The Effect of *Helicobacter pylori* Eradication Therapy on the Development of Gastroesophageal Reflux Disease

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Abstract: *Background:* It is uncertain whether the *Helicobacter pylori* eradication therapy makes a role in the progression of gastroesophageal reflux disease (GERD). *Methods:* A meta-analysis was undertaken to investigate the effect of *H pylori* eradication therapy on the development of GERD. *Results:* Overall, 16 cohort studies were included. The authors demonstrated that *H pylori* eradication had no significant effect on the occurrence of GERD in these cohort studies (odds ratio = 0.87, 95% confidence interval = 0.66–1.14, I^2 = 32.4%, P = 0.103). *Conclusions:* In general, *H pylori* eradication has no significant effect on the development of GERD in the long term. However, eradication therapy should be taken once there is *H pylori* infection, because *H pylori* infection is acknowledged to be a major cause of acute and chronic gastritis and peptic ulcer diseases and has been established as a definite etiologic factor for gastric cancer.

Key Indexing Terms: *H pylori*; Eradication; Therapy; Gastroesophageal reflux disease. **[Am J Med Sci 2015;349(4):364–371.]**

Gastroesophageal reflux disease (GERD) and *Helicobacter pylori* infection are common conditions around the world. GERD is defined as such a condition that the reflux of stomach contents causes tissue damage, troublesome symptoms and/or complications.[1] The prevalence of GERD in western countries is about 10% to 20%, which is higher than in Asian population (2.5%–6.7%); however, the prevalence is increasing in Asian countries. *H pylori* infection is acknowledged to be a major cause of acute and chronic gastritis and peptic ulcer disease[2] and has been established as a definite etiologic factor for gastric cancer.[3] Proton-pump inhibitors (PPIs) are widely used to treat GERD, peptic ulcer and other acid-related digestive diseases in current guidelines. However, long-term PPI therapy for those patients with *H pylori* infection may cause some adverse effects, such as increasing risk of progression of gastric atrophy and intestinal metaplasia to gastric cancer and development of a subtype of esophageal squamous cell carcinoma.[4,5] Thus, it is recommended that *H pylori* infection should be eradicated, especially in the patients with peptic ulcer and a family history of gastric cancer.[6]

However, the risk of *H pylori* eradication is still controversial. Many individual studies have been performed in patients with or without GERD to explore the effect of *H pylori* eradication on the symptomatic or endoscopic reflux disease but produced inconsistent and inconclusive results.[7–28]

The aim of the present meta-analysis is to clarify whether *H pylori* eradication develops GERD symptoms and erosive esophagitis in patients with or without a GERD history.

METHODS

Search Strategy

An electronic search of the literature was performed. This search included the PubMed, MEDLINE, ScienceDirect, Google Scholar and Embase databases of all relevant citations published in English up to January 2014. Cochrane review articles and several sources for congress abstracts were also reviewed. Additionally, we conducted a manual search from the references of the papers retrieved. The initial search term was used in the combination of the following keywords: "*Helicobacter pylori*/*Helicobacter pylori* infection/Hp/*H pylori*," with "gastroesophageal reflux/esophagitis/reflux esophagitis/GERD/gastro-esophageal reflux, disease/gastro-oesophageal reflux disease/GORD" and "eradication/cure/therapy/treatment/anti-."

Inclusion and Exclusion Criteria for Included Studies

Inclusion Criteria

Only cohort studies were included in the present meta-analysis. Cohort studies were defined as prospective studies in which *H pylori*–positive patients were all treated with *H pylori* eradication therapy, and the symptomatic or endoscopic assessments of GERD before and after treatment were compared between patients with successful *H pylori* eradication versus those with persistent infection.

In the included studies, GERD was defined as having heartburn/reflux symptom more than once a week or having endoscopic erosions (erosive esophagitis) according to the Savary-Miller system or Los Angeles classification. *H pylori* infection status was detected by an accepted method: culture, urea breath test or histology. All enrolled participants must have the same baseline diseases, that is, GERD, peptic ulcer or dyspepsia in each study. The specific eradication regimens must be described. All the analyzed groups must have been similar in all important characteristics except the treatment regimens. *H pylori* infection status was detected between 1 and 3 months after eradication therapy and was categorized into positive or negative.

Exclusion Criteria

All editorials, position papers, comments, letters, book chapters, review articles, case reports and meta-analysis were excluded. Papers that were not published in English, without full text, carried out in pediatric, not a human study, without control group and assessed by other outcomes rather than heartburn/regurgitation or endoscopic assessment were also excluded. If more than 1 article was published by the same authors using the same case series, the article with the largest number of cases was selected. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis was applied to evaluate the quality of cohort studies.[29]

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Data Extraction

A consistent standard data collection form was created and used to extract the data from each publication, including (1) first author's name and country in which the study was carried out; (2) sample size (the number included in the analysis/the total number), patients' age and gender, baseline diseases, eradication regimen, the number of active treatment group (with successful eradication) and control group (with persistent infection), follow-up time, NOS score; and (3) outcome measure: patients' population with GERD symptoms or esophagitis at baseline and at the end of the trial.

Final article selection, data extraction and quality control were performed independently by 2 investigators (J.T. and X.S.). A third investigator (W.C.) was involved if conflict occurred. The selection process is shown in Figure 1.

Statistics

Meta-analysis for the effect of *H pylori* eradication treatment on the development of GERD was carried out by calculating pooled estimates of GERD symptoms and erosive esophagitis. Heterogeneity was examined by using χ^2 tests ($P < 0.1$ was considered significant). I^2 metric, which describes the proportion of variability across studies that is because of score heterogeneity, was used to enhance the confidence of the results of the statistics when the number of combined studies was lacking. If $I^2 = 0$, there was no heterogeneity. $I^2 > 50\%$ was considered to be indicative of heterogeneity. Larger values indicated greater heterogeneity. A random-effects model was used if heterogeneity was significant; otherwise, a fixed-effects model was used. Pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) were determined by the inverse variance weighted fixed-effect model or random-effect model. Subgroup analyses were carried out according to the regions, ages, baseline diseases and follow-up duration. Sensitivity analysis was carried out to characterize possible sources of statistical heterogeneity by excluding certain studies from the analysis. Egger and Begg's tests, which measured the degree of funnel plot asymmetry, were used to assess publication bias ($P > 0.05$ indicated no publication bias). The meta-analysis was conducted by using the Stata Software (Stata 12.0; Stata Corp LP, College Station, TX).

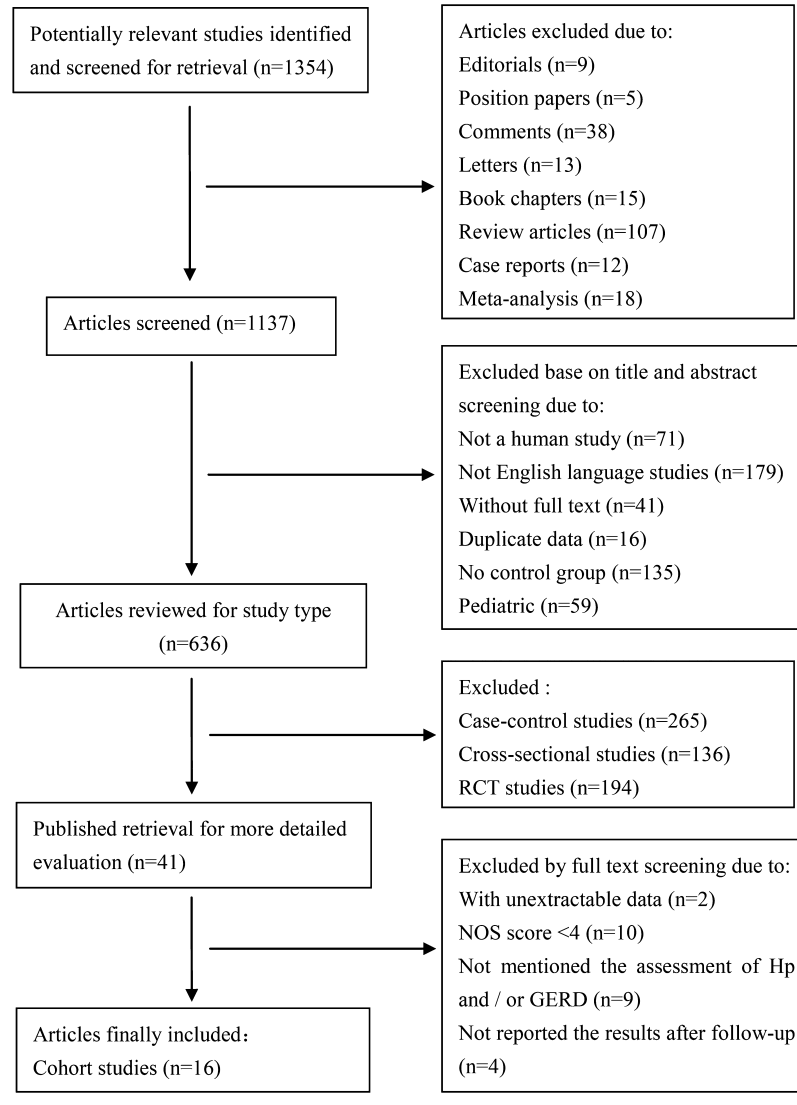

FIGURE 1. Flow chart of the study selection process for the meta-analysis.