Assessing the risks and benefits of treating *Helicobacter pylori* infection

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Therapeutic Advances in Gastroenterology

(2009) 2(3) 141–147

DOI: 10.1177/
1756283X08100279

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Introduction

Since the discovery of *Helicobacter pylori* by Warren and Marshall [Marshall and Warren, 1984] in 1982, much has been learned about this Gram-negative microaerophilic bacterium and its associated pathology. In 1994, the National Institutes of Health recognized that most recurrent duodenal and gastric ulcers were caused by *H. pylori* and antibiotic treatment was recommended. In the same year, the International Agency for Research on Cancer (IARC) declared *H. pylori* to be a group I human carcinogen for gastric adenocarcinoma [IARC, 1994]. Since then, physicians have been working diligently in diagnosing and treating *H. pylori*. Despite the fact that evidence has shown clearly *H. pylori* to be the culprit for gastritis, peptic ulcers and gastric malignancies including mucosa associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma, the effect of *H. pylori* treatment in patients with gastroesophageal reflux disease remains controversial. In this review, we will discuss the risks and benefits of the treatment of *H. pylori* in different disease entities. This is summarized in Table 1.

Evidence of the clinical benefits of *H. pylori* eradication

Gastric and duodenal ulcer

The strong association between *H. pylori* infection and peptic ulcer disease is unarguable. Meta-analysis studies have showed superior ulcer remission rate for both gastric and duodenal ulcer in patients successfully eradicated of *H. pylori* infection [Singh and Ghoshal, 2006; Leodolter *et al.* 2001]. *H. pylori* eradication therapy was also more superior and cost-effective than maintenance acid suppressive therapy in preventing duodenal ulcer [Ford *et al.* 2004]. A study by Sharma *et al.* [2001] also found that *H. pylori* eradication

was more successful in decreasing recurrent gastroduodenal ulcer bleeding compared with ulcer healing treatment alone (17% versus 4% respectively). Maintenance acid suppression therapy was also not necessary after successful *H. pylori* eradication and ulcer healing [Liu *et al.* 2003].

MALT lymphoma

Multiple studies have demonstrated a strong association between *H. pylori* infection and MALT lymphoma [Parsonnet *et al.* 1994; Wotherspoon *et al.* 1991]. Both the American College of Gastroenterology (ACG) [Chey and Wong, 2007] and the Maastricht III consensus conference (MCC III) 2006 [Malfertheiner *et al.* 2007] have proposed *H. pylori* eradication as the first-line treatment for infected patients with stage I low-grade gastric MALT lymphoma, with favorable long-term outcome. In a large prospective series from Germany [Fischbach *et al.* 2004], 62% of patients with low-grade gastric MALT lymphoma had complete remission after *H. pylori* eradication within 12 months. Another study from Taiwan also suggested that anti-*H. pylori* therapy might be considered as one of the treatment options for early-stage *H. pylori*-positive gastric diffuse large B-cell lymphoma [L.T. Chen *et al.* 2005].

Gastric cancer

Gastric cancer is the second most common cause of cancer-related death in the world [Talley *et al.* 2008]. Both animal and human studies have demonstrated a clear association between *H. pylori* infection and gastric adenocarcinoma [Eslick *et al.* 1999; Huang *et al.* 1998; Watanabe *et al.* 1998]. The Cag-A-positive strains of *H. pylori* further increases the risk for gastric carcinoma over the risk of infection with non-Cag-A strains [Huang *et al.* 2003]. The IARC estimates that *H. pylori* causes 36% and

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Table 1. Summary of benefits and risks of *H. pylori* eradication.

	Definite evidence of benefits	Supportive evidence of benefits	Potential risks
<i>H. pylori</i> -positive disease			
Gastric and duodenal ulcer	✓		
MALToma	✓		
Early gastric cancer after resection	✓		
Uninvestigated dyspepsia	✓		
Family history of gastric cancer		✓	
Atrophic gastritis		✓	
Non-ulcer dyspepsia		✓	
NSAIDs		✓	
Iron deficiency anemia		✓	
ITP		✓	
Lymphocytic gastritis, gastric hyperplastic polyps, Menetrier's disease		✓	
GERD		✓ Antral-predominant gastritis	✓ Corpus-predominant gastritis Insignificant
Barrett's metaplasia and esophageal carcinoma			
Childhood asthma and allergic rhinitis			Causal relationship not well established
Antimicrobial resistance			✓ Failure of first-line eradication increases secondary resistance

GERD, gastroesophageal reflux disease; ITP, immune thrombocytopenic purpura; MALT, mucosa associated lymphoid tissue; NSAIDs, non-steroidal anti-inflammatory drugs.

47% of all gastric cancers in developed and developing countries respectively [IARC, 1994]. The epidemiological study EUROGAST included populations from both Asian and Western countries and demonstrated a six-fold increased risk of gastric cancer in *H. pylori* infected populations compared with uninfected populations [EUROGAST Study Group, 1993]. Furthermore, *H. pylori* can cause chronic active and atrophic gastritis, both are early steps in the carcinogenesis process [Siurala, 1966]. *H. pylori* eradication prevents development of these preneoplastic changes of the gastric mucosa, including atrophic gastritis and intestinal metaplasia [Asaka *et al.* 2001; Ohkuma *et al.* 2000; Kuipers *et al.* 1997]. Randomized control studies have shown that regression of these precancerous lesions or a decrease in progression is possible by *H. pylori* eradication [Zhou *et al.* 2003]. A study from China over a period of 7.5 years demonstrated that eradication of *H. pylori* significantly decreased the development of gastric cancer in *H. pylori* carriers without precancerous lesions [Wong *et al.* 2004]. Recently the Japanese Gast Study Group found that eradication of *H. pylori* in 544 patients after

endoscopic resection of early gastric cancer significantly reduced the risk of developing metachronous gastric carcinoma [Fukase *et al.* 2008]. Most of these patients had either intestinal metaplasia or moderate-to-severe gastric atrophy. The risk of subsequent cancer reduced from 4 per 100 every year to 1.4 per 100 every year in the eradication group. The overall consensus is that *H. pylori* should be eradicated as soon as possible and best before precancerous lesions are present. The 2007 Asia-Pacific Consensus Conference recommended that population-based screening and antibiotic treatment of *H. pylori* in high-risk regions should be performed [Fock *et al.* 2008].

Uninvestigated dyspepsia

The MCC III recommended the *H. pylori* 'test and treat' strategy among adult patients under the age of 45 presenting with persistent dyspepsia [Malfertheiner *et al.* 2007]. The ACG recommended a cut-off age of 55 [Chey and Wong, 2007]. This recommendation is validated by a study in Canada, which concludes that *H. pylori* eradication has a small but statistically significant

effect in *H. pylori*-positive uninvestigated dyspepsia [Chiba *et al.* 2002]. Another study from Malaysia also found that *H. pylori* 'test and treat' strategy is more cost effective but less satisfying than prompt endoscopy in the management of young Asian patients with uninvestigated dyspepsia [Mahadeva *et al.* 2008].

Supportive evidence of clinical benefits for *H. pylori* eradication

Functional dyspepsia

It remains controversial whether eradicating *H. pylori* infection is of clinical benefit in patients with functional dyspepsia. Several studies have demonstrated a beneficial effect in terms of symptomatic improvement in *H. pylori* eradication for functional dyspepsia [McNamara *et al.* 2002; McColl *et al.* 1998] but not supported by other studies. The latest meta-analyses, however, have shown a small but statistically significant clinical benefit in a subgroup of patients with functional dyspepsia after eradication of *H. pylori* infection [Hsu *et al.* 2001].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

H. pylori infection and NSAIDs independently increase the risk of peptic ulcer bleeding by 1.79- and 4.86-fold respectively and by 6.13-fold when both factors are combined [Huang *et al.* 2002]. These two risk factors are at least additive if not synergistic in causing peptic ulcer bleed. *H. pylori* eradication was associated with a reduced incidence of peptic ulcer in patients taking NSAIDs (OR 0.43, 95% CI 0.20–0.93) [Vergara *et al.* 2005]. Both long-term NSAIDs and aspirin users with history of peptic ulcer should be tested for *H. pylori* and receive eradication therapy if proven positive [Papatheodoridis and Archimandritis, 2005]. Proton pump inhibitor maintenance is necessary after eradication. In naïve NSAID patients, *H. pylori* eradication may prevent peptic ulcer and bleeding.

Other intestinal and extraintestinal disease

Recent studies have supported an association between *H. pylori* infection, unexplained iron deficiency anemia [DuBois and Kearney, 2005] and immune thrombocytopenic purpura (ITP) [Gasbarrini *et al.* 1998]. The MCG III recommended that *H. pylori* infection should be sought for and treated in patients with

unexplained iron deficient anemia and in those with ITP [Tsutsumi *et al.* 2005]. The Third Chinese National Consensus Report has also added other *H. pylori*-related gastric diseases such as lymphocytic gastritis, gastric hyperplastic polyps and Menetrier's disease as supportive indications for *H. pylori* eradication [Hu *et al.* 2008].

Possible risks of *H. pylori* eradication

The Blaser's hypothesis

The major concern over a potential negative outcome associated with *H. pylori* eradication is the risk of provoking gastroesophageal reflux disease (GERD) and esophageal carcinoma. Blaser first raised this concern in 1999 [Blaser, 1999] based on circumstantial evidence that not all *H. pylori*-infected patients would develop significant clinical consequences in their lifetime and the possible commensal role of *H. pylori*, since this bacterium was infecting humans 58,000 years ago before migration out of East Africa [Linz *et al.* 2007]. He suggested that colonization with Cag-positive strains appears protective against proximal diseases including GERD, Barrett's esophagus, and adenocarcinomas of the gastric cardia and lower esophagus. Eradication of *H. pylori* may remove some beneficial strains and provoke esophageal disease or gastric cancer at the cardia [Hunt, 2001]. This hypothesis was subsequently debated on and the clinical evidence will be discussed [Graham *et al.* 2007].

GERD

The prevalence of *H. pylori* in patients with GERD is lower than in those without reflux disease [Metz and Kroser, 1999]. A meta-analysis found that *H. pylori*-negative status was associated with a significantly increased risk of GERD (pooled OR 1.34, 95% CI 1.15–1.55) [Cremonini *et al.* 2003]. Despite this, studies did not show *H. pylori* to have a direct pathogenic effect on GERD. It has no effect on gastroesophageal junction competence [Shirota *et al.* 1999] and it does not decrease the pressure of the lower esophageal sphincter. There was no significant change in the 24-hour esophageal pH before and after *H. pylori* eradication [Tefera *et al.* 1999]. GERD patients who failed *H. pylori* eradication also relapsed earlier than negative GERD controls and GERD patients who had successful eradication of *H. pylori* [Schwizer *et al.* 2001]. An analysis of eight double-blind prospective trials of *H. pylori*

therapy in patients with duodenal ulcer disease confirmed that eradication of *H. pylori* did not worsen GERD but may improve symptoms in patients with pre-existing GERD [Laine and Sugg, 2002]. Eradication of *H. pylori* may be associated with a mild worsening of GERD in patients with corpus-predominant gastritis but an improvement in patients with antral-predominant gastritis. Blaser suggested that colonization with the Cag-positive strains may be protective against GERD. Unfortunately, Cag-A-positive strains have also been associated with gastric adenocarcinoma [Huang *et al.* 2003].

Barrett's esophagus and esophageal carcinoma

Similar to GERD, a lower prevalence of Barrett's metaplasia and esophageal adenocarcinoma has been described in *H. pylori*-positive patients [Weston *et al.* 2000]. However, in a systematic review by Nakajima and Hattori [2004] the expected annual incidence of gastric cancer in patients with corpus atrophy with persistent infection was at least 5.8-fold higher than that for esophageal adenocarcinoma after the eradication of infection at all ages. For patients with underlying reflux esophagitis or Barrett's esophagus, the expected incidence of either gastric or esophageal adenocarcinoma with persistent infection was higher than that of esophageal adenocarcinoma after eradication of infection. This suggests that *H. pylori* plays an insignificant role in the pathogenesis of Barrett's esophagus and esophageal adenocarcinoma.

Childhood asthma

Two recent studies by Chen and Blaser [2008, 2007] suggested an inverse association of *H. pylori* infection with childhood asthma and allergic rhinitis. The presence of Cag-A-positive *H. pylori* strains in a child was inversely related to ever having asthma and this inverse association was stronger than that with adult-onset asthma. The author concluded that childhood acquisition of *H. pylori* is associated with reduced risks of asthma and allergy. Nevertheless, more prospective studies are needed to demonstrate a causal relationship between *H. pylori* eradication in childhood and subsequent development of asthma.

Antimicrobial resistance

There is an increasing trend of *H. pylori* treatment failure with traditional triple therapy

containing proton pump inhibitors, amoxicillin, clarithromycin or metronidazole in many parts of the world [Graham and Shiotani, 2008]. Empirical therapies that do not reliably yield a greater than 90% successful rate should not be prescribed. A study has shown that unsuccessful treatments significantly increase resistance [Romano *et al.* 2008]. It is therefore important to choose the most effective first-line treatment regime in order to avoid treatment failure and subsequent secondary resistances.

Conclusion

The overall evidence strongly supports that the benefits of eradication of *H. pylori* in indicated patients far outweigh the risks (Table 1). Failure to eradicate *H. pylori* in patients with peptic ulcer disease is associated with a 60% annual ulcer recurrence rate compared with 10% after eradication and a two to three times increased risk of gastric adenocarcinoma [Marshall, 1994]. We therefore advocate the eradication of *H. pylori* in indicated patients as listed in the MCC III and ACG guidelines.

Conflict of interest

All authors have no conflicts to disclose.

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