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Increasing Rates of Esophageal Stricture and Dilation Over 2 Decades in Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a clinicopathologic condition that is characterized by chronic inflammation with variable manifestations.[1] Esophageal strictures are one of the fibrotic remodeling features of EoE and are more commonly seen with diagnostic delay.[2] Recognition of strictures is important given their role in complications of EoE, such as food impactions, and because dilation of strictures can safely provide significant symptomatic benefit.[3,4] While it has been frequently demonstrated that the incidence and prevalence of EoE have been increasing, it is unknown if the prevalence of strictures in EoE patients has changed over time. We aimed to determine whether the prevalence of strictures and the performance of dilation have changed over the prior 2 decades in a large population of EoE patients.

We conducted a retrospective cohort study utilizing the University of North Carolina EoE clinicopathologic database from inception (2001) through the end of 2020. The development and characteristics of the database have been previously reported.[4,5] Subjects in the study were adults and children with an incident diagnosis of EoE per consensus guidelines at the time of diagnosis, including symptoms of esophageal dysfunction, > 15 eosinophils per high-power field (eos/hpf), and exclusion of competing causes of eosinophilia; all had active EoE. Patient demographics, clinical characteristics, report of symptoms, and procedural data were extracted from medical records, including duration of symptoms before diagnosis, the presence or absence of esophageal strictures or narrowing (defined by the performing endoscopist's visual assessment), and whether dilation was performed during the diagnostic endoscopy; subsequent endoscopic exams, even if they had dilations, were not assessed

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Reporting Guidelines:
STROBE.

for this study. Given that this was an observational study, dilations were performed at the discretion of the endoscopist as clinically indicated. Endoscopic severity was calculated using the EoE Endoscopic Reference Score (EREFS), when this was available, and using an Endoscopic Severity Score, which was available for all patients. The Endoscopic Severity Score is the sum of the presence or absence of the same endoscopic findings in EREFS (exudates, rings, edema, furrows, and stricture) and ranges from 0 to 5, with higher scores being more severe. The prevalence of strictures, narrowing, or dilation was calculated by the year of diagnosis. Diagnostic timeframe was also categorized by 5-year intervals and by time intervals related to diagnostic guideline publications (2001–2007; 2007–2017; 2018–2020). Patient characteristics were compared across the 5-year time intervals using analysis of variance for continuous variables and chi-squared for categorical variables. Multivariate logistic regression was performed to assess for overall trends in the odds of esophageal stricture while accounting for changes in patient age and symptom length prior to diagnosis over time.

We analyzed 1064 EoE patients, with a mean age of 29.4 years, 36% children < 18 years, 86% white, 68% male, 59% with at least one atopic condition, and mean symptom length prior to diagnosis of 7.5 ± 8.3 years. When assessing patient baseline characteristics for each 5-year period over the last 20 years (Table), age increased steadily with time (from 17.9 years at diagnosis for 2001–2005 to 33.8 years in 2016–2020; $P < .001$), as did frequency of dysphagia (from 61% to 83%; $P < .001$) and food impaction (from 27% to 40%; $P = .01$); frequency of abdominal pain decreased (from 26% to 12%; $P < .001$).

Overall, stricture prevalence and dilation frequency significantly increased over time, from 8% for each in 2004 to as high as 54% and 59%, respectively, in 2019 ($P < .001$). On multivariate analysis with the year as a continuous variable, the odds of stricture increased by 18% annually even after accounting for changes in patient age and symptom length prior to diagnosis (adjusted odds ratio [aOR] 1.18, 95% confidence interval [CI]: 1.12–1.23). When evaluating 5-year intervals, there was a significant increase in the prevalence of strictures, narrowing, and dilation (Figure A). Within these intervals, after accounting for changes in age and symptom length, the odds of stricture doubled for each interval (aOR 2.11, 95% CI 1.69–2.65). Similar results were noted for EoE guideline intervals (Figure B). Compared to pre-guidelines time period, there were increased odds of stricture for both the second period (aOR 2.75, 95% CI 1.29–5.83) and the most recent time-period (aOR 6.80, 95% CI 3.12–14.8), after controlling for age and symptom length prior to diagnosis.

We found that the prevalence of esophageal strictures in newly diagnosed EoE patients has markedly increased over the past 2 decades, with an associated increase in dilation. This doubling of stricture prevalence persists after accounting for changing demographic and disease factors, including age at diagnosis and symptom duration prior to diagnosis, which are associated with a higher likelihood of fibrostenotic phenotype.[2] Potential explanations for our findings could include increasing recognition of strictures, a changing phenotype, or a combination of both, though the exact reason is difficult to determine with our study design. While there is a broader recognition of EoE over the past 20 years, the incidence of EoE continues to outpace the rate of biopsies for the condition.[6] Additionally, studies have demonstrated that our ability to endoscopically detect strictures has been limited,

particularly when compared to other diagnostic modalities such as barium esophagram.[7,8] This may be due to EoE causing more subtle or diffuse strictures as compared to other more focal forms of stricturing such as in peptic disease.[8] Because it is possible for endoscopists to maximize their detection of strictures with a focused and thorough endoscopic exam[9] and for even severe strictures to be successfully treated,[10] enhanced stricture detection is likely a major reason for our observed increase. However, improved ways to assess fibrostenosis in routine practice (such as standard use of techniques like impedance planimetry) and whether our findings may also represent a shifting phenotype require future research. Limitations of this study, including the single-center retrospective design, lack of ability to prospectively define strictures or narrowing, and potential variability in EREFS reporting over time, are balanced by the large population size, detailed patient characterization, and long study timeframe. In conclusion, the rate of strictures detected at the time of EoE diagnosis has been rising over the past 2 decades, with a concomitant increase in the rate of esophageal dilation.

Conflicts of Interest:

These authors disclose the following: Dr Dellon is a consultant for Abbott, Abbvie, Adare/ Ellodi, Aimmune, Akesobio, Alfasigma, ALK, Allakos, Amgen, Arena, Aslan, AstraZeneca, Avir, Biorasi, Calypso, Celgene/ Receptos/BMS, Celldex, Eli Lilly, EsoCap, Eurpaxia, Ferring, GSK, Gossamer Bio, Holoclara, Invea, Landos, LucidDx, Morphic, Nexstone Immunology, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/ Alimentiv, Salix, Sanofi, Shire/Takeda, Target RWE, Upstream Bio; receives research funding from Adare/Ellodi, Allakos, Arena, AstraZeneca, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Revolo, Shire/ Takeda; and has received an educational grant from Allakos, Banner, Holoclara, and Invea. The remaining authors disclose no conflicts.

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Abbreviations

aOR	adjusted odds ratio
CI	confidence interval
EoE	eosinophilic esophagitis
EREFS	Endoscopic Reference Score

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Data Transparency Statement:

Data may be made available to other researchers upon request to the corresponding author.

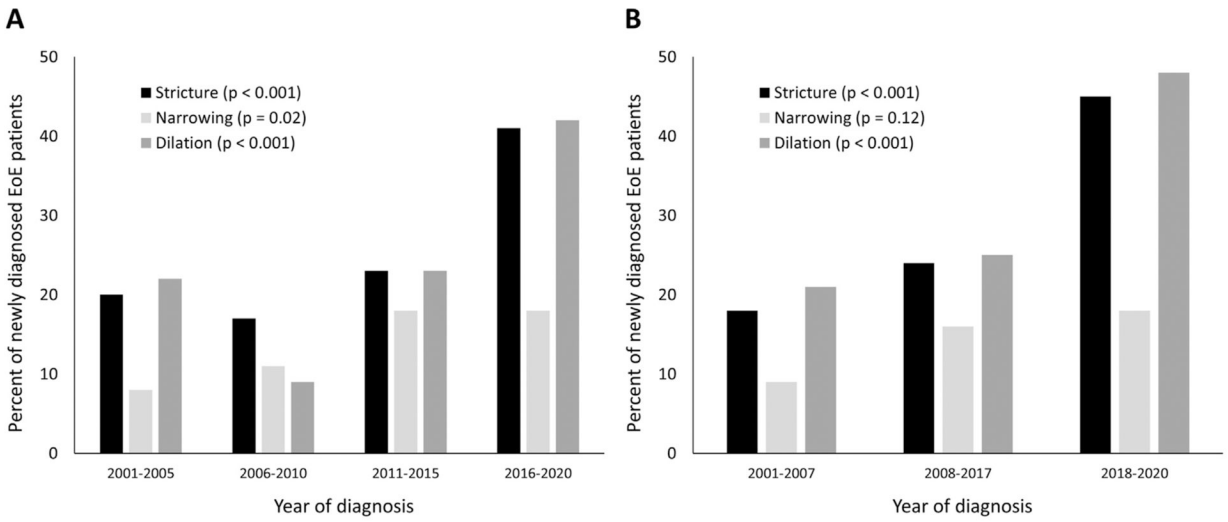

Figure.

Increasing prevalence of stricture (black bars), narrowing (light gray bars), and dilation (dark gray bars) over (A) 5-year intervals and (B) time intervals based on published EoE guidelines. EoE, eosinophilic esophagitis.

Table.

Comparison of Clinical Characteristics Across Each of the 5-year Intervals (n = 1064)

	2001–2005 (n = 49)	2006–2010 (n = 262)	2011–2015 (n = 331)	2016–2020 (n = 422)	*P* [b]
Age at diagnosis (mean years ± SD)	17.9 ± 15.1	26.4 ± 19.5	27.9 ± 17.9	33.8 ± 20.2	<.001
Male (n, %)	44 (90)	185 (71)	212 (64)	283 (67)	.003
White (n, %)	39 (80)	215 (82)	287 (89)	367 (88)	.05
Any atopic condition (n, %)	27 (73)	120 (53)	196 (60)	254 (61)	.07
Symptom length prior to diagnosis (mean years ± SD)	3.9 ± 4.9	6.7 ± 8.4	8.2 ± 9.0	7.6 ± 7.9	.03
Symptoms (n, %)					
Dysphagia	30 (61)	158 (62)	255 (77)	350 (83)	<.001
Food impaction	12 (27)	68 (28)	107 (32)	168 (40)	.01
Heartburn	19 (44)	90 (37)	136 (41)	135 (32)	.05
Chest pain	1 (2)	26 (11)	42 (13)	38 (9)	.12
Abdominal pain	11 (26)	55 (22)	73 (22)	50 (12)	<.001
Endoscopic findings (n, %)					
Exudates	6 (12)	58 (22)	152 (46)	209 (50)	<.001
Rings	12 (24)	108 (41)	171 (52)	248 (59)	<.001
Edema	3 (6)	34 (13)	146 (44)	220 (52)	<.001
Furrows	4 (8)	109 (42)	245 (74)	334 (79)	<.001
Stricture	10 (20)	44 (17)	75 (23)	171 (41)	<.001
Narrowing	4 (8)	28 (11)	61 (18)	75 (18)	.02
Dilation	11 (22)	50 (19)	77 (23)	177 (42)	<.001
Total EREFS (mean ± SD)[a]	n/a	n/a	3.5 ± 2.2	3.9 ± 1.8	.16
Total ESS (mean ± SD)[a]	0.7 ± 0.7	1.3 ± 1.2	2.4 ± 1.5	2.8 ± 1.5	<.001
Peak eosinophil count (mean eos/hpf ± SD)	72.2 ± 69.7	63.4 ± 37.5	66.1 ± 47.6	64.8 ± 44.0	.81

EREFS, Endoscopic Reference Score; SD, standard deviation.

[a]EREFS data available for n = 466; ESS, endoscopic severity score, for which all data available.

[b]Means compared with ANOVA; proportions compared with chi-squared.