We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Helicobacter pylori Infection

*Todor Asenov Angelov, Mila Dimitrova Kovacheva-Slavova,
Hristo Ilianov Iliev, Hristo Yankov Valkov
and Borislav Georgiev Vladimirov*

Abstract

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral bacterium commonly found in the stomach. Major part of the world's population is infected with *H. pylori* and is at increased risk of severe gastritis, peptic ulcer disease, and gastric cancer. Most studied virulence factors of the bacterium are the cytotoxin-associated gene (CagA) and the vacuolating cytotoxin A (VacA). The *H. pylori* infection is diagnosed by invasive (histological examination, culture, and rapid urease test, which require endoscopy and biopsy) and noninvasive methods (serology, urea breath test, and stool antigen test). *H. pylori* eradication is preferred for a long-term prevention of complications. Current treatments consist of antibiotics and adequate PPI dose and can be divided into two strands—with or without bismuth. Achieving an eradication rate of >90% is an indicator for effective treatment. Due to the increasing levels of antibiotic resistance, the standard triple therapy is largely replaced with a quadruple therapy, especially in countries with high resistance rates. Antimicrobial susceptibility testing should be performed after the second-line treatment failure, leading to an individualized patient treatment. Clear explanations and patients' compliance are of great importance for a better outcome.

Keywords: *Helicobacter pylori*, virulence factors, diagnostic methods, treatment

1. Introduction

In the early 1980s, *Helicobacter pylori* (*H. pylori*) was discovered by Barry Marshall and Robin Warren. They reported its presence on mucosal tissue from the stomach of patients with gastritis and peptic ulcers [1]. Today, it is known that more than half of Earth's population is infected with this Gram-negative spiral bacterium. In most cases, the infection is completely asymptomatic, but it is far from harmless as 10–15% of those infected will develop peptic ulcer disease or gastric cancer [2]. The type and severity of the disease depends on several factors, as characteristics of the colonizing strain, host immune response, smoking, high-salt diet, and presence of other concurrent infections [3].

H. pylori strains from different geographical areas show clear phylogeographic features. The bacterium follows the human migration and has co-evolved with humans for over at least 60,000 years [4]. The fecal-oral and oral-oral routes of transmission are most common, with close person-to-person contact required. Strains of *H. pylori* are usually isolated from gastric biopsy tissue specimens, but the bacterium can be recovered also from saliva, gastric reflux fluid, diarrhea, and vomitus. Isolation and transmission from contaminated water supplies and farm animals has also been reported [5].

H. pylori is “special” in many ways as it possesses several important enzymes that enable its survival in the hostile acidic environment. Such an enzyme is the urease,

which breaks down the urea to ammonia and carbon dioxide, hence neutralizing the hydrochloric acid. Moreover, *H. pylori* avoids clearance with the gastric emptying with a number of adhesion molecules and its 4–6 flagella. Important virulence factors are the cytotoxin-associated gene A (CagA) and the vacuolating cytotoxin A (VacA).

Even though *H. pylori* colonization is usually asymptomatic, it leads to chronic active gastritis in most patients and is associated with a number of other gastroduodenal diseases, including gastric and duodenal ulcer disease, distal gastric adenocarcinoma, primary gastric mucosal-associated lymphoid tissue (MALT) lymphoma, dyspepsia, atrophic gastritis, iron deficiency anemia, and idiopathic thrombocytopenic purpura.

This is why *H. pylori* eradication is preferred for a long-term prevention of the above-mentioned complications. Current *H. pylori* treatment consists of antibiotics and adequate PPI dose and can be divided into two strands—with or without bismuth. Achievement of an eradication rate >90% is an indicator for effective treatment [6].

2. *H. pylori* virulence factors

H. pylori strains are more virulent and are associated with more severe gastric mucosal damages when there is a cytotoxin-associated gene pathogenicity island (cag PAI) in their genome. The cag PAI region contains ~30 genes encoding a type IV secretion system (T4SS) as well as cytotoxin-associated gene A (CagA). The CagA is delivered into host gastric epithelial cells via T4SS. Inside the cells, CagA undergoes tyrosine phosphorylation at the Glu-Pro-Ile-Tyr-Al (EPIYA) motifs by Src kinases. There is a higher risk for gastric cancer development in chronic infection with *H. pylori* cagA-positive strains. Carcinogenesis requires two major events. One is inactivation of tumor suppressor, and the other is the activation of oncoprotein. *H. pylori* CagA interacts with both of them and successfully disturbs their functions [7].

Vacuolating Cytotoxin (VacA) is also a major virulence factor present in almost all strains, and is highly polymorphic. VacA affects the cells with the induction of vacuole formation, mitochondrial dysfunction, modulation of signal transduction pathways, inhibition of T cell proliferation, and production of inflammatory cytokines. To favor its action, VacA binds to receptors such as receptor protein tyrosine phosphatases (RPTP α and RPTP β), low-density lipoprotein receptor-related protein-1 (LRP1), fibronectin, CD18, and sphingomyelin. RPTP β promote to ulceration and LRP1 is involved in the induction of autophagy. There is an interaction between cagA and VacA molecules, which is associated with the pathogenesis of gastric diseases. Therefore, further research on VacA may increase the knowledge of its role in the development of gastric disorders in *H. pylori* infection [7].

H. pylori expresses several major adhesins including BabA, SabA, LabA, OipA, and AlpAB. A closer association of the bacteria with the epithelium is thought to be mediated by them. They also increase the inflammation and damage of gastric mucosa by enhanced exposure to other virulence factors.

Duodenal ulcer-promoting gene A, dupA, is present in the tfs4 gene cluster and also the presence of the iceA1 allele of iceA is associated with increased risk for duodenal ulcer disease.

3. *Helicobacter pylori*-associated diseases

3.1 Dyspepsia

According to Rome III, functional dyspepsia (FD) is a symptomatic dyspepsia in the absence of structural or biochemical explanation after appropriate

investigation [8]. There are gastrointestinal symptoms that are associated with chronic dyspepsia as epigastric pain, epigastric burning, uncomfortable postprandial fullness, and early satiation.

FD is one of the most common gastrointestinal diseases which affects the quality of life. Chronic dyspepsia symptoms, which are thought to be caused by *H. pylori* infection, are decided to be separated from FD and defined as *H. pylori*-associated dyspepsia (HpD) in the Kyoto Global Consensus Conference held on January 30–February 1, 2014 [9]. In this meeting, patients who remain symptom free 12 months after eradication are considered to be cases of HpD, while patients who continue to experience dyspepsia even after *H. pylori* eradication will be considered as FD [10].

The evidence of the association between *H. pylori* infection and dyspepsia has been increasing. However, it is still unknown why most of individuals with *H. pylori* infection have no symptoms, while some of them have chronic dyspepsia symptoms. Recent meta-analysis of 103 reports containing 312,415 individuals showed that the prevalence of uninvestigated dyspepsia was higher in *H. pylori*-positive individuals (OR 1.18; 95% CI 1.04–1.33) [11]. There is evidence of a small but statistically significant benefit in eradicating *H. pylori* in *H. pylori*-positive dyspepsia. Therefore, the eradication therapy is recommended as first-line therapy for *H. pylori*-positive dyspepsia. Zhao et al. reviewed 14 randomized controlled trials which contained information on the long-term (12 months or more) effects of *H. pylori* eradication on dyspeptic symptoms, and a sub-group analysis on geographical regions was conducted [12].

3.2 Gastritis

H. pylori swims through the layers of protective mucus of the gastric mucosa to avoid damage from gastric acid and digestive enzymes. The bacterium is able to interact with the mucins via major adhesins the blood group antigen-binding adhesin (BabA), sialic acid-binding adhesin (SabA), and the lacdiNAc-specific adhesin, LabA [13–15].

H. pylori activates inflammatory gene when the bacterium reach to gastric epithelial cells. This is possible due to interaction with Toll-like receptor 2 and NOD1 [16], and inflammasomes [17, 18]. Inflammatory signaling in gastric epithelial cells is activated by a number of different mechanisms, resulting in the secretion of cytokines and chemokines, including interleukin-8 (IL-8), IL-1b, tumor necrosis factor alpha (TNFa), IL-6, IL-12, CCL2-5, CCL20, and CXCL1-3 [19]. The chemokines leads to the accumulation of neutrophils, macrophages, mast cells, dendritic cells (DCs), innate lymphoid cells, and lymphocytes—gastritis [4].

Neutrophils, macrophages, and NK cells contribute to gastritis via the secretion of inflammatory and tissue-damaging factors including reactive oxygen and nitrogen species (ROS and RNS) [20], perforin, and granzymes [21]. However, DCs are semi-mature and tolerogenic in *H. pylori*-infected gastric mucosa that stimulate the development of regulatory T cells (Tregs), which suppress inflammation [22].

It has recently been shown that retinoic acid (RA) is produced by human gastric epithelial cells and DCs regulates the level of inflammation. More intense inflammation and mucosal damage have been observed during *H. pylori* infection, because of reduction in RA [23]. Autoreactive antibodies against molecules, such as the parietal cell H⁺ and K⁺-ATPase, frequently induce the molecular mimicry of *H. pylori*. These antibodies may enhance inflammation and damage in the stomach [24]. In addition, the cytokines interferon-gamma (IFNc) and TNFa, secreted by Th1 cells, stimulate macrophages to secrete further pro-inflammatory factors. IL-17A, IL-17F, IL-21, and IL-22, secreted by Th17 cells, also stimulate the expression of ROS, RNS, and chemokines, leading to further inflammation and neutrophil recruitment [25].

All of the above makes it clear that the hosts' immune response is one of the major factors involved in the *H. pylori* infection pathogenesis. Thus, cytokines and other chemokines, prostaglandins, and their metabolites, as products of the innate response may be involved in the etiology of *H. pylori*-related diseases.

3.3 Peptic ulcer disease

Around 95% of duodenal ulcers and around 70% of gastric ulcers are *H. pylori* infection related [26, 27]. Hemorrhage or perforation are relatively common complications and are associated with a significant mortality.

H. pylori infection leads to destruction of delta cells by chronic inflammation of the antrum. This leads to a reduction in the level of somatostatin secretion and therefore impaired inhibition of gastrin production by the G cells, causing hypergastrinemia. The elevated gastrin levels overstimulate the acid-producing parietal cells of the undamaged corpus (in the case of antral-predominant gastritis) resulting in hyperchlorhydria. The increased gastric acid output can result in gastric metaplasia of the duodenal epithelium. This allows *H. pylori* to colonize it and cause inflammation, possibly leading to duodenal ulceration.

On the other hand, in patients with corpus-predominant atrophy or pan-gastritis, the acid output can be normal or reduced, explained by the loss of parietal cells. A state of hypochlorhydria is established, despite increased gastrin production from the *H. pylori*-infected antrum, preventing development of duodenal ulcers. Gastric ulcers develop due to inflammation and damage to the gastric mucosa. Pre-malignant lesions and gastric adenocarcinoma may also develop [4, 28].

In those with reduced numbers of Tregs in their gastric mucosa, peptic ulceration is more frequently found thus impaired capacity to control the inflammation [19, 29]. The inflammation and damage are enhanced by gastric Th1 and Th17 cells inducing epithelial cells to express higher levels of MHC class II and activation of mitogen-activated protein (MAP) kinases and transcription factors AP-1 and NF- κ B [30].

3.4 Gastric adenocarcinoma

There are approximately 100,000 new cases of gastric cancer each year [31]. A majority of cases are registered in developing countries, half of them occurring in Eastern Asia. It is the fifth most common malignancy worldwide and the third most common cause of cancer-related death diagnosed usually at a late stage [32].

Depending on the location the gastric cancer can be divided into two subtypes:

- Cardia—arising from epithelial cells at the gastroesophageal junction.
- Non-cardia—arising from the distal stomach.

Cardia gastric cancers are thought to be mostly unrelated to *H. pylori* infection and have similar risk factors to those for esophageal adenocarcinoma and Barrett's esophagus [30]. Up to 89% of cases of non-cardia gastric cancer is attributed to the infection with *H. pylori*. The risk of gastric cancer development for an infected individual is 1–2% [33].

The gastric cancer is classified histologically as two types [34]:

- intestinal—usually exophytic, often ulcerating, and are associated with intestinal metaplasia of the stomach and are more common in proximal (fundus) location.

- diffuse-type—poorly differentiated infiltrating lesions, which lead to the thickening of the stomach (linitis plastica) and predominate in younger patients.

Patients with intestinal-type tumors appear to have a better prognosis than those with diffuse-type.

Chronic gastritis caused by *H. pylori* infection after several decades, leads to gastric gland atrophy, intestinal metaplasia, dysplasia, and finally adenocarcinoma. *H. pylori* eradication therapy reduces the incidence of atrophic gastritis, but the risk of gastric cancer development is reduced only if the eradication is administered prior to pre-malignant changes [35]. ROS/RNS-mediated DNA damage, the silencing of tumor suppressor genes via DNA methylation, histone epigenetic modifications, and epithelial-mesenchymal transition are associated with gastric carcinogenesis [36].

Genetically determined high expression of pro-inflammatory cytokines (IL-6, IL-8, TNF α , IL-1b), low expression of anti-inflammatory cytokines (IL-10, TGF β), or enhanced responsiveness to bacterial components (Toll-like receptors 1, 2, 4, 5, and 9) are associated with a higher risk of gastric adenocarcinoma [37, 38]. In the future, identification of molecular profiles for gastric cancer subtypes will lead to more personalized clinical management, therapeutic targets and biomarkers for screening, prognosis, prediction of response to treatment, and monitoring of gastric cancer progression [39].

3.5 MALT lymphoma

Almost all patients with gastric MALT lymphoma have an active *H. pylori* infection with frequency of approximately 0.8 per 100,000 per year. Around 10% of cases are thought to be independent of *H. pylori*, but may be due to perhaps gastric non-pylori Helicobacters or undiagnosed *H. pylori* infection. Formation of lymphoid follicles in the gastric mucosa is induced by *H. pylori*-mediated inflammation, which is not present in the uninfected stomach [40]. Chronic inflammation and continuous antigenic stimulation lead to uncontrolled expansion of marginal zone B cells in these lymphoid follicles [41]. The tumor cells are commonly localized in the gastric mucosa and often remain to this site. However, in approximately 40% of cases, spreading to regional lymph nodes and more distant mucosal sites occurs. In around half of gastric lymphoma, low-grade MALT lymphomas may transform into more aggressive diffuse large B cell lymphomas (DLBCL), which have a considerably worse prognosis [41]. After *H. pylori* eradication treatment, there is a regression of the low-grade B cell MALT lymphomas. In one-quarter of cases a chromosomal translocation t(11; 18) is found. This is the most common genetic aberration in gastric MALT lymphoma. The non-responsiveness of gastric MALT lymphoma to *H. pylori* eradication therapy is also predicted by the presence of t(11; 18) [42]. Fusion between the activator protein-12 (AP-12) and MALT-1 genes lead to this chromosomal breakage and translocation. The product of this fusion stimulates activation of the transcription factor NF- κ B, which regulates the expression of anti-apoptotic genes and cell survival [41]. Mutations in immunoglobulin heavy chain variable region (IGHV) genes are also frequently present [43]. There is growing evidence that host genetic factors play an important role in developing gastric MALT lymphoma.

4. Diagnosis

Diagnosis of *H. pylori* infection can be done with noninvasive methods—serology, urea breath test (UBT), stool antigen test (SAT)—and invasive methods—histology, culture, PCR, rapid urease test (RUT). Only locally validated tests should

be used. PPIs have an anti-*H. pylori* activity and decrease the load of *H. pylori* leading to false-negative results on urease test, UBT, and SAT [44]. H2 receptor antagonists have been shown to have minimal effect on the sensitivity of UBT, and antacids do not impair the sensitivity of UBT or SAT. H2-blockers do not have anti-*H. pylori* activity [45–47]. In contrast, the antibacterial activity of antibiotics and bismuth compounds necessitate their discontinuation for 4 weeks to allow an increase of a detectable bacterial load.

From the noninvasive methods, ¹³C-UBT is the best approach to the diagnosis of *H. pylori* infection, with high sensitivity and specificity [48–50]. It cannot be used in children and pregnant women, because it exposes the patients to radiation [51]. SAT may be less acceptable in some societies, but has a high sensitivity and specificity [6]. Under certain clinical circumstances, it leads to a low bacterial load in the stomach and to a decreased sensitivity of all diagnostic methods except serology. These clinical situations include GI bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric carcinoma. Because serology is able to detect past infection with *H. pylori*, it should not be used as a method to monitor effectiveness of eradication.

In clinical practice, when there is an indication for endoscopy, and there is no contraindication for biopsy, the rapid urease test (RUT) is recommended as a first-line diagnostic test [6]. The sensitivity of biopsy urease tests is approximately 90%, and specificity is in the range of 95–100% [52]. It has been shown that the best biopsy sites for detection of *H. pylori* and assessment of atrophy are the lesser and greater curvature of the mid antrum, and the middle gastric body at the lesser and greater curvature [53]. This is supported by the updated Sydney System [54]. A maximum approach for gastric biopsies includes the incisura region at the lesser curvature. In the case of detection of gastric polyps, ulcerations, and suspicious focal lesions, further biopsies are necessary.

Most cases of *H. pylori* infection can be diagnosed from gastric biopsies using histochemical staining alone. In cases of chronic (active) gastritis in which *H. pylori* is not detected by histochemistry, immunohistochemical testing of *H. pylori* can be used as an accessory test. In the case of normal histology, no immunohistochemical staining should be performed [6].

The value of culture is primarily to perform AST for clarithromycin, levofloxacin, metronidazole, rifamycin, and eventually, amoxicillin and tetracycline. Several studies, using tailored treatments based on *H. pylori* susceptibility to antibiotics in comparison with standard empirical triple therapy, have shown a better eradication rate and may be cost-effective [55, 56].

A panel of serological tests (GastroPanel), including serum Pg (PgI and PgII), gastrin 17 (G-17), and anti-*H. pylori* antibodies, has recently been proposed as “serological biopsy” in dyspeptic patients [57, 58]. In populations with a low prevalence of atrophic gastritis, the negative predictive value of the GastroPanel in identifying atrophic gastritis is as high as 97% (95% CI 95–99%) [59].

In the post-treatment evaluation, UBT is a valid and reliable test in the assessment of *H. pylori* eradication [60]. SAT can be used as an alternative [61]. Testing to prove eradication should be performed at least 4–8 weeks after completion of *H. pylori* therapy. PPI should be discontinued for at least 2 weeks [48, 61–63].

5. Treatment

Recommended treatment regimens [64]:

Clarithromycin triple—PPI (standard or double dose twice daily) + clarithromycin (500 mg twice daily) + amoxicillin (1 g twice daily) **OR** metronidazole (500 mg three times daily) for 14 days.

Bismuth quadruple—PPI (standard dose twice daily) + bismuth subcitrate (120–300 mg 4 times daily) or subsalicylate (300 mg 4 times daily) + tetracycline (500 mg 4 times daily) + metronidazole (250 mg 4 times daily or 500 mg 3–4 times daily) for 10–14 days.

Concomitant—PPI (standard dose twice daily) + clarithromycin (500 mg twice daily) + amoxicillin (1 g twice daily) + nitroimidazole (500 mg twice daily).

Suggested [64]:

Sequential—PPI (standard dose twice daily) + amoxicillin (1 g twice daily) for 5–7 days **then** PPI + clarithromycin (500 mg twice daily) + nitroimidazole5 (500 mg twice daily) for 5–7 days.

Hybrid—PPI (standard dose twice daily) + amoxicillin (1 g twice daily) for 7 days **then** PPI + amoxicillin + clarithromycin (500 mg twice daily) + nitroimidazole (500 mg twice daily) 7 days.

Levofloxacin triple—PPI (standard dose twice daily) + levofloxacin (500 mg daily) + amoxicillin (1 g twice daily) for 14 days.

Levofloxacin sequential—PPI (standard or double dose twice daily) + amoxicillin (1 g twice daily) for 5–7 days **then** PPI + levofloxacin (500 mg daily) + nitroimidazole5 (500 mg twice daily) for 5–7 days.

LOAD—Levofloxacin (250 mg daily) + omeprazole (double dose daily) + nitazoxanide (500 mg twice daily) + doxycycline (100 mg daily) for 7–10 days.

Eradication rates of *H. pylori* have been declining, because of the increasing resistance rates to antibiotics worldwide [65]. Such evidence comes from studies in Europe, Japan, Korea, China, Iran, Greece, Bulgaria, and others [66–71]. Clarithromycin resistance rates have now reached ~30% in Italy and Japan, ~40% in Turkey, and ~50% in China, although rates in Sweden and Taiwan were ~15%. The standard triple therapy is less effective nowadays, because of a number of reasons such as lower compliance, high gastric acidity, high bacterial load, and bacterial strains, but mainly due to the increase in *H. pylori* resistance to clarithromycin. *H. pylori* is now an inconstantly susceptible bacterium (10–50% resistant) except in Northern Europe. The choice of therapy should be based on the frequency of metronidazole and dual clarithromycin and metronidazole resistance. If metronidazole resistance is almost negligible (e.g., Japan), replacing clarithromycin for metronidazole in triple therapy (i.e., PPI-metronidazole-amoxicillin) shows excellent cure rates [72]. However, metronidazole resistance can be partially overcome by increasing the dose, frequency, and duration of the antibiotic.

All non-BQTs will be less effective in regions with dual resistance to clarithromycin and metronidazole >15% [73]. Non-bismuth quadruple concomitant therapy, prescribed for 14 days, can be an effective alternative in regions with high clarithromycin resistance (15–40%) but low to intermediate metronidazole resistance (<40%) [74]. Bismuth-containing quadruple therapies are the treatment of choice when we have high (>15%) dual clarithromycin and metronidazole resistance. Ideally, clarithromycin should be avoided and a combination of alternative antibiotics. If bismuth is not available in high dual clarithromycin and metronidazole resistance areas, levofloxacin [75], rifabutin [76], and high dose dual (PPI + amoxicillin) [77] treatments can be considered. Quadruple therapy with a PPI, bismuth, and a combination of two antibiotics, among furazolidone, tetracycline, metronidazole, and amoxicillin, has been successfully tested (>90% cure rates) against *H. pylori* strains resistant to metronidazole, fluoroquinolones, and clarithromycin [78] and now is the recommended first-line treatment [79]. BQT should be considered effective provided the doses are sufficient and the duration should be extended to 14 days, unless 10 day therapies are proven effective locally [80, 81]. The combination of PPI, bismuth, metronidazole, and tetracycline

lasting 10–14 days achieved $\geq 85\%$ eradication rate, even in areas with a high prevalence of metronidazole resistance [82–84].

Sequential therapy is more complex and requires switching of antibiotic drugs during the treatment course, which can confuse the patients. Concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) is easier and similar to standard triple therapy and should be the preferred non-bismuth quadruple therapy. Sequential therapy achieves lower cure rates compared to concomitant therapy against clarithromycin-resistant strains [85, 86]. All non-BQTs (concomitant, hybrid, triple, and sequential) lead to excellent cure rates against susceptible *H. pylori* strains, but the cure rate will always be $< 90\%$ when the rate of dual resistant strains is $> 5\%$, $> 9\%$, or $> 15\%$, respectively [73].

Response to PPI is individual and determined by cytochrome 2C19 and MDR polymorphisms. Caucasian subjects show a higher prevalence of high metabolizers (56–81%) compared to Asian [74]. Esomeprazole and rabeprazole provide better overall *H. pylori* eradication rates, especially esomeprazole 40 mg twice daily, whereas rabeprazole 10 and 20 mg twice daily [87–92]. By raising pH, *H. pylori* enters the replicative state and become susceptible to amoxicillin and clarithromycin [93].

For second-line treatment, after failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended [94]. In theory, any treatment could be used after failure of BQT, including repeating the same BQT with longer duration and high metronidazole dosage. However, treatment that has already failed seems wiser never to be repeated. Bismuth therapies are usually proposed as first-line treatments for areas of high clarithromycin resistance and using a clarithromycin-containing treatment as second-line therapy after failure of a BQT does not seem to be practical. That is why Levofloxacin-based triple therapy, that is known to be effective as second-line therapy after clarithromycin-containing therapy, should also be recommended after failure of a bismuth-containing quadruple regimen [95, 96]. The incidence of side effects are lower with levofloxacin-containing triple therapy than with bismuth-containing quadruple therapy [97]. A sub-group analysis showed similar eradication rates with 500 and 1000 mg of levofloxacin [97]. However, the efficacy of levofloxacin-based regimens may be affected by an increased prevalence of levofloxacin resistance [98]. Therefore, 14-day bismuth quadruple therapy is a valid second-line treatment for *H. pylori* eradication, especially in areas with high fluoroquinolones resistance. Combining bismuth and levofloxacin in a 14-day quadruple therapy is an effective ($\geq 90\%$ cure rate), simple, and safe second-line strategy in patients [99]. Bismuth overcomes clarithromycin and levofloxacin resistance, because of the synergistic effect with antibiotics [100, 101]. Therefore, the levofloxacin/bismuth-containing quadruple therapy constitutes an encouraging second-line strategy not only in patients failing previous standard triple therapy, but also in non-bismuth quadruple “sequential” or “concomitant” treatments.

After failure of the first-line treatment (clarithromycin based) and second-line treatment (with bismuth-containing quadruple regimen), it is recommended to use the fluoroquinolone-containing regimen as a rescue therapy. After failure of the first-line treatment (triple or non-bismuth quadruple) and second-line treatment (fluoroquinolone-containing therapy), it is recommended to use the bismuth-based quadruple therapy. Furthermore, BQT is not influenced by clarithromycin and fluoroquinolone resistance [102]. However, if a second-line treatment fails, culture with susceptibility testing (AST) or molecular determination of genotype resistance is recommended. Susceptibility-guided triple therapies proved more effective than empirical triple therapies in first-line treatment [55, 103].

6. *Helicobacter pylori* and extragastric diseases

Chronic infection with *H. pylori* may be favorable for certain gastroesophageal diseases, asthma, and other allergic disease manifestations and inflammatory bowel diseases (IBD). The beneficial role of *H. pylori* in GERD, Barrett's esophagus (BE), and esophageal adenocarcinoma (EA) requires further clinical and experimental confirmation.

The reflux of gastric contents and the failure of the esophagus to clear by peristaltic contractions lead to GERD. The severity of the disease depends strongly on the pH of the refluxed gastric juice [104, 105]. Chronic GERDs most likely to cause BE—replacement of the stratified squamous epithelium with a metaplastic columnar epithelium. The inflammation caused by chronic acid exposure appear to promote the development of EA from BE [106]. Patients subjected to endoscopy for any indications have the prevalence of BE, which is approximately 1–2% up to 5–15% in patients with GERD symptoms. Patients with BE have a 30- to 125-fold higher risk for developing EA, in comparison with the general population [107].

In 2013, Rubenstein et al. found an inverse correlation of *H. pylori* with erosive esophagitis, especially in patients harboring CagA-positive strains [108]. This evidence was further supported by Korean and Japanese studies, in which *H. pylori* could be negatively linked with the risk and severity of erosive esophagitis [109, 110].

In 2012, Fischbach et al. documented a decreased risk of EA predominantly in patients infected with CagA-positive *H. pylori* strains and recently confirmed a negative association of *H. pylori* with the risk of BE [41, 111]. Nie et al. also found that CagA-positive *H. pylori* strains were associated with a decreased risk of EA in all populations, irrespective of geographical location [112].

Numerous studies have addressed whether *H. pylori* eradication promotes the development of GERD or associated diseases. However, recent studies have failed to corroborate an important clinical impact on GERD of *H. pylori* eradication.

Inflammatory bowel diseases (IBDs) are chronic relapsing disorders of increasing incidence and two main forms—Crohn's disease and ulcerative colitis. Intestinal inflammation and epithelial injury are characterized for the diseases. In Crohn's disease, inflammation is discontinuous and can affect any part of the gastrointestinal tract and all layers of the bowel wall. In contrast, ulcerative colitis expands continuously from the rectum and affect the superficial layer of the mucosa. Modern hygienic practices and diet have been proposed to account for the increasing incidence of IBD in Western societies associated with changes in the human microbiota composition [113]. A correlation between *H. pylori* infection and IBD has long been suspected by gastroenterologists. There is a lower prevalence of *H. pylori* in IBD patients confirmed by studies, in which active *H. pylori* infection was detected by urea breath test rather than serum IgG or IgA [114–116]. A strong negative association between *H. pylori* colonization and IBD is presented in all meta-analyses and almost all original articles covering the topic [117–119].

7. *H. pylori* and the human microbiota

H. pylori is its best-known component of the stomach microbiota. In healthy conditions the main representatives of gastric microbiota are Streptococcus, Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria [120–124]. The exact composition of a healthy gastric microbiota remains uncharacterized. The interaction between the normal microbiota and *H. pylori* has not yet been fully defined. There is some evidence suggesting a predominance of *H. pylori* over other microbes

[120]. Non-*H. pylori* *Helicobacter* species can cause gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma [125–130].

H. pylori eradication therapy can impair the healthy gut microbiota. The most relevant shifts involved are, respectively, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterobacteriaceae*, and *Lactobacillus* [131]. The most common GI side effects correlated with antibiotic therapy include diarrhea, nausea, vomiting, bloating, and abdominal pain [132]. Antibiotic administration is the main risk factor for the development of *C. difficile* infection [133]. There is insufficient evidence on the effect of different eradication regimens and long-lasting impact of *H. pylori* eradication on the composition of gut microbiota. There are encouraging results, that probiotic supplementation reduce the side effects of eradication [134–144]. Certain probiotics strains may have a better beneficial effect. There are evidence that *Saccharomyces boulardii* decreases the risk and overall adverse effects (RR 0.44, 95% CI 0.31 to 0.64) [145]. A number of meta-analyses of RCTs show a positive result that probiotics has the capacity to increase the efficacy of *H. pylori* eradication therapies [134–144]. Despite these encouraging data, probiotics appear to increase the *H. pylori* eradication rate not by direct effects on *H. pylori*, but with reducing the side effects related to the therapy.

8. Conclusion

Helicobacter pylori has been part of the human population and migration since ancient times. Infection with the bacterium is an extremely significant disease and can lead to severe consequences for infected individuals. Treatment and the rising bacterial resistance are challenges that we encounter in everyday practice, according to the latest guidelines recommendations. We hope that in the future our knowledge will expand and we will be ready to present new approaches for *H. pylori* management, because the bacterium will undoubtedly continue to be part of our microbiome.

Acknowledgments

The publication of this work was supported by KRKA.

Author details

Todor Asenov Angelov^{1*}, Mila Dimitrova Kovacheva-Slavova¹, Hristo Ilianov Iliev², Hristo Yankov Valkov¹ and Borislav Georgiev Vladimirov¹

¹ Department of Gastroenterology, University Hospital “Tsaritsa Ioanna-ISUL” Medical University of Sofia, Sofia, Bulgaria

² Medical University of Sofia, Sofia, Bulgaria

*Address all correspondence to: totodari@gmail.com

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;**1**(8390):1311-1315
- [2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*. 2015;**65**(2):87-108. DOI: 10.3322/caac.21262
- [3] Amieva M, Peek RM Jr. Pathobiology of *Helicobacter pylori*-induced gastric cancer. *Gastroenterology*. 2016;**150**(1):64-78. DOI: 10.1053/j.gastro.2015.09.004
- [4] Atherton JC, Blaser MJ. Coadaptation of *Helicobacter pylori* and humans: Ancient history, modern implications. *The Journal of Clinical Investigation*. 2009;**119**(9):2475-2487. DOI: 10.1172/JCI38605
- [5] Breckan RK, Paulssen EJ, Asfeldt AM, Kvamme JM, Straume B, Florholmen J. The all-age prevalence of *Helicobacter pylori* infection and potential transmission routes. A population-based study. *Helicobacter*. 2016;**21**(6):586-595. DOI: 10.1111/hel.12316
- [6] Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection—The Maastricht V/Florence Consensus Report. *Gut*. 2017;**66**(1):6-30. DOI: 10.1136/gutjnl-2016-312288
- [7] Suzuki H, Warren R, Marshall B. *Helicobacter pylori*. Japan: Springer; 2016. DOI: 10.1007/978-4-431-55705-0. ISBN: 978-4-431-55704-3
- [8] Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al., European Helicobacter and Microbiota Study Group and Consensus Panel. Functional gastroduodenal disorders. *Gastroenterology*. 2006;**130**(5):1466-1479. DOI: 10.1053/j.gastro.2005.11.059
- [9] Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut*. 2015;**64**(9):1353-1367. DOI: 10.1136/gutjnl-2015-309252
- [10] Miwa H, Kusano M, Arisawa T, Oshima T, Kato M, Joh T, et al. Evidence-based clinical practice guidelines for functional dyspepsia. *Journal of Gastroenterology*. 2015;**50**(2):125-139. DOI: 10.1007/s00535-014-1022-3
- [11] Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: A meta-analysis. *Gut*. Jul 2015;**64**(7):1049-1057. DOI: 10.1136/gutjnl-2014-307843
- [12] Zhao B, Zhao J, Cheng WF, Shi WJ, Liu W, Pan XL, et al. Efficacy of *Helicobacter pylori* eradication therapy on functional dyspepsia: A meta-analysis of randomized controlled studies with 12-month follow-up. *Journal of Clinical Gastroenterology*. 2014;**48**(3):241-247. DOI: 10.1097/MCG.0b013e31829f2e25
- [13] Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, et al. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science*. 1998;**279**(5349):373-377
- [14] Mahdavi J, Sonden B, Hurtig M, Olfat FO, Forsberg L, Roche N, et al. *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. *Science*. 2002;**297**(5581):573-578. DOI: 10.1126/science.1069076
- [15] Rossez Y, Gosset P, Boneca IG, Magalhaes A, Ecobichon C, Reis CA, et al. The lacdiNAc-specific adhesin LabA mediates adhesion of *Helicobacter pylori* to human gastric mucosa.

The Journal of Infectious Diseases. 2014;**210**(8):1286-1295. DOI: 10.1093/infdis/jiu239

[16] Viala J, Chaput C, Boneca IG, Cardona A, Girardin SE, Moran AP, et al. Nod1 responds to peptidoglycan delivered by the *Helicobacter pylori* cag pathogenicity island. Nature Immunology. 2004;**5**(11):1166-1174

[17] Kim DJ, Park JH, Franchi L, Backert S, Núñez G. The Cag pathogenicity island and interaction between TLR2/NOD2 and NLRP3 regulate IL-1 β production in *Helicobacter pylori* infected dendritic cells. European Journal of Immunology. 2013;**43**(10):2650-2658. DOI: 10.1002/eji.201243281

[18] Vanaja SK, Rathinam VA, Fitzgerald KA. Mechanisms of inflammasome activation: Recent advances and novel insights. Trends in Cell Biology. 2015;**25**(5):308-315. DOI: 10.1016/j.tcb.2014.12.009

[19] Cook KW, Letley DP, Ingram RJ, Staples E, Skjoldmose H, Atherton JC, et al. CCL20/CCR6-mediated migration of regulatory T cells to the *Helicobacter pylori*-infected human gastric mucosa. Gut. 2014;**63**(10):1550-1559. DOI: 10.1136/gutjnl-2013-306253

[20] Italiani P, Boraschi D. From monocytes to M1/M2 macrophages: Phenotypical vs. functional differentiation. Frontiers in Immunology. 2014;**5**:514. DOI: 10.3389/fimmu.2014.00514

[21] Yun CH, Lundgren A, Azem J, Sjöling A, Holmgren J, Svennerholm AM, et al. Natural killer cells and *Helicobacter pylori* infection: Bacterial antigens and interleukin-12 act synergistically to induce gamma interferon production. Infection and Immunity. 2005;**73**(3):1482-1490

[22] Rizzuti D, Ang M, Sokollik C, Wu T, Abdullah M, Greenfield L, et al.

Helicobacter pylori inhibits dendritic cell maturation via interleukin-10-mediated activation of the signal transducer and activator of transcription 3 pathway. Journal of Innate Immunity. 2015;**7**(2):199-211. DOI: 10.1159/000368232

[23] Bimczok D, Kao JY, Zhang M, Cochran S, Mannon P, Peter S, et al. Human gastric epithelial cells contribute to gastric immune regulation by providing retinoic acid to dendritic cells. Mucosal Immunology. May 2015;**8**(3):533-544. DOI: 10.1038/mi.2014.86

[24] Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. *Helicobacter pylori* and autoimmune disease: Cause or bystander. World Journal of Gastroenterology. 2014;**20**(3):613-629. DOI: 10.3748/wjg.v20.i3.613

[25] Oertli M, Sundquist M, Hitzler I, Engler DB, Arnold IC, Reuter S, et al. DC-derived IL-18 drives Treg differentiation, murine *Helicobacter pylori*-specific immune tolerance, and asthma protection. The Journal of Clinical Investigation. 2012;**122**(3):1082-1096. DOI: 10.1172/JCI61029

[26] Ford AC, Gurusamy KS, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive people. Cochrane Database of Systematic Reviews. 2016;**4**:CD003840. DOI: 10.1002/14651858.CD003840.pub5

[27] Malfertheiner P. The intriguing relationship of *Helicobacter pylori* infection and acid secretion in peptic ulcer disease and gastric cancer. Digestive Diseases. 2011;**29**(5):459-464. DOI: 10.1159/000332213

[28] Robinson K, Kenefick R, Pidgeon EL, Shakib S, Patel S, Polson RJ, et al. *Helicobacter pylori*-induced peptic

ulcer disease is associated with inadequate regulatory T cell responses. *Gut*. 2008;**57**(10):1375-1385

[29] Zhou Y, Toh ML, Zrioual S, Miossec P. IL-17A versus IL-17F induced intracellular signal transduction pathways and modulation by IL-17RA and IL-17RC RNA interference in AGS gastric adenocarcinoma cells. *Cytokine*. 2007;**38**(3):157-164. DOI: 10.1016/j.cyt.2007.06.002

[30] Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut*. 2015;**64**(12):1881-1888. DOI: 10.1136/gutjnl-2014-308915

[31] Herrero R, Park JY, Forman D. The fight against gastric cancer—The IARC Working Group report. *Best Practice & Research. Clinical Gastroenterology*. 2014;**28**(6):1107-1114. DOI: 10.1016/j.bpg.2014.10.003

[32] Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to *Helicobacter pylori*. *International Journal of Cancer*. 2015;**136**(2):487-490. DOI: 10.1002/ijc.28999

[33] Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathologica et Microbiologica Scandinavica*. 1965;**64**:31-49

[34] Malfertheiner P, Fry LC, Monkemuller K. Can gastric cancer be prevented by *Helicobacter pylori* eradication? *Best Practice & Research. Clinical Gastroenterology*. 2006;**20**(4):709-719. DOI: 10.1016/j.bpg.2006.04.005

[35] Na HK, Woo JH. *Helicobacter pylori* induces hypermethylation of CpG islands through upregulation of DNA

methyltransferase: Possible involvement of reactive oxygen/nitrogen species. *Journal of Cancer Prevention*. 2014;**19**(4):259-264. DOI: 10.15430/JCP.2014.19.4.259

[36] Ramis IB, Vianna JS, Goncalves CV, von Groll A, Dellagostin OA, da Silva PE. Polymorphisms of the IL-6, IL-8 and IL-10 genes and the risk of gastric pathology in patients infected with *Helicobacter pylori*. *Journal of Microbiology, Immunology, and Infection*. 2015;**9**(12):1535-1547. DOI: 10.1016/j.jmii.2015.03.002

[37] El-Omar EM, Ng MT, Hold GL. Polymorphisms in toll-like receptor genes and risk of cancer. *Oncogene*. 2008;**27**(2):244-252

[38] Tegtmeyer N, Backert S. Molecular Pathogenesis and Signal Transduction by *Helicobacter pylori*. Part of Current Topics in Microbiology and Immunology. Cham, Switzerland: Springer International Publishing AG; 2017;**400**. DOI: 10.1007/978-3-319-50520-6. ISBN: 978-3-319-50519-0

[39] Genta RM, Hamner HW, Graham DY. Gastric lymphoid follicles in *Helicobacter pylori* infection: Frequency, distribution, and response to triple therapy. *Human Pathology*. 1993;**24**(6):577-583

[40] Du MQ, Atherton JC. Molecular subtyping of gastric MALT lymphomas: Implications for prognosis and management. *Gut*. 2006;**55**(6):886-893

[41] Fischbach W. Gastric MALT lymphoma—Update on diagnosis and treatment. *Best Practice & Research. Clinical Gastroenterology*. 2014;**28**(6):1069-1077. DOI: 10.1016/j.bpg.2014.09.006

[42] Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: Biological and therapeutic relevance.

Blood. 2016;**127**(17):2082-2092. DOI: 10.1182/blood-2015-12-624304

[43] Gatta L, Vakil N, Ricci C, et al. Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for *Helicobacter pylori* infection. The American Journal of Gastroenterology. 2004;**99**:823-829

[44] Connor SJ, Ngu MC, Katelaris PH. The impact of short-term ranitidine use on the precision of the 13C-urea breath test in subjects infected with *Helicobacter pylori*. European Journal of Gastroenterology & Hepatology. 1999;**11**:1135-1138

[45] Savarino V, Tracci D, Dulbecco P, et al. Negative effect of ranitidine on the results of urea breath test for the diagnosis of *Helicobacter pylori*. The American Journal of Gastroenterology. 2001;**96**:348-352

[46] Dulbecco P, Gambaro C, Bilardi C, et al. Impact of long-term ranitidine and pantoprazole on accuracy of [13C] urea breath test. Digestive Diseases and Sciences. 2003;**48**:315-321

[47] Gisbert JP, Calvet X. *Helicobacter pylori* 'test-and-treat' strategy for management of dyspepsia: A comprehensive review. Clinical and Translational Gastroenterology. 2013;**4**:e32

[48] Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of *Helicobacter pylori* infection—A critical review. Alimentary Pharmacology & Therapeutics. 2004;**20**:1001-1017

[49] Nocon M, Kuhlmann A, Leodolter A, et al. Efficacy and cost-effectiveness of the 13C-urea breath test as the primary diagnostic investigation for the detection of *Helicobacter pylori* infection compared to invasive and

non-invasive diagnostic tests. GMS Health Technology Assessment. 2009;**5**:Doc14

[50] Ferwana M, Abdulmajeed I, Alhajiahmed A, et al. Accuracy of urea breath test in *Helicobacter pylori* infection: Meta-analysis. World Journal of Gastroenterology. 2015;**21**: 1305-1314

[51] Gisbert JP, de la Morena F, Abaira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: A systematic review and meta-analysis. The American Journal of Gastroenterology. 2006;**101**:1921-1930

[52] El-Zimaity HM, Al-Assi MT, Genta RM, et al. Confirmation of successful therapy of *Helicobacter pylori* infection: Number and site of biopsies or a rapid urease test. The American Journal of Gastroenterology. 1995;**90**:1962-1964

[53] Satoh K, Kimura K, Taniguchi Y, et al. Biopsy sites suitable for the diagnosis of *Helicobacter pylori* infection and the assessment of the extent of atrophic gastritis. The American Journal of Gastroenterology. 1998;**93**:569-573

[54] Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. The American Journal of Surgical Pathology. 1996;**20**:1161-1181

[55] Wenzhen Y, Yumin L, Quanlin G, et al. Is antimicrobial susceptibility testing necessary before first-line treatment for *Helicobacter pylori* infection? Meta-analysis of randomized controlled trials. Internal Medicine. 2010;**49**:1103-1109

[56] Sugimoto M, Furuta T. Efficacy of tailored *Helicobacter pylori* eradication therapy based on antibiotic

susceptibility and CYP2C19 genotype. *World Journal of Gastroenterology*. 2014;**20**:6400-6411

[57] Dinis-Ribeiro M, Areia M, de Vries AC, et al. Management of precancerous conditions and lesions in the stomach (MAPS): Guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSg), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia. 2012;**44**:74-94

[58] Leja M, Kupcinskas L, Funka K, et al. Value of gastrin-17 in detecting antral atrophy. *Advances in Medical Sciences*. 2011;**56**:145-150

[59] McNicholl AG, Forné M, Barrio J, et al. Accuracy of GastroPanel for the diagnosis of atrophic gastritis. *European Journal of Gastroenterology & Hepatology*. 2014;**26**:941-948

[60] Leodolter A, Domínguez-Muñoz JE, von Arnim U, et al. Validity of a modified 13C-urea breath test for pre- and posttreatment diagnosis of *Helicobacter pylori* infection in the routine clinical setting. *The American Journal of Gastroenterology*. 1999;**94**:2100-2104

[61] Vaira D, Vakil N, Menegatti M, et al. The stool antigen test for detection of *Helicobacter pylori* after eradication therapy. *Annals of Internal Medicine*. 2002;**136**:280-287

[62] Chey WD, Metz DC, Shaw S, et al. Appropriate timing of the 14C-urea breath test to establish eradication of *Helicobacter pylori* infection. *The American Journal of Gastroenterology*. 2000;**95**:1171-1174

[63] Neil GA, Suchower LJ, Ronca PD, et al. Time of *Helicobacter pylori* eradication assessment following treatment. *Helicobacter*. 1997;**2**:13-20

[64] Chey WD, Leontiadis GI, Howde CW, et al. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. *The American Journal of Gastroenterology*. 2017;**112**:212-238. DOI: 10.1038/ajg.2016.563

[65] Thung I, Aramin H, Vavinskaya V, et al. Review article: The global emergence of *Helicobacter pylori* antibiotic resistance. *Alimentary Pharmacology & Therapeutics*. 2016;**43**:514-533

[66] Kobayashi I, Murakami K, Kato M, et al. Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005. *Journal of Clinical Microbiology*. 2007;**45**:4006-4010

[67] Lee JW, Kim N, Kim JM, et al. Prevalence of primary and secondary antimicrobial resistance of *Helicobacter pylori* in Korea from 2003 through 2012. *Helicobacter*. 2013;**18**:206-214

[68] Khademi F, Poursina F, Hosseini E, et al. *Helicobacter pylori* in Iran: A systematic review on the antibiotic resistance. *Iranian Journal of Basic Medical Sciences*. 2015;**18**:2-7

[69] Karamanolis GP, Daikos GL, Xouris D, et al. The evolution of *Helicobacter pylori* antibiotic resistance over 10 years in Greece. *Digestion*. 2014;**90**:229-231

[70] Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2013;**62**:34-42

[71] Boyanova L, Gergova G, Evstatiev I, et al. *Helicobacter pylori* resistance to six antibiotics by two breakpoint systems and resistance evolution in Bulgaria. *Infectious Diseases (London)*. 2016;**48**:56-62

- [72] Nishizawa T, Maekawa T, Watanabe N, et al. Clarithromycin versus metronidazole as first-line *Helicobacter pylori* eradication: A multicenter, prospective, randomized controlled study in Japan. *Journal of Clinical Gastroenterology*. 2015;**49**:468-471
- [73] Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: Evidence-based medicine rather than medicine-based evidence. *Clinical Gastroenterology and Hepatology*. 2014;**12**:177-186
- [74] Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance. *World Journal of Gastroenterology*. 2014;**20**:10338-10347
- [75] Federico A, Nardone G, Gravina AG, et al. Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of *Helicobacter pylori* infection. *Gastroenterology*. 2012;**143**:55.e1-61.e1; quiz e13-14
- [76] Toracchio S, Capodicasa S, Soraja DB, et al. Rifabutin based triple therapy for eradication of *H. pylori* primary and secondary resistant to tinidazole and clarithromycin. *Digestive and Liver Disease*. 2005;**37**:33-38
- [77] Ince AT, Tozlu M, Baysal B, et al. Yields of dual therapy containing high-dose proton pump inhibitor in eradication of *H. pylori* positive dyspeptic patients. *Hepato-Gastroenterology*. 2014;**61**:1454-1458
- [78] Liang X, Xu X, Zheng Q, et al. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant *Helicobacter pylori* infections in a prospective study. *Clinical Gastroenterology and Hepatology*. 2013;**11**:802.e1-807. e1
- [79] Liu WZ, Xie Y, Cheng H, et al. Fourth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *Journal of Digestive Diseases*. 2013;**14**:211-221
- [80] Fischbach L, Evans EL. Meta-analysis: The effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Alimentary Pharmacology & Therapeutics*. 2007;**26**:343-357
- [81] Graham DY, Shiotani A. Which therapy for *Helicobacter pylori* infection? *Gastroenterology*. 2012;**143**:10-12
- [82] Salazar CO, Cardenas VM, Reddy RK, et al. Greater than 95% success with 14-day bismuth quadruple anti- *Helicobacter pylori* therapy: A pilot study in US Hispanics. *Helicobacter*. 2012;**17**:382-390
- [83] Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. *Nature Reviews. Gastroenterology & Hepatology*. 2011;**8**:79-88
- [84] Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori*: Lessons from China. *European Journal of Gastroenterology & Hepatology*. 2013;**25**:1134-1140
- [85] Liou JM, Chen CC, Chen MJ, et al. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: A multicentre, open-label, randomised trial. *Lancet*. 2013;**381**:205-213
- [86] Gatta L, Vakil N, Vaira D, et al. Global eradication rates for *Helicobacter pylori* infection: Systematic review and meta-analysis of sequential therapy. *BMJ*. 2013;**347**:f4587
- [87] Tang HL, Li Y, Hu YF, et al. Effects of CYP2C19 loss-of-function variants

on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: A meta-analysis of randomized clinical trials. *PLoS One*. 2013;**8**:e62162

[88] Padol S, Yuan Y, Thabane M, et al. The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: A meta-analysis. *The American Journal of Gastroenterology*. 2006;**101**:1467-1475

[89] Zhao F, Wang J, Yang Y, et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: A meta-analysis. *Helicobacter*. 2008;**13**:532-541

[90] McNicholl AG, Linares PM, Nyssen OP, et al. Meta-analysis: Esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Alimentary Pharmacology & Therapeutics*. 2012;**36**:414-425

[91] Tokoro C, Inamori M, Koide T, et al. Does pretreatment with proton pump inhibitors influence the eradication rate of *Helicobacter pylori*? *Hepato-Gastroenterology*. 2010;**57**:1645-1649

[92] Yoon SB, Park JM, Lee JY, et al. Long-term pretreatment with proton pump inhibitor and *Helicobacter pylori* eradication rates. *World Journal of Gastroenterology*. 2014;**20**:1061-1066

[93] Labenz J. Current role of acid suppressants in *Helicobacter pylori* eradication therapy. *Best Practice & Research. Clinical Gastroenterology*. 2001;**15**:413-431

[94] Marin AC, McNicholl AG, Gisbert JP. A review of rescue regimens after clarithromycin-containing triple therapy failure (for *Helicobacter pylori* eradication). *Expert Opinion on Pharmacotherapy*. 2013;**14**:843-861

[95] Gisbert JP, Morena F. Systematic review and meta-analysis: Levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Alimentary Pharmacology & Therapeutics*. 2006;**23**:35-44

[96] Saad RJ, Schoenfeld P, Kim HM, et al. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: A meta-analysis. *The American Journal of Gastroenterology*. 2006;**101**:488-496

[97] Di Caro S, Fini L, Daoud Y, et al. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for *Helicobacter pylori* eradication in second-line. *World Journal of Gastroenterology*. 2012;**18**:5669-5678

[98] Saracino IM, Zullo A, Holton J, et al. High prevalence of primary antibiotic resistance in *Helicobacter pylori* isolates in Italy. *Journal of Gastrointestinal and Liver Diseases*. 2012;**21**:363-365

[99] Gisbert JP, Romano M, Gravina AG, et al. *Helicobacter pylori* second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. *Alimentary Pharmacology & Therapeutics*. 2015;**41**:768-775

[100] Malfertheiner P. Infection: Bismuth improves PPI-based triple therapy for *H. pylori* eradication. *Nature Reviews. Gastroenterology & Hepatology*. 2010;**7**:538-539

[101] Liao J, Zheng Q, Liang X, et al. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. *Helicobacter*. 2013;**18**:373-377

[102] Malfertheiner P, Link A, Selgrad M. *Helicobacter pylori*: Perspectives and time trends. *Nature Reviews*.

Gastroenterology & Hepatology. 2014;**11**:628-638

[103] López-Góngora S, Puig I, Calvet X, et al. Systematic review and meta-analysis: Susceptibility-guided versus empirical antibiotic treatment for *Helicobacter pylori* infection. The Journal of Antimicrobial Chemotherapy. 2015;**70**:2447-2455

[104] Collen MJ, Johnson DA, Sheridan MJ. Basal acid output and gastric acid hypersecretion in gastroesophageal reflux disease. Correlation with ranitidine therapy. Digestive Diseases and Sciences. 1994;**39**(2):410-417

[105] Gardner JD, Sloan S, Robinson M, Miner PB Jr. Frequency analyses of gastric pH in control and gastro-oesophageal reflux disease subjects treated with a proton-pump inhibitor. Alimentary Pharmacology & Therapeutics. 2004;**20**(11-12):1381-1386. DOI: 10.1111/j.1365-2036.2004.02279.x

[106] Lao-Sirieix P, Corovic A, Jankowski J, Lowe A, Triadafilopoulos G, Fitzgerald RC. Physiological and molecular analysis of acid loading mechanisms in squamous and *Helicobacter pylori* and extragastric diseases 343 columnar-lined esophagus. Diseases of the Esophagus. 2008;**21**(6):529-538. DOI: 10.1111/j.1442-2050.2007.00807.x

[107] Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology Clinics of North America. 2015;**44**(2):203-231. DOI: 10.1016/j.gtc.2015.02.001

[108] Rubenstein JH, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, et al. Association between *Helicobacter pylori* and Barrett's esophagus, erosive esophagitis,

Helicobacter pylori and extragastric diseases 345 and gastroesophageal reflux symptoms. Clinical Gastroenterology and Hepatology. 2014;**12**(2):239-245. DOI: 10.1016/j.cgh.2013.08.029

[109] Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy EB, et al. Gut immune maturation depends on colonization with a host-specific microbiota. Cell. 2012;**149**:1578-1593. DOI: 10.1016/j.cell.2012.04.037

[110] Minatsuki C, Yamamichi N, Shimamoto T, Kakimoto H, Takahashi Y, Fujishiro M, et al. Background factors of reflux esophagitis and non-erosive reflux disease: A cross-sectional study of 10,837 subjects in Japan. PLoS One. 2013;**8**(7):e69891. DOI: 10.1371/journal.pone.0069891

[111] Fischbach LA, Nordenstedt H, Kramer JR, Gandhi S, Dick-Onuoha S, Lewis A, et al. The association between Barrett's esophagus and *Helicobacter pylori* infection: A meta-analysis. Helicobacter. 2012;**17**(3):163-175. DOI: 10.1111/j.1523-5378.2011.00931.x

[112] Nie S, Chen T, Yang X, Huai P, Lu M. Association of *Helicobacter pylori* infection with esophageal adenocarcinoma and squamous cell carcinoma: A meta-analysis. Diseases of the Esophagus. 2014;**27**(7):645-653. DOI: 10.1111/dote.12194

[113] Baumgart DC, Bernstein CN, Abbas Z, Colombel JF, Day AS, D'Haens G, et al. IBD around the world: Comparing the epidemiology, diagnosis, and treatment: Proceedings of the World Digestive Health Day 2010—Inflammatory bowel disease task force meeting. Inflammatory Bowel Diseases. 2011;**17**(2):639-644. DOI: 10.1002/ibd.21409

[114] Pearce CB, Duncan HD, Timmis L, Green JR. Assessment of the prevalence of infection with *Helicobacter pylori*

in patients with inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology*. 2000;**12**(4):439-443

[115] Pronai L, Schandl L, Orosz Z, Magyar P, Tulassay Z. Lower prevalence of *Helicobacter pylori* infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease—Antibiotic use in the history does not play a significant role. *Helicobacter*. 2004;**9**(3):278-283. DOI: 10.1111/j.1083-4389.2004.00223.xHEL223

[116] Piodi LP, Bardella M, Rocchia C, Cesana BM, Baldassarri A, Quatrini M. Possible protective effect of 5-aminosalicylic acid on *Helicobacter pylori* infection in patients with inflammatory bowel disease. *Journal of Clinical Gastroenterology*. 2003;**36**(1):22-25

[117] Wu XW, Ji HZ, Yang MF, Wu L, Wang FY. *Helicobacter pylori* infection and inflammatory bowel disease in Asians: A meta-analysis. *World Journal of Gastroenterology*. 2015;**21**(15): 4750-4756. DOI: 10.3748/wjg.v21.i15.4750

[118] Rokkas T, Gisbert JP, Niv Y, O'Morain C. The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis. *United European Gastroenterology Journal*. 2015;**3**(6):539-550. DOI: 10.1177/205064061558088910.1177_2050640615580889

[119] Castano-Rodriguez N, Kaakoush NO, Lee WS, Mitchell HM. Dual role of *Helicobacter* and *Campylobacter* species in IBD: A systematic review and meta-analysis. *Gut*. Feb 2017;**66**(2):235-249. DOI: 10.1136/gutjnl-2015-310545

[120] Andersson AF, Lindberg M, Jakobsson H, et al. Comparative analysis

of human gut microbiota by barcoded pyrosequencing. *PLoS One*. 2008;**3**:e2836

[121] Bik EM, Eckburg PB, Gill SR, et al. Molecular analysis of the bacterial microbiota in the human stomach. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;**103**:732-737

[122] Li XX, Wong GLH, To KF, et al. Bacterial microbiota profiling in gastritis without *Helicobacter pylori* infection or non-steroidal anti-inflammatory drug use. *PLoS One*. 2009;**4**:e7985

[123] Yang I, Nell S, Suerbaum S. Survival in hostile territory: The microbiota of the stomach. *FEMS Microbiology Reviews*. 2013;**37**:736-761

[124] Yang I, Woltemate S, Piazuolo MB, et al. Different gastric microbiota compositions in two human populations with high and low gastric cancer risk in Colombia. *Scientific Reports*. 2016;**6**:18594

[125] Debongnie JC, Donnay M, Mairesse J, et al. Gastric ulcers and *Helicobacter heilmannii*. *European Journal of Gastroenterology & Hepatology*. 1998;**10**:251-254

[126] Matsumoto T, Kawakubo M, Akamatsu T, et al. *Helicobacter heilmannii* sensu stricto-related gastric ulcers: A case report. *World Journal of Gastroenterology*. 2014;**20**:3376-3382

[127] Morgner A, Bayerdörffer E, Meining A, et al. *Helicobacter heilmannii* and gastric cancer. *Lancet*. 1995;**346**:511-512

[128] Morgner A, Lehn N, Andersen LP, et al. *Helicobacter heilmannii*-associated primary gastric low-grade MALT lymphoma: Complete remission after

curing the infection. *Gastroenterology*. 2000;**118**:821-828

[129] Haesebrouck F, Pasmans F, Flahou B, et al. Gastric *Helicobacters* in domestic animals and nonhuman primates and their significance for human health. *Clinical Microbiology Reviews*. 2009;**22**:202-223

[130] Stolte M, Kroher G, Meining A, et al. A comparison of *Helicobacter pylori* and *H. heilmannii* gastritis. A matched control study involving 404 patients. *Scandinavian Journal of Gastroenterology*. 1997;**32**:28-33

[131] Ladirat SE, Schols HA, Nauta A, et al. High-throughput analysis of the impact of antibiotics on the human intestinal microbiota composition. *Journal of Microbiological Methods*. 2013;**92**:387-397

[132] Marteau P, Rambaud JC. Potential of using lactic acid bacteria for therapy and immunomodulation in man. *FEMS Microbiology Reviews*. 1993;**12**:207-220

[133] Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *The New England Journal of Medicine*. 2015;**372**:825-834

[134] Dang Y, Reinhardt JD, Zhou X, et al. The effect of probiotics supplementation on *Helicobacter pylori* eradication rates and side effects during eradication therapy: A meta-analysis. *PLoS One*. 2014;**9**:e111030

[135] Lv Z, Wang B, Zhou X, et al. Efficacy and safety of probiotics as adjuvant agents for *Helicobacter pylori* infection: A meta-analysis. *Experimental and Therapeutic Medicine*. 2015;**9**:707-716

[136] Tong JL, Ran ZH, Shen J, et al. Meta-analysis: The effect of supplementation with probiotics on eradication rates and adverse events

during *Helicobacter pylori* eradication therapy. *Alimentary Pharmacology & Therapeutics*. 2007;**25**:155-168

[137] Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in *Helicobacter pylori* eradication therapy. *Journal of Clinical Gastroenterology*. 2013;**47**:25-32

[138] Zhang M-M, Qian W, Qin Y-Y, et al. Probiotics in *Helicobacter pylori* eradication therapy: A systematic review and meta-analysis. *World Journal of Gastroenterology*. 2015;**21**:4345-4357

[139] Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases *Helicobacter pylori* eradication rate: Evidence from a meta-analysis. *Revista Española de Enfermedades Digestivas*. 2013;**105**:445-453

[140] Zhu R, Chen K, Zheng Y-Y, et al. Meta-analysis of the efficacy of probiotics in *Helicobacter pylori* eradication therapy. *World Journal of Gastroenterology*. 2014;**20**:18013-18021

[141] Zou J, Dong J, Yu X. Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for *Helicobacter pylori* eradication. *Helicobacter*. 2009;**14**:97-107

[142] Vladimirov B. Treatment of helicobacter-pylori associated diseases. In: Boyanova L, editor. *Helicobacter pylori*. Norfolk, UK: Caister Academic Press; 2011:237-251

[143] Li S, Huang XL, Sui JZ, et al. Meta-analysis of randomized controlled trials on the efficacy of probiotics in *Helicobacter pylori* eradication therapy in children. *European Journal of Pediatrics*. 2014;**173**:153-161

[144] Sachdeva A, Nagpal J. Effect of fermented milk-based probiotic preparations on *Helicobacter pylori* eradication: A systematic review and meta-analysis of randomized-controlled trials. *European Journal of Gastroenterology & Hepatology*. 2009;**21**:45-53

[145] Szajewska H, Horvath A, Kołodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Alimentary Pharmacology & Therapeutics*. 2015;**41**:1237-1245