Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-022-07610-9

ORIGINAL ARTICLE

Worsened Fibrostenotic Outcomes in Eosinophilic Esophagitis Patients Due to COVID-19-Related Endoscopy Cancellations

Adolfo A. Ocampo[1] · **Evan S. Dellon**[1,2]

Received: 13 May 2022 / Accepted: 27 June 2022

Abstract

Background Indirect consequences of COVID-19 in eosinophilic esophagitis (EoE) are not known.

Aim To determine the impact of COVID-19-related endoscopy cancellations on outcomes in EoE patients.

Methods In this retrospective cohort study, we assessed whether adult EoE patients who had routine endoscopy scheduled from mid-March 2020 to May 2020 (pandemic start) were canceled or proceeded, and if canceled, ultimately returned. We extracted clinical, endoscopic, and histologic data for their pre-COVID procedure as well as the next procedure performed, if a patient returned. Outcomes included histologic response (< 15 eos/hpf) and endoscopic severity. Those with delayed care were compared to those who returned as scheduled.

Results Of 102 patients identified, 75 had procedures canceled, and 20 (27%) never returned. For the 55 who were canceled but returned, mean time between procedures was 1.1 ± 0.7 years with a delay of 0.5 ± 0.3 years. While treatment rates were similar between the pre- and delayed post-COVID EGD, more patients required a dilation after their return (71% vs 58%; $p = 0.05$) and their esophageal diameter had significantly decreased (16.8 mm to 15.0 mm; $p < 0.001$). Of 17 individuals who did not have stricture, narrowing, or dilation pre-pandemic, during their next endoscopy 5 (29%) had a stricture, 1 (6%) had a narrowing, and 7 (41%) required dilation.

Conclusion Of EoE patients with canceled endoscopies during the beginning of the COVID-19 pandemic, > 25% never returned for care, which is a previously unmeasured impact of the pandemic. Those who returned had > 1 year between procedures with progression of fibrotic features and need for esophageal dilation.

Keywords Eosinophilic esophagitis · Outcomes · Fibrosis · Stricture · Dilation · COVID-19

Introduction

Eosinophilic esophagitis (EoE) is an inflammatory and allergic disease that is characterized by increased numbers of eosinophils in the esophageal mucosa which lead to symptoms of esophageal disfunction [1–4]. While there is currently some controversy related to the most appropriate monitoring intervals for patients with EoE under control after treatment, there is substantial evidence that with increasing symptom duration prior to diagnosis, EoE will present as a fibrostenotic phenotype in the majority, but not all, patients [2, 5–9]. In addition, even after diagnosis EoE can progress to fibrostenosis if patients do not have regular monitoring [10, 11].

In the current pandemic, coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is also now known to involve the gastrointestinal (GI) tract [12, 13]. Given the unprecedented nature of COVID-19, it has had a substantial impact on the field of GI overall, including restricting non-urgent endoscopic procedures, and impacting operations and staffing of endoscopy units as well as endoscopic training and education [14–19]. In addition, data have begun to emerge on the direct impact of COVID-19 on EoE and other eosinophilic gastrointestinal disorders (EGIDs).

✉ Evan S. Dellon
edellon@med.unc.edu

[1] Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., Chapel Hill, NC 27599-7080, USA

[2] Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, USA

Published online: 05 July 2022

Interestingly, patients with EGIDs have not been found to have an increased risk of COVID-19 infection or complications [20–25]. This may be due to patients with eosinophilic gastrointestinal disorders having reduced RNA levels of Angiotensin Converting Enzyme (ACE) type 2 and serine protease TMPRSS2, both important mediators for SARS-CoV-2 entry into host cells [20, 23].

Despite this ongoing research into the effects of COVID-19 in patients with EoE, the non-infectious impact the pandemic has caused in these patients has not been previously explored. For example, at the beginning of the pandemic, we observed that many EoE patients at our center had their scheduled endoscopies canceled and delayed, but the scope of this and ultimate effect on patients were not known, particularly given the potential for disease progression in EoE. Therefore, we aimed to determine the impact of COVID-19-related endoscopy cancellations on clinical outcomes in EoE patients. We hypothesized that patients who had their endoscopic procedures canceled because of the pandemic would have worse clinical, endoscopic, and histological outcomes once they returned.

Methods

Study Design and Patient Selection

We conducted a retrospective cohort study of the University of North Carolina (UNC) EoE Clinicopathologic database, which has been previously described [26–31]. In brief, this database includes data from newly diagnosed EoE cases of all ages based on consensus guidelines at the time of their diagnosis [2, 4, 32, 33]. For this study, patients were included if they were originally scheduled to undergo an upper endoscopy at our center during the period of time between mid-March and May of 2020. This period was specifically chosen because it was at the beginning of the pandemic and a time when the number of non-urgent medical procedures that were performed was abruptly limited [34, 35]. At our center, all elective outpatient endoscopies were canceled during this time period. In order for a procedure to be retained on the schedule and performed, justification was required to document the clinical urgency and patient benefit as balanced by the risk of COVID-19 in the expanding pandemic. We felt that this situation therefore provided an opportunity for a natural experiment to determine outcomes in this set of EoE patients with their procedures canceled. This study was approved by the UNC Institutional Review Board.

Data Elements and Outcomes

Once patients were identified, data were extracted from the medical record using a standardized collection form. Data of interest included clinical, endoscopic, and histological features. Specifically, we collected demographics, EoE historical data, treatments, details about endoscopy done most recently prior to the pandemic ("pre-pandemic endoscopy"), and, for patients who returned for their next procedure during the pandemic, details about that endoscopy ("next endoscopy").

The primary outcome of interest was histologic response (defined as < 15 eos/hpf) [36, 37]. Endoscopic findings were compiled individually as dichotomous variables (for example, rings: yes/no), and with the EoE Endoscopic Reference Score (EREFS) [38, 39]. For this, the overall worse score from throughout the esophagus was extracted (exudates: 0–2; rings: 0–3; edema: 0–1; furrows: 0–2; stricture: 0–1) [40]. When present, the smallest diameter of an esophageal stricture or area of narrowing was estimated by the endoscopist (typically using the dilator to measure the size) [41], and if dilation was performed, the post-dilation largest size achieved was also noted. Because this was a retrospective study, we were not able to assess validated or prospectively obtained patient-reported outcomes. Instead, we extracted the global patient-reported symptom response, as indicated in the chart, which is a metric we have successfully used previously [28, 31, 42].

Analysis

We used descriptive statistics to summarize the characteristics of the study population. Patients who were scheduled during the study timeframe were divided into several groups: those who had the procedure as scheduled, those who were canceled, and of those who were canceled, those who ultimately returned for a procedure. We compared features and outcomes between several groups (Fig. 1). These comparisons included patients who were canceled to those who were not canceled for their pre-pandemic endoscopy, as well for their next endoscopy. Additionally, we compared in paired fashion the pre-pandemic endoscopy for canceled patients who then ultimately returned to the next endoscopy. For all comparisons, two-sample t-tests and Chi-squares were used for means and proportions, respectively, for between group comparisons, and paired t-tests and McNemar's tests were used for means and proportions, respectively, for within-group comparisons. Analyses were performed using Stata version 12 (StataCorp, College Station, TX).

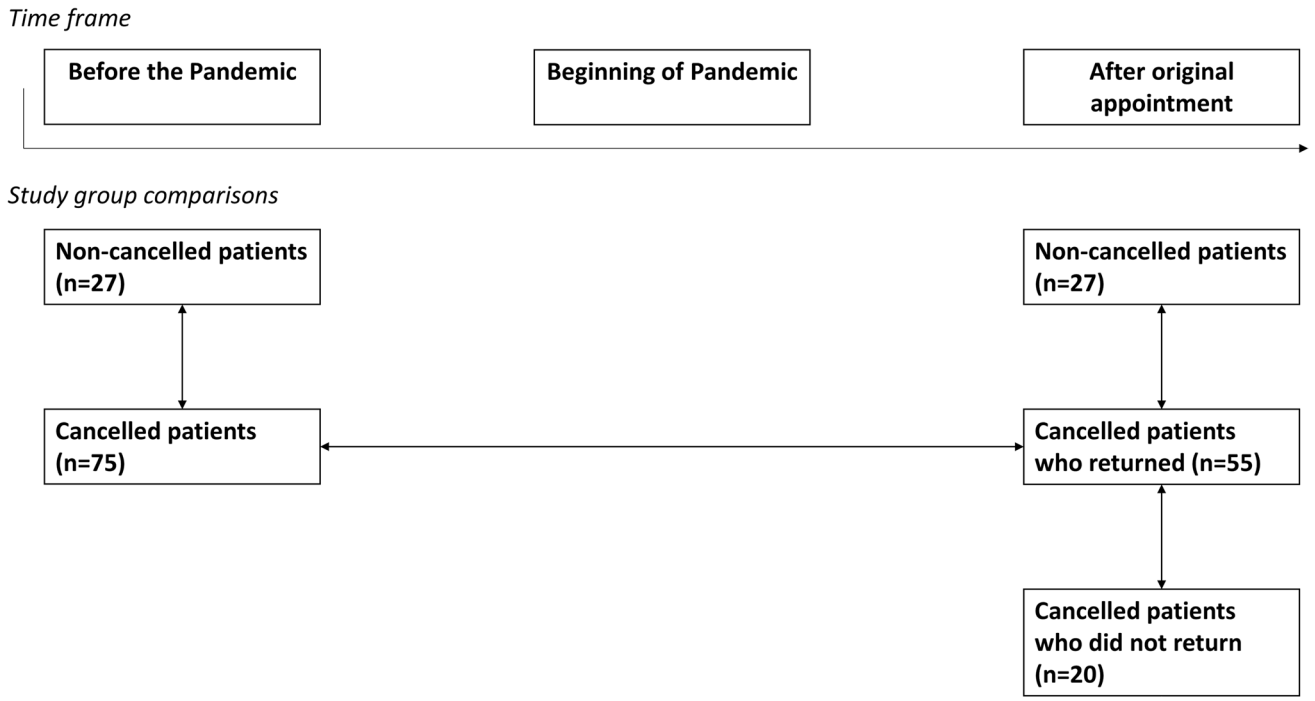

Fig. 1 Patient groups, time points, and comparisons for the study. The timeline is noted at the top of the figure, and comparisons are indicated with double-headed arrows

Results

There were 102 patients who had an endoscopy scheduled for EoE during our specified timeframe. Of these, 27 underwent their endoscopy as planned and 75 had their procedure canceled because of the pandemic. When comparing patients who had their endoscopy canceled to those who did not, most demographic and clinical features were similar (Table 1). However, compared to those who were canceled, patients who were not canceled had previously required more esophageal dilation (100% vs 75%; $p = 0.004$), had more severe fibrosis (pre-dilation esophageal diameter 13.6 vs 15.1 mm; $p = 0.04$), and were more likely to have a higher proportion on an elimination diet (56% vs 33%; $p = 0.04$). Of the 75 patients who had their original endoscopy canceled, 20 (27%) never returned. Few differences were detected when we compared the patients whose appointment was originally canceled but returned to those who were canceled but did not return, though those who returned had a higher use of topical corticosteroids (tCS) (51% vs 15%; $p = 0.005$) and were more likely to be returning for a surveillance endoscopy (Supplemental Table 1).

Of the subgroup of patients whose appointment was canceled but who eventually returned ($n = 55$), the mean time between their pre-pandemic endoscopy and the rescheduled next endoscopy was 1.1 ± 0.7 years. The mean time between the endoscopy that was canceled and their eventual next endoscopy was 0.5 ± 0.3 years. When these two endoscopies were compared, even though treatments, most endoscopic findings, and symptom and histologic responses were similar, after the COVID-induced cancellation and delay a higher proportion of patients required dilations (71% vs 58%; $p = 0.05$) and had a smaller esophageal diameter than the size achieved before the start of the pandemic (16.8 mm to 15.0 mm; $p < 0.001$) (Table 2). In addition, there were 17 patients in this group who did not have strictures, narrowing, or required dilation during their pre-pandemic endoscopy. Of these, 5 (29%) progressed to have strictures, 1 (6%) to narrowing, and 7 (41%) to dilation when they returned for their next endoscopy.

We were not able to identify features related to treatment or adherence that were associated with progression as the majority of patients remained on some treatment (PPI, steroids, or diet) and were adherent to treatment (Table 2). Of the 22 patients on diet elimination 17 were on a stable diet and 5 were in the reintroduction phase, and there was no pattern related to this or the type of diet elimination and progression; the types of diet were variable ($n = 3$ for 6FED, none for 4FED, 1 for 3FED, 7 for 2FED, and 11 for other types of elimination). There were 17 patients identified who were on PPI but not on diet or steroids, and only 6

Table 1 Clinical, endoscopic and histologic data for EoE patients who underwent endoscopy during the initial part of the COVID-19 pandemic compared to those whose procedure was canceled

	Scoped ($n=27$)	Canceled ($n=75$)	p†
Age (mean years ± SD)	33.8 ± 11.3	39.8 ± 13.9	0.05
Male (n, %)	18 (67)	54 (72)	0.60
White (n, %)	26 (96)	73 (97)	0.63
EoE historical details			
Duration of EoE (mean years ± SD)	4.3 ± 4.2	4.1 ± 3.5	0.82
Ever had histologic response (n, %)*	16 (59)	43 (57)	0.86
Ever had esophageal dilation (n, %)	27 (100)	56 (75)	0.004
Details about last "pre-COVID-19" EGD			
Reason for EGD (n, %)			0.10
Diagnostic procedure	2 (7)	11 (15)	
Treatment change	15 (56)	51 (68)	
Surveillance on stable treatment	10 (37)	13 (17)	
Treatments (n, %)			
PPI	11 (41)	36 (48)	0.52
Topical steroids	9 (33)	31 (41)	0.47
Elimination diet	15 (56)	25 (33)	0.04
Adherent to treatment	24 (89)	60 (80)	0.30
Endoscopic findings (n, %)			
Exudates	17 (63)	40 (54)	0.46
Rings	17 (63)	49 (66)	0.76
Edema	15 (56)	46 (62)	0.55
Furrows	17 (63)	54 (73)	0.33
Stricture	22 (81)	49 (66)	0.14
Narrowing	7 (26)	8 (11)	0.06
Crepe-paper	2 (7)	2 (3)	0.28
Dilation performed	19 (70)	43 (58)	0.26
Initial size (mean mm ± SD)	13.6 ± 3.5	15.1 ± 2.2	0.04
Final size (mean mm ± SD)	15.5 ± 3.1	17.0 ± 1.9	0.02
Total EREFS (mean ± SD)	3.8 ± 2.3	3.7 ± 1.9	0.69
Symptom response (n, %)	13 (48)	44 (59)	0.35
Peak eosinophil count (eos/hpf ± SD)	44.9 ± 40.3	35.0 ± 38.9	0.27
Histologic response (n, %)*	8 (30)	22 (30)	0.99

*Histologic response defined as < 15 eos/hpf

†Means compared with 2 sample t-tests; proportions compared with chi-square

(35%) were in histologic remission when they returned for the endoscopy.

When we compared the second endoscopy from the non-canceled patients to the endoscopy after the eventual return of the canceled patients, non-canceled patients more frequently had strictures (93% vs 65%; $p=0.008$), narrowing (33% vs 9%; $p=0.006$) and dilation (93% vs 71%; $p=0.03$), with narrower esophageal calibers (pre-dilation esophageal diameter 13.4 vs 15.0 mm; $p=0.01$) compared to those who were canceled but eventually returned (Table 3).

Discussion

EoE is a chronic condition, and upper endoscopy is important for monitoring endoscopic and histologic response, and for performing esophageal dilations in patients with strictures or narrowing. The COVID-19 pandemic has not only had a direct impact on patients with EoE and on GI practice in general [14–20, 23], but indirect impacts are likely though not yet extensively studied. The goal of our study, therefore, was to determine the impact of endoscopic procedure cancellations due to COVID-19 on outcomes in our EoE patient population. There were several notable findings of this natural experiment. First, of the 75 patients canceled, just over a quarter never returned for their routinely scheduled care. This is a surprisingly high number for a set of patients who were being followed, had previously had an endoscopy, and were already scheduled for a monitoring procedure. However, emerging data have highlighted loss to follow-up as a problem in EoE patients, both at the time of presentation with a food impaction, and after diagnosis [43, 44]. Second, of the patients who ultimately returned, their follow-up was delayed by an average of 6 months (with the next endoscopy more than a year after the previously scheduled procedure), and when they returned they tended to require higher rates of dilation and lost some esophageal caliber; some had even developed de-novo fibrostenosis. This adds to the emerging literature about EoE disease progression even after diagnosis and may inform discussions about the most appropriate monitoring intervals [10, 11].

A survey conducted by Spindel and colleagues assessed reasons why patients missed healthcare appointments during the beginning of the COVID-19 pandemic [45]. This study, as well as others, found that procedural appointments, such as endoscopies, were missed much more often than primary care appointments due to the increased use of telehealth visits and associated fear of contracting COVID-19 during an in-person visit [34, 35, 45, 46]. Although our study could not assess reasons that a large number of canceled patients did not return despite being contacted to reschedule, these explanations have face validity in EoE as well. Other studies implicate reasons outside patient's control, such as: hospital policy limiting the number of procedures [14, 22, 34], being unable to secure a pre-procedure COVID screening test [35, 46], and testing positive on a screening test and having to cancel again [34, 46, 47].

Table 2 Clinical, endoscopic, and histologic data for patients who were canceled and ultimately returned for their endoscopy, comparing the pre-COVID endoscopy to the next endoscopy performed during the pandemic ($n=55$)

	Last procedure (pre-COVID)	After returned (during COVID)	p†
Treatments (n, %)			
PPI	27 (49)	24 (44)	0.44
Topical steroids	28 (51)	24 (44)	0.29
Elimination diet	19 (35)	22 (40)	0.26
Adherent to treatment	41 (75)	46 (84)	0.16
Endoscopic findings (n, %)			
Exudates	30 (55)	26 (47)	0.41
Rings	38 (69)	35 (64)	0.37
Edema	32 (58)	32 (58)	1.0
Furrows	39 (71)	24 (62)	0.25
Stricture	38 (69)	36 (65)	0.48
Narrowing	8 (15)	5 (9)	0.26
Crepe-paper	2 (4)	0 (0)	0.16
Dilation performed	32 (58)	39 (71)	0.05
Initial size (mean mm ± SD)	14.9 ± 2.4	15.0 ± 2.7**	0.67
Final size (mean mm ± SD)	16.8 ± 2.0**	16.8 ± 1.8	0.70
Total EREFS (mean ± SD)	3.5 ± 1.9	3.1 ± 2.1	0.19
Symptom response (n, %)	35 (64)	32 (58)	0.47
Peak eosinophil count (eos/hpf ± SD)	29.9 ± 34.1	34.9 ± 42.3	0.35
Histologic response (n, %)*	18 (33)	21 (38)	0.65

*Histologic response defined as < 15 eos/hpf

†Means compared with paired t-tests; proportions compared with McNemar's test

**For the comparison of the final size (pre-COVID) to initial size (during), the decrease is significant, $p<0.001$

In our study population, it is also interesting to note that approximately one quarter of EoE patients were not canceled in the first place. Per health system policies put into place at the beginning of the pandemic, procedures could only be performed if there was a compelling indication with a risk–benefit ratio that still favored patient benefit. It is not surprising, then, that these subjects had more severe fibrostenotic disease, all procedures were therapeutic (100% underwent dilation), and a subset had already embarked on food elimination dietary therapy and monitoring for response was also needed. For the canceled patients, an important finding was the worsened fibrostenotic features compared to their pre-pandemic endoscopy. In a previous study by Chang and colleagues, the longer that there was a "gap" in routine EoE care and monitoring, the higher the chance of having increased stricture, narrowing, and dilation rates [10]. While that study evaluated a minimum gap of 2 years (with some patients having as long as 8 or more years), our study suggests that a shorter mean delay may lead to the same type of progression, though we note that our study population tended to be more severe and had high rates of fibrostenosis as demonstrated by esophageal dilation in 58%-70% at baseline. A recent study by Bon and colleagues analyzed long-term follow-up in the Swiss EoE cohort and found that absence of close follow-up, defined as a year or less, was associated with stricture develop after controlling for potential confounding factors. These data are also consistent with our findings [11].

There are several limitations to our study. First, we recognize that this study stems from a single academic center. However, we believe the study design and population were appropriate to test our hypothesis, but acknowledge that the results may not be generalizable given the relatively severe baseline features of our population. Second, given the retrospective nature of the study, we were not able to use validated patient-reported outcomes and instead had to rely on global symptom response, but this is still informative. Third, we were not able to explore the reasons why people did not reschedule their appointments, and future work should investigate these reasons to facilitate follow-up in EoE and minimize disease progression. Strengths of the study included utilization of a natural experiment design, with procedure cancellations from the COVID-19 pandemic that could not be mimicked in a different setting, rigorous and standardized data collection, and a well-characterized patient population.

In conclusion, a large number of EoE patients had their endoscopies canceled during the initial part of the COVID-19 pandemic. Many of the patients who were not

Table 3 Comparison of the follow-up endoscopy for patients who were not canceled at the beginning of the pandemic to return endoscopy after for patients who were initially canceled

	Next exam of those initially scoped ($n=27$)	After return for those initially canceled ($n=55$)	p†
Time between prior EGD and return EGD (mean years ± SD)	0.8 ± 0.6	1.1 ± 0.7	0.02
Treatments (n, %)			
PPI	6 (22)	24 (44)	0.06
Topical steroids	12 (44)	24 (44)	0.95
Elimination diet	15 (56)	22 (40)	0.18
Adherent to treatment	26 (96)	46 (84)	0.13
Endoscopic findings (n, %)			
Exudates	18 (67)	26 (47)	0.10
Rings	20 (74)	35 (64)	0.35
Edema	21 (78)	32 (58)	0.08
Furrows	19 (70)	24 (62)	0.45
Stricture	25 (93)	36 (65)	0.008
Narrowing	9 (33)	5 (9)	0.006
Crepe-paper	1 (4)	0 (0)	0.15
Dilation performed	25 (93)	39 (71)	0.03
Balloon	12 (48)	23 (59)	0.39
Savary	13 (52)	16 (41)	0.39
Initial size (mean mm ± SD)	13.4 ± 3.0	15.0 ± 2.7	0.01
Final size (mean mm ± SD)	15.8 ± 2.2	16.8 ± 1.8	0.01
Total EREFS (mean ± SD)	4.1 ± 1.9	3.1 ± 2.1	0.05
Symptom response (n, %)	14 (52)	32 (58)	0.59
Peak eosinophil count (eos/hpf ± SD)	43.6 ± 36.3	34.9 ± 42.3	0.30
Histologic response (n, %)*	8 (30)	21 (38)	0.45

*Histologic response defined as < 15 eos/hpf

†Means compared with 2 sample t-tests; proportions compared with chi-square

canceled demonstrated more fibrostenosis and required more dilations than those who were canceled. Moreover, greater than 25% of those canceled never returned for care, which is an unmeasured impact of the pandemic, and it is uncertain whether EoE findings have worsened in this group. Those whose appointment was canceled had progression of some fibrostenotic features once they returned for endoscopy, which took longer than a year from their prior procedure, with an average delay of 6 months. More work is needed in the future to better understand the reasons behind the progression of EoE over a relatively short period of time in this population. However, these worsened EoE outcomes provide additional justification to a growing literature that should stress the importance of routine follow-up and monitoring endoscopy in many EoE patients, and especially those with pre-existing fibrostenosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-022-07610-9.

Author's Contribution AAO: Study design, data collection and interpretation, manuscript drafting, critical revision. ESD: Project conception, study design, data collection, data analysis/interpretation, manuscript drafting, critical revision.

Funding This study was supported in part by NIH T35 DK007386.

Declarations

Conflict of interest None of the author report any potential conflicts of interest related to this manuscript.

References

1. O'Shea KM, Aceves SS, Dellon ES et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology.* 2018;154:333–345. https://doi.org/10.1053/j.gastro.2017.06.065.
2. Liacouras CA, Furuta GT, Hirano I et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128:3–22. https://doi.org/10.1016/j.jaci.2011.02.040.

3. Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. *Gastroenterology.* 2018;154:319-332.e3. https://doi.org/10.1053/j.gastro.2017.06.067.
4. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology. 2018;155(4):1022–1033.e10. doi:https://doi.org/10.1053/j.gastro.2018.07.009
5. Schoepfer AM, Safroneeva E, Bussmann C et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology.* 2013;145:1230–6.e62. https://doi.org/10.1053/j.gastro.2013.08.015.
6. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc.* 2014;79:577–85.e4. https://doi.org/10.1016/j.gie.2013.10.027.
7. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, Smout AJPM, Bredenoord AJ. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. *Am J Gastroenterol.* 2018;113:836–844. https://doi.org/10.1038/s41395-018-0052-5.
8. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. *J Clin Gastroenterol.* 2016;50:134–140. https://doi.org/10.1097/MCG.0000000000000297.
9. Koutlas NT, Dellon ES. Progression from an Inflammatory to a Fibrostenotic Phenotype in Eosinophilic Esophagitis. Case Rep Gastroenterol. 2017;11(2):382–388. Published 2017 Jun 15. doi:https://doi.org/10.1159/000477391
10. Chang NC, Thakkar KP, Ketchem CJ, Eluri S, Reed CC, Dellon ES. A Gap in Care Leads to Progression of Fibrosis in Eosinophilic Esophagitis Patients [published online ahead of print, 2021 Oct 27]. Clin Gastroenterol Hepatol. 2021;S1542–3565(21)01141–1. doi:https://doi.org/10.1016/j.cgh.2021.10.028
11. Bon L, Safroneeva E, Bussmann C et al. Close follow-up is associated with fewer stricture formation and results in earlier detection of histological relapse in the long-term management of eosinophilic esophagitis. *United European Gastroenterol J.* 2022;10:308–318. https://doi.org/10.1002/ueg2.12216.
12. Galanopoulos M, Gkeros F, Doukatas A et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World J Gastroenterol.* 2020;26:4579–4588. https://doi.org/10.3748/wjg.v26.i31.4579.
13. McDermott CV, Cox EJ, Scanlan JM, Alicic RZ. COVID-19 and Gastrointestinal Tract Symptoms: Recognition, Containment, and Learning From the Past. *Mayo Clin Proc.* 2020;95:2320–2324. https://doi.org/10.1016/j.mayocp.2020.08.023.
14. Ekmektzoglou K, Tziatzios G, Siau K et al. Covid-19: exploring the "new normal" in gastroenterology training. *Acta Gastroenterol Belg.* 2021;84:627–635. https://doi.org/10.51821/84.4.014.
15. Iacucci M, Cannatelli R, Labarile N, et al. Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period [published correction appears in Lancet Gastroenterol Hepatol. 2021 Mar;6(3):e2]. Lancet Gastroenterol Hepatol. 2020;5(6):598–606. doi:https://doi.org/10.1016/S2468-1253(20)30119-9
16. Gralnek IM, Hassan C, Beilenhoff U et al. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. *Endoscopy.* 2020;52:483–490. https://doi.org/10.1055/a-1155-6229.
17. Perisetti A, Goyal H, Sharma N. Gastrointestinal Endoscopy in the Era of COVID-19. Front Med (Lausanne). 2020;7:587602. Published 2020 Nov 26. doi:https://doi.org/10.3389/fmed.2020.587602
18. Irisawa A, Furuta T, Matsumoto T et al. Gastrointestinal endoscopy in the era of the acute pandemic of coronavirus disease 2019: Recommendations by Japan Gastroenterological Endoscopy Society (Issued on April 9th, 2020). *Dig Endosc.* 2020;32:648–650. https://doi.org/10.1111/den.13703.
19. Tan X, Guo J, Chen Z, Königsrainer A, Wichmann D. Systematic review and meta-analysis of clinical outcomes of COVID-19 patients undergoing gastrointestinal endoscopy. Therap Adv Gastroenterol. 2021;14:17562848211042185. Published 2021 Aug 30. doi:https://doi.org/10.1177/17562848211042185
20. Chiang AWT, Duong LD, Shoda T et al. Type 2 Immunity and Age Modify Gene Expression of Coronavirus-induced Disease 2019 Receptors in Eosinophilic Gastrointestinal Disorders. *J Pediatr Gastroenterol Nutr.* 2021;72:718–722. https://doi.org/10.1097/MPG.0000000000003032.
21. Savarino E, Lorenzon G, Ghisa M et al. Lack of complications in patients with eosinophilic gastrointestinal diseases during SARS-CoV-2 outbreak. *J Allergy Clin Immunol Pract.* 2020;8:2790-2792.e1. https://doi.org/10.1016/j.jaip.2020.06.041.
22. Savarino EV, Iovino P, Santonicola A, et al. Clinical and Psychological Impact of COVID-19 Infection in Adult Patients with Eosinophilic Gastrointestinal Disorders during the SARS-CoV-2 Outbreak. J Clin Med. 2020;9(6):2011. Published 2020 Jun 26. doi:https://doi.org/10.3390/jcm9062011
23. Zevit N, Chehade M, Leung J, Marderfeld L, Dellon ES. Eosinophilic Esophagitis Patients Are Not at Increased Risk of Severe COVID-19: A Report From a Global Registry. *J Allergy Clin Immunol Pract.* 2022;10:143-149.e9. https://doi.org/10.1016/j.jaip.2021.10.019.
24. Qeadan F, Chehade M, Tingey B, Egbert J, Dellon ES, Peterson KA. Patients with eosinophilic gastrointestinal disorders have lower in-hospital mortality rates related to COVID-19. *J Allergy Clin Immunol Pract.* 2021;9:4473-4476.e4. https://doi.org/10.1016/j.jaip.2021.09.022.
25. Franceschini L, Macchiarelli R, Rentini S, Biviano I, Farsi A. Eosinophilic esophagitis: is the Th2 inflammation protective against the severe form of COVID-19? *Eur J Gastroenterol Hepatol.* 2020;32:1583. https://doi.org/10.1097/MEG.0000000000001909.
26. Eluri S, Runge TM, Hansen J, et al. Diminishing Effectiveness of Long-Term Maintenance Topical Steroid Therapy in PPI Non-Responsive Eosinophilic Esophagitis. Clin Transl Gastroenterol. 2017;8(6):e97. Published 2017 Jun 15. doi:https://doi.org/10.1038/ctg.2017.27
27. Reed CC, Corder SR, Kim E et al. Psychiatric Comorbidities and Psychiatric Medication Use Are Highly Prevalent in Patients With Eosinophilic Esophagitis and Associate With Clinical Presentation. *Am J Gastroenterol.* 2020;115:853–858. https://doi.org/10.14309/ajg.0000000000000597.
28. Reed CC, Fan C, Koutlas NT, Shaheen NJ, Dellon ES. Food elimination diets are effective for long-term treatment of adults with eosinophilic oesophagitis. *Aliment Pharmacol Ther.* 2017;46:836–844. https://doi.org/10.1111/apt.14290.
29. Runge TM, Eluri S, Cotton CC et al. Outcomes of Esophageal Dilation in Eosinophilic Esophagitis: Safety, Efficacy, and Persistence of the Fibrostenotic Phenotype. *Am J Gastroenterol.* 2016;111:206–213. https://doi.org/10.1038/ajg.2015.399.
30. Sperry SL, Woosley JT, Shaheen NJ, Dellon ES. Influence of race and gender on the presentation of eosinophilic esophagitis. *Am J Gastroenterol.* 2012;107:215–221. https://doi.org/10.1038/ajg.2011.342.
31. Ketchem CJ, Thakkar KP, Xue A et al. Older patients with eosinophilic esophagitis have high treatment response to topical steroids. *Dig Liver Dis.* 2022;54:477–482. https://doi.org/10.1016/j.dld.2021.10.004.

32. Furuta GT, Liacouras CA, Collins MH et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology.* 2007;133:1342–1363. https://doi.org/10.1053/j.gastro.2007.08.017.
33. Dellon ES, Gonsalves N, Hirano I et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol.* 2013;108:679–693. https://doi.org/10.1038/ajg.2013.71.
34. Whaley CM, Pera MF, Cantor J, et al. Changes in Health Services Use Among Commercially Insured US Populations During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(11):e2024984. Published 2020 Nov 2. doi:https://doi.org/10.1001/jamanetworkopen.2020.24984
35. Ni B, Gettler E, Stern R, et al. Disruption of medical care among individuals in the southeastern United States during the COVID-19 pandemic. J Public Health Res. 2021;11(1):2497. Published 2021 Sep 24. doi:https://doi.org/10.4081/jphr.2021.2497
36. Wolf WA, Cotton CC, Green DJ et al. Evaluation of Histologic Cutpoints for Treatment Response in Eosinophilic Esophagitis. *J Gastroenterol Hepatol Res.* 2015;4:1780–1787. https://doi.org/10.17554/j.issn.2224-3992.2015.04.562.
37. Reed CC, Wolf WA, Cotton CC et al. Optimal Histologic Cutpoints for Treatment Response in Patients With Eosinophilic Esophagitis: Analysis of Data From a Prospective Cohort Study. *Clin Gastroenterol Hepatol.* 2018;16:226-233.e2. https://doi.org/10.1016/j.cgh.2017.09.046.
38. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut.* 2013;62:489–495. https://doi.org/10.1136/gutjnl-2011-301817.
39. Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the Eosinophilic Esophagitis Endoscopic Reference Score in Diagnosis and Determining Response to Treatment [published correction appears in Clin Gastroenterol Hepatol. 2016 Jun;14 (6):919]. Clin Gastroenterol Hepatol. 2016;14(1):31–39. doi:https://doi.org/10.1016/j.cgh.2015.08.040
40. Ma C, Bredenoord AJ, Dellon ES, et al. Reliability and responsiveness of endoscopic disease activity assessment in eosinophilic esophagitis [published online ahead of print, 2022 Feb 1]. Gastrointest Endosc. 2022;S0016–5107(22)00082–7. doi:https://doi.org/10.1016/j.gie.2022.01.014
41. Eluri S, Tappata M, Huang KZ, et al. Distal esophagus is the most commonly involved site for strictures in patients with eosinophilic esophagitis. Dis Esophagus. 2020;33(2):doz088. doi:https://doi.org/10.1093/dote/doz088
42. Ketchem CJ, Reed CC, Stefanadis Z, Dellon ES. Treatment with compounded fluticasone suspension improves the clinical, endoscopic, and histologic features of eosinophilic esophagitis. Dis Esophagus. 2021;34(7):doaa120. doi:https://doi.org/10.1093/dote/doaa120
43. Chang JW, Olson S, Kim JY, et al. Loss to follow-up after food impaction among patients with and without eosinophilic esophagitis. Dis Esophagus. 2019;32(12):doz056. doi:https://doi.org/10.1093/dote/doz056
44. Chang NC, Ketchem CJ, Eluri S, et al. Loss to Follow-Up and Health Care Utilization After Initial Diagnosis of Eosinophilic Esophagitis [published online ahead of print, 2021 Sep 28]. Dig Dis Sci. 2021;https://doi.org/10.1007/s10620-021-07259-w. doi:https://doi.org/10.1007/s10620-021-07259-w
45. Spindel JF, Spindel J, Gordon K, Koch J. The Effects of The COVID-19 Pandemic on Primary Prevention. *Am J Med Sci.* 2022;363:204–205. https://doi.org/10.1016/j.amjms.2021.12.003.
46. Czeisler MÉ, Marynak K, Clarke KE, et al. Delay or Avoidance of Medical Care Because of COVID-19–Related Concerns — United States, June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1250–1257. DOI: http://dx.doi.org/https://doi.org/10.15585/mmwr.mm6936a4external icon
47. Spalletta G, Porcari DE, Banaj N, Ciullo V, Palmer K. Effects of COVID-19 Infection Control Measures on Appointment Cancelation in an Italian Outpatient Memory Clinic. Front Psychiatry. 2020;11:599844. Published 2020 Nov 30. doi:https://doi.org/10.3389/fpsyt.2020.599844