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***Helicobacter pylori*: Friend or foe?**

Malnick S *et al*. *H. pylori*: Friend or foe?

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a gram negative spiral bacterium that is present in nearly half of the world’s population. It is the major cause of peptic ulcer disease and a recognized cause of gastric carcinoma. In addition it is linked to non-ulcer dyspepsia, vitamin B12 deficiency, iron-deficient anemia and immune thrombocytopenic purpura. These conditions are indications for testing and treating according to current guidelines. An additional indication according to the guidelines is “anyone with a fear of gastric cancer” which results in nearly every infected person being eligible for eradication treatment. There may be beneficial effects of *H. pylori* in humans including protection from gastroesophageal reflux disease and esophageal adenocarcinoma. In addition universal treatment will be extremely expensive (more than $32 billion in the United States), may expose the patients to side-effects such as anaphylaxis and *Clostridium difficile* infection, as well as contributing to antibiotic resistance. There may also be an as yet uncertain effect on the fecal microbiome. There is a need for robust clinical data to assist in decisions regarding treatment of *H. pylori* infection.

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**Key words:** *Helicobacter pylori*; Treatment; Cost; Benefit; Cancer

**Core tip:** *Helicobacter pylori* (*H. pylori*) is found in more than half of the world's population. It is a major cause of peptic ulcer disease and gastric carcinoma. The overwheming majority of those infected will not suffer any consequences during their lifetime. Furthermore, there may be a beneficial effect of *H. pylori* infection on allergy and asthma in young children and a protection against gastroesophageal reflux disease and its feared complication of esophageal carcinoma. Universal eradication will be prohibitively expensive, have side-effects and needs to be evaluated on the basis of robust clinical data that is not yet available.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) is a gram negative bacterium found on the luminal surface of the gastric epithelium[1]. It induces chronic inflammation of the underlying mucosa. The infection is usually contracted in the first years of life and persists indefinitely unless treated[2]. The prevalence varies with age and socio-economic status in childhood and therefore varies between countries[3].

Approximately 50% of the world's population is infected with *H. pylori*[2]. *H. pylori* infection has been linked to gastric and duodenal ulcers (in 1%-10% of infected patients), gastric carcinoma (0.1%-3%) and gastric mucosa-associated lymphoid tissue lymphoma (less than 0.01%)[4]. However, the vast majority of the infected population will never develop symptoms related to *H. pylori* infection.

Consensus guidelines have been developed and updated[5] (Table 1). The recommendations for treatment include peptic ulcer, MALT-lymphoma, gastric cancer, first-degree relatives of patents with gastric cancer, unexplained iron-deficiency anemia and immune thrombocytopenia. In addition, the Maastricht Guidelines state that “*H. pylori* positive patients with fear of gastric cancer should receive eradication treatment”[5]. This last recommendation makes it likely that anyone found to be *H. pylori* positive will receive eradication treatment.

**EPIDEMIOLOGY**

The prevalence of *H. pylori* infection varies from 20% to 50% in industrialized countries to over 80% in developing countries[4,6]. In developing countries, the majority of children are infected before the age of 10 and peaks at the more than 80% before the age of 50. In developed countries infection in children is unusual but becomes more common in adulthood. Serology is negative in the vast majority before the age of 10, increases to 10% in those between 18 and 30 and to 50% in those older than 60[7].

The route for infection by *H. pylori* is unclear[8]. It seems most likely to be by the oral-fecal or oral-oral route[9].

The risk of acquiring *H. pylori* is related to socioeconomic status and early life living conditions[10]. In some countries there is a link between a decline in *H. pylori* prevalence and economic development. In Japan, 70%-80% of adults born before 1950, 45% of those born between 1950-1960 and 25% of those born between 1960 and 1970 are infected[11].

Reinfection with *H. pylori* following successful bacterial cure is unusual. In adults the rate is less than 2% per year[12] which is similar to the primary adult acquisition of infection[13].

**DISEASES ASSOCIATED WITH *HELICOBACTER PYLORI***

*H. pylori* is present in the majority of the patients with uncomplicated duodenal ulcers, especially in those with no history of recent non-steroidal anti-inflammatory drug consumption[14]. *H. pylori* is not found in up to 27% of patients with endoscopically proven duodenal ulcers[15] and thus needs to be tested for. In addition *H. pylori* is found in the majority of uncomplicated gastric ulcers[16]. *H. pylori* infection has also been linked with unexplained iron deficiency anemia[17], vitamin B12 deficiency[18] and immune thrombocytopenic purpura[19]. It is clear that *H. pylori* should be examined for and treated to eradication in the above cases.

*H. pylori* is also linked to gastric cancer. There is a six fold increase in the risk for gastric cancer in *H. pylori* positive populations compared with uninfected populations[20]. In a nested case control study of Japanese Americans living in Hawaii, *H. pylori* seropositvity was present in 94% of those with gastric cancer compared to 76% of matched controls (an odds ratio of 6.0)[21].

There is also an association between *H. pylori* infection and mucosa-associated lymphoid tissue (MALT) lymphoma[22] as well as a link between. In addition MALT lymphoma regresses following successful treatment for *H. pylori*.

*H. pylori* infection has also been linked to iron-deficiency anemia[17] and vitamin B12 deficiency[18].

In summary, *H. pylori* infection is clearly linked to peptic ulcer disease, gastric cancer and MALT lymphoma, immune thrombocytopenia and some cases of vitamin B12 and iron deficiency. In such situations, it is reasonable to proceed to eradication.

**DIAGNOSIS OF *H. PYLORI* INFECTION**

There are several methods for diagnosing *H. pylori* infection, both noninvasive and invasive. The invasive tests are performed on specimens obtained at endoscopy These include biopsy urease testing, histology and less commonly bacterial culture and sensitivity. The sensitivity of a biopsy urease test is between 90%-95% and the specificity is 95%-100%[15].

In addition, there are non-invasive tests including breath urease testing, stool antigen testing and serology. The urea breath test is based on the hydrolysis of urea by *H. pylori* to produce carbon dioxide and ammonia[23]. A labeled carbon isotope is given by mouth and *H. pylori* liberate tagged carbon dioxide that can be detected in the exhaled air.

Laboratory based enzyme-linked immunosorbent assay testing to detect immunoglobulin G is inexpensive and non invasive. There is a high sensitivity (90% to 100%), but variable specificity (76% to 96%). In low prevalence areas, a positive serology result has a low predictive value for active infection. In such areas stool antigen or breath testing is recommended. Conversion of positive serology to negative one year after treatment suggests bacterial cure[24].

The presence of *H. pylori* in the stool of infected patients has enabled the development of fecal assays[15]. This has a high sensitivity, specificity and diagnostic accuracy[25].

In summary, there are a range of tests, both invasive and non-invasive, that are available for the diagnosis of *H. pylori* infection.

**INDICATIONS FOR *H. PYLORI* ERADICATION**

***Peptic ulcer disease***

*H. pylori* is found in the majority of duodenal ulcers[14], especially if there is no history of consumption of NSAIDS. In those patients with a duodenal ulcer who do not have *H. pylori* infection, there seems to be a worse prognosis with a higher incidence of ulcer relapse, non-healed ulcer and relapse of severe dyspeptic symptoms in the *H. pylori* negative patients[26].

*H. pylori* seems to be associated with the majority of gastric ulcers[16] but again there is an increasing proportion of patients with gastric ulcer in whom *H. pylori* is not detected. Some of these cases may be related to surreptitious use of NSAIDS.

Thus in cases of peptic ulcer disease routine testing and treating of *H. pylori* is recommended and justified. The recommendations for testing and treating of *H. pylori* are shown in Table 1.

***Carcinoma of the stomach***

*H. pylori* is linked to the development of chronic active gastritis and atrophic gastritis which are early stages in the carcinogenesis sequence. There is a clear association between *H. pylori* infection and gastric adenocarcinoma. *H. pylori* has been recognized as a grade 1 carcinogen by the International Agency for Research on Cancer (IARC)[27]. It is thought that long-term chronic inflammation caused by *H. pylori* is the main mechanism for the developemnt of gastric carcinoma[28].

In spite of the definite connection between gastric carcinoma and *H. pylori* infection, it has not been convincingly shown that *H. pylori* eradication decreases the incidence of gastric carcinoma. This is due to the fact in order to perform trials with cancer as the endpoint, more than 18000 patients will need to be recruited and will need to be followed up for 10 to 20 years[29].

In addition it may be unethical to include an untreated arm since *H. pylori* has been classified as a type 1 carcinogen. There are only two randomized controlled interventional trials with gastric cancer development as the primary outcome[30,31] (Table 2). Both of these studies were performed in high risk areas of the Far East. In the study of Wong *et al*[30] 1630 *H. pylori* positive patients were followed up for 7 years. In the eradication group 7/817 (0.9%) of the patients developed gastric carcinoma compared to 11/813 (1.3%) in the placebo group, *P* = 0.33. It is of interest to note that none of the patients without precancerous lesions at baseline histology developed cancer. The authors suggest that the chemo preventive effect of *H. pylori* eradication is only effective before preneoplastic lesions have developed.

The majority of intestinal-type gastric carcinoma arises from atrophic gastric mucosa. Although eradication of *H. pylori* results in a decrease of inflammation, it is not clear that mucosal atrophy is improved by *H. pylori* eradication[32-35]. One study with follow-up of 13.7 years after *H. pylori* eradication found no significant inflammatory cell infiltration at the time of cancer diagnosis. This suggests that the decrease in mucosal inflammation resulting from *H. pylori* eradication is insufficient to prevent gastric carcinoma once severe mucosal atrophy has developed[25]

Fukase *et al*[31] enrolled 544 patients in a multi-center study and a 3 year follow-up. The odds ratio for developing gastric cancer was 0.353 in the eradciation group (*P* = 0.009).

A meta-analysis of published trials found gastric cancer in 33/3112 (1%) of eradication patients *vs* 50/3031 (1.6%) of untreated patients[36]. This is a relative risk of 0.65, *P* = 0.05.

In addition the influence of *H. pylori* eradication may decrease with time. In a study of 268 *H. pylori*+ patients who had undergone endoscopic resection of early gastric cancer, there were 177 patients who had undergone successful *H. pylori* eradication and 91 who had persistent *H. pylori* infection[37]. Although the incidence of metachronous gastric carcinoma was lower in the eradicated group at 5 years of follow up (*P* = 0.007), this difference was no longer significant in the follow-up period extending to 11.1 years (*P* = 0.262). Interestingly, in this study too, multivariate analysis showed severe mucosal atrophy, but not *H. pylori* status to be an independent risk factor for metachronous gastric cancer.

There may be a precancerous state, with moderate to severe gastric mucosal atrophy or intestinal metaplasia representing a point of no return in terms of developing gastric cancer, from which *H. pylori* eradication can no longer prevent gastric cancer. It thus may be preferable to try to identify those patients at risk for developing atrophic gastritis and then treat for *H. pylori* eradication. It has been suggested that *H. pylori* eradication will be most beneficial in terms of preventing cancer in patients who have chronic atrophic gastritis and negative serum pepsinogen[38].

***Functional dyspepsia***

Dyspepsia is a common symptom with an extensive differential diagnosis. It is thought to be present in about 25% of the population in any year, although the majority of affected people do not seek medical care. About 25% of those suffering from dyspepsia have an underlying organic cause, but the remainder have nonulcer dyspepsia in which there is no clear organic cause after diagnostic evaluation. Functional dyspepsia is classified into postprandial distress syndrome and epigastric pain syndrome[39].

*H. pylori* eradication has been associated with significant benefits in a subset of patients suffering from functional dyspepsia[40]. Four hundred and four patients with functional dyspepsia who were infected with *H. pylori* were randomized to receive placebo or eradication treatment of *H. pylori*. On 12 mo follow up patients in whom *H. pylori* was eradicated were more likely to have symptomatic improvement as compared to the control group (49% *vs* 36%, *P* = 0.01). In addition, a systematic review of 17 randomized controlled trials including 3566 patients with functional dyspepsia, eradication of *H. pylori* was associated with a small but significant benefit. 14 patients needed to be treated in order to cure one case of functional dyspepsia[41].

However, it is possible that alterations in the upper gastrointestinal tract microbiome may result in the development of dyspepsia. Dyspepsia is more likely to occur after an episode of gastroenteritis[42,43].It has been suggested that the effect of *H. pylori* therapy in improving the symptoms of functional dyspepsia is due to its impact on the gut microbiome rather than the eradication of *H. pylori* alone[44]. The clinical management of *H. pylori* infection has recently been reviewd[45].

**BENEFICIAL EFFECTS OF *H. PYLORI* INFECTION**

*H. pylori* has been colonizing the human stomach for more than 58000 years[46] and has been found in Egyptian mummies. This long-standing relationship suggests that there may be some adverse effects to altering the colonization of the human microbiome.

There does appear to be an inverse relationship between *H. pylori* infection and Barretts esophagus[47]. Sonnenberg *et al*[48] reported a study of more than 78000 US patients who underwent upper GI endoscopy and histopathological analysis of gastric biopsies. They found that there was a strong correlation between the presence of *H. pylori*, chronic gastritis and intestinal metaplasia. In addition, there was an inverse association with Barretts esophagus. Barrett's esophagus is thought to be an intermediate lesion along the pathway between reflux esophagitis and esophageal adenocarcinoma. In recent years, there has been an increase in the incidence of esophageal adenocarcinoma in the developed world, together with an increase in the incidence of Barretts esophagus and esophageal reflux (Table 3)[49-53].

*H. pylori* infection is usually acquired in childhood and generally persists for life[54]. Thus *H. pylori* has infected the majority of the world's population for the majority of their lifetime[54] and in most cases causes no symptoms. In recent years there has been a decrease in the prevalence of *H. pylori* infection in developed countries. In the United States less than 6% of children are infected by *H. pylori*[55]. A similar trend is becoming apparent in the other parts of the developed world[56,57].

In addition, there have been reports of an inverse association between childhood-onset asthma and *H. pylori* infection[55,58,59] and protection from other infections[60,61] (Table 3).

Recently, it is becoming clear that the gut microbiota has an important effect on many disease processes[62] and that disturbing the balance of the bacteria by antibiotics can produce a state of dysbiosis with an effect on pathogen evolution[63]. *Clostridium difficile* infection linked to antibiotic use is one example of a deleterious effect related to antibiotic consumption and its effect on the microbiome.

Many organisms that are considered as commensals such as *Kelbsiella*, *Strep viridans* and *Candida* can become opportunistic pathogens, especially in the aged population. There is no coordinated attempt to eradicate these organisms from the human population and we suggest that there should not be a similar effort to eradicate *H. pylori*. There is a complex biological relationship between humans and commensal bacteria that is only now beginning to be understood. The “test and treat” approach to *H. pylori* does not address this issue at all.

**COST OF ERADICATION OF *H. PYLORI***

The current recommendations for treating *H. pylori* make a strong case for universal eradication. The insertion of “*H. pylori* positive patients with fear of gastric cancer should receive eradication treatment”[5] makes it likely that the majority of the world's infected population will receive treatment. The economic implications are enormous.

In the United States the population in 2012 was approximately 300 million people.A urease breath test costs $15 and thus the cost of testing is approximately $4.5 billion. Assuming 30% positivity rate, then retesting to confirm eradication will need to be performed on 90 million people for an additional cost of $1.5 billion.

First line therapy consisting of amoxycillin 1 g *bid*, omeprazole 20 mg *bid*, and clarithromycin 500 mg *bid* for 10 d costs $203 (based on [www.goodrx.com](http://www.goodrx.com/)). This will cost $18.27 billion for the 90 million people who are *H. pylori* positive. This treatment is about 80% effective and thus 18 million people will still be infected with *H. pylori*. Second line therapy with omeprazole, bismuth subsalicylate, tetracycline and metronidazole costs $2.68 billion and is expected to be about 70% successful. Repeat testing of these 18 million people will cost $270 million and there will still be 5.4 million people infected with *H. pylori*.

Further treatment will require gastroscopy, biopsy, bacterial culture and sensitivity testing. The cost of gastroscopy to medicare in an ambulatory surgery clinic is $341 for the center and $351 for the physician and thus the total cost for 5.4 million people is $3.74 billion. The cost of a helicon acted culture is $159 with a further $222 for susceptibility testing for 4 drugs (Ellie Goldstein, personal communication).This will result in a total cost of $2 billion for 5.4 million people. Thus the total cost for eliminating *H. pylori* from the population of the United States is in the region of $33 billion dollars!

**IS ERADICATION OF *H. PYLORI* COST-EFFECTIVE ?**

The question of whether eradication of *H. pylori* is cost-effective is complex. There is a difference between treating anyone found to be positive, or those with non-ulcer dyspepsia, or people with a high risk for gastric cancer. In addition there is still not a complete understanding of the beneficial effects of commensal *H. pylori* infection as well as the risks associated with universal treatment.

There have been studies estimating the financial implications of screening for *H. pylori* in a subpopulation of dyspeptic patients, or related to one *H. pylori*-associated disease such as peptic ulcer or gastric cancers[64-65]. In these studies screening for and treating *H. pylori* was found to be cost effective in patients with peptic ulcer or for preventing gastric cancer[65]. Furthermore it has been estimated that screening and treatment for *H. pylori* is likely to be cost effective taking into account both gastric cancer and peptic ulcer disease[66,67]. A meta-analysis of trials of eradication therapy in *H. pylori* positive peptic ulcer disease found a reduction in the recurrence of peptic ulcer disease and concluded that it was cost effective[68]. A comparison of a strategy of screening and treating everyone found to be positive *vs* test and treat only if symptoms arise found an incremental cost per case of $26 in the screening cohort[69].

A comprehensive cost-benefit analysis is difficult to perform since not all of the variables are known. The effect on the fecal microbiome of widespread eradication is not known. In addition, the decrease in prevalence of *H. pylori* will cause a corresponding decrease in the incidence of new infection in the next generation. To the best of our knowledge, a cost-benefit analysis incorporating these variables has not been performed.

In summary, *H. pylori* is a common infection of the human stomach. It is a major cause of peptic ulcer disease, a recognized carcinogen and linked to both iron and vitamin B12 deficiency. It may have some beneficial effects protecting from gastroesophageal reflux disease and associated esophageal carcinoma, as well as protecting young children from asthma and allergic diseases.

Near universal eradication, consistent with current guidelines, will be prohibitively expensive.

Furthermore, it is likely there will be some fatalities from previously unknown allergic reactions to antibiotics employed, drug side-effects, an increase in bacterial antibiotic resistance in treated populations, an increase in *Clostridium difficile* infection and unknown effects on the fecal microbiome.

There is an urgent need for robust clinical data to enable and support decisions regarding treatment of *H. pylori* infection before committing to a huge expenditure of limited health-care resources for which the overall impact is uncertain.

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**Table 1 Reccomendations for testing and treating of *Helicobacter pylori* infection[5]**

|  |
| --- |
| **Reccomendations** |
| Do not test if not prepared to treat |
| Peptic ulcers |
| Unexplained iron deficiency anemia |
| Idiopathic thrombocytopenic purpura |
| Vitamin B12 deficiency |
| Long-term proton pump inhibitor therapy |
| Functional dyspepsia? |
| Family history of gastric cancer |

**Table 2 Randomized controlled trials of *Helicobacter pylori* eradication and risk of gastric cancer**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Province, country** | **Gastric cancer per 105** | **No patients**  **Treatment/control** | **Follow up (yr)** | **No patients with gastric cancer** |  | ***P*** |
| Wong *et al*[30] | Fujian, China | 99/105 | 817/813 | 7.5 | 7 (0.9)/11 (1.4) |  | 0.33 |
| Fukase *et al*[31] | Japan | 62/105 | 272/272 | 3 | 9 (3.3)/24 (8.8) |  | 0.009 |

**Table 3 Inverse association of *Helicobacter pylori* with asthma and allergy[52]**

|  |  |  |
| --- | --- | --- |
| ***H. pylori* status(*H. pylori*/cagA)** | **< 15 yr OR** | **> 15 yr OR** |
| - | 1 | 1 |
| +/- | 0397 (0.65-1.45) | 0.95 (0.68-1.33) |
| +/+ | 0.63 (0.43-0.93) | 0.97 (0.72-1.32) |

*H. pylori: Helicobacter pylori*.