Polish Journal of Microbiology
2012, Vol. 61, No 4, 239–246

MINIREVIEW

The Controversy over Anti-*Helicobacter pylori* Therapy

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Received 11 May 2012, revised 14 September 2012, accepted 18 September 2012

Abstract

Helicobacter pylori is a Gram-negative spiral-shaped bacterium, member of ε-Proteobacteria specifically colonizing the gastric epithelium of humans. It causes one of the most common infections worldwide, affecting about half of the world's population. However, it should be noted that the prevalence of *H. pylori*, particularly in the Western world, has significantly decreased coinciding with an increase of some autoimmune and allergic diseases, such as asthma. Various epidemiological studies have also documented a negative association between *H. pylori* colonization and the presence of GERD (gastroesophageal reflux disease) and risk of esophageal cancer. Additionally, an upward trend of obesity recently observed in inhabitants of developed countries raised a question about the relationship between *H. pylori* infection and the human body mass index. The first part of this review describes common, recommended anti-*H. pylori* treatments. The second part, presents the results of recent experiments aimed at evaluating the association between *H. pylori* infections and gastro-esophageal diseases, the level of stomach hormones, the human body mass index and allergic diseases. Although some studies suggest an inverse association of *H. pylori* infection with some health problems of the modern world such as asthma, obesity or GERD, *H. pylori* should be considered as a harmful human pathogen responsible for serious and sometimes lethal diseases. Thus, many scientists advocate the eradication of *H. pylori.*

Key words: *Helicobacter pylori*, allergy, GERD, NAP protein, obesity, therapy

Introduction

Helicobacter pylori is a Gram-negative spiral-shaped bacterium, belonging to ε-Proteobacteria, which specifically colonizes the gastric epithelium of humans causing one of the most common infection worldwide. It affects about half of the world's population; yet, its prevalence varies geographically. Currently, *H. pylori* infections are highly prevalent in developing countries, but are disappearing in developed countries. There are 40% of infected individuals in the general Polish population (84% of the infected adult population) (Dzieniszewski and Jarosz, 2008). *H. pylori* infections induce both acute and chronic gastritis and peptic ulcers. It is also considered to be a high risk factor for the development of mucosa-associated lymphoid tissue lymphoma and adenocarcinoma of the stomach. Although most infected individuals have no symptoms, approximately 10–20% of cases of *H. pylori* infections will lead to development of peptic ulcers and approximately 1% to gastric cancer. Based on results of clinical studies, the World Health Organization has assigned *H. pylori* infections as class I carcinogens. There is significant evidence indicating that the bacterial genotype is the most important factor determining the type of induced pathology. Additional factors include host genotype and environmental aspects, such as nutrition.

Upon infection, *H. pylori* activates in epithelial cells multiple intracellular pathways, which affect various cellular functions. Many virulence factors produced by all or just some *H. pylori* clinical isolates are involved in the development of disease symptoms. Among them, the most extensively studied are various adhesins (involved in bacterial adhesion to gastric mucosal cells), ureases (which neutralize the acidic environment of the stomach), cytotoxin-associated gene A (CagA) protein and the CagA pathogenicity island (involved in interactions with many host signal-transduction pathways), vacuolating cytotoxin A (VacA, which modulates the host immune cell physiology), neutrophil-activating protein A (NapA) and products of genes located within "plasticity zone" such as duodenal ulcer promoting protein (DupA, which is a risk marker for development of duodenal ulcer and a protective factor against gastric cancer). It has recently been shown that *H. pylori* infections induce aberrant methylation in a number of gene

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promoters in gastric mucosa, which are known to be methylated in cancer patients (Cover and Blanke, 2005; Ding *et al.*, 2010; Douraghi *et al.*, 2008; Tegtmeyer *et al.*, 2011; Yamaoka, 2008).

Sequencing of several *H. pylori* genomes and comparative genomics experiments revealed a high level of genome diversity. At first, by comparing the genomes of 15 *H. pylori* strains Salama *et al.* determined that *H. pylori* genes constituting the core set count 1 281 genes (Salama *et al.*, 2000). The growing number of genomes included in microarray analyses resulted in redefining the number of core genes in *H. pylori* genomes. At present, it is widely assumed that *H. pylori* core genes consist of about 1 100 genes. Auxiliary genes amount to 22–27% of the genome, encoding mainly proteins of unknown function, the Cag protein, outer-membrane proteins (OMP) and proteins involved in DNA metabolism (Dong *et al.*, 2009; Gressmann *et al.*, 2005). Some strain-specific genes are disease-specific. The diversity of *H. pylori* genomes is not only noticeable when evaluating the number of common genes, but also when examining gene nucleotide sequences. Genetic variety among *H. pylori* strains arises from intra-genomic diversifications (for example – point mutations, recombination and slipped-strand mispairing) as well as inter-genomic recombination – the ability of *H. pylori* to take up exogenous DNA and incorporate it into its genome (Dorer *et al.*, 2009). The process allows the pathogen to adapt to various niches within the same host or to the changing environments during long-lasting infections.

Recommended anti-*Helicobacter* therapies

According to several international guidelines, different drug regimens are recommended for treatment of *H. pylori* infections. These include triple, quadruple, (sequential or concomitant) therapy regimens. Treatment regimen should be selected according to areas of low or high claritromycin resistance. Standard triple therapy which involves administration of a proton pump inhibitor combined with clarithromycin and amoxicillin or metronidazol for 7 to 14 days was the most commonly recommended first-line treatment by guidelines published in Europe and North America since the mid 1990s (Chey and Wong, 2007; Malfertheiner *et al.*, 2012). However, the recent data showed that this drug combination has lost some efficacy and according to recently published worldwide guidelines should be abandoned when the clarithromycin resistance rate in the region is more than 15–20% (Malfertheiner *et al.*, 2012). Increased doses of proton pump inhibitors had small effects on eradication rates (Fuccio *et al.*, 2007; Vakil and Connor, 2005). Bismuth-based quadruple and levofloxacin-based triple regimens are also frequently recommended, but as second-line therapies. Third-line options (empiric regimes tailored to individual antibiotic sensitivities) include treatments based on rifabutin (an antituberculous agent) and furazolidone. However, susceptibility testing is not common, but, when it is employed, it is only carried out in specialist research-oriented centers. Sequential therapy is an alternative to standard triple therapy for eradication of *H. pylori* (Gisbert, 2010; Gisbert *et al.*, 2010). It aims to overcome clarithromycin resistance. During the first stage of therapy, amoxicillin is administered to weaken the bacterial cell wall, which otherwise prevents the formation of channels that block clarithromycin from entering the bacterial cell and, in effect, cause resistance to the antibiotic. Subsequently, clarithromycin and nitroimidazole are administered for a further 5 days in the second phase of the therapy. Administration of the proton-pump inhibitor is continuously employed throughout the treatment. Generally, the sequential therapy has a better rate of curing *H. pylori* infection than classical triple therapy. However, clinically the sequential administration of the two drug combinations is relatively complex. As an alternative the concomitant quadruple therapy including the same four drugs as sequential therapy given concomitantly has been tested. It appears to be equally effective as sequential therapy but less complex (Essa *et al.*, 2009; Wu *et al.*, 2010).

Treatment against *H. pylori* still fails in more than 20% of patients and a more acceptable eradication level is greatly anticipated. Two main obstacles against effective therapy are the resistance of *H. pylori* to different antibiotics (*i.e.* clarithromycin, metronidazole, amoxicillin, levofloxacin), correlated with the consumption of antibiotics in the general population, and lack of strict abidance to the rules of drug administration, which involves the efforts of both doctor and patient. The prescribed defined therapy is long and complicated. It is uncomfortable for patients and impedes complying with the recommended procedures. In view of these facts, there is an urgent need to intensify the fight against *H. pylori* by developing alternative methods of treating *Helicobacter pylori* infections (De Francesco *et al.*, 2010; O'Connor *et al.*, 2010). It was documented that the addition of probiotics to a standard antibiotic treatment improved slightly *H. pylori* eradication rate and considerably reduced therapy-associated adverse effects (Lionetti *et al.*, 2010; Vitor and Vale, 2011; Zou *et al.*, 2009).

The alarming rise of antibiotic resistant pathogenic microorganisms renewed interest in antibacterial, including anti-*Helicobacter*, research and forced scientists to search for new drugs with novel modes of action. Some new anti-*Helicobacter* drugs are currently under

development. New, potentially effective agents should fulfill several requirements, at least display strong, specific antibacterial activity against *Helicobacter*, when used in mono-therapy, and exhibit activity in low pH. Examples of such agents are: the TG44 molecule synthesized by the Nagase ChemeteX Corporation and acyl-lysyl oligomers (OAKs). The former compound, tested so far only in *in vitro* experiments, is a highly specific anti-*Helicobacter* molecule, which activity is based on the disruption of the cell outer membrane (Kamoda *et al.*, 2006). Latter compounds are synthetic antimicrobial peptides (AMPs) of broad specificity, which demonstrate high efficacy against *Helicobacter* in *in vitro* and *in vivo* tests (Makobongo *et al.*, 2009; Makobongo *et al.*, 2012). They are a unique and diverse group of molecules produced by many tissues and cell types of various organisms. As AMPs have recently elicited interest as new antibacterial drugs, one can expect that new AMPs will be tested as anti-*Helicobacter* agents soon (Brogden, 2005). However, it should be kept in mind that AMP therapy might potentially enable pathogens to overcome the innate immune response of an immunocompetent host (Brodsky and Gunn, 2005).

Unexpected consequences of *Helicobacter pylori* infection/eradication

Impact of *Helicobacter pylori* infection on esophageal diseases. Symptoms of the gastro-esophageal reflux disease (GERD) appear when the impairment of motility of the gastric system allows for the contact of the gastric content with the esophagus epithelium. This may lead to development of Barrett esophagus (BE), which is recognized as a risk factor for the subsequent development of esophageal adenocarcinoma (EAC). The pathogenesis of these diseases is complex and multifactorial, but acidity of the refluxate is a crucial factor inducing GERD development.

The decreasing prevalence of *H. pylori* infections and related diseases, especially in developed countries, and, at the same time, an increase in the recognition of gastro-esophagal reflux symptoms and its complications, raise a question whether *H. pylori* is a likely etiological factor for this changing epidemiology. This phenomenon has been observed in many countries, at different geographic locations, such as Japan or USA (Blaser, 2008; Kim *et al.*, 2011; Rajendra, 2011; Yang *et al.*, 2009). The causal relationship between *H. pylori* infections and the gastro-esophageal disease has been examined in a large number of epidemiological studies. The first observations were made by Labenz *et al.*, who reported that *H. pylori* eradication in patients with duodenal peptic ulcer stimulates the development of reflux eosophagitis (Labenz *et al.*, 1997). Comparative analyses concentrated on assessing the rate of *H. pylori* infection in patients with reflux esophagitis compared to those with a normal esophagus as well as on the evaluation of the effect of *H. pylori* eradication on the development of reflux esophagitis. Although some studies confirmed the inverse associations between these two analyzed phenomena, contradictory results also have been reported. For more details we recommended review papers, such as by Graham *et al.*, 2007; Hung and Wong, 2009; Sharma and Vakil, 2003; Souza and Lima, 2009. Lack of consensus between various studies may be due to many factors, such as difficulties in evaluating the clinical aspects of *H. pylori* infection or the differences in the genotype of the infecting strain. It was documented that *H. pylori* can colonize various parts of the stomach and that the site of infection is an important factor influencing the consequences of colonization. Antrum gastritis is related to high inflammation and high acid secretion, whereas corpus gastritis correlates with low acid secretion. Another important factor is the genetic and immunological status of the host. Three recent meta-analysis studies conducted by Islami and Kamangan, Qian *et al.* and Yaghoobi *et al.* summarized the data published during last twenty years (Islami and Kamangar, 2008; Qian *et al.*, 2011; Yaghoobi *et al.*, 2010) Islami and Kamangar used 19 carefully selected studies to examine the association between *H. pylori* infection and esophageal adenocarcinoma (EAC). Presented data suggested inverse association of the CagA-positive *H. pylori* colonization with risk of EAC. Meta-analysis of Yaghoobi *et al.* evaluated the risk of GERD development due to *H. pylori* eradication and showed that the frequency of GERD does not increase after *H. pylori* eradication among dyspeptic patients, whereas a two-fold higher risk of GERD development in patients with peptic ulcers was observed. Meta-analysis conducted by Qian *et al.* did not show any association between *H. pylori* eradication and the occurrence of symptomatic GERD. Potential mechanism of the protective effect of *H. pylori* gastric colonization against esophageal diseases still remains unexplainable. Apart from changes in gastric acidity, stomach colonization by *H. pylori* influences the level of at least two hormones: leptin and ghrelin (see below), which can influence the esophagus epithelium as esophagus cells contain leptin receptors. The recent progress in sequencing technology in combination with the development of new bioinformatic tools allows us to study the microbiome (a set of bacterial genes present in a specific ecological niche) of the stomach and esophagus. It is expected that this strategy will permit tracing changes in the microbiome that are correlated with disease development or are due to *H. pylori* eradication. Analysis of the stomach microbiota revealed that it is much more complex than it was assessed before. *H. pylor*i was found to be

the most abundant phylotype in the stomach of individuals tested as *H. pylori*-positive by standard methods (Bik *et al.*, 2006). Structure of the human gastric bacterial community was determined to be dependent on the *H. pylori*-induced disease. For instance, the stomach microbiota of gastric cancer patients differs significantly compared to microbiota of dyspeptic individuals (Dicksved *et al.*, 2009; Maldonado-Contreras *et al.*, 2011). Metagenomic study of the esophagal microbiome also revealed its astonishing complexity and significant changes in the microbiome structure connected to pathological alterations of the esophageal epithelium (Yang *et al.*, 2009). As even short term antibiotic treatment of *H. pylori* infections has tremendous repercussions for the gut microbiome structure, it may also be a factor of GERD development (Jakobsson *et al.*, 2010). Further metagenomic studies are required to shed more light on the contribution of stomach or esophagus dysbiosis on disease development.

Correlation between *Helicobacter pylori* infection and asthma and allergic diseases. In recent years, a rise in the prevalence of bronchial asthma in developed countries has been observed. Many environmental factors, such as tobacco smoke, air pollution or allergen exposure, are without doubt responsible for this documented upward tendency. However, the influence of human microbiota on allergic diseases should be also taken into account. As over the past years the prevalence of *H. pylori* infection has been decreasing, the causal relationship between *H. pylori* infection and asthma was carefully evaluated in many epidemiological studies. The relationship between these two diseases was noted for the first time in 1997 by Kosunen *et al.* (Kosunen *et al.*, 1997). Although the conducted studies provided controversial results, it is rather accepted that human colonization with *H. pylori* CagA-positive strains may have an inverse effect on development of bronchial asthma. However more studies are required to prove a real association between *H. pylori* eradication in childhood and subsequent development of asthma (Hung and Wong, 2009). At this point it should be also pointed out that *H. pylori* CagA positive strains which potentially may be protective against GERD or asthma are strongly associated with gastric cancer, which is the second leading cause of cancer-related deaths worldwide (Huang and Hunt, 2003).

For more data from epidemiological studies see papers cited by Roussos *et al.*, D'Elios *et al.* and Malferheiner *et al.* (D'Elios *et al.*, 2009; Malfertheiner *et al.*, 2011; Roussos *et al.*, 2005).

Despite the lack of a clear hypothesis explaining the link between these two diseases, some data suggest that this inverse association might be due to the differences in the type of immune response induced.

According to the WHO definition, asthma is a chronic inflammatory disease of the airways associated with a predominant activation of CD4+ Th2 lymphocytes, which produce several Th2 cytokines, including IL-4 and IL-5 (Del Prete *et al.*, 1993; Robinson *et al.*, 1992).

In contrast, *H. pylori* gastric colonization preferentially elicits a Th1 mucosal immune response with the production of IFN-γ, IL-12, IL-18, IL-23 and TNF-α (D'Elios *et al.*, 2009). *H. pylori* neutrophil-activating protein (HP-NAP) is a main *H. pylori* virulence factor responsible for this effect. HP-NAP is a 200 kDa ball-shaped dodecamer formed by four-helix bundled subunits (17 kDa) with a hollow central part (Tsuruta *et al.*, 2012). Structurally it belongs to the Dps (DNA protecting protein under starved condition) protein family. The role of this protein in bacterial cells is still controversial. Analysis of its ability to bind to DNA resulted in incoherent data. Additionally, although HP-NAP is a bacterioferritin able to bind up to 500 atoms of iron per dodecamer, the role of this process in bacterial physiology remains unclear. Furthermore, HP-NAP was described as a cytoplasmic protein, released after cell lysis. Once released in the gastroduodenal mucosa, NAP is transported *via* transcytosis across endothelial cells, (de Bernard and D'Elios, 2010) stimulating subsequently human neutrophils, monocytes and dendritic cells *via* activation of the Toll-like receptor 2 (TLR2). In consequence, high upregulation of both the production of IL-12 and IL-23 occurs (D'Elios and de Bernard, 2010). HP-NAP activity also causes the decrease of IL-4-secreting cells. As a result, HP-NAP supported by other *H. pylori* factors induces the production of IL-12 and IL-23 that both promote the preferential development of Th-1 cells and repress the Th-2 allergic response (Amedei *et al.*, 2010; Amedei *et al.*, 2006; Cappon *et al.*, 2010). Administration of HP-NAP has a beneficial effect in case of asthma. Arnold *et al.* proved that *H. pylori* infections induced T regulatory cells (Tregs) and protected mice from asthma, especially when mice were infected neonatally. After *H. pylori* eradication due to antibiotic treatment, the protection effect was abolished (Arnold *et al.*, 2011). The efficacy of HP-NAP against asthma was also confirmed by D'Elios *et al.,* who documented that systemic and mucosal administrations of HP-NAP result in reduction of the amount of eosinophil cells, immunoglobulin E and Th2 cytokines in the mice bronchitis model. This suggests that *H. pylori* infection is able to induce long lasting Th1 type of immune response. Taking the above into account, HP-NAP seems to be an effective factor for prevention and treatment of asthma and allergic diseases (D'Elios *et al.*, 2009).

Apart from playing a role in induction of Th1 inflammation and inhibition of the Th2 response, HP-NAP may potentially be used in cancer therapy. As a very

powerful inducer of IL-12 and IL-23, HP-NAP represent the most effective cytokine in regard to tumor eradication, anti-metastatic activity and long-term anti-tumor immunity (Colombo and Trinchieri, 2002). IL-12 was recently ranked third in a comprehensive list of immunotherapeutic agents with high potential in treating cancer. Codolo and colleagues showed that local administration of HP-NAP decreases tumor growth by triggering tumor necrosis in a mouse model of bladder cancer. HP-NAP-treated tumors show also a reduced vascularization due to the anti-angiogenic activity of IFN-γ induced by treatment of cancer implants with HP-NAP (Codolo *et al.*, 2012a; Codolo *et al.*, 2012b). In sum it should be pointed out that even persistent infection with *H. pylori* may be linked to protection from some autoimmune diseases, it is not recommended to leave *H. pylori* infection untreated in asthmatic patients. (D'Elios and de Bernard, 2010). However based on the performed studies it is tempted to speculate that administration of rHP-NAP might be beneficial not only against allergic diseases, but also to fight cancer.

Impact of *H. pylori* infection and anti-*Helicobacter* therapy on obesity. The decreasing prevalence of *H. pylori* infections during the second half of the 20th century and the beginning of the 21th is noticeable across the whole developed world. For example, in some countries currently less than 10% of school children are carriers of this microorganism (Chen and Blaser, 2008; Rothenbacher *et al.*, 1998; Segal *et al.*, 2008). At the same time, the incidence of obesity among the same population group has been observed. It prompts many research groups to evaluate the impact of *H. pylori* infection on body weight.

Two hormones, leptin and ghrelin, play a crucial role in body weight balance by regulating food intake and energy disbursement. Leptin is a 16 kDa protein, the product of the *ob* gene, which is synthesized and secreted mainly by adipocytes (Zhang *et al.*, 1994). However, it has recently been shown that this hormone is also present in rat and human gastric mucosa (Bado *et al.*, 1998; Sobhani *et al.*, 2000). As leptin deficiency causes obesity in humans and mice and since *H. pylori* induced gastritis may influence the leptin level, many comparative epidemiological studies have recently been conducted to examine the effect of *H. pylori* infections on gastric leptin expression and on the body mass index (BMI). Most of these studies compared infected and non-infected individuals by CagA-positive and CagA-negative strains. Infection by CagA-positive *H. pylori* strains was shown to result in more severe gastritis and more often led to gastric cancer than infection by CagA-negative *H. pylori*. Majority of obtained data has not implied any associations between the plasma leptin level and *H. pylori* infection (Azuma *et al.*, 2001; Chuang *et al.*, 2009; Ioannou *et al.*, 2005). However, a study examining prepubertal children conducted by Pacifico *et al.* indicated that the serum leptin level was significantly lower in *H. pylori* positive patients than in *H. pylori* negative individuals (Pacifico *et al.*, 2008). In contrast to data concerning the plasma leptin level, many investigators provided convincing results showing that *H. pylori* infection results in a significant increase of gastric leptin expression (Azuma *et al.*, 2001; Jun *et al.*, 2007) what, in turn, might led to weight loss.

Conflicting results have also been published regarding the effect of *H. pylori* infection on ghrelin level. Ghrelin is a 28 amino acid peptide predominantly produced by the stomach, which is thought to be the most potent growth hormone releaser (Kojima *et al.*, 1999). Ghrelin has also been implicated in the control of food intake (Nakazato *et al.*, 2001). It was determined to affect metabolic functions and evoke weight gain (Wren *et al.*, 2001). In the study performed by Gokcel *et al.*, no differences in the plasma ghrelin concentration between adults positive and negative for *H. pylori* have been observed (Gokcel *et al.*, 2003). In contrast, many studies performed on Japanese patients revealed a strong negative impact of *H. pylori* infection on the plasma ghrelin level, which was positively correlated with gastric ghrelin mRNA expression (Isomoto *et al.*, 2005a; Isomoto *et al.*, 2005b; Shiotani *et al.*, 2005). Additionally, some analyses indicated that this effect is dependent on the severity of the disease and influenced by the patient's gender (Chuang *et al.*, 2009).

Although *H. pylori* infection modulates the plasma ghrelin and stomach leptin level, epidemiological studies do not document any associations between *H. pylori* infection and the body max index of the analyzed patients. A large US-based population study showed that there is no correlation between the presence of *H. pylori* and the genetic status of the colonizing strain (CagA-positive *vs.* CagA-negative strains) as well as the weight of the analyzed individual (Cho *et al.*, 2005; Ioannou *et al.*, 2005).

The second set of experiments was directed towards analyzing the effect of *H. pylori* eradication, plasma leptin or ghrelin level and the increase in BMI. They provided rather consistent results. In many studies, it has been reported that *H. pylori* eradication is associated with the increase of the circulating leptin level, the decrease of the ghrelin level resulting in an increase in BMI. This effect was independent of the examined population and was observed both among adult Japanese as well as American individuals who underwent anti-*Helicobacter* therapy. Additionally, similar long-term effect of *H. pylori* eradication was observed among prepubertal children (Francois *et al.*, 2011; Fujiwara *et al.*, 2002; Osawa *et al.*, 2006; Pacifico *et al.*, 2008). However,

Suto *et al.* noticed that the effect of *H. pylori* eradication on BMI is dependent on the serum pepsinogen I/II ratio (Suto *et al.*, 2009). Interestingly, experiments conducted by Nwokolo *et al.*, who for the first time examined the effect of *H. pylori* eradication in *H. pylori* asymptomatic patients, showed a significant increase of the ghrelin level after therapy. Authors have thus concluded that lowering the prevalence of *H. pylori* infections in developed countries might lead to the observed increase in obesity (Nwokolo *et al.*, 2003).

Summary

Collectively, it is obvious that the decreased *H. pylori* prevalence among populations of Western countries could lead to significant changes in human health. However, the plausible mechanism is extremely complex as it is influenced not only by the genotype of the pathogen, but also by the immunological and genetic status of the host. As *H. pylori* infection is almost always acquired during childhood, the microorganism is able to alter the resident stomach microbiota over a years, what leads to other pathologies such as EAC. Thus eradication of *H. pylori* can also stop transmission to healthy persons and prevent other pathologies connected with stomach microbiota changes.

Helicobacter pylori has accompanied humans since the dawn of time and coevolved together with its host. Thus, it is not surprising that the interrelation between the microorganism and its host is complex – the bacterium behaves as a pathogen causing some severe diseases, such as the peptic ulcer disease or gastric cancer, while, at the same time, as a commensal protecting from other infections. According to dr M. Blaser, gastroenterologists should re-think recommendations for *H. pylori* therapy and decide under what conditions such infections should be eradicated. We will be faced with the necessity of deciding how to react when human *H. pylori* infection is not so prevalent. Evidences collected so far indicate that the benefits of eradication of *H. pylori* outweigh the risks. *H. pylori* CagA positive strains which potentially may be protective against GERD or asthma are strongly associated with gastric cancer, which is the second leading cause of cancer-related deaths worldwide.

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