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Helicobacter pylori Infection

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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 (RPTPα and RPTPβ), low-density lipoprotein receptor-related protein-1 (LRP1), fibronectin, CD18, and sphingomyelin. RPTPβ 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 pangastritis, 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. Premalignant 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-jB [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, TNFa, IL-1b), low expression of anti-inflammatory cytokines (IL-10, TGFb), 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-jB, 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 specific-ity [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 lym-phoma, 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, levofloxa-cin, 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 assess-ment 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) + clarithro-mycin (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 ≥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 (≥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 stains 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

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