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Clinical Trial Report: Eradication of *Helicobacter pylori* Reduces the Risk for Subsequent Gastric Cancer

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Rating

• Of importance.

Introduction

*Helicobacter pylori* is a carcinogen and has been associated with the development of gastric cancer. The hypothesis to be tested in this meta-analysis is to determine whether eradication of this organism is associated with a long-term reduction in the risk for development of gastric cancer.

**Aims**

The study’s purpose is to examine whether eradication of *H. pylori* infection can reduce the risk for the development of gastric cancer.

**Methods**

The authors examined the results of seven studies that met inclusion criteria by using relevant clinical trials. Relevant trials were identified through searching PubMed, Embase, Google Scholar, and the Cochrane Library. To be eligible to include subjects in this analysis, the randomized clinical trials were required to compare an eradication treatment group to an untreated group and to provide an analysis of the number of gastric cancers occurring during follow-up evaluation.

**Results**

A total of seven studies were considered adequate to meet the inclusion criteria. One of the studies was excluded after further analysis. Overall, 27 of 3388 (1.1%) treated patients in the *H. pylori* antibiotic treatment group were identified as having gastric cancer, compared to 56 of 3307 (1.7%) in those subjects who did not undergo treatment. The authors identified the relative risk for gastric cancer as 0.65 (95% CI, 0.43–0.98).

**Discussion**

The authors conclude that eradication of *H. pylori* reduces gastric cancer risk.
Comments

This section compares the meta-analysis under discussion with other studies that evaluate the role of treatment of *H. pylori* infection in reference to the potential positive effects on prevention of gastric cancer. These studies collectively provide the reader with perspective when confronted with a patient with an active infection.

The current article evaluates the protective effects of treating *H. pylori* on the potential risk for the later development of gastric cancer. This article has worldwide impact, given the high incidence of this infection in developing nations, particularly in Asia. This meta-analysis has accordingly focused on enrolling studies from areas of the world that have a high incidence of infection. Although this focus could be viewed as a possible weakness of the inclusion study design, the inclusion of studies from areas with high disease incidence make this study more relevant. This study is supported by a clinical trial evaluating early *H. pylori* eradication in reducing the risk of gastric cancer in patients with peptic ulcer disease [1]. As a corollary, one study showed that *H. pylori* infection is associated with a reduced risk of esophageal cancer [2].

*H. pylori* is a bacterium that colonizes the relatively acidic human stomach. Like *Escherichia coli*, it is a neutralophile, an organism that requires nearly neutral pH for optimal growth. *H. pylori* has evolved acid acclimation and resistance mechanisms to combat gastric acidity, which permits the colonization of the acidic gastric mucosa. A major adaptation of the organism to the acidic gastric environment is the constitutive production of large amounts of intrabacterial urease [3]. Activation of urease at acidic pH is a result of the opening of the proton-gated urea channel, UreI. Opening this channel allows rapid entry of urea into the cytoplasm of the organism, where it is hydrolyzed by urease and the production of NH₃ and CO₂.

*H. pylori* colonization, if left untreated, results in a persistent, lifelong infection [4, 5]. In developing nations, the incidence of infection is greater than 80% in adults, whereas industrialized countries report an incidence of 20–50%. Immigration of persons from endemic areas of the world to the United States results in regional increases in the incidence of disease. Accordingly, *H. pylori* infection will remain endemic in the United States for at least another century [6]. It is estimated that 15–20% of patients with *H. pylori* infection develop peptic ulcers and 3% of infected patients develop gastric cancer [7]. The two primary forms of gastric cancer that have been associated with *H. pylori* infection include adenocarcinoma and, less commonly, mucosa-associated lymphoid tumors (MALToma) or lymphomas [4]. Eradication of *H. pylori* in patients with duodenal or gastric ulcer cures the disease, prevents relapse, and reduces the risk of cancer [6–8].

The diagnosis of *H. pylori* infection can be established by several methods: endoscopy with biopsy, serum antibody testing, urea breath testing, and, more recently, stool antigen assay. During endoscopy, the biopsy results may be confirmed by one of three methods: biopsy, urease test, and histology. Although gastric biopsy is usually considered the gold standard, more studies now rely on less invasive testing. Accordingly, noninvasive testing is the preferred method for establishing a diagnosis and confirming eradication. The sensitivity of urea breath testing is about 88–95%, and specificity is about 95–100% [9]. Another method of establishing the diagnosis is laboratory-based serologic testing using enzyme-linked immunosorbent assay technology to detect IgG antibodies. Although this test has a uniform high sensitivity (90%–100%), the variable specificity (76%–96%) and low accuracy (83%–98%) would exclude this methodology for confirming eradication. The presence of *H. pylori* in the stool of infected patients has led to the development of a stool antigen test, which is now a commercially available enzyme immunoassay (Premier Platinum HpSA Immunoassay; Meridian Diagnostics, Cincinnati, OH), thus enabling this method as an accurate modality for establishing eradication [10]. The accuracy of the test was evaluated in a study involving 270 patients in whom the diagnosis of *H. pylori* was established by endoscopy and urea breath testing; test sensitivity was 94% and specificity was 86%. Thus, it has been well established that the stool antigen assay appears to be useful for documenting whether eradication was successful. Furthermore, the stool antigen assay is a noninvasive test that, unlike endoscopic tests, does not place patients at risk of developing complications. A 2007 guideline from the American College of Gastroenterology recommends that biopsy for histopathology is only appropriate if urea breath testing or antibody testing, urea breath testing, and, more recently, stool antigen testing is about 88–95%, and specificity is about 95–100% [9]. Another method of establishing the diagnosis is laboratory-based serologic testing using enzyme-linked immunosorbent assay technology to detect IgG antibodies. Although this test has a uniform high sensitivity (90%–100%), the variable specificity (76%–96%) and low accuracy (83%–98%) would exclude this methodology for confirming eradication. The presence of *H. pylori* in the stool of infected patients has led to the development of a stool antigen test, which is now a commercially available enzyme immunoassay (Premier Platinum HpSA Immunoassay; Meridian Diagnostics, Cincinnati, OH), thus enabling this method as an accurate modality for establishing eradication [10]. The accuracy of the test was evaluated in a study involving 270 patients in whom the diagnosis of *H. pylori* was established by endoscopy and urea breath testing; test sensitivity was 94% and specificity was 86%. Thus, it has been well established that the stool antigen assay appears to be useful for documenting whether eradication was successful. Furthermore, the stool antigen assay is a noninvasive test that, unlike endoscopic tests, does not place patients at risk of developing complications. A 2007 guideline from the American College of Gastroenterology recommends that biopsy for histopathology is only appropriate if urea breath testing or stool antigen testing is not feasible or during follow-up of complicated ulcer disease, and that serologic testing is not useful for follow-up because many patients continue to have antibodies for months or years after eradication therapy [11]. In the meta-analysis under review, four of the clinical studies relied on urea breath testing and two of the studies relied on the rapid urease test. Histology was used for confirmation in three of the studies.

*H. pylori* bacterial infection is prevalent in certain US populations, and leads to the development of peptic ulcer disease and a predisposition to gastric cancer [2]. Eradication of *H. pylori* prevents peptic ulcer disease and reduces the risk of gastric cancer, and thus is an important therapeutic strategy for most clinicians [1, 6–8]. Current *H. pylori* eradication therapy requires a combination treatment approach using a proton pump inhibitor (PPI)
and at least two antibiotics. This approach is known as “triple therapy.” Standard eradication therapy requires treatment for 10–14 days and has a success rate of less than 75% [12]. The efficacy of various triple-therapy regimens is undermined by the development of antimicrobial resistance by H. pylori [13] and may well contribute to development of antibiotic resistance of other important bacterial pathogens [14]. In H. pylori infection, primary resistance to amoxicillin has not been described. However, the frequency of clarithromycin resistance is 17–45.4% in the United States and even higher in Japan. It is estimated that the resistance rate worldwide is increasing. Metronidazole resistance ranges between 25% and 48% in both men and women in developing countries, because of the frequent use of nitro-imidazoles to treat other diseases [15]. In a recent meta-analysis, primary resistance to clarithromycin decreased the eradication rate by 50%, whereas primary resistance to metronidazole decreased the rate of eradication by 37% [16]. The rate of eradication using the triple-therapy approach has fallen below 80% in many regions, as noted in the Maastricht III consensus report, and the results differ by regions of the world [17].

The development of antimicrobial resistance by H. pylori is a major factor in unsuccessful eradication, and clarithromycin treatment may contribute to development of antibiotic resistance of other important pathogens [13, 14, 18, 19]. Antibiotic therapy is associated with diarrhea and the potential for the development of pseudomembranous colitis. Poor patient compliance is also a factor in unsuccessful eradication. Twice-daily administration of a PPI and twice-daily administration of two antibiotics for 14 days requires 84 tablets; moreover, compliance with before-meal administration is necessary because of the acid secretion–dependent mechanism of the PPI. Additionally, PPI-based acid control has considerable variability because of variability in absorption and drug-drug interactions owing to metabolism by CYP2C19, which may account for the lack of universal eradication with triple therapy. Although the meta-analysis reviewed here does not specifically address antimicrobial resistance, this issue is critically important and its omission may result in this study underestimating the potential relative risk reduction of the development of gastric cancer. The importance of eradication is not only for the prevention and cure of peptic ulcer disease, but also for the prevention of gastric adenocarcinoma, which is the third leading cause of cancer deaths in the United States.

Overall, the available data suggest that H. pylorus is a carcinogen and in certain persons leads to the development of gastric cancer. Although clinical and epidemiologic studies show an increase in relative risk for the development of gastric cancer in individuals infected with this organism, the exact mechanism that explains the link between this organism and carcinogenesis is not known. Thus, a review of the available literature indicates strong clinical evidence suggesting that successful eradication of this organism is related to a reduction in the risk of gastric cancer. Clearly, a better understanding of this pathophysiologic association is needed to better define the pathways involved in carcinogenesis.

Disclosure No potential conflict of interest relevant to this article was reported.

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