

Original Article

Age-based Differences in the Diagnosis and Management of Esophageal Eosinophilia

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What is already known about this topic? The criteria for the diagnosis and evaluation of esophageal eosinophilia and eosinophilic esophagitis continue to evolve. Diagnostic criteria do not differ by age, nor does the decision to initiate treatment or seek allergy involvement.

What does this article add to our knowledge? Irrespective of consensus guideline recommendations and the use of a proton-pump inhibitor trial, in symptomatic patients with esophageal eosinophilia, patient age had significance influence regarding allergy referral, steroid treatment, and repeated endoscopy for disease monitoring.

How does this study impact current management guidelines? Of a referral center population of patients with esophageal eosinophilia, numerous age-based differences in care existed regarding the management of symptomatic patients, although consensus guidelines do not specify different pathways of care based on age.

BACKGROUND: Eosinophilic esophagitis (EoE) is hallmarked by esophageal eosinophilia, >15 eosinophils(eos)/high-powered field (hpf), unresponsive to acid inhibition, and varied symptomatology. EoE consensus guidelines do not discriminate based on age for initiating treatment.

OBJECTIVE: To evaluate if age-related differences exist in managing esophageal eosinophilia and EoE within a university population.

METHODS: In a retrospective cohort study from a referral center, the medical records of 426 pediatric and adult patients with at least 1 presenting symptom of esophagitis, reflux, or upper gastrointestinal dysfunction, who underwent esophageal biopsy between 2009 and 2011 were analyzed for age-based differences in care in diagnosing and managing esophageal eosinophilia.

RESULTS: For these patients, 79.6% (336/426) had ≥ 15 eos/hpf in biopsy specimens, which was not associated with age. Significantly fewer adults than children with ≥ 15 eos/hpf were diagnosed with EoE ($P < .001$), referred for allergy evaluation ($P < .001$), started on swallowed steroid therapy ($P < .001$), or underwent repeated biopsy ($P < .001$). Increasing age, atopy, and increasing biopsy peak eos count moderated these effects, but the adjusted predicted probabilities for these outcomes were significantly lower among adults. Restriction for an 8-week prebiopsy proton-pump inhibitor trial did not alter the age-based relationships for an allergy referral or repeated biopsy. **CONCLUSIONS:** Numerous age-based differences in the management of symptomatic patients with esophageal eosinophilia existed in this cohort. Adults were significantly less likely than children to receive a clinical diagnosis of EoE, allergy referral, or steroid treatment, or to have a repeated biopsy. Even

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Abbreviations used

BMI- Body mass index
 EoE- Eosinophilic esophagitis
 eos- Eosinophil
 GERD- Gastroesophageal reflux disease
 GI- Gastrointestinal
 hpf- High-powered field
 OR- Odds ratio
 PPI- Proton-pump inhibitor
 REE- Responsive esophageal eosinophilia
 TIGER- The International Gastrointestinal Research Group

when stratified for an 8-week prebiopsy proton-pump inhibitor trial, advancing age was associated with lower odds of referral or repeated biopsy. Further study is necessary to better understand why discrepancies exist and their potential ramifications. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

Key words: Eosinophilic esophagitis; Eosinophil; Health disparities; Care pathways; Swallowed steroid therapy; Esophagogastroduodenoscopy; Allergy; TIGER; GERD; Dysphagia; Age; Children; Adults; Biopsy; Dilation; Dietary therapy; Esophageal biopsy

Eosinophilic esophagitis (EoE) is a distinct clinicopathologic entity characterized by elevated esophageal eosinophil (eos) counts (≥ 15 eos per high-powered field [hpf]) and widely varied symptomatology, which ranges from solid food dysphagia in adults to vomiting and feeding difficulties in children. EoE also must be distinguished from other types of esophageal eosinophilia, either by symptom presentation and/or trial use of a proton-pump inhibitor (PPI). Although other histologic features besides eos peak count can aid in the diagnosis of EoE, none are diagnostic of EoE.^{1,2} Presenting symptoms are poorly predictive of disease status, and a diagnosis can only be made in the presence of an esophageal biopsy specimen with ≥ 15 eos/hpf, typically after multiple esophageal sites are sampled.¹⁻³ The International Gastrointestinal Research Group (TIGER) has published 2 sets of conjoint guidelines on the management and treatment of EoE, with input from both allergists and gastroenterologists, most recently in 2011. Although there are notable differences in presenting symptoms of EoE by age, the recommendations to initiate treatment for biopsy-proven disease or to refer a patient for evaluation by an allergist do not vary by age in the TIGER or American College of Gastroenterology guidelines.¹⁻³

There is limited previous exploration regarding variations in pathways of care that pertain to the diagnosis and management of esophageal eosinophilia and EoE, and no known study that has modeled this as an effect of the patient, provider, or specialty level.^{1,4,5} Differences have been noted in the choice of steroid agent,⁶⁻¹¹ the use of dietary management,¹²⁻¹⁶ the order of preference in initiating diet versus steroid therapy,¹ and the age-specific differential diagnosis to consider in symptomatic patients (eg, consideration for esophageal cancers, erosive esophagitis, relative response to PPI [PPI-responsive esophageal eosinophilia [PPI-REE], gastroesophageal reflux disease [GERD]]).^{1,3,4,16,17} The current study seeks to evaluate if age-based differences in

pathways to care exist in the diagnosis and management of esophageal eosinophilia and EoE, and to compare any differences across a large, age-diverse sample of patients undergoing endoscopy with esophageal biopsy at a large academic medical center.

METHODS

This study was approved by the University of Michigan Medical School Institutional Review Board. A retrospective chart review was conducted of 503 pediatric and adult patients who underwent an esophageal biopsy with the biopsy specimen read at the University of Michigan between March 2009 and April 2011, and who were seen in the University of Michigan adult gastroenterology, pediatric gastroenterology, or allergy clinics, or were directly referred for endoscopy. Patients ages 6 months or older were selected from the Department of Pathology database based on the presence of the key words “esophagitis” or “eosinophil” in the diagnostic line of the pathology report.⁵ This included biopsy specimens obtained by providers outside the system, but re-read by a University of Michigan pathologist (M.E., J.G.). A comprehensive medical record review was performed to examine patient characteristics, presenting symptoms, treatments, and diagnoses given just before or at the time of (including during immediate follow-up visits for) an *esophagogastroduodenoscopy* with esophageal biopsy.

Patient attributes

Patient characteristics abstracted from the chart review included age, sex, race, and body mass index. Examined elements of the patient's presentation included the following: type of symptoms; dysphagia frequency and triggers; GERD and associated symptoms and/or treatments (including the duration of treatment) such as chest or abdominal pain, water-brash, or regurgitation; overchewing of food, or excessive liquid intake to swallow a bite; nausea and/or vomiting; food impaction; esophageal dilatation; globus sensation; bloating; hoarse voice; chronic cough; decreased appetite, food refusal and/or early satiety; food aversion; a history of esophageal stricture or ring; hematochezia; failure to thrive and/or weight loss; and nocturnal awakening due to abdominal pain. Additional information was collected related to the patient's history of comorbid atopy (asthma, eczema, allergic rhinitis, and/or food allergies as noted in the medical history) and medications taken for treatment of these conditions; history of other prior known gastrointestinal disorders (eg, inflammatory bowel disease, celiac disease, gastric ulcer disease, history of prior fundoplication, or history of *Helicobacter pylori* infection); and alcohol and tobacco history. Each patient's record also was evaluated for a family history of dysphagia, EoE, esophageal stricture, eczema, or atopic disease. The cohort was further narrowed to exclude patients who had undergone a prior *esophagogastroduodenoscopy* or had no presenting symptoms of esophageal dysfunction and abdominal or epigastric pain, which left 426 individuals remaining for analysis.

Gross visual and pathologic findings

Endoscopic findings obtained from a review of the endoscopy report were evaluated for the presence of the following features: subjective reported presence of erythema, esophagitis, furrows, plaques, corrugation (eg, a ringed esophagus and/or feline appearance), ulcers and/or tears, small-caliber esophagus, stenosis, Barrett mucosal change, stricture, duodenal ulcer, Schatzki ring, and hiatal hernia. Pathology reports were reviewed for the

presence of the following features: peak eos count (categorized by location in the esophagus, when such a notation had been made), the presence of microabscesses, presence of fibrosis, surface layering, elongation of the rete pegs, and lymphocytic infiltrate. All eos counts and associated histologic features were reverified by a pathologist blinded to the original count for the specific purposes of the study.

Outcomes and statistical analyses

Prior studies that explored the relationship between biopsy outcome and symptom presentation or symptom scoring for EoE, dysphagia, or gastroesophageal reflux also were reviewed in selecting predictor variables for chart abstraction.¹⁸⁻²¹ Four main outcomes of interest were evaluated as pathways of care: (a) the probability of having a biopsy with eos counts suggestive of EoE (≥ 15 eos/hpf) predicted from presenting symptoms, (b) therapies initiated for management of biopsy specimens with cell counts indicative of EoE, (c) referral to an allergist/immunologist, and (d) if a repeated *esophagogastroduodenoscopy* with biopsy was performed. Data were analyzed by using Stata IC, Version 12 (StataCorp, College Station, Texas) by frequency analysis, proportional analysis between adult and pediatric cases by using the χ^2 test or Fisher exact test, logistic regression for binary outcomes, and negative binomial regression for models predictive of log absolute eos count numbers or days between interventions (cell count treated as an overdispersed count variable, coefficients expressed as incident rate ratios). Colinearity of the regression models was assessed by using inspection of variance inflation. Sensitivity analyses were performed on these models by restricting analysis to just the cohort that had completed an 8-week PPI trial before the initial biopsy, which represented the strictest interpretation of the 2007 diagnostic guidelines. For the sensitivity analysis, there was limited removal of nonsignificant covariates due to statistical power-related issues of event-per-variable constraints in a reduced sample-size pool.²² Subgroup and interaction effects were assessed through analysis of adjusted marginal means to provide predicted outcome probabilities (by using the Stata margins command).²³

RESULTS

Population characteristics

Among 426 patients included in the analysis, the median age was 38 years, and 19.5% ($n = 83$) were 18 years old or younger. Within the study population, 67.1% were male patients ($n = 342$), 80.4% were white ($n = 337$), 53.9% had a history of atopy ($n = 271$), and 27.8% were evaluated by a gastrointestinal provider outside of the health care system ($n = 118$). The differences in the demographic trends between the pediatric and adult subjects in the study are compared in Table I. The overall frequency of key presenting symptoms and the endoscopic and microscopic features by age are displayed in Table II. Several statistically significant differences were noted between these groups in both tables. Overall, 79.6% ($n = 336$) of the total population had a biopsy with ≥ 15 eos/hpf, a count level associated with histologic diagnostic criteria for EoE. Neither age nor atopy were significantly associated with eos counts ≥ 15 eos/hpf at a bivariate level, nor in an adjusted logistic regression model (adjusted for symptoms, gross visual findings, histologic findings, and comorbid atopy) (the full model is not shown) that explored presenting symptoms, gross visual endoscopic findings, and associated biopsy histologic features (age odds ratio [OR] 0.99

TABLE I. Demographic data ($n = 426$)

Characteristic	Total	Pediatric	Adult
Male subjects (%) ($n = 342$)	67.1	67.5	67
White (%) ($n = 337$)	80.4	85.4	93.8
Age ≤ 18 y (%) ($n = 83$)	19.5	—	—
Median age (y) ($n = 426$)	38	10	41
Median BMI (kg/m^2) ($n = 426$)	25.5	17	27.4
Had at least 1 atopic condition (%) ($n = 271$)	53.9	59.3	52.3
Seen by outside GI provider (%) ($n = 118$)	27.8	33	6.1

BMI, Body mass index; GI, gastrointestinal.

TABLE II. Age-stratified presenting symptoms, endoscopic visual, and histologic features ($n = 426$)

Finding	Total	Pediatric	Adult
Dysphagia (%) ($n = 248$)	58.2	44.6	61.5*
Abdominal pain (%) ($n = 126$)	29.6	42.2	26.5*
Vomiting (%) ($n = 84$)	19.7	51.8	12*
GERD (%) ($n = 295$)	69.3	56.6	72.3*
Failure to thrive and/or weight loss (%) ($n = 49$)	11.5	34.9	5.8*
Early satiety (%) ($n = 52$)	12.2	30.1	5.6*
Luminal narrowing (%) ($n = 99$)†	23.2	6	27.4*
Median time symptomatic (mo)	30	14	36*
Esophageal corrugation (%) ($n = 159$)	37.3	10.8	43.7*
Whitish plaques (%) ($n = 42$)	9.9	21.7	7*
Odynophagia (%) ($n = 51$)	10.1	9.7	10.3
Furrows (%) ($n = 154$)	36.1	44.6	34.1
Ulcers and/or tears (%) ($n = 25$)	5.9	8.4	5.3
Food impaction (%) ($n = 73$)	17.1	18.1	16.9
Biopsy specimen with ≥ 15 eos/hpf (%) ($n = 336$)	79.6	79.5	79.6
Median peak no. eos/hpf	31	33	31

* $P < .05$, which indicates a significant difference in proportion (χ^2 test or Fisher exact test).

†Includes the presence of Shatzki ring, stenosis, small-caliber esophagus, described narrowing, or stricture.

[95% CI, 0.97-1.01], $P = .24$; atopy OR 1.18 [95% CI, 0.64-2.18], $P = .59$). Age, furthermore, was not associated with the peak number of eos/hpf (age adjusted incidence rate ratio 1 [95% CI, 0.98-1.02], $P = .93$; atopy adjusted incidence rate ratio 1.11 [95% CI, 0.94-1.31], $P = .20$) (full model not shown). PPI use (per additional month) was associated with lower odds of eos counts ≥ 15 eos/hpf in the logistic model (OR 0.98 [95% CI, 0.97-0.99], $P = .05$) but was not significantly associated with the log count of the peak number of eos.

Management strategies initiated for esophageal eosinophilia in symptomatic adult and pediatric patients are compared in Table III. Several significant differences were noted between these age groups in how this was managed. Notably, in this population, the adults were less frequently given a clinical diagnosis of EoE when their biopsy specimen had ≥ 15 eos/hpf compared with children (31.3% vs 68.7%; $P < .0001$). Additional significant age-based differences were noted in the proportional rates of having dilation performed at the time of the biopsy, of initiating swallowed topical steroid therapy to treat a diagnostic biopsy, of initiating dietary therapy to treat a

TABLE III. Prebiopsy and postbiopsy management (n = 426)

Treatment or therapy	Total	Pediatric	Adult
If biopsy specimen with ≥ 15 eos/hpf (n = 334), diagnosed with EoE (%) (n = 185)	55.4	68.7	31.3*
Esophageal dilation (%) (n = 111)	26.2	4.8	31.4*
Swallowed steroid begun (if biopsy specimen with ≥ 15 eos/hpf) (%) (n = 149)	44.7	64.3	30.7*
Dietary modification begun (if biopsy specimen with ≥ 15 eos/hpf) (%) (n = 80)	23.8	66.7	13.3*
Referral to allergist (if biopsy specimen with ≥ 15 eos/hpf) (%) (n = 123)	36.9	84.6	25.4*
Used PPI > 8 wk before biopsy (%) (n = 154)	36.1	33.7	36.7
Median duration of PPI use (mo)	0.25	0	0.5

*Indicates a statistically significant difference in proportion when using the χ^2 test or the Fisher exact test.

diagnostic biopsy, and of referring patients to see an allergist when there was a diagnostic biopsy.

Comparisons of differential pathways of care

Given differences in allergy referral and swallowed steroid treatment based on age were noted, 2 separate adjusted logistic regression models were created to explore factors predictive of these outcomes. Allergy referral was significantly associated with the initiation of swallowed steroids (OR 14.8 [95% CI, 7.4-29.6]; $P < .0001$), age per year (OR 0.85 [95% CI, 0.79-0.91]; $P < .0001$), and dysphagia (OR 3.2 [95% CI, 1.44-7.11]; $P = .004$) (Table IV). There was a significant interaction of age with itself (age²), which indicated a plateauing of the relationship between the inverse association of advancing age and referral to allergy. This is demonstrated graphically in Figure 1, A.

Initiation of swallowed steroid therapy (Table V) was associated with age (OR 1.09 [95% CI, 1.11-4.42]; $P = .024$), peak eos biopsy specimen count (OR 1.02 [95% CI, 1.01-1.03]; $P = .005$), dysphagia (OR 0.33 [95% CI, 0.16-0.66]; $P = .002$), allergist referral (OR 9.77 [95% CI, 4.43-21.5]; $P < .0001$), and dietary modification (OR 2.34 [95% CI, 1.16-4.8]; $P = .018$). As noted in the bivariate analysis (Table III and Figure 1, B), there is an inverse association between age (stratified at ≤ 18 years vs ≥ 19 years) and steroid treatment. However, after adjusting for several variables, including allergy referral and the interaction of age with itself, a plateau is shown in the positive association between steroid treatment and increasing age, which indicates that this relationship also is nonlinear (Figure 1, C).

Despite the fact that 79.6% (n = 336) of the cohort had biopsy specimens with ≥ 15 eos/hpf, only 16.4% (n = 70) underwent a second biopsy for disease surveillance within the 2-year study period. Significantly more children than adults underwent a second biopsy for surveillance (37.4% children vs 11.4% adults; $P < .001$). An adjusted logistic regression model also was created to investigate factors that influenced having a biopsy repeated (Table VI). Increasing age and the presence of furrowing on visual inspection were significantly associated with lower odds of having a repeat biopsy. GERD symptoms, esophageal corrugation, and increasing peak eos counts were associated with increased odds of having a second biopsy. However, the peak eos count number interacted with itself (eosinophil count²), and there was a plateau in the positive

TABLE IV. Mutually adjusted associations with referral to an allergist

Factors predictive of allergy referral	OR (95% CI)	P
Swallowed steroid treatment initiated	14.8 (7.40-29.6)	<.001
Age (per y)	0.85 (0.79-0.91)	<.001
Age*Age interaction*	1.0002 (1.001-1.0025)	.002
Dysphagia	3.2 (1.44-7.11)	.004
Atopy	1.44 (0.75-2.8)	.28
Months of duration of PPI trial	1.00 (0.98-1.01)	.91
Symptoms >6 mo	1.85 (0.77-4.45)	.17
Food impaction	0.66 (0.27-1.63)	.37
Peak eos count	1.00 (0.90-1.02)	.61
GERD	1.02 (0.51-2.06)	.95
Male sex	0.99 (0.49-1.98)	.98
Furrowing and/or longitudinal marking	0.65 (0.31-1.39)	.27
Esophageal corrugation	1.67 (0.75-3.73)	.21
Esophageal plaques	2.62 (0.76-9)	.13
Esophageal luminal narrowing	0.54 (0.24-1.22)	.14

*Age/age interaction reflects squaring the term to investigate nonlinear relationships as age advances.

association between eos count and a follow-up procedure. In addition, age also interacts with itself, and there is a plateau in the negative association between age and a follow-up procedure (Figure 1, D).

Sensitivity of the findings

Detailed sensitivity analysis was performed on the data set, restricted to only those who had been on a PPI for 8 weeks before the initial biopsy (n = 154), to test the applicability of our models according to the most complete diagnostic recommendations in the 2007 TIGER guidelines (cell count, symptoms, PPI trial).² There were no differences in the relationship between age and the predicted probabilities of allergy referral, repeated biopsy, or initiating steroid therapy (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

To our knowledge, this is the first study to examine specific differences in pathways to care in how esophageal eosinophilia and EoE are diagnosed and managed in a cohort of pediatric and adult patients at an academic medical center. The intent was to characterize practice style and to provide evidence as to how providers interpreted past EoE guidelines, which may help influence future specific recommendations. We observed that significant age-based differences exist in how esophageal eosinophilia and EoE are managed, many of which are discrepant with the approach outlined in the 2007 TIGER guidelines, the active guidelines during the time that these patients were evaluated. These guidelines make no recommendation that symptoms and/or histologic evidence should be handled differently as a function of patient age (a theme continued in both the 2011 TIGER and 2013 American College of Gastroenterology guidelines). Furthermore, these age-related findings that we observed were unchanged when reanalyzed for only the group that underwent the 8-week PPI trial.

We found that children with histologic findings of esophageal eosinophilia, ≥ 15 eos/hpf, at our center were more likely than

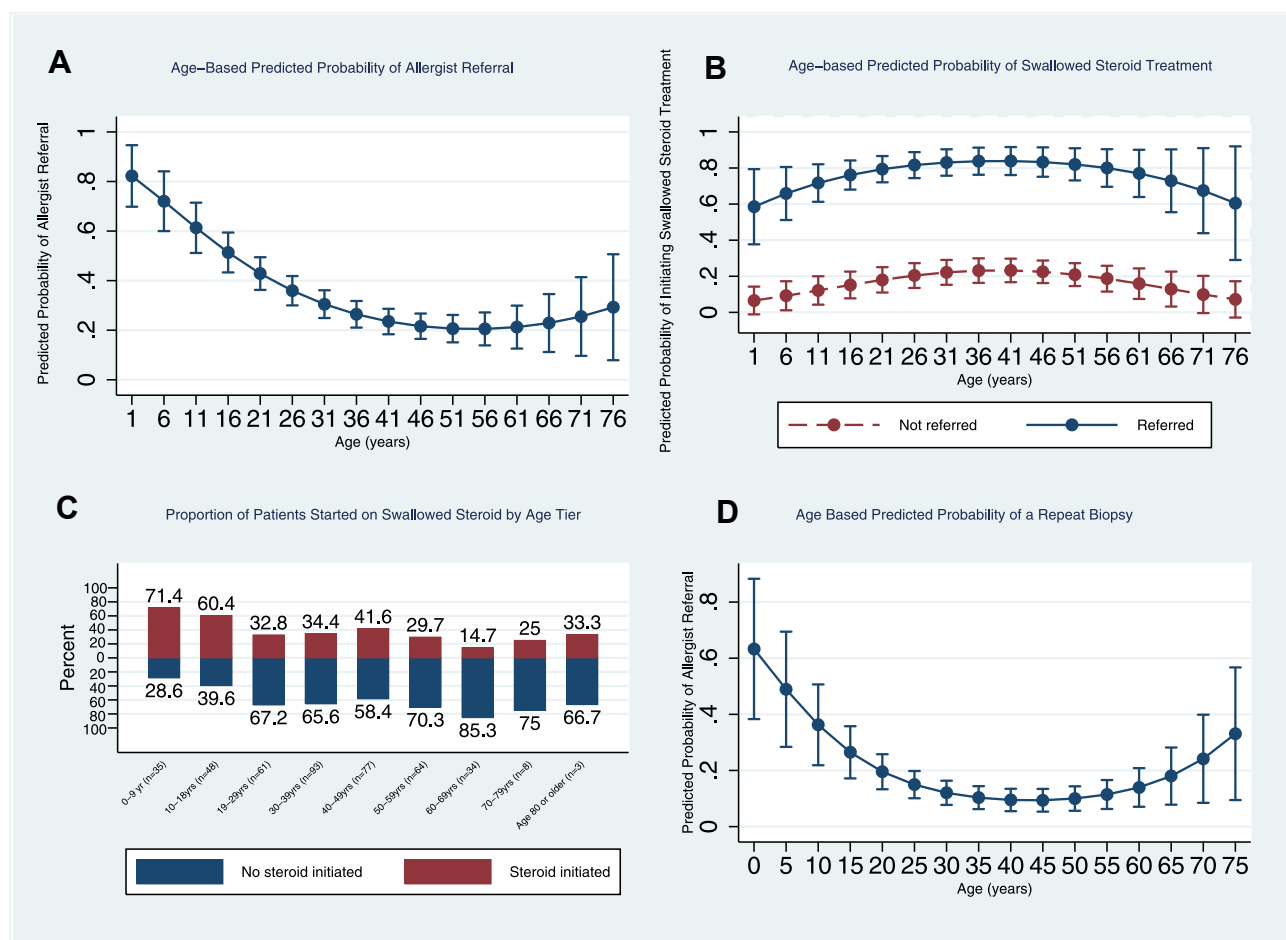


FIGURE 1. A, Predicted probability of an allergy referral, by age, stratified by allergy referral, based on the adjusted regression model highlighted in Table IV; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression; error bars represent the 95% CI of the prediction. B, Unadjusted proportional differences, by age tier, of receiving swallowed steroid treatment. C, Predicted probability of initiating swallowed steroid, by age, based on the adjusted regression model highlighted in Table V; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression and stratified by allergist referral; error bars represent the 95% CI of the prediction. D, Predicted probability of having a repeated endoscopy and/or biopsy, by age, based on the adjusted regression model highlighted in Table VI; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression; error bars represent the 95% CI of the prediction.

adults to be given a clinical diagnosis of EoE, to be referred to an allergist, and to undergo a repeated endoscopy and biopsy. Furthermore, being prescribed steroid treatment was significantly influenced by referral to an allergist, and was also nonlinear with respect to advancing patient age (eg, certain ages of both children and adults were more likely to receive this therapy). The ramifications of these differing pathways are unclear, given limited data regarding the natural history of EoE.

The low overall observed rate of repeated biopsy to monitor disease (16.6%) is puzzling at any age, as was the observation that repeated biopsies occurred more commonly in the children in our population (given potential anesthesia concerns). From our data, it is difficult to speculate if provider bias influenced these rates, if these rates were a by-product of the other age-related differential pathways identified, or if these rates were the result of limited data regarding the optimal interval for repeated

endoscopy. The 2007 guidelines did not specify a frequency of repeated endoscopy but did note the need for staged endoscopic follow up in both children and adults.² More data are needed about this key measurement, given that having repeated tissue findings impacts many other outcomes.

We note that only 55.4% of patients with a biopsy specimen count that exceeded 15 eos/hpf were clinically diagnosed with EoE overall, and this occurred in twice as many children as adults. This may be explained by the belief in PPI-REE and that eos counts between 15 and 30 eos/hpf (and possibly as high as 60 eos/hpf) may respond to aggressive PPI treatment, particularly with adults.^{3,24-33} PPI-REE is a newer concept, not discussed in the 2007 TIGER guidelines, which simply recommended an 8-week PPI trial before endoscopy to distinguish EoE from severe GERD (evidence grade C).^{2,26} Subsequent guidelines have continued to recommend a PPI trial to help rule out a multitude

TABLE V. Mutually adjusted associations with initiation of swallowed steroid as a treatment for EoE

Factor predictive of steroid treatment	OR (95% CI)	P
Received dilation	2.21 (1.11-4.42)	.02
Age	1.09 (1.01-1.18)	.03
Age*Age (interaction term)*	0.99 (0.997-0.999)	.03
Peak eos/hpf	1.02 (1.01-1.03)	.005
Dysphagia	0.33 (0.16-0.66)	.002
Referral to allergist	9.77 (4.43-21.5)	<.001
Dietary modification made	2.34 (1.16-4.8)	.02
Symptoms persist >6 mo	1.61 (0.73-3.6)	.25
Ringed and/or corrugated esophagus	0.48 (0.23-1.03)	.06
History of impaction	0.78 (0.36-1.3)	.55
Months duration of PPI use	0.99 (0.97-1.01)	.27
Atopy	0.93 (0.5-1.72)	.82
GERD	0.68 (0.36-1.3)	.24
Male sex	1.14 (0.6-2.2)	.69
Furrowing and/or longitudinal markings	1.89 (0.92-3.9)	.09
Whitish plaques	1.16 (0.38-3.6)	.8
Esophageal luminal narrowing present	1.39 (0.67-2.89)	.37
Multilevel biopsy taken	1.72 (0.87-3.4)	.12
Weight loss and/or failure to thrive	2.33 (0.8-6.8)	.12

*Age/age interactions reflect squaring the terms to determine underlying nonlinear relationships as age advances.

of potential causes of esophageal eosinophilia which may be PPI-responsive (labeled PPI-REE), including, but not limited to, GERD.³ In our population, only 36% (n = 154) had an 8-week PPI trial, which did not differ significantly by age. However, the PPI trial had little influence on our management outcomes of interest, and the sensitivity analysis noted no difference in the relationship between age and the predicted probabilities of allergy referral, repeated biopsy, or initiation of steroid therapy. We cannot explain the low rate of use of PPI before the biopsy within our cohort or reasons why this recommendation was not more closely followed. Evidence that supports a PPI trial at the time was, and still remains, unsupported by high-quality data; there are no large or randomized, controlled prospective studies, just uncontrolled series or retrospective analyses.^{27,28,30-33} Analysis of recent data for PPI-REE suggests that the PPI treatment effect is heterogeneous, the definition of improvement inconsistent, and the effectiveness limited (approximately 30%-40% of adults show improvement).³¹⁻³³ Only 1 study to date elucidates any potential anti-eosinophilic mechanism of action for a PPI independent of acid blockade.²⁹ Additional data are needed to better understand the prebiopsy role of PPI.

Limitations of this study include use of a retrospective population, referral bias, selection bias, and loss to follow up. A large proportion of the population did have ≥ 15 eos/hpf in their biopsy specimen, and this study was conducted at a large, academic medical center, which may have resulted in clustering. Use of slightly more diverse search criteria may have enabled more "negative" biopsy specimens to be identified. Only one-third of the patients underwent an 8-week PPI trial, although a sensitivity analysis showed that this did not alter the outcomes of interest that we report. However, this will shape future studies because prebiopsy PPI treatment has now been recommended in 3 separate guidelines. We were not able to assess provider-level familiarity with the TIGER guidelines or assess provider beliefs

TABLE VI. Mutually adjusted associations with repeated biopsy

Factors predictive of a surveillance biopsy	OR (95% CI)	P
Peak eos/hpf	1.07 (1.01-1.13)	.014
Peak Count*Peak Count interaction*	0.99 (0.998-0.999)	.021
Age	0.86 (0.79-0.93)	<.001
Age*Age interaction*	1.001 (1.001-1.002)	<.001
GERD	1.48 (1.40-7.97)	.006
Furrowing and/or longitudinal marking	0.11 (0.11-0.6)	.002
Esophageal corrugation	1.64 (1.54-8.82)	.003
Atopy	0.94 (0.48-1.13)	.88
Odynophagia	1.03 (0.37-2.86)	.95
Failure to thrive and/or weight loss	0.87 (0.28-2.67)	.81
Nausea	1.55 (0.62-3.88)	.35
Vomiting	1.31 (0.54-3.19)	.55
Dysphagia	1.39 (0.62-3.2)	.43
Nocturnal awakening with abdominal pain	2.32 (0.49-10.84)	.29
Esophageal plaques	1.54 (0.49-4.79)	.46
Esophageal luminal narrowing	1.19 (0.29-4.86)	.81
Months of duration of PPI trial	0.99 (0.98-1.01)	.51
Early satiety	0.90 (0.31-2.58)	.84
Food impaction	0.60 (0.22-1.63)	.32
Multilevel biopsy specimen taken	0.68 (0.81-3.75)	.15
Symptoms >1 y	0.21 (0.25-1.18)	.12
Dietary modification initiated	0.41 (0.45-2.23)	.99
Referred to allergist	0.51 (0.33-2.73)	.92
Swallowed steroid treatment initiated	0.61 (0.57-3.3)	.49
PPI therapy initiated postbiopsy	0.42 (0.39-2.23)	.88

*Count/count and age/age interactions reflect squaring the terms to determine underlying nonlinear relationships as counts or age advance.

regarding EoE at the time, which may have influenced practice style significantly. This will be a focus of future study. EoE research in general has a lack of prospective, controlled studies, which forces a reliance on small, retrospective cohorts from large referral centers.¹⁻³ It is unclear how practice style may be influenced by guidelines that are formulated with limited high quality evidence. This may account for differential interpretation of guideline recommendations. Finally, the current study was limited to symptomatic patients who were undergoing their initial diagnostic biopsy, which may have excluded some potential disease phenotypes associated with less typical presentations. Further study at other large centers is needed to validate our findings and to assess for any variation in practice style or patient clustering that could be unique to the institution in this particular study.

We present unique data from a large, academic-center sample that age-based differences exist that pertain to the diagnosis and treatment of EoE. These differences were still apparent irrespective of analysis with or without an 8-week PPI trial, which suggests true differential pathways of care based on age. In this population, pediatric patients were significantly more likely to have management in accordance with 2007 TIGER guidelines, whereas adults had a differential pathway of care with respect to clinical diagnosis, allergy referral, and initiation of swallowed steroids, and with undergoing surveillance biopsy. It is unclear why we observed age-based differences in management because this is not recommended in EoE consensus treatment guidelines. Given no physiologic rationale for using age as a determining

factor to guide initiation of steroid therapy, referral for allergy services, or to obtain a repeated biopsy, analysis of these data may suggest that the age-based differences were due to variation in provider decision making between pediatric and adult physicians.^{2,7,8,11,34} However, further study is needed to better define and understand the effects of provider variation. Consideration also should be given for distinct EoE guidelines specific to children and to adults if additional evidence supports that true age-based differential care pathways exist. The long-term ramifications of age-based differences in the approach to care are unknown but differential pathways of care could significantly alter the natural history of illness as well as health service utilization.

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SUPPLEMENTAL MATERIAL

Sensitivity Analysis of the Age Based Outcomes

We noted that increasing age remained associated with a reduced odds of allergist referral (OR 0.89, CI 0.89-0.96 and OR 1.001, CI 1-1.002 for the age/age interaction), reduced odds of undergoing repeat biopsy (OR 0.94, CI 0.9-0.98) and reduced odds of predicting ≥ 15 Eos/HPF on biopsy from presenting symptoms (OR 0.97, CI 0.93-1; age remained non-significant in the biopsy peak count model). Age (the average effect for age) was no longer significantly associated with swallowed steroid therapy, but allergy referral remained significantly associated. Adjusted

predicted probabilities (the probability per increasing individual age as a predictive margin) for referral, biopsy, and referral-stratified initiation of swallowed steroids based on age were also largely unchanged, showing significantly lower probabilities of these outcomes with respect to increasing age. The shape of the referral-stratified steroid curve changed given significant age/age interaction. In fact, the predicted probability of receiving swallowed steroid, stratified by allergy referral, now declines with advancing age (Supplemental figure 1, compared to figure 1). Thus, the effect of restricting analysis to just the 8-week PPI trial subset had limited impact on the previous findings.

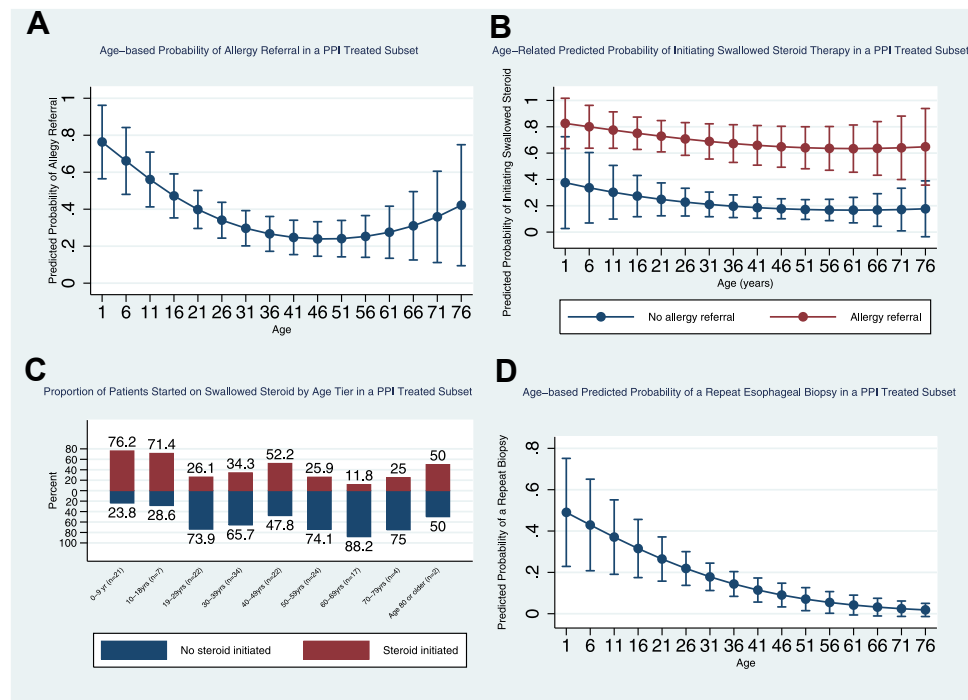


FIGURE E1. A, Predicted probability of an allergy referral, by age, stratified by allergy referral, based on the adjusted regression model highlighted in Table IV, restricted to the $n = 154$ subset of patients who underwent an 8-week PPI trial; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression; error bars represent the 95% CI of the prediction. B, Unadjusted proportional differences, by age tier, of receiving swallowed steroid treatment, restricted to the $n = 154$ subset of patients who underwent an 8-week PPI trial. C, Predicted probability of initiating swallowed steroid, by age, based on the adjusted regression model highlighted in Table V, restricted to the $n = 154$ subset of patients who underwent an 8-week PPI trial; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression and stratified by allergist referral; error bars represent the 95% CI of the prediction. D, Predicted probability of having a repeated endoscopy and/or biopsy, by age, based on the adjusted regression model highlighted in Table VI, restricted to the $n = 154$ subset of patients who underwent an 8-week PPI trial; the points represent the average adjusted predicted probability per representative age when using the observed values for the other variables in the regression; error bars represent the 95% CI of the prediction.