REVIEW

Current understanding and management of *Helicobacter pylori* infection: an updated appraisal [version 1; referees: 3 approved]

Shamshul Ansari¹, Yoshio Yamaoka¹,²

¹Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu-City, Oita, 879-5593, Japan
²Department of Medicine-Gastroenterology, Baylor College of Medicine, 2002 Holcombe Boulevard, Houston, TX, 77030, USA

### Abstract

In addition to its role in gastric conditions, *Helicobacter pylori* has been found to contribute to the development of several non-gastric issues in recent years. Eradication therapy is the only effective management strategy to minimize the *H. pylori*-related gastric cancer and extra-gastric complications. For an effective “test and treat” strategy, diagnosis and therapy are both important. Because the infection is usually asymptomatic, patient selection is a critical issue for timely diagnosis and many clinical and demographic factors should be considered. Clarithromycin and metronidazole resistance rates also need to be considered while eradication therapy is offered. In this report, we discuss the issues which must be taken into account for the correct and timely diagnosis and for the antibiotic therapy-based management of *H. pylori* infection.

### Keywords

Helicobacter pylori, virulence factors, eradication therapy, antibiotics resistance

---

Open Peer Review

Referee Status: ✔ ✔ ✔

Invited Referees

| version 1 | 1 | 2 | 3 |
|-----------|---|---|---|
| published | ✔ | ✔ | ✔ |
| 11 Jun 2018 | | | |

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1. **Steven Moss**, Warren Alpert Medical School of Brown University, USA
2. **Francis Mégraud**, Université de Bordeaux, France
3. **Peter Malfertheiner**, Otto-von-Guericke University Magdeburg, Germany

Discuss this article

Comments (0)
Corresponding author: Yoshio Yamaoka (yyamaoka@bcm.edu)

Author roles: Ansari S: Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; Yamaoka Y: Funding Acquisition, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Ansari S and Yamaoka Y. Current understanding and management of Helicobacter pylori infection: an updated appraisal [version 1; referees: 3 approved] F1000Research 2018, 7(F1000 Faculty Rev):721 (doi: 10.12688/f1000research.14149.1)

Copyright: © 2018 Ansari S and Yamaoka Y. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: This work was supported by grants-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan (16H05191) (YY) and by the Japan Society for the Promotion of Science (Core-to-Core Program) (YY) and by National Institutes of Health grant DK62813 (YY). SA is a PhD student supported by the Japanese Government (MEXT) Scholarship Program for 2015. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

First published: 11 Jun 2018, 7(F1000 Faculty Rev):721 (doi: 10.12688/f1000research.14149.1)
**Introduction**

*Helicobacter pylori* is the causative agent of chronic gastric infections, and it has been estimated that at least half of the world’s population is infected. A recent meta-analysis on the global prevalence of *H. pylori* infection has shown an overall prevalence of 44.3%, and estimated prevalences are as high as 89.7% in Nigeria and as low as 10.0% in Indonesia and 8.9% in Yemen. Socio-economic status, together with the level of urbanization and sanitation conditions, likely reflects the differences of *H. pylori* prevalence from country to country. The exact route of this bacterium’s transmission is unclear; however, evidence supports person-to-person transmission via oral–oral or fecal–oral route between family members. After it has transited to the gastric lumen, *H. pylori* localizes to specific locations such as the antrum and corpus, where it is well adapted to survive in acidic conditions and establish persistent infection. Once infection is established, several gastro-duodenal complications such as gastritis, gastric ulcer, duodenal ulcer, dyspeptic symptoms, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphomas may develop. Gastric cancer persists as a major public health issue and ranks as the third most common cause of cancer-related mortality; in 2012, it led to the deaths of about 723,100 individuals. In addition to its association with gastro-duodenal complications, *H. pylori* in recent years has been reported to cause several extra-gastric complications.

Epidemiological studies have suggested an association between *H. pylori* infection and certain other extra-gastric complications such as ischemic heart disease, neurodegenerative diseases, and hematological disorders (iron deficiency anemia, immune-thrombocytopenic purpura, and vitamin B12 deficiency). Bellos et al. recently found that *H. pylori* infection in pregnant women increases the risk of developing preeclampsia, which is a potent contributor to maternal and fetal morbidity and mortality. Another complication, hyperemesis gravidarum, can be found in up to 2.0% of women with early pregnancy and its onset has been associated with *H. pylori* infection. Cen et al., in a meta-analysis comprising 18 studies involving 1,544 participants, found an overall threefold increased risk for gall bladder disease, such as cholecystitis and cholelithiasis, in association with *H. pylori* infection. In Asian populations, the risk is higher than in non-Asian populations. Serological evidence for *H. pylori* infection was found to be associated with the development of hepatic diseases such as non-alcoholic fatty liver disease. With regard to the conclusive evidence linking *H. pylori* infection with hematological disorders (iron deficiency anemia, immune-thrombocytopenic purpura, and vitamin B12 deficiency), the Maastricht V/Florence consensus recommended *H. pylori* eradication therapy for these complications in addition to the gastric complications.

Eradication therapy significantly decreases the risk of developing gastric cancer if given before the onset of pre-cancerous lesions (atrophy, intestinal metaplasia, and dysplasia) and has proven to be the only effective strategy for reducing the development of gastric cancer. When a population-based “test and treat” strategy in a geographic region is being considered, which tests are preferred for the diagnosis of *H. pylori* infection, which subjects should be offered the diagnosis, and which treatment should be prescribed remain critical issues. The main aim of this review is to summarize the information regarding the strategic approaches and indications for the diagnosis of *H. pylori* as well as appropriate antibiotic therapy-based management.

**Virulence factors implicated in gastro-duodenal diseases**

Although a declining trend of *H. pylori* infection has been reported in many countries, the incidence of gastric cancer remains a major public health issue for cancer-related deaths worldwide. Despite the role of host factors and environmental conditions of the stomach, bacterial virulence factors play an important role in *H. pylori*-related pathogenicity. The virulence factors such as cytoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are the most studied and closely associated with gastric epithelial cell apoptosis and the development of severe gastric complications. *CagA* is an oncogenic protein that possesses an EPIYA motif (Glu–Pro–Ile–Tyr–Ala) motif; after CagA’s internalization in the host epithelium by the type 4 secretory system (T4SS), which forms a needle-like structure, the tyrosine of the EPIYA motif undergoes phosphorylation. CagA can possess four different types of EPIYA motifs—EPIYA-A, -B, -C, and -D—depending on the geographic region. *H. pylori* strains from Western countries usually possess CagA with EPIYA-A, -B, and -C (one to three EPIYA-C), whereas those from most of the East Asian countries possess EPIYA-A, -B, and -D. EPIYA-A and -B are carried by almost all CagA, and the third EPIYA motif (C or D) is a geographic, genotypic, and virulence characteristic. The presence and characteristics of the third EPIYA motif (EPIYA-C or -D) determine the virulent characteristics of CagA. In a recent meta-analysis, CagA with a single EPIYA-D motif was significantly associated with the development of gastric cancer while CagA with multiple EPIYA-C motifs was found to be a significant risk factor for peptic ulcer disease (PUD) in Asian countries; however, in the US and Europe, CagA with multiple EPIYA-C motifs was associated with the development of gastric cancer. The VacA is an exotoxin which affects multiple cellular pathways and induces host cell vacuolation and cell death (reviewed in 22).

Blood group antigen-binding adhesin (BabA) is a major outer membrane protein and another major virulence factor that is involved in the attachment of bacteria to the host epithelium, which leads to double-strand DNA breaks and translocation of CagA to the host cells. The specific location of *bab*-paralogous genes in three loci (babA/babB/c) was found to be associated with the development of pre-cancerous lesion (atrophy) and peptic ulcer. The role and characteristics of many other proteins have been implicated in the development of *H. pylori*-related pathogenicity. The outer inflammatory protein A (OipA), duodenal ulcer-promoting gene A (Dupa), sialic acid-binding adhesin (Saba), and protein which is induced by contact with epithelium (IceA) are implicated in the triggering of gastric epithelial cell apoptosis and the development of severe gastric complications such as peptic ulcer and gastric cancer.
In addition to its acid-neutralization function, urease, a potent virulence factor, was recently reported to induce angiogenesis, the formation of new blood vessels from pre-existing vasculature, which is important for tumor growth and metastatic dissemination and plays a key role in the progression of gastric cancer.11,12. In a study using in vitro endothelial cell tube formation assay and in vivo chorioallantoic membrane (CAM), the addition of H. pylori urease was found to induce the formation of tube-like structures by human umbilical vascular endothelial cells and CAM, respectively.13. Another gene, hp0169, the only gene annotated as collagenase in H. pylori that encodes the protein HpPrtC, which belongs to the protease family, was found to affect pathogenicity through cell viability, proliferation, and apoptosis.14. The H. pylori strains harboring these virulence factors are considered more pathogenic than the strains lacking these factors. Therefore, evaluation of these virulence factors provides insight for risk stratification and clinical outcome.

Diagnostic approaches for H. pylori infections

Currently, the diagnosis of H. pylori infection is carried out by invasive (for example, endoscopy and endoscopic biopsy for histopathology, culture, and rapid urease test) and non-invasive (for example, urea breath tests, stool antigen test, and serological tests) methods.15. However, the diagnostic preferences are based on the prevalence of H. pylori infection and age-related gastric cancer incidence in each area. For example, the non-invasive methods are preferred mostly in areas where the gastric cancer incidence is low, whereas endoscopy is recommended in those patients who have a high likelihood of developing gastric cancer, such as those over 60 years of age (or even in younger patients in some European countries), and who have a family history of gastric cancer or are in geographic regions with a high incidence of gastric cancer. The guidelines of the Japanese Society for Helicobacter Research put forth its recommendations suggesting that the diagnosis of H. pylori infection is performed by using at least one of several invasive and non-invasive methods; however, increased accuracy is obtained by using multiple diagnostic tests.16. Despite their high accuracy, the endoscopy-based diagnostic methods are not recommended for screening purposes and this is because of their invasiveness, high cost, and unavailability.17. The Maastricht V/Florence consensus report recommended using non-invasive methods such as locally validated serological tests over endoscopic procedures for the diagnosis of H. pylori infection in patients with dyspeptic symptoms.18. Moreover, the American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology, considering the adverse effects that may occur because of endoscopy, suggested the use of upper gastrointestinal endoscopy in patients who present with dyspeptic symptoms and are over 60 years of age or if the patient belongs to a high-risk family or a region with gastric cancer.19. However, in some European countries, endoscopy is recommended in patients over 45 years of age who have predisposing factors such as a high chance of developing gastric cancer.20. In this context, the non-invasive methods are considered the preferred and recommended methods for the mass screening of H. pylori infection despite the possible drawbacks they may have. For example, the urea breath test is currently recommended as the best approach for the screening of H. pylori infection because of its non-invasiveness and high sensitivity; on the other hand, it is relatively expensive and requires mass spectrometric analysis (which may not be available at resource-limited centers) and false-positive and -negative results may occur (albeit rarely). For example, Neisseria flavescens and Pseudomonas fluorescens, the urease-producing bacteria that were found to colonize the stomach of patients with gastritis, are potential pathogens that can give a false-positive result using the urea breath test.21. The stool antigen test is the preferred method for the detection of H. pylori infection in children; however, low sensitivity and specificity have been reported in patients with low bacterial density and in those with peptic ulcer bleeding.22. Therefore, the preference of appropriate diagnostic tests depends on many factors such as the patient’s choice and the test’s accuracy and availability as well as its cost-effectiveness.

Indications for “test and treat” strategy

Almost all H. pylori-infected individuals have chronic active gastritis on biopsy, and the clinical outcome of the infection is quite unpredictable, ranging from asymptomatic to a severe complication such as peptic ulcer and gastric cancer; however, these are mostly preventable by eradication therapy.23. Several studies have reported that eradication therapy for H. pylori in healthy and asymptomatic patients reduces the risk of developing gastric cancer; however, in patients with pre-neoplastic lesions, such as intestinal metaplasia and dysplasia, reversal of this pathological progression was hardly achieved by eradication therapy.24,25. However, reports have found significant improvement in prognosis and reversal of atrophy and even intestinal metaplasia after successful therapy, though to a lesser degree in the case of intestinal metaplasia.26-28. Moreover, a recent clinical trial conducted in South Korea reported that eradication therapy is able to significantly prevent the development of gastric cancer after endoscopic removal of early gastric cancer lesions.29. Treatment also reduces the risk of infection transmission from individual to individual, and therefore the financial burden that is associated with H. pylori infections may be avoided. The Kyoto global consensus report involving members of the Japanese Society of Gastroenterology, the European Helicobacter Study Group, the Asian Pacific Association of Gastroenterology, the Healthy Stomach Initiative, and the working group members of gastroenterology for International Classification of Diseases-11th revision (ICD-11) recommended screening for H. pylori gastritis after the age of 12 years and proposed that all positive cases be treated with eradication therapy even if they have no related symptoms or conditions.30. With regard to the Kyoto global consensus report, the Maastricht V/Florence consensus recommended the “test and treat” strategy for patients with dyspeptic symptoms. This report also made an important recommendation that patients with hematological disorders (iron deficiency anemia, immune-thrombocytopenic purpura, and vitamin B12 deficiency) be administered eradication therapy because there is considerable evidence linking these complications with H. pylori infection.31. However, because of the low incidence of H. pylori-associated gastric cancer in the US, the ACG recommended testing for H. pylori infection in patients with predisposing factors such as PUD, a history of...
PUD, low-grade gastric MALT lymphoma, or a history of endoscopic resection of early gastric cancer13, whereas the Bangkok consensus report for the Association of Southeast Asian Nations (ASEAN) countries (Indonesia, Thailand, the Philippines, Malaysia, Singapore, Vietnam, Myanmar, Cambodia, Laos, and Brunei) emphasized that *H. pylori* infection is more common in dyspeptic patients than in asymptomatic ones and recommended testing for *H. pylori* infection in patients with chronic dyspeptic symptoms34. Thus, the diagnosis of *H. pylori* infection in a particular geographic region should take into account the prevalence of infection, the incidence of severe complications such as gastric cancer in that geographic region, predisposing factors, and the age of the patient (for example, screening using non-invasive tests in younger patients and endoscopy-based methods in patients in the upper extremity of life, usually over 60 years, or over 45 years in some European countries). Irrespective of the diagnostic methods used, all patients with diagnosed *H. pylori* infection should be offered eradication therapy, which is based on the antibiotic resistance rate of that geographic region.

**Current first-line therapeutic strategies**

The therapeutic strategy that is offered as the initial course (first-line) to patients with diagnosed *H. pylori* infection provides the greatest chance for eradication overall. Therefore, the first-line eradication therapy plays a key role in the cure of *H. pylori* infections. Additionally, careful selection of the pertinent first-line therapy is mandatory and this should be based on the local resistance rates of the antibiotic constituents. Clarithromycin (a macrolide) has been an important constituent of *H. pylori* eradication therapy, but proton pump inhibitor (PPI)-clarithromycin-based triple therapy with PPI, clarithromycin, and amoxicillin (or metronidazole where its resistance rate is low) is now recommended as the first-line eradication therapy only when clarithromycin resistance is below 15%. However, if clarithromycin resistance exceeds 15%, bismuth quadruple therapy (bismuth, PPI, tetracycline, and metronidazole) or non-bismuth quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole; also known as concomitant therapy) may be offered for 10–14 days as an alternative to first-line triple therapy15,53. In most of the ASEAN countries, metronidazole resistance is high, and an increasing rate of clarithromycin resistance in recent years confers difficulty in achieving the goal of clarithromycin- and metronidazole-based therapy. A meta-analysis on primary antibiotic resistance conducted in the Asia-Pacific region in 2017 reported an increasing pattern of clarithromycin resistance rate in recent years, whereas metronidazole resistance rates were as high as 75% in Vietnam, 84% in Bangladesh, and 88% in Nepal35. However, in most areas, amoxicillin resistance is rare (below 5%), and in some parts clarithromycin resistance is also lower than 15%; therefore, PPI-clarithromycin-based triple therapy for 14 days is effective44. Another recent meta-analysis based on randomized controlled trials regarding eradication efficacy found an 84.3% cure rate by sequential therapy with PPI, amoxicillin, clarithromycin, and metronidazole in 2013 and this was superior to 7- or 10-day triple therapy but not to 14-day triple therapy and bismuth- or non-bismuth-based therapy46. The ACG also included sequential therapy—consisting of PPI and amoxicillin for 5–7 days followed by PPI, clarithromycin, and metronidazole for a further 5–7 days—as an option for first-line triple therapy53. The clarithromycin and metronidazole resistance rate in a particular geographic region determines the preferred constituents of eradication therapy. For example, in a geographic region where clarithromycin resistance exceeds 15%, it may be replaced with levofloxacin (a fluoroquinolone), and a levofloxacin-based triple therapy consisting of PPI, levofloxacin, and amoxicillin for 10–14 days or sequential therapy consisting of PPI and amoxicillin for 5–7 days followed by PPI, levofloxacin, and metronidazole for a further 5–7 days may be prescribed as an option for first-line therapy53. However, the efficacy of sequential therapy may vary depending on geographic region and antibiotic resistance rate. In a meta-analysis conducted in China, the authors found that 10-day concomitant therapy was more efficacious than 10-day sequential therapy for infection with metronidazole-resistant strains or together with clarithromycin-resistant strains57. The meta-analysis conducted in the Asia-Pacific region in 2017 also reported that in these countries with clarithromycin resistance higher than 15–20%, clarithromycin-based triple therapy as well as sequential and concomitant therapy showed less than 80% eradication efficacies58. In countries with a high incidence of *H. pylori*-associated gastric cancer and clarithromycin resistance exceeding 15–20%, it is better to use alternative approaches to clarithromycin-based eradication therapy. Finally, after the completion of first-line antibiotic treatment, the eradication therapy’s efficacy should be assessed using the urea breath test15. In agreement with the development of multi-drug resistance in other bacterial species, antibiotic resistance in *H. pylori* is an increasing trend because of the overuse and misuse of antibiotics for the treatment of other infections, especially in developing countries46. Currently, the novel polymerase chain reaction-based approach is sensitive for the detection of *H. pylori* DNA in stool samples together with detecting mutations causing clarithromycin resistance46. This non-invasive method could be able to significantly decrease endoscopy-based biopsy sampling for antibiotic resistance determination.

**Geographic distribution of clarithromycin and metronidazole resistance**

Although the antibiotic resistance rate differs from country to country and even a regional variation may be found within a country, an overall increasing pattern of resistance with time is an emerging problem in many countries46. In 2017, based on the threat that may be imposed, *H. pylori* was listed in the World Health Organization’s “priority list of antibiotic resistance bacteria” and was ranked as top of the most common causes of community-acquired infections if the strain is clarithromycin-resistant61. In general, the clarithromycin and metronidazole resistance rates predict the success rate of standard therapy, as these antibiotics are primary constituents of standard therapy and also resistance to these two antibiotics is frequently seen; therefore, to prescribe the therapy, one must have sound knowledge of regional resistance rates to these antibiotics. In European regions such as Sweden62, Belgium63, Iceland64, Germany64, and the UK65, generally lower resistance rates to both clarithromycin and metronidazole (lower than 15% and 30%, respectively) have been reported (Figure 1, area I). In countries such as Costa
Rica, Spain, Nigeria, and Lithuania and in some Asia-Pacific regions such as Thailand, Bhutan, Russia, and Australia, clarithromycin resistance is lower than 15%; however, metronidazole resistance rates of higher than 30% have been reported (Figure 1, area II). According to a meta-analysis conducted in Asia-Pacific regions, no clarithromycin resistance was found in Bhutan, although more than 80% of the H. pylori strains were metronidazole-resistant. In Nigeria, metronidazole resistance was reported to be up to 99%. On the other hand, in South Africa, Peru, Algeria, Canada, and Morocco and in other European countries such as Poland and France, together with other Asia-Pacific regions (for example, India, Iran, Saudi Arabia, South Korea, China, and Vietnam), higher resistance rates than the threshold levels for both clarithromycin and metronidazole have been reported (Figure 1, area III). In most regions, the frequent use of antibiotics is the main contributor to drug resistance and the declining efficacy of eradication therapies. However, hetero-resistance (both resistant and susceptible strains together in one patient’s stomach) has also been reported to contribute to the reduced efficacy of eradication therapy. The resistance rate of metronidazole usually remains high in developing countries because it is most widely used for the treatment of parasitic infestations, whereas in the developed world its resistance tends to be low. In the US, Austria, and Japan, overall clarithromycin resistance was more than 15%; however, metronidazole resistance was lower than 30% (Figure 1, area IV).

Last but not least

Regarding the current therapeutic management of H. pylori infections, we, the authors, are deeply concerned with two main points. First, we are well aware that the misuse and overuse of antibiotics pose a great threat to reaching the goal of eradication therapy efficacy and also can create a problem for the future by increasing the rate of antibiotic resistance, as “what does not kill you makes you stronger” and similarly “weaker antibiotics

---

**Figure 1. Geographic distribution of clarithromycin and metronidazole resistance.** The dotted lines show the threshold levels for clarithromycin and metronidazole resistance rates (15% and 30%, respectively). Both clarithromycin and metronidazole resistance rates are low in countries belonging to area I. Clarithromycin resistance is low but metronidazole resistance is high in countries of area II, whereas in the countries belonging to area III both clarithromycin and metronidazole resistance rates are high. In countries of area IV, the clarithromycin resistance is high but metronidazole resistance is low.
make stronger bacteria”. Thus, the selection of the most appropriate therapeutic strategy based on regional resistance rate is of the utmost importance. Second, *H. pylori* is transmitted from person to person and usually between family members, so there is the possibility of re-infection in cured patients living in the same geographic locality. Moreover, first-line eradication therapy is the most efficacious; therefore, the choice of therapy should be based on the local resistance rate to clarithromycin and metronidazole primarily. Finally, after the completion of therapy, the eradication of *H. pylori* should be assessed.

**Competing interests**

The authors declare that they have no competing interests.

**Grant information**

This work was supported by grants-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan (16H05191) (YY) and by the Japan Society for the Promotion of Science (Core-to-Core Program) (YY) and by National Institutes of Health grant DK62813 (YY). SA is a PhD student supported by the Japanese Government (MEXT) Scholarship Program for 2015.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Key points and conclusions**

As *H. pylori*-associated gastric complications are a challenging threat to public health, their effective management is of the utmost importance. Diagnosis and therapy are the major arms of management. Non-invasive methods should be the preferred option for diagnosis unless the patient has some predisposing factors necessitating endoscopy. A population-based approach to *H. pylori* eradication should be based on the prevalence of *H. pylori* infection and incidence of gastric cancer in that geographic locality. Moreover, first-line eradication therapy is the most efficacious; therefore, the choice of therapy should be based on the local resistance rate to clarithromycin and metronidazole primarily. Finally, after the completion of therapy, the eradication of *H. pylori* should be assessed.

**References**

1. Zamani M, Ebrahimtabar F, Zamani V, et al.: Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2018; 47(7): 868–76. PubMed Abstract | Publisher Full Text | F1000 Recommendation

2. Noori JKY, Lai WY, Ng WK, et al.: Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. *Gastroenterology*. 2017; 153(2): 420–9. PubMed Abstract | Publisher Full Text | F1000 Recommendation

3. Marnishi S, Eshaghi H, Mahmoudi S, et al.: Intrafamilial transmission of *Helicobacter pylori*: genotyping of faecal samples. *Br J Biomed Sci*. 2016; 73(1): 38–43. PubMed Abstract | Publisher Full Text

4. Bui D, Brown HE, Harris RB, et al.: Serologic Evidence for Fecal-Oral Transmission of *Helicobacter pylori*. *Am J Trop Med Hyg*. 2016; 94(1): 82–8. PubMed Abstract | Publisher Full Text | Free Full Text

5. Ansari S, Yamaoka Y: Survival of *Helicobacter pylori* in gastric acidic territory. *Helicobacter*. 2017; 22(4): e12386. PubMed Abstract | Publisher Full Text | Free Full Text

6. Jiang J, Chen Y, Shi J, et al.: Population attributable burden of *Helicobacter pylori*-related gastric cancer, coronary heart disease, and ischemic stroke in China. *Eur J Clin Microbiol Infect Dis*. 2017; 36(2): 199–212. PubMed Abstract | Publisher Full Text | F1000 Recommendation

7. Ferlay J, Soerjomataram I, Dikshit R, et al.: Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136(3): E359–86. PubMed Abstract | Publisher Full Text

8. Torre LA, Bray F, Siegel RL, et al.: Global cancer statistics, 2012, CA Cancer J Clin. 2015; 65(2): 87–108. PubMed Abstract | Publisher Full Text

9. Franceschi F, Gasbarrini A, Polyzos SA, et al.: *Extragastric Diseases and Helicobacter pylori*. *Helicobacter*. 2015; 20 Suppl 1: 40–6. PubMed Abstract | Publisher Full Text

10. Goni E, Franceschi F: *Helicobacter pylori* and extragastric diseases. *Helicobacter*. 2016; 21 Suppl 1: 45–56. PubMed Abstract | Publisher Full Text

11. Bellos I, Daskalakis G, Pergialiotis V: *Helicobacter pylori* infection increases the risk of developing preclampsia: A meta-analysis of observational studies. *Int J Clin Pract*. 2018; 72(2): e13064. PubMed Abstract | Publisher Full Text | F1000 Recommendation

12. Ng GX, Venkatnarayanan N, De Deyn MLZQ, et al.: A meta-analysis of the association between Helicobacter pylori (*H. pylori*) infection and hyperemesis gravidarum. *Helicobacter*. 2018; 23(1): e12455. PubMed Abstract | Publisher Full Text | F1000 Recommendation

13. Chen L, Pan J, Zhou B, et al.: *Helicobacter pylori* Infection of the gallbladder and the risk of chronic cholecystitis and cholelithiasis: A systematic review and meta-analysis. *Helicobacter*. 2018; 23(1): e12457. PubMed Abstract | Publisher Full Text | F1000 Recommendation

14. Polyzos SA, Kountouras J, Papatheodorou A, et al.: *Helicobacter pylori* Infection in Patients with Nonalcoholic Fatty Liver Disease. *Metabolism*. 2015; 64(1): 121–6. PubMed Abstract | Publisher Full Text

15. Maiertheiner P, Megraud F, O’Morain CA, et al.: Management of Helicobacter pylori Infection—the Maastricht V/Florence Consensus Report. *Gut*. 2017; 66(1): 6–30. PubMed Abstract | Publisher Full Text | F1000 Recommendation

16. Rokkas T, Rokka A, Portincasa P: A systematic review and meta-analysis of the role of Helicobacter pylori eradication in preventing gastric cancer. *Ann Gastroenterol*. 2017; 30(4): 414–23. PubMed Abstract | Publisher Full Text | F1000 Recommendation

17. Wandel AM, Guillen KM: Transgenic expression of the Helicobacter pylori virulence factor CagA promotes apoptosis or tumorigenesis through JNK activation in Drosophila. *PLoS Pathog*. 2012; 8(10): e1002939. PubMed Abstract | Publisher Full Text | Free Full Text

18. Akazawa Y, Isomoto H, Matsuhashi K, et al.: Endoplasmic reticulum stress contributes to Helicobacter pylori vacA-induced apoptosis. *PLoS One*. 2013; 8(12): e82322. PubMed Abstract | Publisher Full Text | Free Full Text

19. Zenotti G, Cendron L: Structural and functional aspects of the Helicobacter pylori secretome. *World J Gastroenterol*. 2014; 20(6): 1402–23. PubMed Abstract | Publisher Full Text | Free Full Text

20. Tchidpurou A: CagA-mediated pathogenesis of *Helicobacter pylori*. *Microb Pathog*. 2016; 93: 44–55. PubMed Abstract | Publisher Full Text

21. Li Q, Liu J, Gong Y, et al.: Association of CagA EPIYA-D or EPIYA-C with...
phosphorylation sites with peptic ulcer and gastric cancer risks: A meta-analysis. Med Hypotheses. 2017; 96(7): 167–74. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

22. Thi Huyen Trang T, Thanh Binh T, Yamaguchi Y: Relationship between vac Types and Development of Gastrudodenal Diseases. Toxins (Basel). 2018; 8(6): pii: E126. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

23. Toller IM, Neelen KJ, Steger M, et al.: Carcinogenic bacterial pathogen Helicobacter pylori triggers DNA double-strand breaks and a DNA damage response in its host cells. Proc Natl Acad Sci U S A. 2011; 108(6): 13484–9. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

24. Ishijima N, Suzuki M, Ashida H, et al.: BabA-mediated adherence is a potentializer of the Helicobacter pylori type IV secretion system activity. J Biol Chem. 2011; 286(9): 7056–64. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

25. Ansari S, Kabamba ET, Shrestha PK, et al.: Helicobacter pylori infection in Japan: 2009 revised edition. J Clin Microbiol. 2010; 48(2): 626–31. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

26. Teymournejad O, Mobarez AM, Hassan ZM, et al.: Binding of the Helicobacter pylori OipA causes apoptosis of host cells via modulation of Bax/Bcl-2 levels. Sci Rep. 2017; 7(1): 8036. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

27. Takahashi A, Shota S, Matsunori O, et al.: Intact long-type dupA as a marker for gastroduodenal diseases in Okinawan subpopulation, Japan. Helicobacter. 2013; 18(1): 66–72. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

28. Yu J, Leung WK, Go MY, et al.: Relationship between Helicobacter pylori babA2 status with gastric epithelial cell turnover and premalignant gastric lesions. Gut. 2002; 51(4): 480–4. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

29. Yamaguchi Y: Increasing evidence of the role of Helicobacter pylori SabA in the pathogenesis of gastroduodenal disease. J Infect Dev Ctries. 2008; 2(3): 174–81. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

30. Ma YJ, Duan GC, Zhang RG, et al.: Urease: Contributions to Angiogenesis. Gut. 2013; 62(11): e6620. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

31. De Palma M, Biziato D, Petrova TV, et al.: Helicobacter pylori pylori characterization in clinical isolates from Bhutan, Myanmar, Nepal and Bangladesh. PLoS One. 2012; 7(11): e0187255. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

32. F1000 Recommendation: Treatment of Helicobacter pylori infection - a prospective study for up to 10 years. Am J Gastroenterol. 2017; 112(5): 552–59. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

33. Bellaire EM, Smith L, Sorensen NA, et al.: Global eradication rates for Helicobacter pylori infection: a systematic review and meta-analysis. J Clin Microbiol. 2018; 56(12): pii: e02503-17. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

34. Gemma M, Matsuoka K, Nakano Y, et al.: Helicobacter pylori infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up eradication trial. Gut. 2017; 66(7): pii: gutjnl-2016-311685. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

35. F1000 Recommendation: Functional study of gene hp0169 as a marker to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014; 348: g174. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

36. Lee YC, Chang TH, Chou CK, et al.: Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology. 2016; 150(5): 1113–1124.e5. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

37. Kodama M, Murakami K, Okimoto T, et al.: Ten-year prospective follow-up of histological changes at five points on the gastric mucosa as recommended by the updated Sydney system after Helicobacter pylori eradication. J Gastroenterol. 2012; 47(4): 386–93. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

38. F1000 Recommendation: Helicobacter pylori infection in the Asia-Pacific region: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017; 2(10): 707–15. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

39. F1000 Recommendation: Helicobacter pylori gastriis. Gut. 2015; 64(9): 1353–67. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

40. Chey WD, Lonnqvist G, Howden CW, et al.: ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol. 2017; 112(2): 212–39. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

41. F1000 Recommendation: Antibiotic susceptibility of Helicobacter pylori: a prospective study for up to 10 years. Helicobacter. 2013; 18(11): 1–10. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

42. Smith G, Boyle B, Brennan D, et al.: The Irish Helicobacter pylori Working Group consensus for the diagnosis and treatment of H. pylori infection in adult patients in Ireland. Eur J Clin Microbiol Infect Dis. 2017; 36(5): 552–9. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

43. F1000 Recommendation: Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Lancet Gastroenterol Hepatol. 2018; 3(1): 37–56. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

44. F1000 Recommendation: Gastritis, Helicobacter pylori, and after therapy. Gastroenterol Clin. 2009; 38(1): 1–24. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

45. F1000 Recommendation: Helicobacter pylori pylori as a marker to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014; 348: g174. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

46. F1000 Recommendation: Ileal-ileal bile acid malabsorption May Predict Clarithromycin Resistance and Eradication of Helicobacter pylori pylori in the Asia-Pacific region: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017; 2(10): 707–15. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

47. F1000 Recommendation: Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. BMJ. 2013; 347: f14587. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

48. F1000 Recommendation: Sequential versus concomitant therapy for treatment of Helicobacter pylori infection: an updated systematic review and meta-analysis. Eur J Clin Pharmacol. 2018; 74(1): 1–13. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

49. F1000 Recommendation: Primary antibiotic resistance in Helicobacter pylori in the Asia-Pacific region: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017; 2(10): 707–15. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

50. F1000 Recommendation: Current recommendations for Helicobacter pylori pylori therapies in a world of evolving resistance. Lancet Gastroenterol Hepatol. 2018; 3(12): 941–50. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

51. F1000 Recommendation: A Novel Stool PCR Test for Helicobacter pylori pylori May Predict Clarithromycin Resistance and Eradication of Infection at a High Rate. J Clin Microbiol. 2018; 56(8): 2400–9. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

52. F1000 Recommendation: Global eradication rates for Helicobacter pylori pylori infection: systematic review and meta-analysis. Eur J Clin Pharmacol. 2018; 74(1): 1–13. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

53. F1000 Recommendation: Helicobacter pylori pylori strains in a random adult Swedish population. Helicobacter. 2006; 11(4): 224–30. Published Abstract | Publisher Full Text | Free Full Text
Open Peer Review

Current Referee Status: ✔ ✔ ✔

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 Peter Malfertheiner Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

**Competing Interests:** No competing interests were disclosed.

1 Francis Mégraud Department of Bacteriology, INSERM U1053, Université de Bordeaux, Bordeaux, France

**Competing Interests:** No competing interests were disclosed.

1 Steven Moss Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI, USA

**Competing Interests:** No competing interests were disclosed.

The benefits of publishing with F1000Research:

• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com