World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i27.8979

World J Gastroenterol 2014 July 21; 20(27): 8979-8985
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Helicobacter pylori: Friend or foe?

Stephen David Howard Malnick, Ehud Melzer, Malka Attali, Gabriel Duek, Jacob Yahav

Stephen David Howard Malnick, Department of Internal Medicine C, Kaplan Medical Center, 76100 Rehovot, Israel
Ehud Melzer, Gabriel Duek, Gastroenterology Institute, Kaplan Medical Center, 76100 Rehovot, Israel
Malka Attali, Department of Internal Medicine B, Kaplan Medical Center, 76100 Rehovot, Israel
Jacob Yahav, Kaplan Medical Center, Affiliated to the Hebrew University, Jerusalem, 76100 Rehovot, Israel
Author contributions: Malnick SDH developed the concept and wrote the manuscript; Melzer E, Attali M and Duek G developed the theme and researched the literature; Yahav J contributed to the writing and revision of the manuscript, in addition to developing the concept.
Correspondence to: Stephen David Howard Malnick, Director, Department of Internal Medicine C, Kaplan Medical Center, PO Box 1, 76100 Rehovot, Israel. stephen@malnick.net
Telephone: +97-289-441371 Fax: +97-289-441852
Received: September 24, 2013 Revised: January 23, 2014
Accepted: April 21, 2014
Published online: July 21, 2014

Abstract

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral bacterium that is present in nearly half 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 treatment 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 adverse 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 decision-making regarding treatment of *H. pylori* infection.

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

Core tip: *Helicobacter pylori* (*H. pylori*) is found in more than half the world's population. It is a major cause of peptic ulcer disease and gastric carcinoma. The overwhelming 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 adverse effects and needs to be evaluated on the basis of robust clinical data that is not yet available.

Malnick SDH, Melzer E, Attali M, Duek G, Yahav J. *Helicobacter pylori*: Friend or foe? *World J Gastroenterol* 2014; 20(27): 8979-8985 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i27/8979.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i27.8979

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 socioeconomic 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

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

Recommendations
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

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, mucosa-associated lymphoid tissue (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 the prevalence peaks at 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 under the age of 10, increases to 10% in those between 18 and 30 years 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 socio-economic 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 and 1960 and 25% of those born between 1960 and 1970 are infected[11].

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

DISEASES ASSOCIATED WITH *H. 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 tested and treated to eradication in the above cases.

H. pylori is also linked to gastric cancer. There is a 6-fold increase in the risk of 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 with 76% of matched controls (OR = 6.0)[21].

There is also an association between *H. pylori* infection and MALT lymphoma[22]. In addition MALT lymphoma regresses following successful treatment for *H. pylori*.

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 urea breath 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* liberates 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%-100%), but variable specificity (76%-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 1 year after treatment suggests bacterial eradication[24].

The presence of *H. pylori* in the stool of infected patients has enabled the development of fecal assays[15] which have 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.

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

Ref.	Province, country	Gastric cancer per 10^5	No. of patients treatment/control	Follow up (yr)	No. of patients with gastric cancer	*P* value
Wong *et al*[30]	Fujian, China	$99/10^5$	817/813	7.5	7 (0.9)/11 (1.4)	0.330
Fukase *et al*[31]	Japan	$62/10^5$	272/272	3	9 (3.3)/24 (8.8)	0.009

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 non-steroidal antiinflammatory drugs (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[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 ulcers 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 treatment 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[27]. It is thought that long-term chronic inflammation caused by *H. pylori* is the main mechanism for the development 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 10-20 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 with 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 chemopreventive 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 in 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 multicenter study with a 3 year follow-up. The odds ratio for developing gastric cancer was 0.353 in the eradication 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 had a relative risk of 0.65 ($P = 0.05$).

The influence of *H. pylori* eradication may decrease with time. In a study of 268 *H. pylori*-positive 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, as 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 of 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%

Table 3 Inverse association of *Helicobacter pylori* with asthma and allergy[55]

H. pylori status (*H. pylori*/cagA)	< 15 yr OR (95%CI)	> 15 yr OR (95%CI)
-	1	1
+/-	0.97 (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*.

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 (FD) 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 FD[40]. Four hundred and four patients with FD who were infected with *H. pylori* were randomized to receive placebo or eradication treatment of *H. pylori*. At 12-mo follow-up, patients in whom *H. pylori* was eradicated were more likely to have symptomatic improvement compared with the control group (49% *vs* 36%, $P = 0.01$). In addition, a systematic review of 17 randomized controlled trials, including 3566 patients with FD, found that 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 FD[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 FD 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 reviewed[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 in altering the colonization of the human microbiome.

There does appear to be an inverse relationship between *H. pylori* infection and Barrett's esophagus[47]. Sonnenberg *et al*[47] reported a study of more than 78000 patients in the United States who underwent upper gastrointestinal 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 Barrett's 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 Barrett's esophagus and esophageal reflux (Table 3)[48-53].

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 other parts of the developed world[56,57].

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 has become 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 assertion that "*H. pylori*-positive patients with a 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. A urease breath test costs $15 and thus the cost of testing would be approximately $4.5 billion. Assuming a 30% positivity rate, then retesting to confirm eradication would need to be performed on 90 million people with 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). This would cost $18.27 billion for 90 million people who are *H. pylori*-positive. This treatment is about 80% effective and thus 18 million people would still be infected with *H. pylori*. Second-line therapy with omeprazole, bismuth sub-

salicylate, tetracycline and metronidazole costs $2.68 billion and is expected to be about 70% successful. Repeat testing of these 18 million people would cost $270 million and there would still be 5.4 million people infected with *H. pylori*.

Further treatment would 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 *Helicobacter* culture is $159 with a further $222 for susceptibility testing for 4 drugs (Ellie Goldstein, personal communication).This would 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* testing and treatment only if symptoms arise found an incremental cost per case of $26 in the screened 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 is 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 adverse 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.

REFERENCES

1 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023]
2 **Everhart JE**. Recent developments in the epidemiology of Helicobacter pylori. *Gastroenterol Clin North Am* 2000; **29**: 559-578 [PMID: 11030073]
3 **Woodward M**, Morrison C, McColl K. An investigation into factors associated with Helicobacter pylori infection. *J Clin Epidemiol* 2000; **53**: 175-181 [PMID: 10729690]
4 **McColl KE**. Clinical practice. Helicobacter pylori infection. *N Engl J Med* 2010; **362**: 1597-1604 [PMID: 20427808 DOI: 10.1056/NEJMcp1001110]
5 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
6 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]
7 **Pounder RE**, Ng D. The prevalence of Helicobacter pylori infection in different countries. *Aliment Pharmacol Ther* 1995; **9** Suppl 2: 33-39 [PMID: 8547526]
8 **Cave DR**. Transmission and epidemiology of Helicobacter pylori. *Am J Med* 1996; **100**: 12S-17S; discussion 17S-18S [PMID: 8644777]
9 **Mégraud F**. Transmission of Helicobacter pylori: faecal-oral versus oral-oral route. *Aliment Pharmacol Ther* 1995; **9** Suppl 2: 85-91 [PMID: 8547533]
10 **Webb PM**, Knight T, Greaves S, Wilson A, Newell DG, Elder J, Forman D. Relation between infection with Helicobacter pylori and living conditions in childhood: evidence for person to person transmission in early life. *BMJ* 1994; **308**: 750-753 [PMID: 8142828]
11 **Asaka M**, Kimura T, Kudo M, Takeda H, Mitani S, Miyazaki T, Miki K, Graham DY. Relationship of Helicobacter pylori to serum pepsinogens in an asymptomatic Japanese population. *Gastroenterology* 1992; **102**: 760-766 [PMID: 1537513]
12 **Archimandritis A**, Balatsos V, Delis V, Manika Z, Skandalis N. "Reappearance" of Helicobacter pylori after eradication: implications on duodenal ulcer recurrence: a prospective 6 year study. *J Clin Gastroenterol* 1999; **28**: 345-347 [PMID: 10372933]
13 **Parsonnet J**. The incidence of Helicobacter pylori infection. *Aliment Pharmacol Ther* 1995; **9** Suppl 2: 45-51 [PMID: 8547528]
14 NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in Peptic Ulcer Disease. *JAMA* 1994; **272**: 65-69

[PMID: 8007082]
15 **Chey WD**, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007; **102**: 1808-1825 [PMID: 17608775 DOI: 10.1111/j.1572-0241.2007.01393.x]
16 **Laine L**. Helicobacter pylori, gastric ulcer, and agents noxious to the gastric mucosa. *Gastroenterol Clin North Am* 1993; **22**: 117-125 [PMID: 8449561]
17 **DuBois S**, Kearney DJ. Iron-deficiency anemia and Helicobacter pylori infection: a review of the evidence. *Am J Gastroenterol* 2005; **100**: 453-459 [PMID: 15667507 DOI: 10.1111/j.1572-0241.2005.30252.x]
18 **Kaptan K**, Beyan C, Ural AU, Cetin T, Avcu F, Gülşen M, Finci R, Yalçín A. Helicobacter pylori--is it a novel causative agent in Vitamin B12 deficiency? *Arch Intern Med* 2000; **160**: 1349-1353 [PMID: 10809040]
19 **Papagiannakis P**, Michalopoulos C, Papalexi F, Dalampoura D, Diamantidis MD. The role of Helicobacter pylori infection in hematological disorders. *Eur J Intern Med* 2013; **24**: 685-690 [PMID: 23523153 DOI: 10.1016/j.ejim.2013.02.011]
20 An international association between Helicobacter pylori infection and gastric cancer. The EUROGAST Study Group. *Lancet* 1993; **341**: 1359-1362 [PMID: 8098787]
21 **Nomura A**, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991; **325**: 1132-1136 [PMID: 1891021 DOI: 10.1056/NEJM199110173251604]
22 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176 [PMID: 1682595]
23 **Howden CW**, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2330-2338 [PMID: 9860388 DOI: 10.1111/j.1572-0241.1998.00684.x]
24 **Feldman M**, Cryer B, Lee E, Peterson WL. Role of seroconversion in confirming cure of Helicobacter pylori infection. *JAMA* 1998; **280**: 363-365 [PMID: 9686554]
25 **Trevisani L**, Sartori S, Ruina M, Caselli M, Rossi MR, Costa F, Bellini M, Iaquinto G, Gardullo N, Todisco A. Helicobacter pylori stool antigen test: clinical evaluation and cost analysis of a new enzyme immunoassay. *Dig Dis Sci* 1999; **44**: 2303-2306 [PMID: 10573378]
26 **Bytzer P**, Teglbjaerg PS; Danish Ulcer Study Group. Helicobacter pylori-negative duodenal ulcers: prevalence, clinical characteristics, and prognosis--results from a randomized trial with 2-year follow-up. *Am J Gastroenterol* 2001; **96**: 1409-1416 [PMID: 11374675 DOI: 10.1111/j.1572-0241.2001.03774.x]
27 **Helicobacter and Cancer Collaborative Group**. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353 [PMID: 11511555]
28 **Sotoudeh M**, Derakhshan MH, Abedi-Ardakani B, Nouraie M, Yazdanbod A, Tavangar SM, Mikaeli J, Merat S, Malekzadeh R. Critical role of Helicobacter pylori in the pattern of gastritis and carditis in residents of an area with high prevalence of gastric cardia cancer. *Dig Dis Sci* 2008; **53**: 27-33 [PMID: 17492381 DOI: 10.1007/s10620-007-9817-1]
29 **Graham DY**, Shiotani A. The time to eradicate gastric cancer is now. *Gut* 2005; **54**: 735-738 [PMID: 15888771 DOI: 10.1136/gut.2004.056549]
30 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
31 **Fukase K**, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392-397 [PMID: 18675689 DOI: 10.1016/S0140-6736(08)61159-9]
32 **Zhou LY**, Lin SR, Ding SG, Huang XB, Zhang L, Meng LM, Cui RL, Zhu J. The changing trends of the incidence of gastric cancer after Helicobacter pylori eradication in Shandong area. *Chin J Dig Dis* 2005; **6**: 114-115 [PMID: 16045599 DOI: 10.1111/j.1443-9573.2005.00204.x]
33 **Mera R**, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, Correa P. Long term follow up of patients treated for Helicobacter pylori infection. *Gut* 2005; **54**: 1536-1540 [PMID: 15985559 DOI: 10.1136/gut.2005.072009]
34 **Ito M**, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, Sumii M, Tanaka S, Yoshihara M, Chayama K. Helicobacter pylori eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. *Aliment Pharmacol Ther* 2002; **16**: 1449-1456 [PMID: 12182744]
35 **Sung JJ**, Lin SR, Ching JY, Zhou LY, To KF, Wang RT, Leung WK, Ng EK, Lau JY, Lee YT, Yeung CK, Chao W, Chung SC. Atrophy and intestinal metaplasia one year after cure of H. pylori infection: a prospective, randomized study. *Gastroenterology* 2000; **119**: 7-14 [PMID: 10889149]
36 **Fuccio L**, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, Grilli D, Bazzoli F. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009; **151**: 121-128 [PMID: 19620164]
37 **Maehata Y**, Nakamura S, Fujisawa K, Esaki M, Moriyama T, Asano K, Fuyuno Y, Yamaguchi K, Egashira I, Kim H, Kanda M, Hirahashi M, Matsumoto T. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. *Gastrointest Endosc* 2012; **75**: 39-46 [PMID: 22018552 DOI: 10.1016/j.gie.2011.08.030]
38 **Yanaoka K**, Oka M, Ohata H, Yoshimura N, Deguchi H, Mukoubayashi C, Enomoto S, Inoue I, Iguchi M, Maekita T, Ueda K, Utsunomiya H, Tamai H, Fujishiro M, Iwane M, Takeshita T, Mohara O, Ichinose M. Eradication of Helicobacter pylori prevents cancer development in subjects with mild gastric atrophy identified by serum pepsinogen levels. *Int J Cancer* 2009; **125**: 2697-2703 [PMID: 19610064 DOI: 10.1002/ijc.24591]
39 **Talley NJ**; American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; **129**: 1753-1755 [PMID: 16285970 DOI: 10.1053/j.gastro.2005.09.019]
40 **Mazzoleni LE**, Sander GB, Francesconi CF, Mazzoleni F, Uchoa DM, De Bona LR, Milbradt TC, Von Reisswitz PS, Berwanger O, Bressel M, Edelweiss MI, Marini SS, Molina CG, Folador L, Lunkes RP, Heck R, Birkhan OA, Spindler BM, Katz N, Colombo Bda S, Guerrieri PP, Renck LB, Grando E, Hocevar de Moura B, Dahmer FD, Rauber J, Prolla JC. Helicobacter pylori eradication in functional dyspepsia: HEROES trial. *Arch Intern Med* 2011; **171**: 1929-1936 [PMID: 22123802 DOI: 10.1001/archinternmed.2011.533]
41 **Moayyedi P**, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D. Eradication of Helicobacter pylori for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2005; **(1)**: CD002096 [PMID: 15674892 DOI: 10.1002/14651858.CD002096.pub2]
42 **Mearin F**, Pérez-Oliveras M, Perelló A, Vinyet J, Ibañez A, Coderch J, Perona M. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. *Gastroenterology* 2005; **129**: 98-104 [PMID: 16012939]
43 **Ford AC**, Thabane M, Collins SM, Moayyedi P, Garg AX,

Clark WF, Marshall JK. Prevalence of uninvestigated dyspepsia 8 years after a large waterborne outbreak of bacterial dysentery: a cohort study. *Gastroenterology* 2010; **138**: 1727-1736; quiz e12 [PMID: 20117111 DOI: 10.1053/j.gastro.2010.01.043]
44 **Moayyedi P**. Helicobacter pylori eradication for functional dyspepsia: what are we treating?: comment on "Helicobacter pylori eradication in functional dyspepsia". *Arch Intern Med* 2011; **171**: 1936-1937 [PMID: 22123803 DOI: 10.1001/archinternmed.2011.541]
45 **Malfertheiner P**, Venerito M, Selgrad M. Helicobacter pylori infection: selected aspects in clinical management. *Curr Opin Gastroenterol* 2013; **29**: 669-675 [PMID: 24100726 DOI: 10.1097/MOG.Ob012e328365d443]
46 **Linz B**, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, Falush D, Stamer C, Prugnolle F, van der Merwe SW, Yamaoka Y, Graham DY, Perez-Trallero E, Wadstrom T, Suerbaum S, Achtman M. An African origin for the intimate association between humans and Helicobacter pylori. *Nature* 2007; **445**: 915-918 [PMID: 17287725 DOI: 10.1038/nature05562]
47 **Sonnenberg A**, Lash RH, Genta RM. A national study of Helicobactor pylori infection in gastric biopsy specimens. *Gastroenterology* 2010; **139**: 1894-1901.e2; quiz e12 [PMID: 20727889 DOI: 10.1053/j.gastro.2010.08.018]
48 **Shaheen N**, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: scientific review. *JAMA* 2002; **287**: 1972-1981 [PMID: 11960540]
49 **Lagergren J**, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831 [PMID: 10080844 DOI: 10.1056/NEJM199903183401101]
50 **Devesa SS**, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; **83**: 2049-2053 [PMID: 9827707]
51 **Pohl H**, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97**: 142-146 [PMID: 15657344 DOI: 10.1093/jnci/dji024]
52 **Bollschweiler E**, Wolfgarten E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 2001; **92**: 549-555 [PMID: 11505399]
53 **Bresalier RS**. Barrett's Esophagus and esophageal adenocarcinoma. *Annu Rev Med* 2009; **60**: 221-231 [PMID: 18783330 DOI: 10.1146/annurev.med.59.061206.112706]
54 **Atherton JC**, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. *J Clin Invest* 2009; **119**: 2475-2487 [PMID: 19729845 DOI: 10.1172/JCI38605]
55 **Chen Y**, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]
56 **Segal I**, Otley A, Issenman R, Armstrong D, Espinosa V, Cawdron R, Morshed MG, Jacobson K. Low prevalence of Helicobacter pylori infection in Canadian children: a cross-sectional analysis. *Can J Gastroenterol* 2008; **22**: 485-489 [PMID: 18478134]
57 **Rothenbacher D**, Bode G, Berg G, Gommel R, Gonser T, Adler G, Brenner H. Prevalence and determinants of Helicobacter pylori infection in preschool children: a population-based study from Germany. *Int J Epidemiol* 1998; **27**: 135-141 [PMID: 9563707]
58 **Chen Y**, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. *Arch Intern Med* 2007; **167**: 821-827 [PMID: 17452546 DOI: 10.1001/archinte.167.8.821]
59 **Janson C**, Asbjornsdottir H, Birgisdottir A, Sigurjonsdottir RB, Gunnbjörnsdottir M, Gislason D, Olafsson I, Cook E, Jögi R, Gislason T, Thjodleifsson B. The effect of infectious burden on the prevalence of atopy and respiratory allergies in Iceland, Estonia, and Sweden. *J Allergy Clin Immunol* 2007; **120**: 673-679 [PMID: 17586034 DOI: 10.1016/j.jaci.2007.05.003]
60 **Rothenbacher D**, Blaser MJ, Bode G, Brenner H. Inverse relationship between gastric colonization of Helicobacter pylori and diarrheal illnesses in children: results of a population-based cross-sectional study. *J Infect Dis* 2000; **182**: 1446-1449 [PMID: 11015236 DOI: 10.1086/315887]
61 **Chang AH**, Haggerty TD, de Martel C, Leung CW, Parsonnet J. Effect of Helicobacter pylori infection on symptoms of gastroenteritis due to enteropathogenic Escherichia coli in adults. *Dig Dis Sci* 2011; **56**: 457-464 [PMID: 20635147 DOI: 10.1007/s10620-010-1309-z]
62 **Pflughoeft KJ**, Versalovic J. Human microbiome in health and disease. *Annu Rev Pathol* 2012; **7**: 99-122 [PMID: 21910623 DOI: 10.1146/annurev-pathol-011811-132421]
63 **Stecher B**, Maier L, Hardt WD. 'Blooming' in the gut: how dysbiosis might contribute to pathogen evolution. *Nat Rev Microbiol* 2013; **11**: 277-284 [PMID: 23474681 DOI: 10.1038/nrmicro2989]
64 **Briggs AH**, Sculpher MJ, Logan RP, Aldous J, Ramsay ME, Baron JH. Cost effectiveness of screening for and eradication of Helicobacter pylori in management of dyspeptic patients under 45 years of age. *BMJ* 1996; **312**: 1321-1325 [PMID: 8646042]
65 **Parsonnet J**, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 1996; **348**: 150-154 [PMID: 8684154]
66 **Mason J**, Axon AT, Forman D, Duffett S, Drummond M, Crocombe W, Feltbower R, Mason S, Brown J, Moayyedi P. The cost-effectiveness of population Helicobacter pylori screening and treatment: a Markov model using economic data from a randomized controlled trial. *Aliment Pharmacol Ther* 2002; **16**: 559-568 [PMID: 11876711]
67 **Roderick P**, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, Patel P. The cost-effectiveness of screening for Helicobacter pylori to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model. *Health Technol Assess* 2003; **7**: 1-86 [PMID: 12709294]
68 **Ford AC**, Delaney BC, Forman D, Moayyedi P. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol* 2004; **99**: 1833-1855 [PMID: 15330927 DOI: 10.1111/j.1572-0241.2004.40014.x]
69 **Leivo T**, Salomaa A, Kosunen TU, Tuominen R, Färkkilä M, Linna M, Sintonen H. Cost-benefit analysis of Helicobacter pylori screening. *Health Policy* 2004; **70**: 85-96 [PMID: 15312711 DOI: 10.1016/j.healthpol.2004.02.004]

P- Reviewers: Ihara E, Kim YJ, Suk KT **S- Editor**: Gou SX
L- Editor: Cant MR **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327