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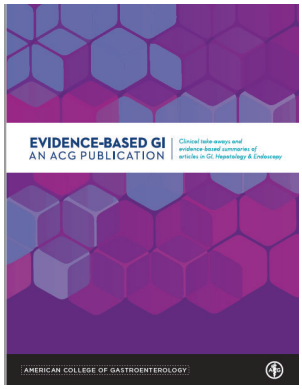

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Does Prophylactic Clipping Prevent Delayed Bleeding After EMR of Large Proximal Colonic Polyps?

Ahmad Abu-Heija, MBBS
Associate Editor

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his article reviews Kemper G, Turan AS, Schreuder RM, et al. The effect of prophylactic clipping on delayed bleeding after proximal colonic endoscopic mucosal resection: a multicenter randomized controlled trial (CLIPPER). Endoscopy. 2025 Jul 22; DOI: 10.1055/a-2637-3180.

Correspondence to Ahmad Abu-Heija, MD, Associate Editor. Email: EBGI@gi.org

Keywords: Colorectal adenoma; colorectal neoplasia; endoscopic polypectomy; therapeutic endoscopy; delayed bleeding; post polypectomy bleeding

STRUCTURED ABSTRACT

Question: Does prophylactic clip closure after endoscopic mucosal resection (EMR) of large (≥20 mm) nonpedunculated polyps in the proximal colon reduce delayed post-EMR bleeding in routine clinical practice?

Design: Multicenter, randomized controlled clinical trial (Dutch EMR Study Group).

Setting: Conducted at 19 Dutch hospitals (6 academic, 13 non-academic) between 2018 and 2021.

Patients: A total of 356 adult patients with large, nonpedunculated colorectal polyps (≥20 mm) were included.

Intervention: Patients were randomly assigned (1:1) to prophylactic clipping vs no clipping after hot snare EMR.

Outcomes: Primary outcome was delayed bleeding within 30 days (hematochezia, requiring emergency department (ED) visit, transfusion, hospitalization, or reintervention). Secondary outcomes were clip closure rate, perforation, post-polypectomy syndrome, and bleeding severity.

Data Analysis: Statistical comparisons were made using intention-to-treat (ITT) analysis.

Funding: Dutch Digestive Foundation (MLDS) supported this study with a research grant. Olympus (Japan) provided the Quick Clip Pro without charge for this trial. The funder had no role in study design, data collection, analysis, or manuscript preparation.

Results:
Bleeding. Between May 2018 and December 2021, 356 patients (177 clipping vs 179 control) with a median polyp size of 30 mm (IQR 25-40 mm). Delayed bleeding occurred in 9.0% in the prophylactic clipping group vs 6.1% in the control group; $P = 0.30$. All bleeding was mild or moderate without severe bleeding or deaths. No difference between academic and non-academic centers.

Complete clip closure. Achieved in 71.8% of clipping group. Delayed bleeding: 4.8% (complete closure) vs 19.6% (partial closure) vs 6.1% (control) – not statistically significant.

Risk factors for delayed bleeding. Cecal polyps (RR 2.23; 95% CI 1.08–4.61) and anticoagulant use (RR 3.23; 95% CI 1.51–6.91).

Clinical relevance. Prophylactic clipping did not reduce delayed bleeding following EMR of large (≥20 mm) proximal nonpedunculated polyps in this pragmatic, nationwide RCT. Bleeding rates and adverse event severity were similar in both groups.

COMMENTARY

Why Is This Important?

Previous RCTs assessing the benefit of prophylactic clipping in large, nonpedunculated polyps have shown mixed results.[1-4]

- Albéniz et al.: Nonsignificant reduction in bleeding (12.1% → 5%; $P = 0.05$).
- Pohl et al.: Significant reduction for proximal lesions (9.6% → 3.3%; $P = 0.001$).
- Gupta et al.: Significant reduction with clipping (10.6% → 3.4%; $P = 0.03$).
- Feagins et al.: No benefit, possibly due to inclusion of smaller (10–19 mm) lesions.

A pooled individual patient data meta-analysis (IPDMA) found delayed bleeding rates of 3.5% (clipped) vs 9.0% (unclipped) (95% CI 0.17–0.54), suggesting benefit.[5]

However, the current study did not find a significant benefit. Possibly explained by:

- Variability in bleeding definitions among trials.
- Effectiveness depending on complete clip closure, which aids wound healing.
- Variability in clips used in the other studies compared to the 'Olympus Quick Clip Pro' used in this study.
- In this study, even with a high complete closure rate (72%), delayed bleeding was 4.8% vs. 6.1% ($P = 0.13$), while partial closure had a much higher rate (19.6%).

This contrasts with prior pooled data showing partial closure still reduced bleeding (1.7% vs 9.0%; $P = 0.001$).[5]

Key Study Findings

In this multicenter RCT of 356 patients across 19 hospitals, prophylactic clipping after EMR of large (≥20 mm) proximal colon polyps did not reduce delayed bleeding (9.0% vs. 6.1%, $P = 0.30$).

Caution

This study had several important limitations. Although it reflected real-world clinical practice by including both academic and community hospitals, endoscopists varied widely in EMR experience and clip closure proficiency, which may have influenced bleeding outcomes. Endoscopists in training also participated, potentially diluting the protective effect of clipping seen in expert settings. Because randomization occurred after EMR, difficult-to-close lesions may have been unintentionally excluded, introducing selection bias. Additionally, the study could not independently verify closure completeness due to limited image documentation, and center-level differences were not adjusted for

statistically. These factors may have limited the ability to detect a modest true benefit of prophylactic clipping.

My Practice

I primarily utilize cold snare EMR for resection of large non-pedunculated polyps which is associated with significantly lower risk of bleeding.6 When using hot snare EMR, I tend to utilize clips in certain patient subgroups including right colonic lesions, patients on anticoagulants/antiplatelets, and larger polyps. Given these procedures tend to take more time, I prioritize allocating adequate time in my schedule for these cases to ensure adequate clip closure and use clips with anchor prongs (Boston Scientific – Mantis Clip) to aid in defect closure of large EMR sites.

For Future Research

Whether targeted prophylactic clipping in more defined high-risk subgroups (e.g., cecal lesions, large lesions >40 mm, anticoagulant use) reduces bleeding. As well as the role of endoscopist experience and training in optimizing closure success and bleeding prevention. Furthermore, studying the impact of newer clip designs with anchor prongs on risk of delayed bleeding.

Conflict of Interest

Dr. Abu-Heija reports no potential conflicts of interest for this summary.

Abbreviations

ED, emergency department; EMR, endoscopic mucosal resection; IPDMA, individual patient data meta-analysis; ITT, intention-to-treat.

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EVIDENCE-BASED GI
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GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity: A New Chapter in Metabolic Oncology?

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OBESITY

This summary reviews This summary reviews Dai H, Li Y, Lee YA, et al. GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity. JAMA Oncol. 2025 Aug 21:e252681. doi: 10.1001/jamaoncol.2025.2681.

Correspondence: Rahul S. Dalal, MD, MPH. Associate Editor. Email: EBGI@gi.org
Keywords: GLP-1 receptor agonists; obesity; cancer risk; gastrointestinal oncology; precision medicine

STRUCTURED ABSTRACT

Question: Is the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) associated with cancer incidence among adults who are overweight or obese?

Design: Target trial emulation using a retrospective new-user cohort design with 1:1 time-dependent propensity score matching.

Setting: OneFlorida+ network, consisting of 14 health systems, and ~20 million patients from 2014–2024.

Patients: Adults ≥18 years eligible for anti-obesity medication. Excluded patients <18 years with active malignancy or who were pregnant at baseline.

Exposure: GLP-1RA initiation (liraglutide, semaglutide, tirzepatide).

Outcomes: Incidence of 13 obesity-related cancers (bladder, colorectal, kidney, breast, endometrial, thyroid, pancreatic, meningioma, liver, upper gastrointestinal, ovarian, multiple myeloma, and prostate) and lung cancer.

Data Analysis: Matching with Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs; prespecified site-specific analyses, sensitivity checks, heterogeneity of treatment effect (HTE), and individualized treatment effect analyses using machine learning.

Funding: This study was funded by the National Institutes of Health's (NIH) National Institute of Diabetes and Digestive and Kidney Diseases.

Results: In 86,632 matched adults (43,317 GLP-1RA initiators and 43,315 nonusers; mean age 52.4 years; 68.2% women; 50.7% with type 2 diabetes), overall cancer incidence was lower among GLP-1RA users compared with nonusers (13.6 vs 16.4 per 1,000 person-years), corresponding to an HR of 0.83 (95% CI, 0.76–0.91; $P = 0.02$) (**Figure 1**).[1] Site-specific analyses showed reduced risks for endometrial (HR 0.75; 95% CI, 0.57–0.99; $P = 0.05$), ovarian (HR 0.53; 95% CI, 0.29–0.96; $P = 0.04$), and meningioma (HR 0.69; 95% CI, 0.48–0.97; $P = 0.05$), with a possible increased risk of kidney cancer (HR 1.38; 95% CI, 0.99–1.93; $P = 0.04$).

Sensitivity analyses, including Fine-Gray competing risk models and a composite gynecologic cancer model, confirmed robustness of results (HR 0.69; 95% CI, 0.48–0.97 for combined endometrial/ovarian cancer). Heterogeneity analyses suggested the strongest benefit among younger women and those with metabolic risk, while the kidney cancer signal was more pronounced in patients <65 years and overweight (BMI 27–29.9).

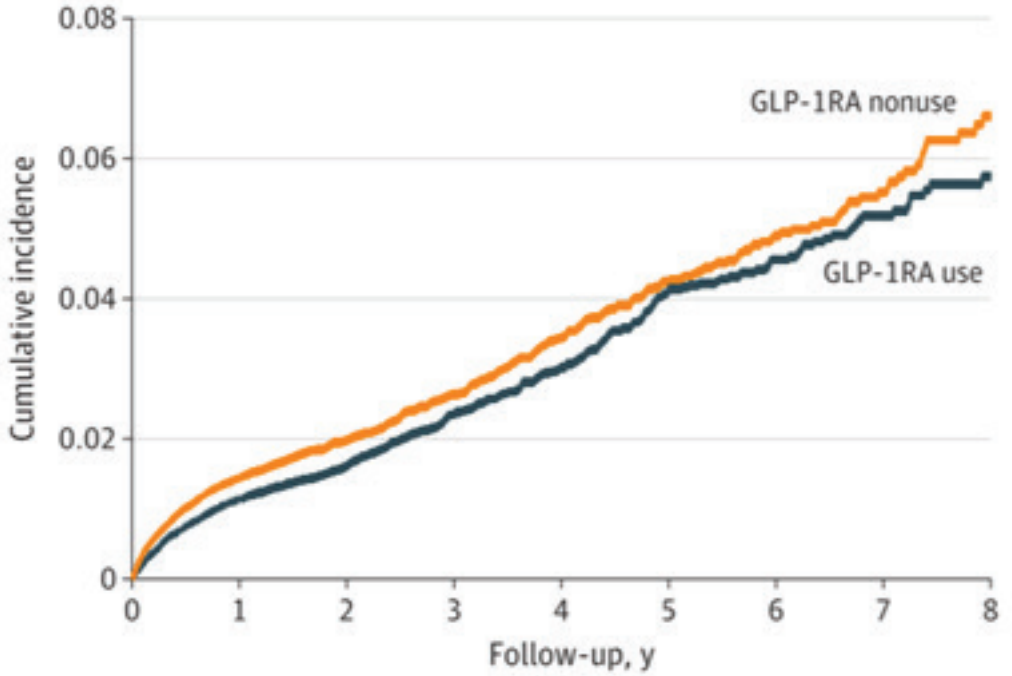

Figure 1. Cumulative incidence of overall cancer in patients receiving GLP-1RAs compared with patients not receiving GLP-1RAs. Kaplan-Meier curves demonstrating lower cumulative incidence of overall cancer among GLP-1RA initiators (blue line) compared with matched nonusers (orange line) during up to 8 years of follow-up.

COMMENTARY

Why Is This Important?

GLP-1RAs have transformed obesity and diabetes care, providing substantial cardiometabolic benefits.[2,3] However, safety concerns, particularly around cancer risk, have persisted since early rodent thyroid studies.[4] With over 137 million US adults now eligible for GLP-1RAs, even modest changes in cancer risk carry major public health implications.

Obesity is also a leading driver of gastrointestinal (GI) and hepatobiliary cancers, from colorectal cancer to hepatocellular carcinoma, making any therapy that modifies obesity-related cancer risk directly relevant to gastroenterology practice.[5]

This study offers contemporary evidence on GLP-1RA association with overall cancer risk in adults with obesity, particularly for hormonally driven malignancies, while raising questions about kidney cancer that warrant ongoing vigilance. This study provides the most rigorous, contemporary evidence on GLP-1RA association with overall cancer risk, particularly for hormonally driven malignancies, while raising questions about kidney cancer that warrant ongoing vigilance. Importantly, it highlights heterogeneity of treatment effects, identifying subgroups who may derive the greatest benefit—or, conversely, experience potential harm from GPL1-RA use.[1]

Among 43,317 GLP-1RA users and 43,315 matched nonusers, overall cancer incidence was 13.6 vs 16.4 per 1,000 person-years, translating to a 17% lower risk with GLP-1RAs (HR 0.83; 95% CI 0.76–0.91; $P=0.02$). Reduced risks were seen for endometrial (HR 0.75; 95% CI, 0.57-0.99; $P=0.05$), ovarian (HR 0.53; 0.29-0.96; $P=0.04$), and meningioma cancers (HR 0.69; 95% CI,0.48-0.97]; $P=0.05$), while a possible increased risk of kidney cancer was observed (HR 1.38; 95% CI 0.99–1.93; $P=0.04$). Results were consistent across sensitivity analyses.

Caution

Despite its strengths – including a large sample size and propensity matching – this is an observational study that is subject to confounders and bias. Cancer latency may exceed the study's follow-up period, limiting the ability to detect long-term effects. Some cancers (e.g., ovarian, pancreatic) had relatively few events, producing wide confidence intervals. The kidney cancer signal, while intriguing, requires replication and may represent chance, confounding, or true risk. Generalizability may be limited beyond the OneFlorida+ network. Ultimately, these findings are hypothesis-generating and should not yet alter cancer screening guidelines.

My Practice

In my practice, where I increasingly prescribe GLP-1RAs for obesity and MASLD, these findings are highly reassuring. These findings are also highly relevant considering the recent FDA approval of GLP-1RAs for MASH with F2-3 fibrosis.

I can now counsel patients that GLP-1RAs not only promote weight loss and cardiometabolic benefits but may also reduce overall cancer risk, particularly for endometrial and ovarian cancers; two malignancies strongly linked to obesity and hyperinsulinemia. At the same time, I acknowledge the possible kidney cancer signal, which I discuss with patients as an area of active investigation rather than a reason to withhold therapy. I continue to emphasize adherence to lifestyle interventions and standard cancer screening, while framing GLP-1RAs as part of a comprehensive prevention strategy.

For Future Research

Longer-term studies are needed to capture cancers with long latency and validate site-specific signals. Mechanistic studies should clarify whether benefits arise from weight loss alone or direct GLP-1 receptor effects on tumor biology. Finally, focused work on GI and hepatobiliary cancers (where obesity and metabolic dysfunction are critical drivers) will be essential to fully define the oncologic

role of GLP-1RAs.

Conflict of Interest

The authors of this summary have no conflicts of interest to disclose.

Abbreviations

BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; HTE, heterogeneity of treatment effect; NIH, National Institute of Health.

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Addition of Bedtime Lafutidine Inhibits Nocturnal Acid-Breakthrough and Improves Sleep Quality in GERD Patients on

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Christopher Vélez, MD
Associate Editor

This article reviews Wang D, He R, Zhang X, Duan C, Bai T, Xu J, Xiang X, Hou X. Addition of bedtime lafutidine inhibits nocturnal acid-breakthrough and improves sleep quality in gastroesophageal reflux disease patients on esomeprazole: A randomized controlled trial. Sci Rep. 2025 Jul 2;15(1):23286.

Correspondence to Christopher Vélez, MD, Associate Editor Email: EBGI@gi.org

Keywords: lafutidine, GERD, NERD, RCT.

STRUCTURED ABSTRACT

Question: Is the addition of bedtime lafutidine 10 mg (a new generation histamine 2-receptor antagonist) to esomeprazole 20 mg twice daily effective in inhibiting acid and improving the clinical patient's gastroesophageal reflux disease (GERD) symptoms?

Design: Single-center, observer-blinded, placebo-controlled, randomized trial.

Setting: A single center in China.

Patients: Patients had to meet all of the inclusion criteria for enrollment: 1) aged between 18 and 65-years old; 2) GERD-Q score≥8 with nocturnal symptoms (regurgitation

or heartburn); 3) completed upper endoscopy within the past year; 4) willingness to take part in this study. Patients with any of the following conditions were excluded: 1) there are contraindications to esophageal high-resolution esophageal manometry and 24-h pH monitoring, such as cardiopulmonary dysfunction, esophageal stenosis, or varices; 2) pregnant or lactating women; 3) participating in other clinical studies; 4) taking gastric acid-inhibiting drugs within 1 week.

Interventions/Exposure: The duration of treatment was 1 week. Patients were randomly assigned to either the treatment group (lafutidine+esomeprazole) or the control group (placebo + esomeprazole). Baseline information, symptom evaluation, and sleep quality were assessed at enrollment and upon completion of treatment. High-resolution esophageal manometry and 24-hour multichannel intraluminal impedance monitoring were performed on the last day of the treatment.

Outcome: The primary outcome was the intragastric pH metrics assessed after 1 week of treatment, including the nocturnal acid breakthrough rate and the gastric pH>4 holding time ratio (pH 4 HTR). The secondary outcomes include esophageal pH metrics, changes in symptom scores, and changes in sleep quality scores.

Data Analysis: The authors hypothesized that the incidence of nocturnal acid breakthrough would be 20% in the esomeprazole + lafutidine group and 60% in the esomeprazole + placebo group. A 10% difference between the 2 groups was determined to be clinically significant. Assuming a dropout rate of 10%, for 80% power at an alpha level of 0.05 with a 2-sided test, the required number of 2each group was 30. An interim analysis was conducted when enrollment reached 80% of the calculated sample size. The clinical trial was terminated early due to the demonstration of significant efficacy of the primary outcomes. The primary outcome analysis was conducted in the intention-to-treat (ITT) population, comprising all patients who received at least 1 dose of study medication. Multiple imputations were performed to address missing data for primary outcomes. All outcome analyses were further evaluated in the per-protocol (PP) population, which included patients who adhered to their assigned treatment regimen and completed the 1-week follow-up questionnaire and esophageal measurements.

Funding: National Natural Science Foundation of China and the Natural Science Foundation of Hubei Province, China.

Results: A total of 48 subjects were included from 59 enrolled participants (24 in each arm). The cohort was predominantly male sex (58.3% in both arms). Of the 59 participants, 8 were not willing to participate, 2 had low symptom scores, and 1 person was pregnant.

The addition of bedtime lafutidine to esomeprazole significantly increased nocturnal intragastric pH>4 holding time ratios and decreased the occurrence of nocturnal acid breakthrough (NAB). GERD patients who added lafutidine experienced a more pronounced improvement in sleep quality, and correlated with NAB reduction.

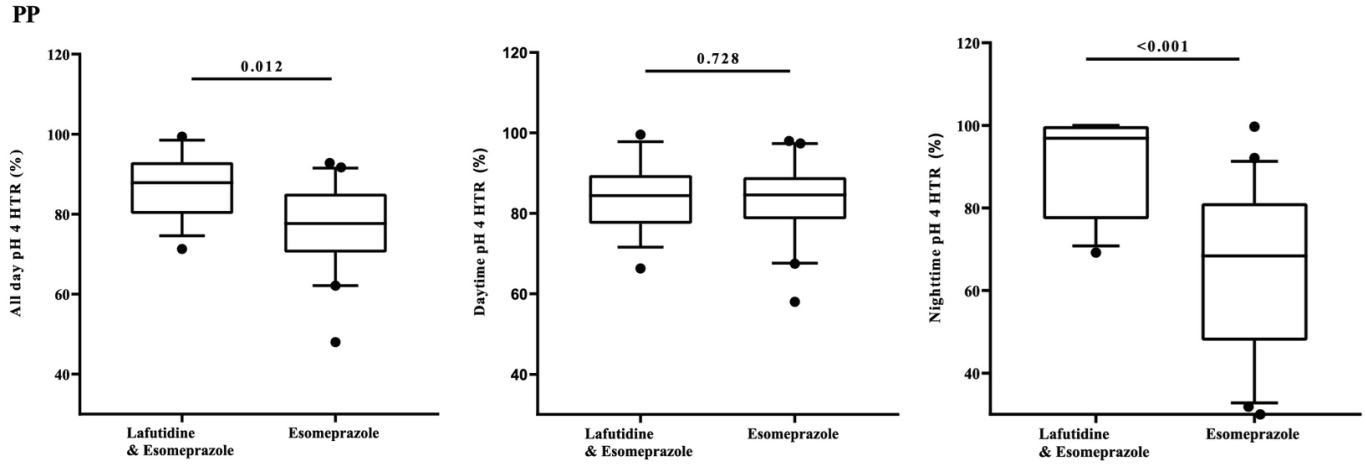

Figure 1. The intragastric 24-h pH parameters of participants of 2 groups. Left: All-day intragastric pH 4 HTR by PP analysis. Middle: Daytime intragastric pH 4 HTR by PP analysis. Right: Nighttime intragastric pH 4 HTR by PP analysis. *Image originally appeared as Figure 2d-f from Wang et al. Reproduced under CCBY-NC-ND 4.0.*

COMMENTARY

Why Is This Important?

The family of illnesses termed "gastroesophageal reflux disease" includes a range of conditions from erosive esophagitis to non-erosive reflux disease (NERD) to reflux hypersensitivity and functional heartburn. The former 2 conditions are marked by acid-related changes to the esophagus, and the latter 2 disorders are thought to be more representative of a nerve hypersensitivity state, including potentially disordered gut-brain interaction (DGBI). It is a common practice to add bedtime/nighttime histamine 2 receptor antagonists when escalation of proton pump inhibitor

therapy to twice daily dosing is not effective.

Through the 2020s, most acid suppression guidelines for the treatment of GERD spectrum complaints center on the penultimately developed treatment class, proton pump inhibitors (PPIs). There was a recognition that histamine 2 receptor antagonists (H2RA) could play an adjunctive role in refractory cases. The American College of Gastroenterology's 2022 GERD guidelines[1] "use of a bedtime H2RA may be beneficial if dosed on an as-needed basis for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment." Lafutidine is thought to have additional benefits over other H2RAs like famotidine.[2] These include possible benefits to mucosal blood flow, with reports of increased plasma concentrations of the calcitonin gene-related peptide and somatostatin. This could offer a more effective treatment compared to older H2Ras.

Key Study Findings

The addition of bedtime lafutidine 10 mg to esomeprazole 20 mg twice daily significantly increased nocturnal intragastric pH >4 holding time ratios and decreased the occurrence of nocturnal acid breakthrough. GERD patients who added lafutidine experienced a more pronounced improvement in sleep quality, correlated with a reduction in nocturnal acid breakthrough. This bolsters existing ACG clinical guidelines for newer-generation H2RAs.

The addition of bedtime lafutidine 10 mg to esomeprazole 20 mg twice daily significantly increased nocturnal intragastric pH >4 holding time ratios and decreased the occurrence of nocturnal acid breakthrough. GERD patients who added lafutidine experienced a more pronounced improvement in sleep quality, correlated with a reduction in nocturnal acid breakthrough. This bolsters existing ACG clinical guidelines for newer-generation H2RAs.

Caution

The major strength of this article is the use of objective assessment of acid exposure time, which has been a significant limitation in other acid reflux spectrum treatments, such as potassium-competitive acid blockers. The caution, paradoxically, can come from this strength – in the community, adding on lafutidine empirically without verified acid exposure status, and potentially missing out on GERD-spectrum conditions like reflux hypersensitivity and functional heartburn that could benefit from central neuromodulation. Rarely do I find patients who fit into a binary classification of "total treatment response" and "total treatment failure." Namely, functional heartburn criteria include the presence of "no" symptom

relief of heartburn symptoms despite optimal use of acid-suppressing therapy. In my clinical practice, at least, rarely does someone describe a total lack of symptom relief from acid suppression therapy, but rather a less-than-expected benefit. I hope those who begin to use lafutidine in their practice keep in mind that there may still be a need to offer pH monitoring[3] (when available) to distinguish among the various GERD-spectrum disorders. Additionally, with the advent of potassium-competitive acid blockers (PCABs), which are potent and independent of meal-based dosing, is there really a market for another H2RA?

My Practice

Based on this trial, I will be on the lookout for lafutidine should it be approved by United States regulatory authorities. The reality is that, despite my pronouncements above, people tend to avoid pH testing unless it is necessary. Often in my very tertiary practice (not reflective o f the typical gastroenterologist's practice), they have already tried adding an H2RA to twice-daily PPI; they would not be in my clinic if they had not. In this instance, I have a greater ability to insist on pH testing. Even so, it is often a hard sell – catheter-based testing is uncomfortable, wireless testing involves endoscopy and anesthesia. But patients are generally willing to consider such testing if they have maximized their acid suppression without significant i mprovement in symptoms. Perhaps acid-based testing can be delayed a little longer, should another tool be available to fight against the GERD burden.

For Future Research

Now that potassium-competitive acid blockers are playing a growing role in the management of GERD, it would be useful to compare PPI + H2RA with PCAB to determine whether one therapy is superior to the other. Another potential avenue is to determine whether this new generation H2RA is effective as needed for the DGBI-spectrum conditions that can be confused with GERD, such as functional heartburn and reflux hypersensitivity. People tend to have concerns about the central neuromodulator agents, given their use in other mental health conditions. Perhaps offering these patients additional pharmacotherapy, such as new-generation acid antagonists, may be effective.

Conflict of Interest

Dr. Vélez has received funding from Ironwood Pharmaceuticals, which has tested and/or offers non-PCAB GERD therapeutics.

Abbreviations

DGBI, disordered gut-brain interaction; GERD, gastroesophageal reflux disease; NAB, nocturnal acid breakthrough; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

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EVIDENCE-BASED GI
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Yield of Esophageal Biopsy Patterns for the Diagnosis of Eosinophilic Esophagitis

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Associate Editor

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This article reviews Muftah M, Harnett DA M, Hiramoto B, et al. Yield of Esophageal Biopsy Patterns for the Diagnosis of Eosinophilic Esophagitis. Gastrointest Endosc. 2025 Aug;102(2):194-201.

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Keywords: Eosinophilic esophagitis (EoE), biopsy, diagnosis.

STRUCTURED ABSTRACT

Question: Does the currently recommended biopsy protocol for the diagnosis of eosinophilic esophagitis (EoE), 6 samples from the distal and either proximal or middle esophagus, adequately capture EoE diagnoses, or is the diagnostic yield improved by altering biopsy site selection?

Design: Retrospective, cross-sectional study of consecutive treatment naive adult patients with newly diagnosed EoE with ≥2 esophageal segments biopsied. Distribution of eosinophilia (≥15 eosinophils [eos]/high-power field [hpf]) in the proximal, middle, and distal esophagus was assessed.

Setting: Three hospitals (2 community and 1 tertiary care center) from 2017-2021.

Patients: Adults presenting with symptoms of esophageal dysfunction and

histopathology showing ≥ 15 eos/hpf on at least 1 esophageal biopsy. All included patients had biopsy samples obtained from ≥ 2 esophageal segments (distal, middle, and/or proximal). Among 727 newly diagnosed patients, mean age was 43.4 ± 14.9 years; 55.9% were male and 89.3% were White. On the index EGD, patient biopsy samples were obtained from 1, 2, and 3 esophageal segments in 216 (29.7%), 451 (62%), and 60 (8.3%) patients, respectively. Thus, 511 patients met inclusion criteria.

Interventions/Exposure: Distribution of esophageal eosinophilia assessed by biopsy site (distal, middle, proximal). Proportion of patients with non-distal disease (<15 eos/hpf in distal biopsies) and segmental eosinophilia patterns were determined.

Outcome: The primary outcome was the distribution of esophageal eosinophilia at the time of diagnostic EGD. Biopsy site was determined by review of endoscopy and pathology reports. Biopsies samples obtained from different sites were placed in separate bottles and labeled as either proximal (proximal to 23 cm), middle (24 to 31 cm), or distal (distal to 32 cm) esophagus. For those with biopsies from 2 sites, proportion of patients with ≥15 eos/hpf from both sites versus 1 site was assessed. For those with 3 sites biopsied, proportion with ≥15 eos/hpf from all 3 biopsy sites versus 2 sites or 1 was assessed. Other outcomes included concordance of esophageal eosinophilia in the proximal and mid esophagus as well as the proportion with and factors associated with non-distal disease.

Data Analysis: Demographic, clinical, endoscopic, and histologic variables of subjects were summarized by using descriptive statistics. Distribution (proximal, middle, and/or distal) of eosinophilia (≥15 eos/hpf) was assessed. Predictors for non-distal disease (<15 eos/hpf on distal biopsy samples) were evaluated by using multivariable logistic regression.

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Results: Among 511 patients with biopsy samples obtained from ≥2 segments, endoscopic features of EoE were seen in 330 (64.6%) and all patients had distal biopsy samples. In this group, 56% had ≥ 1 site with < 15 eos/hpf, and 10% had non-distal disease (i.e., no distal eosinophilia). Among the 254 patients with only 1 site displaying eosinophilia (≥ 15 eos/hpf), 210 (82.7%) had eosinophilia only in the distal segment,

whereas 44 (17.3%) had eosinophilia only in the proximal or middle segment (**Figure 1**).

In those with biopsies from all 3 segments (n=60), 31.7% had eosinophilia in only 1 segment, including 10% with isolated mid esophageal disease and no isolated proximal eosinophilia (**Figure 2**). Discordance between middle and proximal biopsy results occurred in 30% of patients, with 94.4% showing eosinophilia in the middle but not the proximal esophagus. On multivariable analysis, increasing age (odds ratio, 1.02; 95% CI, 1.002-1.04; $P = 0.03$) and male sex (odds ratio, 1.89; 95% CI, 1.002-3.55; $P = 0.049$) were independent predictors of non-distal disease.

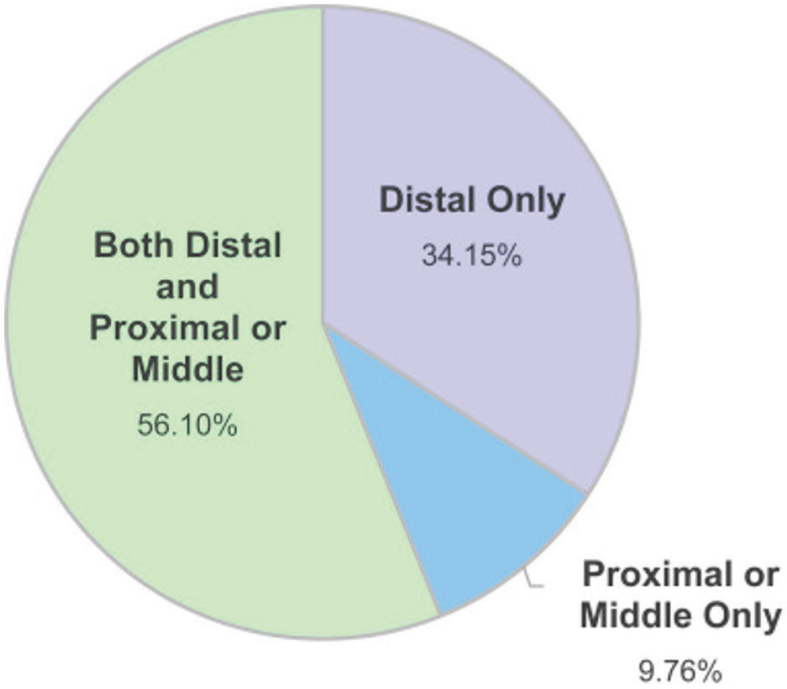

Figure 1. Distribution of eosinophilia in patients with biopsies of 2 esophageal segments.

COMMENTARY

Why Is This Important?

Current consensus guidelines[1] for the diagnosis of EoE recommend obtaining at least 2-4 biopsies from 2 locations in the esophagus: the distal esophagus and either the mid or proximal esophagus. These recommendations are based on limited data[2-4] supporting some key assumptions that (1) nearly all patients with EoE have distal eosinophilia and thus biopsies from this area will have a 100% diagnostic yield; (2) middle and proximal esophageal biopsy specimens are interchangeable; and (3) very few patients have disease isolated to a single esophageal segment. This study is the largest to date to assess the pattern and location of esophageal eosinophilia

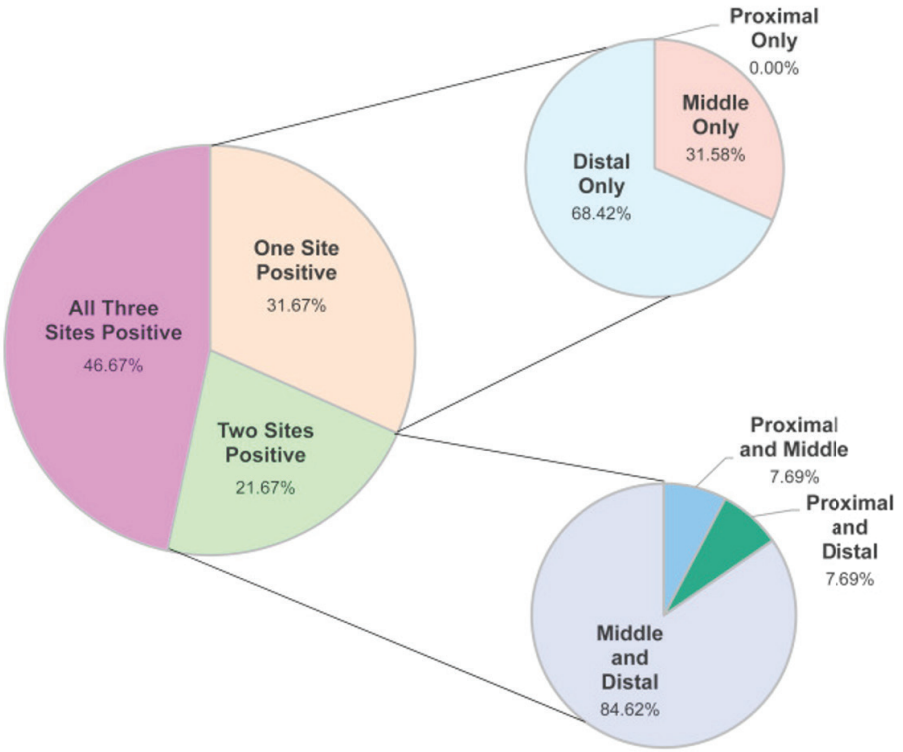

Figure 2. Distribution of eosinophilia in patients with biopsy samples from all 3 esophageal segments.

at the time of initial EoE diagnosis with some findings that potentially challenge current biopsy acquisition recommendations for EoE diagnosis.

Key Study Findings

Aligned with guideline recommendations, 90% of the cohort had distal eosinophilia. However, the study showed that 10% of the cohort had non-distal disease and 30% had discordant findings between eosinophilia in the proximal and middle segment biopsies, with > 90% of them having middle but not proximal eosinophilia. Additionally, 31.7% met diagnostic criteria for EoE with ≥ 15 eos/hpf in only 1 esophageal location. Study findings support current recommendations to obtain multiple biopsies from different locations in the esophagus to maximize the diagnostic yield of EoE.

The results do question the current recommendations that treat mid and proximal esophageal biopsies interchangeably, as in this study the frequency and pattern of discordance in eosinophilia supports greater yield from biopsies obtained from mid esophagus rather than the proximal esophagus. Importantly, although 10% of patients in the subgroup with all 3 sites biopsied had isolated eosinophilia in the middle esophagus, none had proximal-only eosinophilia. Thus, this 10% of patients with EoE could be missed if biopsies were just obtained from the distal and proximal esophagus, which translates to approximately 3,600 missed cases of EoE annually in the United States.[5]

While, independent predictors for non-distal disease were increasing age and male sex, quality and strength of data does not support an individualized biopsy protocol at this time. Finally, in addition to establishing the diagnosis, assessing the distribution of eosinophilia at the time of EoE diagnosis may have implications on management and prognosis. In this study, patients with proximal predominant eosinophilia were less likely to have a histologic response to proton pump inhibitors compared with those with distal predominant eosinophilia, and may provide prognostic information regarding treatment response.

Caution

The study was retrospective and conducted at tertiary care centers, which may limit generalizability. Biopsy site classification relied on endoscopist reporting, and only a minority of patients underwent three-site biopsies, potentially underestimating discordance rates. Selection bias may have influenced which patients received sampling from multiple levels in the esophagus.

My Practice

In my clinical practice, in those patients who I have a suspicion for EoE, I perform biopsies from multiple locations in the esophagus—ideally off PPI therapy. I typically follow current guideline recommendations by routinely sampling the distal and either the proximal or mid esophagus. This study shows that this strategy may miss a meaningful subset of patients with EoE. As a result, I likely will modify my biopsy protocol moving forward and include distal, mid, and proximal esophageal biopsies in all patients with suspected EoE, regardless of endoscopic appearance, to maximize diagnostic yield.

For Future Research

Further studies are needed to determine the utility of characterizing eosinophil distributions and the optimal biopsy protocol for the assessment of EoE. Studies are also needed to define the prognostic and therapeutic implications of eosinophil distribution patterns and to determine the cost-effectiveness of expanded biopsy protocols. Clarifying whether biopsy site selection can potentially guide personalized treatment strategies represents an iportant next step.

Conflict of Interest

The author has no relative conflict of interest.

Abbreviations

EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos, eosinophils; hpf, high-power field; PPI, proton pump inhibitor.

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