

Is *H. pylori* Eradication Associated With GERD in Non-Ulcer Dyspepsia?

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A. Introduction

a. Rationale

Helicobacter pylori is a bacterial pathogen with proven causal association with peptic ulcer disease and gastritis. In addition, this bacterium is known to be carcinogenic with proven association with gastric adenocarcinoma and gut associated lymphoid tissue (GALT) lymphoma. Eradication of *H. pylori* has been shown to reduce peptic ulcer recurrence and to result in the regression of GALT lymphoma. The prevalence of colonization is high as at least 50-60% of individuals in the United States having serologic evidence of *H. pylori* by age 60.¹ *H. pylori* testing and eradication have been recommended for patients under 45 years of age with unclear dyspeptic complaints who do not have "alarm" symptoms (weight loss, dysphagia, evidence of GI bleeding, abdominal mass or lymphadenopathy).² Epidemiologic data has suggested that the prevalence of GERD and esophageal adenocarcinoma has increased as the prevalence of *H. pylori* has decreased in Western societies.³ However, it is unclear if *H. pylori* eradication provokes gastroesophageal reflux disease (GERD). This potential relationship is important as GERD is a risk factor for Barrett's esophagus and esophageal adenocarcinoma. If *H. pylori* were to be found to be protective against GERD, patients with strong indications for eradication would need to be followed closely for the GERD development. A possible protective role for *H. pylori* may also alter the risk-benefit analysis for empiric *H. pylori* eradication in those patients with dyspepsia who have not undergone endoscopy.

b. Review of the Literature

Studies on the effect of *H. pylori* eradication and GERD have had conflicting conclusions.

In one of the earliest studies, retrospective analysis showed a twofold increased risk of reflux esophagitis associated with successful eradication of *H. pylori* for infected patients with a duodenal ulcer (26% vs. 13%, $p < 0.001$).⁴ This study also noted a direct association between severity of gastric corporal inflammation before eradication and the risk of reflux esophagitis. In another study, retrospective analysis showed an almost threefold increased risk of GERD symptoms or esophagitis after successful eradication in infected patients with duodenal ulcer (37% vs. 13%, $p = 0.04$).⁵ A case-control study found substantially increased risk (18% vs. 0.3%, $p < 0.01$) of reflux esophagitis after eradication for infected patients with peptic ulcer or gastritis.⁶ The study also found a direct association between hiatal hernia and corpus gastritis to post-eradication reflux esophagitis. To the contrary, *H. pylori* eradication was found not to exacerbate or induce GERD symptoms for infected patients with peptic ulcer disease in another uncontrolled study.⁷ In addition, a randomized, blinded trial found no association between *H. pylori* eradication and GERD symptoms for infected patients with a duodenal ulcer (22% vs. 15%, $p = 0.47$).⁸ Another randomized study found no difference in relapse rate for infected GERD patients who had *H. pylori* eradicated vs. those who did not.⁹

The proposed mechanism for provocation of GERD after *H. pylori* eradication is the resolution of corporal gastritis caused by the infection. This allows return to normal function of acid-producing parietal cells. This in turn leads to increased risk of GERD and GERD complications. In addition, some studies suggest that *H. pylori* strains with cytotoxin associated gene A (*cagA*) may be associated with a greater inflammatory response¹⁰ and may be more protective against GERD.¹¹

B. Hypothesis/Question

Does eradication of *H. pylori* for patients with nonulcer dyspepsia and *H. pylori* gastritis provoke GERD symptoms or reflux esophagitis?

C. Methods

a. Conceptual and Operational Definitions

Nonulcer dyspepsia will be defined according to the Rome II criteria¹² as the presence of at least 12 weeks, which need not be consecutive, within the preceding 12 months of:

Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and

No evidence of organic disease (including at upper endoscopy) that is likely to explain symptoms; and

No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not irritable bowel syndrome).

Helicobacter pylori infection will be defined as serologic evidence of IgG by ELISA and a positive C¹³ urea breath test. This will be determined before randomization. The presence of the *cagA* genotype will be determined by serum ELISA assay for *cagA* antibody. This will also be determined before randomization, but the result will be blinded. Successful eradication will be defined as negative result on all C¹³ urea breath tests (UBT) after treatment. UBT to confirm eradication will occur at one month after eradication and at the end of the study (either at one year or at the time of a primary outcome event).

Gastritis will be confirmed by the presence of inflammatory cell infiltration of the gastric mucosal epithelium. The presence and location of gastritis will be determined at each endoscopy by two biopsies at the antrum and two at the corpus. The gastritis will be graded according to the Updated Sydney System from zero (none) to three (severe). If two biopsies from the same region have discrepant grades, the higher grade will be used.

The presence of hiatal hernia will also be noted at endoscopy. A hiatal hernia will be defined as the presence of the esophagogastric junction more than 2 cm above the diaphragm.

The primary outcome to be evaluated in this study is the composite outcome of new GERD symptoms, use of proton pump inhibitor (PPI) and/or H₂-receptor antagonist (H₂RA) therapy, or reflux esophagitis. Follow up will be for 12 months. GERD symptoms will be defined as pyrosis, regurgitation, dysphagia, or hypersalivation. These symptoms will be measured by structured interview. Participants will be questioned at monthly follow up regarding use of PPI and/or H₂RA therapy. Reflux esophagitis will be evaluated by endoscopy every 3 months for a one year period. Esophagitis will be defined as graded by the Savary-Miller classification.¹³

b. Study Design

This will be a randomized, double-blind, placebo controlled trial. Participants will have nonulcer dyspepsia and *H. pylori* gastritis verified by endoscopy, endoscopic biopsy, *H. pylori* serology, and UBT before randomization. They will then be randomized to *H. pylori* eradication vs. placebo. The eradication regimen will consist of lansoprazole 30mg po bid, amoxicillin 500mg po bid, and clarithromycin 500mg po bid for a total of 14 days. The placebo arm will receive lansoprazole 30mg po bid and 2 placebo tablets for a total of 14 days. Eradication will be evaluated by UBT as above at one month after the completion of the eradication or placebo regimen. The result will be blinded to the investigators and participants. After eradication/placebo therapy completion, participants will be followed at monthly intervals for a total of 12 months for development of GERD symptoms and for the

need of PPI or H2RA treatment. New GERD symptoms or requirement of PPI and/or H2RA treatment will be considered as a primary outcome event and at that time, the participant will have an endoscopy and no further study follow-up. Esophagogastroduodenoscopy will be performed at months 3, 6, 9, and 12 to evaluate the presence of esophagitis and gastritis. The development of esophagitis will also be considered a primary outcome event with no further study follow-up. The maximum follow up will be 12 months.

c. Statistical Analysis

Since this study will measure time to primary outcome, life table analysis will be used. The two groups will be compared using the log rank test. Analysis will be on intention-to-treat basis. Gastritis scores will be compared using the Mann-Whitney U test. Age, smoking, regular ethanol intake (\geq twice/wk), weight change, presence of hiatal hernia, initial antral gastritis score, initial corporal gastritis score, and presence of cagA genotype will be evaluated for causal relationship with the primary outcome with multivariable logistic regression.

d. Sample Size

Since the primary outcome will be compared with the log rank test which uses the chi-square statistic, this will be used for sample size calculation. Based on a previously published study⁵, I estimate that there will be a 30% prevalence of the combined outcome of GERD symptoms, need for PPI or H2RA treatment, or reflux esophagitis in participants who undergo H. pylori eradication vs. 15% in those who do not. The study will be done with a power of 80% to detect this difference at an alpha level of 0.05. Therefore 134 participants need to be randomized to each arm of the study. Assuming about a 10% loss to follow up proportion, 150 patients will be randomized to each arm giving a total study population of 300.

e. Subject Selection

Inclusion criteria consist of people 18 years of age or older with nonulcer dyspepsia with evidence of active H. pylori and gastritis. Exclusion criteria include: presence of "alarm" symptoms (unexplained weight loss, dysphagia, evidence of GI bleeding, abdominal mass or lymphadenopathy), GERD symptoms, use of PPI or H2RA within 2 weeks, active peptic ulcer disease, H. pylori eradication within 30 days, previous gastric or esophageal surgery, chronic use of NSAIDs, use of prokinetics, scleroderma, gastroparesis, contraindication for any of the 3 eradication drugs used in this study, and life expectancy of less than 12 months. Patients who present to Columbia-Presbyterian affiliated internal medicine or gastroenterology clinics complaining of dyspepsia will be recruited for the study. There should be adequate representation of women and non-caucasian populations in the study. After an initial workup is done to evaluate the dyspepsia, if the patient fulfills the inclusion criteria and not any of the exclusion criteria, s/he will be approached for enrollment. Informed consent will be obtained through a meeting with a research coordinator to explain the study including risks, benefits, and alternatives. An informed consent form will be duly signed. One possible difficulty is that some potential participants may be averse to frequent esophagogastroduodenoscopy. It may also take several months to recruit 300 eligible and consenting participants.

f. Study Drugs (all are approved and will be given in standard dosage)

The eradication regimen will be lansoprazole 30mg po bid, Amoxicillin 1g po bid, and Clarithromycin 500mg po bid for a total of 2 weeks. This regimen has an H. pylori eradication rate of at least 85-90%. The placebo regimen will be lansoprazole plus 2 placebo tablets for 2 weeks.

Lansoprazole - known side effects with frequency 1% to 10%: GI: Abdominal pain (2%), diarrhea (4%, more likely at doses of 60 mg/day), constipation (1%), nausea (1%) Amoxicillin - several infrequent side effects with poorly described frequency

Clarithromycin – known side effects with frequency 1% to 10%: CNS: Headache (adults and children 2%), Derm: Rash (children 3%) GI: Diarrhea (adults 6%, children 6%); vomiting (children 6%); nausea (adults 3%); abnormal taste (adults 7%); heartburn (adults 2%); abdominal pain (adults 2%, children 3%) Hepatic: Elevated prothrombin time (1%) Renal: Elevated BUN (4%)

D. Risk, Benefits, Alternatives

Risks include about a 0.2% risk of major cardiorespiratory complication associated with each upper endoscopy procedure. There is a 1-10% risk of side effect with the eradication medications. There is also a risk of provoking GERD in participants who have H. pylori successfully eradicated if indeed a significant association does exist. Participants may or may not benefit from this study. Participants may potentially benefit from the therapeutic relationship and close follow-up of their functional dyspepsia complaints. Since H. pylori eradication has not been conclusively shown to benefit in nonulcer dyspepsia, it is not unethical to randomize participants to placebo in this study. An alternative would be continued empiric PPI or H2RA therapy but this has not been shown to be conclusively beneficial in this population. The same is true for prokinetic medications (eg, metoclopramide, cisapride).

E. Confidentiality

The study data will be coded. This code will not be a hospital unit number, social security number, subject initials, phone number, or address.

F. Compensation

Participants will be compensated in the form of parking vouchers for clinical visits associated with the study or compensation for bus/train if they use public transportation. They will also receive medications and medical attention associated with the study at no cost.

G. Radiation

The C¹³ urea breath test for H. pylori infection is NOT a radioactive test.

H. References

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Lay Abstract**Title: Is H. pylori Eradication Associated With GERD in Non-Ulcer Dyspepsia?**

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Study Purpose

The purpose is to further evaluate if H. pylori eradication provokes gastroesophageal reflux disease (GERD). This study will evaluate patients with H. pylori gastritis and non-ulcer dyspepsia. This is a good population to study in a randomized, double blind, placebo-controlled fashion as there is not an absolute indication for H. pylori eradication.

Study subjects and method of recruitment

A total of 300 patients will be randomized to either H. pylori eradication or placebo. All participants will be at least 18 years old. Subjects will be recruited after they present to an internal medicine or gastroenterology clinic at CPMC and are shown to meet the inclusion criteria in the absence of exclusion criteria. Physicians will refer patients after it has been determined that the patient is willing to discuss a research study. Announcements will also be posted in the clinics and in the hospital.

Study procedures

Monthly interview to determine presence of GERD symptoms or need for proton pump inhibitor or H2-receptor antagonist therapy

Visits as needed to evaluate patients who have GERD symptoms or need for proton pump inhibitor or H2-receptor antagonist therapy

Esophagogastroduodenoscopy every 3 months within a 12 month total follow up period

Issues

None