Review Article



Impact of *Helicobacter pylori* Status on GERD, Barrett's Esophagus and Esophageal Cancer



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Abstract

Helicobacter pylori (*H. pylori*) is an exceptionally common human pathogen infecting a large proportion of the world's population. It is known to cause gastritis, peptic ulcer disease, non- cardiac gastric adenocarcinoma, and gastric mucosa-assisted lymphoid tissue lymphoma. Test and treat is a widely practiced strategy for *H. pylori* infection worldwide. While there are clear benefits of treating *H. pylori* infection, long-term adverse consequences of widespread eradication of this commonly identified pathogen remain an area of much debate. *H. pylori* infection affects gastric acid secretion and the relationships of the infection with gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC) have been studied but remain controversial topics. Review of the most up-to-date evidence from studies performed in the last 20 years suggests a possible inverse relationship between the prevalence of *H. pylori* infection and GERD. A meta-analysis of a randomized controlled trial showed that eradication of the infection was more likely to cause increased incidence of GERD. Additionally, other studies have noted a significant protective effect of *H. pylori* infection, notably Cag A+ strains, against the development of BE and EAC. In this review article, we will discuss the impact of *H. pylori* infection status on GERD, BE, and esophageal cancer.

Introduction

Helicobacter pylori (*H. pylori*) is a human pathogen that infects as many as 50% of the world's population.¹ It has been implicated in the etiology of gastritis, peptic ulcer disease, and noncardiac gastric adenocarcinoma and gastric mucosa-assisted lymphoid tissue-lymphoma. Given its carcinogenic potential, the current approach to *H. pylori* infection is to test and treat. Over the years, the relationship between *H. pylori* infection and acid reflux related diseases has been re-evaluated. It has been reported that eradication of *H. pylori* infection can lead to worsening symptomatic gastroesophageal reflux disease (GERD), particularly in patients with already weakened lower esophageal sphincter.²

GERD remains one of the most common diseases treated by

gastroenterologists and primary care physicians. It is defined as the retrograde movement of gastric contents into the esophagus causing related symptoms and complications.³ Gastroesophageal reflux is considered part of normal physiology and can occur several times a day in a healthy patient without causing symptoms or mucosal injury.⁴ When the mechanism of luminal clearance and integrity of antireflux barriers are disrupted, pathologic GERD can occur due to prolonged gastric acid exposure to the esophageal mucosa. The most common and classic symptoms of GERD are heartburn and regurgitation, but it can also manifest as chest pain, hoarseness, or chronic cough.³ Mucosal injury can result in erosive esophagitis, peptic strictures, Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC).⁴ While GERD is common, up to 40 to 50 percent of patients with EAC do not experience classic GERD symptoms.³ Five-year survival of EAC after onset of symptoms remains poor at less than 20%.5

The prevalence of GERD and EAC has been increasing in the western hemisphere. While there is no proven causal relationship between *H. pylori* infection and GERD, the prevalence of *H. pylori* infection has been reported to be inversely related to GERD and EAC in earlier observational studies. However, the true effect of *H. pylori* infection on GERD and BE/EAC remains controversial.^{1,6,7} As we continue to treat *H. pylori* to reduce the incidence of gastric cancer and peptic ulcer disease, it is important to evaluate the impact of widespread eradication of *H. pylori* and its effect on gastroesophageal reflux related diseases. Recent American Journal of

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Keywords: *H. pylori*; *Helicobacter pylori*; Gastroesophageal reflux disease; Barrett's esophagus; Esophageal adenocarcinoma; Esophageal cancer.

Abbreviations: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

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Gastroenterology guidelines have suggested a movement toward more noninvasive screening for BE/EAC without requiring GERD as a prerequisite symptom. Understanding all factors that may affect the incidence of GERD and BE/EAC will help targeted and optimal screening efforts to prevent EAC. This review examines the mechanism of how *H. pylori* affects reflux related diseases and the relationship between *H. pylori* infection and its eradication on the incidence of GERD, BE, and EAC.

Methods

A general literature search was conducted in Pubmed, EMBASE, Web of Science, and Google Scholar. Articles that discussed *H. pylori*, reflux disease, BE, and EAC were accessed. The following terms were used: (*H. pylori*) OR (*Helicobacter pylori*) AND ((esophageal cancer) OR (esophageal carcinoma) OR (esophageal adenocarcinoma) OR (Barrett's esophagus) OR (GERD) OR (esophagitis) OR (acid reflux)).

Effect of H. pylori infection and the effect of H. pylori eradication on gastric acid secretion

Gastric acid secretion is thought to play a role in acid reflux disease, which can be affected by *H. pylori* infection in varying degrees based on its distribution in the stomach. Gastric antrum-predominant infection has been shown to increase the production of gastrin (by downregulating somatostatin secreted by antral D cells) leading to increase of acid production by parietal cells found in the gastric corpus.⁸ *H. pylori*-induced corpus gastritis is associated with an inflammatory process that attenuates gastrin's effect on parietal cells, resulting in an overall decrease in acid production, particularly in the setting of severe gastric atrophy.⁸

Eradication of antral-predominant *H. pylori*-associated gastritis may reduce gastrin levels and result in reduction of acid secretion. In those with severe corpus inflammation, eradication may increase acid secretion through removal of functional inhibition on parietal cells from inflammatory products.⁹ Such effects are thought secondary to upregulation of H⁺/K⁺-ATPase mRNA without a change in the number of parietal cells occurring at least after one to three months following *H. pylori* eradication.^{10,11} Data regarding longterm effects on acid secretion following eradication of *H. pylori* infection are lacking, but prolonged, severe corpus inflammation can lead to irreversible loss of parietal cells and achlorhydria.⁸ Thus, most studies have hypothesized that *H. pylori* infection contributes to the GERD-BE-EAC sequence through reduction in acid secretion, especially in the setting of atrophic gastritis.

Other postulated mechanisms on the effect of H. pylori on GERD, BE, and EAC

Kountouras *et al.*¹² argued that the effect of acid secretion on the GERD-BE-EAC pathway was over emphasized. They proposed that *H. pylori* is involved in GERD pathophysiology through induction of inflammatory products such as prostaglandins which relaxes lower esophageal sphincter as well as gastrin induction leading to increased acid secretion that ultimately contributes to development of GERD. Gastrin may also be oncogenic and promotes esophageal carcinomatosis gastrin receptor expression in Barrett's metaplasia specimens and promotion of metaplasia has been demonstrated in mice with hypergastrinemia.¹³ *H. pylori* DNA refluxate in the esophagus might play a role in directly downregulating inflammatory response such as reducing cytokine production that is involved in acceleration of BE development.¹⁴ Association between insulin resistance and *H. pylori* infection

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has been reported with the dysmetabolic state likely promoting GERD-BE-EAC sequence although evidence is limited.¹⁵ High levels of leptin and ghrelin are associated with a higher risk of BE, and *H. pylori* infection may indirectly reduce levels of leptin and ghrelin.^{16,17} Ghrelin stimulates appetite and is associated with obesity, a major risk factor for development of GERD/BE/EAC. *H. pylori* may help maintain normal oral microbiota diversity. Alteration in the oral microbiome with increased gram-negative bacteria and decreased gram-positive bacterial profile has been associated with a higher risk of reflux esophagitis.¹⁸ Lastly, *H. pylori*-induced apoptosis of Barrett's-derived EAC cells has also been reported.¹⁹

H. pylori and GERD

The development of reflux esophagitis after H. pylori eradication was first reported in 1995 by Schutze.²⁰ Early epidemiological data suggested that decreasing prevalence of H. pylori infection in Western populations appeared to be associated with an increasing prevalence of GERD and EAC.²¹ Since then, there have been several studies suggesting potential increase in incidence of reflux disease after H. pylori eradication although such conclusion has remained controversial.²² Some studies have suggested that corpus gastritis may be protective for reflux disease. One Japanese study found that following H. pylori eradication, 33% of patients with corpus gastritis had reflux esophagitis compared to 13% in those without corpus gastritis.²³ In North America, Vakil et al.²⁴ conducted a randomized controlled trial in patients with nonnuclear dyspepsia and H. pylori infection. Antral-predominant H. pylori infection was noted in 55% of patients compared with corpuspredominant H. pylori infection, which was noted in only 6% of patients. The remainder had involvement at both sites. Symptoms of heartburn and regurgitation were found to be significantly improved after eradication in patients with antral-predominant gastritis. Esophagitis was more common in the eradication group but statistical significance was not reached.²⁴ Another recent study done in Iran reported similar findings that GERD was more prevalent and significantly associated with antral gastritis.²⁵ Such a pattern supports the mechanism that the effect of H. pylori on acid production may play a big role in the development of GERD. Antral gastritis is thought to be more common in the Western world, while corpus gastritis is more common in Asia; therefore, eradication of H. pylori would actually lead to less acid reflux disease in the Western world. While these studies may suggest possible regional variation in the pattern of H. pylori infection, larger studies are needed to help determine the true prevalence of antral or corpus-predominant H. pylori in different regions of the world.

Many other observational studies as well as several randomized controlled trials have also looked at the relationship between H. pylori status and incidence of GERD. We examined several metaanalyses on these studies performed in the last 20 years (Table 1). ²⁶⁻³³ In a meta-analysis of observational studies, H. pylori infection was associated with 26% decrease in GERD symptoms and a 30% reduction in erosive esophagitis.²⁶ H. pylori eradication is associated with increased incidence of GERD symptoms and erosive esophagitis, although statistical significance was not reached in the early meta-analyses of randomized controlled trial (RCT) and cohort studies as described in Table 1. Notably, most studies included in the analyses were North American and European studies. A subgroup analysis by Xie et al.²⁷ showed that the incidence of GERD was especially increased in the Asian population after H. pylori eradication. A study by Mou et al.28 which included more Asian studies showed a significant increase in GERD incidence after eradication as well. However, their subgroup analysis did

Table 1.	Meta-analysis of H. pylori infection and the incidence of GERD/erosive esophagitis and the effect of H. pylori treatment on GERD/erosive	sive es-
ophagiti	is	

Reference	Type of studies included in the meta-analysis	Outcome: Incidence of GERD or Erosive esophagi- tis in <i>H. pylori</i> eradicated vs. persistent patients
Yaghoobi <i>et al.,</i> ²⁹ 2010	7 RCTs, 5 cohort studies	Erosive esophagitis OR = 1.11 (95% CI: 0.81–1.53, <i>p</i> = 0.52) Symptomatic GERD OR =1.37 (95% CI: 0.89–2.12, <i>p</i> = 0.15)
Qian <i>et al.,³⁰</i> 2011	11 RCTs	Erosive esophagitis OR = 0.97 (95% CI: 0.67–1.40; <i>p</i> = 0.88) Symptomatic GERD OR = 0.88 (95% CI: 0.63–1.23, <i>p</i> = 0.46)
Saad <i>et al.</i> , ³¹ 2012	10 RCTs	Erosive esophagitis OR = 1.13 (95% CI: 0.72–1.78, <i>p</i> = 0.59) Symptomatic GERD OR = 0.81 (95% CI: 0.56–1.17, <i>p</i> = 0.27)
Xie <i>et al.</i> , ²⁷ 2013	43 Studies including, case– control, corhort, and RCTs	Symptomatic GERD Case-control (untreated patients) OR = 0.64 (95% CI: 0.49–0.83) Cohort studies (eradicated patients) RR = 2.50 (95% CI: 1.46–4.26) RCTs (eradicated patients) RR = 1.99 (95% CI: 1.23–3.22)
Tan <i>et al.,³²</i> 2015	16 Cohort studies	Symptomatic GERD OR = 0.87 (95% CI: 0.66–1.14, <i>p</i> = 0.103)
Mou <i>et al.,</i> ²⁸ 2020	19 RCTs	Symptomatic GERD RR = 1.54 (95% CI: 1.06–2.24, <i>p</i> = 0.02)
Zhao <i>et al.,</i> ³³ 2020	17 RCTs	Erosive esophagitis OR = 1.67 (95% CI: 1.12–2.48, <i>p</i> = 0.01) Symptomatic GERD OR = 1.04 (95% CI: 0.84–1.29, <i>p</i> = 0.71)
Zamani <i>et al.</i> , ²⁶ 2021	36 Cross- sectional and case-control studies	7 Cross–sectional studies Prevalence of <i>H. pylori</i> infection and incidence of symptomatic GERD OR = 0.74 (95% CI: 0.61–0.90) 26 Cross–sectional studies Prevalence of <i>H. pylori</i> infection and incidence of erosive esophagitis OR = 0.70 (95% CI: 0.58–0.84) 4 Case-controlled studies Prevalence of <i>H. pylori</i> infection and incidence of symptomatic GERD OR = 1.10 (95% CI: 0.85–0.143)

CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

not show significant difference in either non-Asian or Asian studies. Of the seven meta-analyses of RCTs and cohort studies, three found significant increases in the incidence of GERD or erosive esophagitis after *H. pylori* eradication while the four other studies did not show significant difference.^{20,27,29–33} While it is unclear how the distribution of antral or corpus gastritis may have affected the outcome, the general trend seen in recent studies that included both Asian and Western populations suggests that *H. pylori* infection may be protective against GERD while its eradication may be associated with increased incidence of GERD and erosive esophagitis.

From a mechanistic point of view, *H.pylori* infection has not been shown to directly impact the competency of the esophagogastric junction or esophageal peristalsis.³⁴ It is also not known whether colonization of esophageal mucosa by *H.pylori* affects mucosal sensitivity to acid exposure. It is likely that the primary effect of *H.pylori* infection on GERD is to modify the nature of the refluxate from the stomach and this may be different in antralpredominant vs. corpus-predominant infection. Another possible explanation is that gastric bicarbonate levels are restored to baseline after *H.pylori* eradication without significant change in acid production.

H. pylori and BE

BE occurs when the esophageal squamous epithelium is replaced by specialized columnar epithelium with goblet cells causing intestinal metaplasia in the distal esophagus.³⁵ Increasing BE segment length is associated with an increased risk of progression to EAC.³⁶ Short-segment BE (<3 cm) and long-segment BE (\geq 3 cm) carry risks of progression to EAC of 0.07%, and 0.25%, respectively.³⁷ BE is closely associated with GERD and is the only known precursor to EAC with increasing incidence in both North America and Europe.³⁸ BE is detected in 10–15% of patients with GERD.³⁹ Given its association with GERD, it would be reasonable to expect that *H. pylori* infection would be protective against BE. However, early data did not reveal a clear trend and studies have shown mixed effects of *H. pylori* infection on incidence of BE.^{40–42}

Table 2 summarizes five meta-analyses of observational studies evaluating the association between H. pylori infection and BE.43-47 Wang et al showed no significant difference in the overall prevalence of *H. pylori* infection in BE and healthy controls.⁴³ Subgroup analysis favored a lower prevalence of H. pylori infection in BE patients. Fischbach et al.44 included 49 observational studies but after accounting for bias and correct measurement of H. pylori infection, only four studies were found acceptable and showed an overall protective effect. A similar result was noted when considering only the USA studies. Subgroup analysis of CagA positivity in seven studies showed a protective effect against BE. An analysis by Eross *et al.*⁴⁵ that included 72 studies also showed that H. pylori infection protected against BE. The protective effect was more pronounced in dysplastic BE and for long-segment BE. Their CagA positivity analysis included four additional studies to Fischbach's analysis and found a significant protective effect. A similar association was found in two other recent studies.46,47

Reference	Type of studies included in the meta-analysis	Outcome: Prevalence of <i>H. pylori</i> infection in patients with or without BE
Wang et al., ⁴³ 2009	12 Case-control studies	42.9% vs. 43.9%, OR = 0.74 (95% CI: 0.40–1.37, <i>p</i> = 0.34) Subgroup analysis: 23.1% vs. 42.7%, OR = 0.50 (95% CI: 0.27–0.93, <i>p</i> = 0.03)
Fischbach <i>et al.</i> , ⁴⁴ 2012	49 Observation studies	4 Studies included after accounting for bias RR = 0.46 (95% CI: 0.35–0.60) 10 USA studies RR = 0.46 (95% CI: 0.40–0.53) 7 studies with CagA-positive infection RR = 0.38 (95% CI: 0.19–0.78)
Eross <i>et al.,</i> ⁴⁵ 2018	72 Observational studies	OR = 0.68 (95% CI: 0.58–0.79, <i>p</i> < 0.001). Dysplastic BE OR = 0.37 (95% CI: 0.26–0.51, <i>p</i> < 0.001) Long-segment BE OR = 0.25 (95% CI: 0.11–0.59, <i>p</i> = 0.001)
Du <i>et al.,</i> ⁴⁶ 2021	46 Observational studies	OR = 0.70 (95% CI: 0.51–0.96, <i>p</i> = 0.03) CagA-positive <i>H. pylori</i> infection OR = 0.28 (95% CI: 0.15–0.54, <i>p</i> = 0.0002) Long-segment BE OR = 0.47 (95% CI: 0.25–0.90; <i>p</i> = 0.02)
Ma et al., ⁴⁷ 2022	24 Observational studies	OR = 0.53 (95% CI: 0.45–0.64; <i>p</i> < 0.001) CagA–positive <i>H. pylori</i> infection OR = 0.25 (95% CI: 0.15–0.44, <i>p</i> = 0.000) Long-segment BE OR = 0.39 (95% CI: 0.18–0.86, <i>p</i> = 0.019)

Table 2.	Meta-analysis of	observational stu	dies comparing t	the prevalence of	f <i>H. pylori</i> infecti	on in patients wit	h or without BE
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BE, Barrett's esophagus; CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

While earlier studies found an inconclusive association between *H. pylori* infection and BE, recent meta-analyses have all reported significant protective effects of *H. pylori*, especially against dysplastic and long-segment disease, which carry a higher potential to progress to EAC. Notably, these studies reported a high level of heterogeneity and many studies used serology as a marker for *H. pylori* positivity.

H. pylori and EAC

EAC has been the most common esophageal cancer in the USA since the 1970s and has shown increasing prevalence in the western hemisphere.48 This appears to coincide with an increased rate of eradication of H. pylori which has been linked to a possible protective effect against EAC in early epidemiologic studies.⁴⁹ EAC has a very low 5-year survival rate; therefore, it is important to identify predisposing factors to help mitigate the risks of developing EAC. The five most recent meta-analysis that were identified are shown in Table 3.48,50-53 Rokkas et al.50 showed that H. pylori infection was less frequently identified in patients with EAC. CagA-positive infection was also significantly lower in patients with EAC. A metaanalysis by Zhuo et al.⁵¹ reported similar findings. Three subsequent studies also agreed with the findings that suggested *H. pylori* infections are less commonly found in patients with EAC.^{48,52,53} All these meta-analyses support an association between H. pylori infection and EAC, with the bacteria exerting a possible protective effect, especially strains that are CagA-positive.

H. pylori and esophageal squamous cell carcinoma (ESCC)

While ESCC is more common in Asian countries and not associated with GERD, studies have looked at its association with *H*.

pylori as well. As shown in Table 3, Most studies did not find a significant relationship between ESCC and *H. pylori*. Two metaanalysis found a possible protective effect of CagA-positive infection against ESCC in Asian studies, but the opposite was found in non-Asian studies.^{48,53}

Conclusions

Evidence from recent studies mostly shows a significant inverse correlation between *H. pylori* infection and GERD, BE, and EAC. Studies of the effect of *H. pylori* eradication on the incidence of GERD have reported more heterogeneous results. The majority of observational data support the notion that *H. pylori* infection protects against the development of BE and EAC. Infection with CagA-positive *H. pylori* strains also appears to confer significant protection. Although these meta-analyses included many of the same individual studies, they still showed a consistent inverse relationship between *H. pylori* infection and GERD-related diseases. While there is more evidence from randomized controlled trials on the effect of *H. pylori* infection on GERD, more prospective cohort studies regarding the effect of *H. pylori* infection on BE and EAC are needed.

However, the trend noted in these meta-analyses is not exactly consistent with what was previously observed in the Western world where *H. pylori* infections were thought to be antrum-predominant, and GERD was expected to improve after the eradication of antrum-predominant *H. pylori* infection following reversal of hypergastrinemia and the consequent reduction in acid secretion. Perhaps this explains the heterogeneity of the results seen in meta-analysis on GERD that included both Asian and Western

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Reference	Type of studies included in the meta-analysis	Outcome: Prevalence of <i>H. pylori</i> infection in patients with or without esophageal cancer (EAC or ESCC)
Rokkas <i>et al.,⁵⁰</i> 2007	18 Observational studies	EAC (10 studies) OR = 52 (95% CI: 0.37–0.73, p < 0.001) CagA-positive <i>H. pylori</i> infection (6 studies) OR = 0.51 (95% CI: 0.31–0.82, p < 0.006) ESCC (5 studies) OR = 0.86 (95% CI: 0.56–1.33, p < 0.48)
Zhuo <i>et al.,⁵¹ 2008</i>	12 Case-control studies	EAC (9 studies) OR = 0.58 (95% CI: 0.48–0.70, <i>p</i> < 0.01) ESCC (5 studies) OR = 0.80 (95% CI: 0.45–1.43, <i>p</i> < 0.05)
Islami <i>et al.,</i> 52 2008	19 Observational studies	EAC (13 studies) OR = 0.56 (95% CI: 0.46–0.68) CagA-positive <i>H. pylori</i> infection (5 studies) OR = 0.41 (95% CI: 0.28–0.62) ESCC (9 studies) OR = 1.10 (95% CI: 0.78–1.55)
Xie <i>et al.</i> , ⁵³ 2013	19 Observational studies	EAC (15 studies) OR = 0.59 (95% CI: 0.51–0.68) EAC CagA-positive <i>H. pylori</i> infection (8 studies) OR = 0.56 (95% CI: 0.45–0.70) ESCC (16 studies) OR = 0.97 (95% CI: 0.76–1.24) Asian studies only OR = 0.66 (95% CI: 0.43–0.89) ESCC CagA-positive <i>H. pylori</i> infection (9 studies) OR = 0.77 (95% CI: 0.65–0.92)
Nie <i>et al.,</i> ⁴⁸ 2014	28 Observational studies	EAC (13 studies) OR = 0.57 (95% CI: 0.44–0.73) EAC CagA-positive <i>H. pylori</i> infection (8 studies) OR = 0.64 (95% CI: 0.52–0.79) ESCC (19 studies) OR = 1.16 (95% CI: 0.83–1.60) ESCC CagA-positive <i>H. pylori</i> infection (7 studies) OR = 0.97 (95% CI: 0.79–1.19). ESCC CagA-positive <i>H. pylori</i> infection with stratified analysis Asian studies OR = 74 (95% CI: 0.57–0.97) non-Asian studies OR = 1.41 (95% CI: 1.02–1.94)

CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

studies. It also suggests that *H. pylori* may have a different degree of impact on each stage of the GERD-BE-EAC sequence as acid secretion is likely not the sole mechanism involved. Its involvement in downregulating tumor-promoting inflammatory response and maintaining oral microbiota balance as well as its interaction with esophageal epithelial cells likely play a role, although more studies are needed to better understand the pathogenesis. A possible inverse relationship between CagA positivity and EAC/ESCC is an interesting observation with unclear mechanism.

Treatment of *H. pylori* is widely adopted in clinical practice to prevent complications such as atrophic gastritis, peptic ulcer disease, and gastric cancer; therefore, it is not appropriate to withhold *H. pylori* treatment to prevent GERD and related complications. While there is no strong evidence that *H. pylori* eradication causes or predisposes to GERD, it may likely unmask pre-existing GERD. However, management of *H. pylori* infected patients at increased risk for GERD or EAC may warrant an individualized approach. With large portions of the Western population developing EAC without having significant GERD symptoms, it is important to identify additional risk factors that increase the risks of EAC. As a different strategy is employed to increase screening for EAC in the absence of chronic GERD, understanding whether *H. pylori* increases the risk of BE/EAC is important to determine if it should be considered as an additional risk factor to be included in the algorithm for EAC screening. More research is needed in this subset of patients to delineate the best management strategy.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to study concept and design (XL, EW, MD), acquisition of data (XL, EW), data analysis (XL, EW), drafting of the manuscript (XL, EW), critical revision of the manuscript (XL, EW, MD), and supervision of the project and final approval (MD).

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