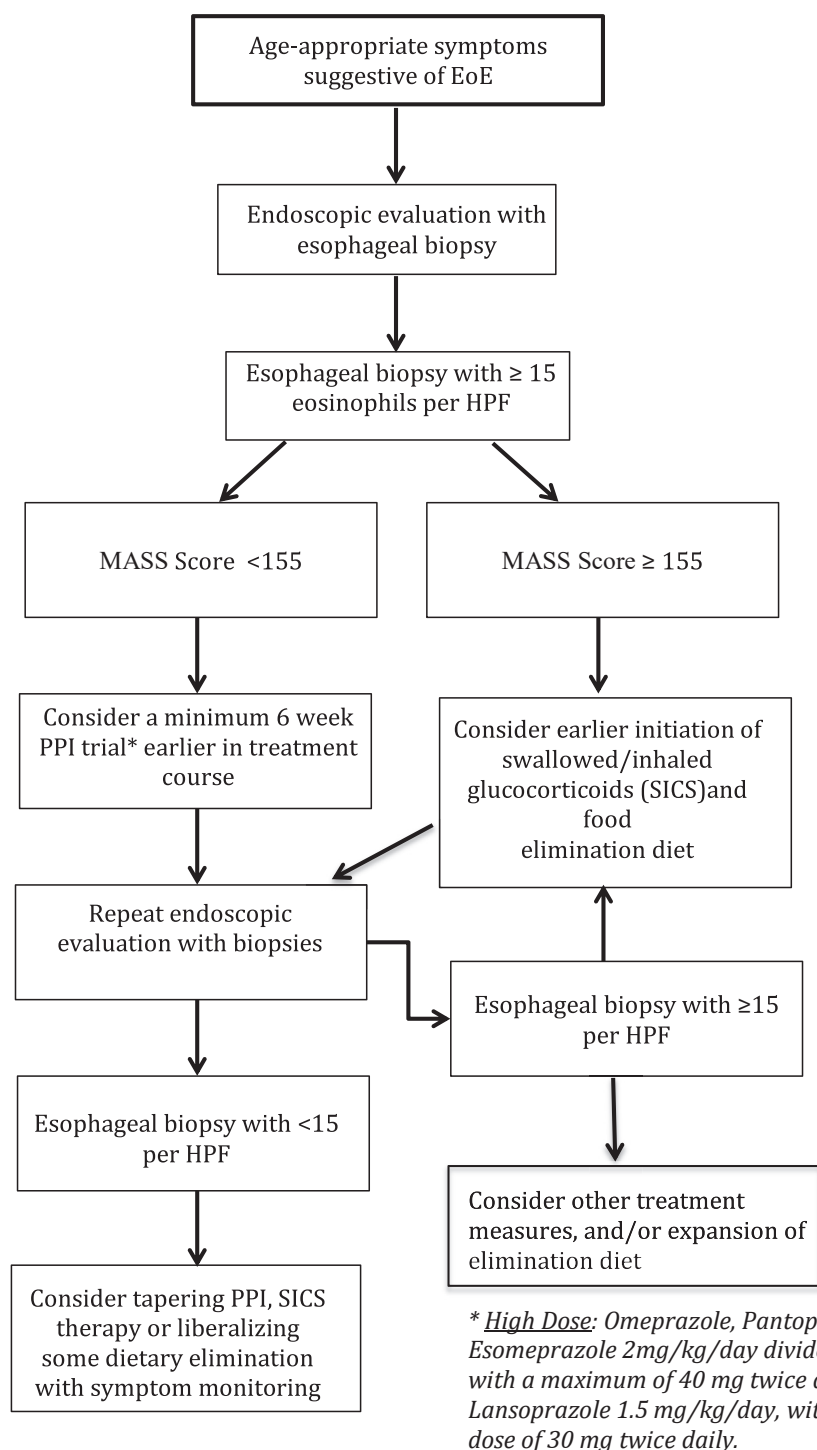


FIGURE 1. Proposed EoE management algorithm. Suggested algorithm for management of EoE, based on MASS score. *EoE*, Eosinophilic esophagitis; *HPF*, high-power-field; *MASS*, Mulder Adapted Scoring System; *PPI*, proton pump inhibitor.

PPI response was 155, with 75.0% (95% CI: 62.6%, 85%) sensitivity and 75.9% (95% CI: 62.4%, 86.5%) specificity. For every 10-unit increase in total score, the odds of not having a PPI response increased by 19.3%. The area under the curve of total score was 0.810 (95% CI: 0.732, 0.888), and the χ^2 test for the ROC curve was statistically significant ($P < .0001$) (Figure E2,

available in this article's Online Repository at www.jaci-inpractice.org). In addition, the positive predictive value (PPV) was 78.7% (95% CI: 66.3%, 88.1%) and the negative predictive value (NPV) was 71.9% (95% CI: 58.5%, 83.0%). The type of PPI used ($P < .486$) was not significantly associated with the PPI response. There was no significant qualitative difference in these

results when only patients ≥ 5 years of age were included in the analysis.

Based on the univariate logistic regression analysis with significance at $P < .05$, patients with pain/heartburn (OR: 0.364, 95% CI: 0.171, 0.776, $P = .0089$) were less likely to have MASS > 155 , and patients with dysphagia (OR: 4.8, 95% CI: 1.787, 12.893, $P = .0019$), furrowing (OR: 5.5, 95% CI: 2.496, 12.238, $P < .0001$), or white papules (OR: 3.1, 95% CI: 1.377, 6.927, $P = .0062$) were more likely to have MASS > 155 (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Based on the results of multivariable logistic regression analysis after backward elimination where $P < .10$ were considered significant, patients without pain/heartburn (OR: 2.358, 95% CI: 0.988, 5.618, $P = .0532$), with dysphagia (OR: 3.153, 95% CI: 1.036, 9.597, $P = .0432$), with furrowing (OR: 5.445, 95% CI: 2.232, 13.282, $P = .0002$), or with white papules/plaques (OR: 3.773, 95% CI: 1.451, 9.812, $P = .0065$) were significantly more likely to have MASS scores above 155 (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). These results are not surprising given that the MASS score assigns greater weight to those features.

Although the MASS has fair sensitivity and specificity at a cutoff of 155, with the NPV of 71.9% and the PPV of 78.7%, this can be improved with higher scores. For example, the MASS of 195 was 94% specific (CI: 84.6%, 98.8%) with the PPV of 88.9% for a lack of response to PPIs, and thus may be useful when determining initial clinical management regarding a PPI trial, swallowed inhaled corticosteroids, or food elimination.

This scoring system may allow for earlier phenotyping of EoE to improve effective targeted management strategies. The 2018 Consensus Guidelines have stated that future directions should include determination of predictors of PPI response.³ Other EoE symptom scores for assessing disease activity have been validated, but they have mainly been studied in older children or adults. Although those scoring methods have found a similar PPI response rate to our cohort, our use of MASS score is novel because no studies in the past have used a weighted combination of demographic, clinical, and endoscopic features to predict PPI response in children only.^{4,7} Although the Pediatric Eosinophilic Esophagitis Scoring System has been validated, it requires a parent proxy, and does not use demographic or endoscopic findings and has not been shown to predict treatment response. Furthermore, although the original findings by Mulder only differentiated between gastroesophageal reflux (< 15 eosinophils/HPF) and EoE (> 15 eosinophils/HPF) in a mixed cohort from pathology records, MASS scores have been used here to predict likelihood of PPI response specifically in children with EoE seen in a clinical setting.

In addition, although it is generally thought that PPI responsive and PPI nonresponsive EoE are indistinguishable at baseline when individual gene expression is studied, there is some weak/preliminary evidence that there may be a subset of genes that are differentially expressed between the two.^{8,9} This is an area of active study. Thus, we cautiously propose consideration of a methodical approach for EoE management in children that integrates this scoring system (Figure 1). However, there are many other reasons to consider when initiating treatment with PPIs. Besides known risks of using PPIs, there is evidence that PPI response may be transient

(affected by seasonality, medication compliance/adherence, changes in diet, or new allergen exposure), and that PPIs may have varying efficacy in subgroups of patients.² Thus, we suggest that this approach should only be used when keeping other aspects supporting and discouraging use of PPI treatment in mind.

The current study's limitations include a small sample size and retrospective design in a single center. We were also limited by the variability of treatment (type of PPI, although this did not show a significant effect in the cohort), and the fact that final response to diet, or steroids, was not studied. Furthermore, the MASS score cutoff proposed is based on the current data, and would have to be studied in other patients from a similar population. All of these limitations can be addressed with a future larger, randomized, prospective, multicenter study using this tool to guide treatment strategy.

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^aDivision of Allergy and Immunology, Department of Pediatrics, Cohen Children's Medical Center, Donald Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY

^bBiostatistics Unit, Feinstein Institute for Medical Research, Great Neck, NY

^cDivision of Pediatric Gastroenterology, Cohen Children's Medical Center, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY

*Co-first authors.

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Corresponding author: Punita Ponda, MD, Northwell Health Division of Allergy and Immunology, 865 Northern Boulevard, Suite 101, Great Neck, NY 11021. E-mail: pponda@northwell.edu.

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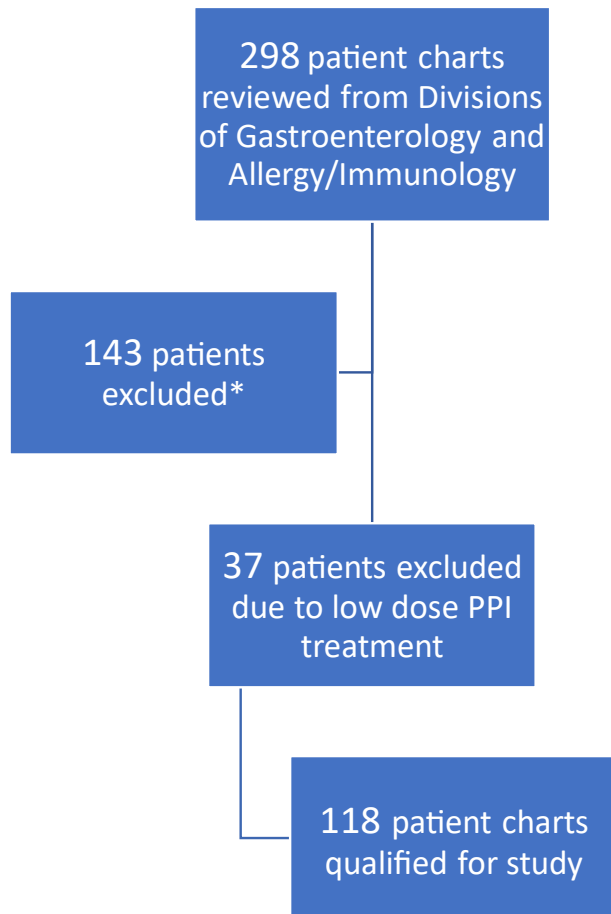


FIGURE E1. Chart review flowsheet. Flowsheet of the study methodology/review. *Incomplete data such that inclusion criteria were not met: no repeat EGD, unavailable initial EGD findings or histology, illegible information, lost to follow-up, or other causes of esophageal eosinophilia. *EGD*, Esophagogastroduodenoscopy; *PPI*, proton pump inhibitor.

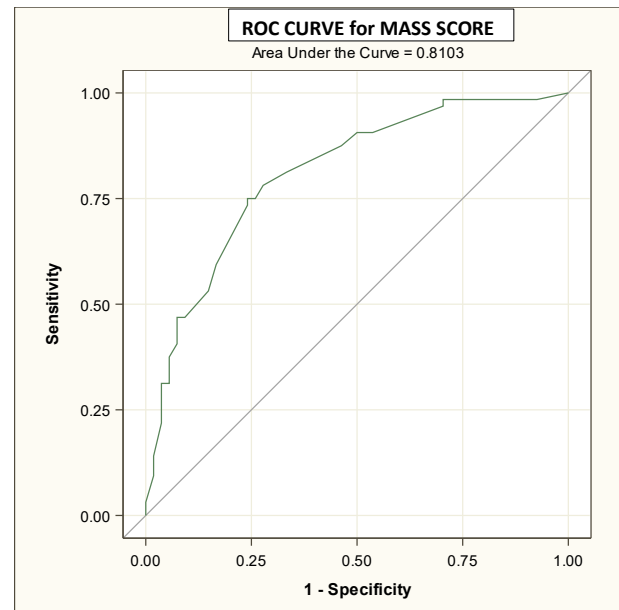


FIGURE E2. ROC curve using the MASS score for all patients. *MASS*, Mulder Adapted Scoring System; *ROC*, receiver operating characteristic.

TABLE E1. Results of univariable logistic regression analysis

Variable	OR	95% CI of OR	P value
Age at service	1.026	0.950-1.108	.5123
Gender			.4589
Male	1.374	0.593-3.182	
Female	†	†	
Dysphagia			.0019*
Yes	4.800	1.787-12.893	
No	†	†	
Pain or heartburn			.0089*
Yes	0.364	0.171-0.776	
No	†	†	
Impaction			.0845
Yes	6.509	0.775-54.683	
No	†	†	
Furrowing			<.0001*
Yes	5.526	2.496-12.238	
No	†	†	
White papules			.0062*
Yes	3.088	1.377-6.927	
No	†	†	
Type of PPI			.4861
Lansoprazole	1.839	0.851-3.975	.1213
Esomeprazole	1.471	0.303-7.136	.6317
Pantoprazole	1.103	0.066-18.457	.9454
Omeprazole	†	†	

CI, Confidence interval; OR, odds ratio; *PPI*, proton pump inhibitor.

*Statistically significant when $P < .05$.

†Reference group for all comparisons.

TABLE E2. Results of multivariable logistic regression analysis after backward elimination

Variable	OR	95% CI of OR	P value
Dysphagia			.0432*
Yes	3.153	1.036-9.597	
No	†	†	
Heartburn			.0532*
Yes	0.424	0.178-1.012	
No	†	†	
Furrowing			.0002*
Yes	5.445	2.232-13.282	
No	†	†	
White papules			.0065*
Yes	3.773	1.451-9.812	
No	†	†	

CI, Confidence interval; OR, odds ratio.

*Statistically significant when $P < .10$.

†Reference group for all comparisons.

TABLE E3. Cohort characteristics*

N = 118	Mean ± SD (median)
Age (y)	8 ± 4.8 (8)
PPI response rate (%)	45.8
MASS total score	145 ± 83.0 (160)
MASS for PPI responsive	98 ± 67.5 (96)
MASS for PPI nonresponsive	185 ± 73.3 (167)

MASS, Mulder Adapted Scoring System; PPI, proton pump inhibitor; SD, standard deviation.

*Description of study population and primary results: patient age at initial EGD, PPI response rate, MASS scores in PPI responsive and nonresponsive subgroups.