Effect of bacterial and host factors on *Helicobacter pylori* eradication therapy

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Abstract

Introduction—A clearer understanding of the factors affecting the cure rate of *Helicobacter pylori* infection might lead to the development of novel prevention strategies and therapeutic targets.

Areas covered—This review covers two important issues that affect the eradication of *H. pylori*: bacterial and host factors. Several virulence factors have been shown to be predictors for gastroduodenal diseases. Successful treatment of *H. pylori* infection also depends on host genetic factors such as cytochrome P450 2C19 (*CYP2C19*) and interleukin (*IL*)*-1B*. The latest evidence on host genetic factors is discussed.

Expert opinion—The authors identify three main targets for achieving effective eradication therapy. The first therapeutic target is to identify counter measures for antibiotic-resistant *H. pylori* strains. Thus, antibiotic susceptibility should be checked in all patients, ideally, before the start of eradication treatment. The second therapeutic target is the inhibition of acid suppression. Maintaining a high intragastric pH for 24 hours increases the effectiveness of some antibiotics and the eradication effects for *H. pylori*. The third therapeutic target is to identify high-risk groups; the *CYP2C19* and *IL-1B* polymorphisms are candidates for significant risk factors. A personalized medical approach will likely increase the cure rate of *H. pylori* infection.

Keywords

antibiotic resistance; cytochrome P450 2C19; *Helicobacter pylori*; interleukin 1B; virulence factors

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1. Introduction

Helicobacter pylori is a gram-negative bacterium that colonizes the gastric epithelium of humans. It is one of the most important human pathogens that are involved in the pathogenesis of atrophic gastritis, gastroduodenal ulcers, gastric cancer, MALT lymphoma, idiopathic thrombocytopenic purpura, iron deficiency anemia, and vitamin B12 deficiency. The prevalence of *H. pylori* infection is >50% worldwide and 63–94% in developing countries [1]. Although it has decreased in developed countries through advanced diagnosis and eradication therapy, the rate of infected patients remains at 27.5–32.5% [2,3]. More progress towards worldwide *H. pylori* elimination needs to be made. In February 2013, the Japanese government approved diagnostic testing and eradication therapy for all *H. pylori*-positive patients confirmed by endoscopy [4].

Although triple therapy with a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole have been used as the first line treatment for *H. pylori* infections, the American College of Gastroenterology suggested that the cure rates were 70–85% in 2007 [5]. Additionally, recent systematic review showed that the cure rates of sequential and standard triple therapy were 84.1% and 75.1%, respectively [6]. The most important factor affecting *H. pylori* cure rates is the antibiotic resistance of *H. pylori* strains. The number of *H. pylori* strains that are resistant to antibiotics is increasing. The cure rate of patients were co-infected with clarithromycin-and metronidazole-resistant strains has been reported to be around 37% (16.2–60.7%) [7].

H. pylori contains several virulence factors, including cytotoxin-associated gene A product (CagA), vacuolating cytotoxin A (VacA), duodenal ulcer promoting gene A product (DupA), outer inflammatory protein A (OipA), and blood group antigen binding adhesin (BabA). These factors affect gastric mucosal inflammation and injury by activating inflammatory cell infiltration. They are predictors of gastric atrophy, intestinal metaplasia, and severe clinical outcomes [8]. Virulence factors also play important roles in gastric mucosal injury and are thus thought to affect the cure rates of *H. pylori* infection [9].

In addition, successful treatment of *H. pylori* infection depends on host genetic factors such as cytochrome P450 2C19 (*CYP2C19*), interleukin 1B (*IL-1B*), and multidrug-resistant transporter-1 (*MDR1*). Although PPIs are indispensable for eradication, the effect of PPIs is related to *CYP2C19* genetic polymorphisms [10]. In this review, we summarize eradication therapy strategies for *H. pylori* infection from the viewpoint of bacterial and host factors.

2. Bacterial factors

2.1 Antibiotic resistance

Clarithromycin-containing triple therapy (PPI twice daily in combination with 2 antibiotics: 200–500 mg clarithromycin and 750–1000 mg amoxicillin or 400 mg metronidazole) for 7–14 days is recommended by several guidelines [5,11,12]. However the cure rates of *H. pylori* infection have declined to 75% in the United States and Europe and 70–75% in China and Korea [13]. Moreover, although prolonged duration of the therapy became 14-days, the cure rate was still poor (70%) [14].

Increasing antibiotic resistance rates of *H. pylori* strains due to the improper usage of antibiotics are thought to be one of the main reasons for the decrease in cure rates. The frequent use of clarithromycin results in resistant bacteria. In Europe, the highest clarithromycin resistance rates; more than 30%, have been reported in Austria, Hungary and Portugal. In contrast, low resistance rate of < 10% have been observed in Northern Europe [15].

This might be due to differences in prescriptions for infectious diseases in these countries. High resistance rates to clarithromycin have been reported in Japan and China (22.7% and 32%, respectively). The resistance rates in both countries increased to >10% in the last decade [16,17]. To address the increased prevalence of clarithromycin resistance, new guidelines have been published in Europe. These recommend choosing eradication therapies based on resistance rates [18]. In regions with low clarithromycin resistance rates (20%), standard therapy containing clarithromycin is still allowed as first line therapy; however, it should be avoided in regions with high clarithromycin resistance rates (>20%) [18].

The antimicrobial effects of clarithromycin are mediated through binding of the compound to the 50S ribosomal subunit, preventing the bacterial ribosome from translating its messenger RNAs to synthesize new proteins. Three point mutations in the peptidyltransferase region of domain V of the 23S ribosomal RNA (rRNA) are responsible for more than 90% of clarithromycin–resistant strains. They include substitutions of adenine to guanine at position 2143 (A2143G) and those from adenine to guanine or cytosine at position 2142 (A2142G or A2142C) [19]. Novel mutations related to single mutations in *infB* or ribosomal protein L 22 (*rpl22*) (either a 9 base pairs [bp] insertion or a 3 bp deletion) have been shown to have synergic effects with mutations in 23S rRNA [20]. In Japan, tailored eradication treatment has been attempted. Clarithromycin susceptibility was analyzed by PCR before the start of eradication therapy; based on these results, the patients were treated by a suitable regimen containing either clarithromycin or metronidazole [21]. The overall cure rate in this study was 96.7% (95% CI 92.5–98.9), and the one of patients infected with clarithromycin-resistant *H. pylori* strains was over 95% after checking the susceptibility since metronidazole was used in their treatment regimen.

The number of metronidazole-resistant *H. pylori* strains has also increased. For the past decades, the prevalence of metronidazole-resistant strains has been around 50% in Latin America [22]. The highest resistance rate (83%) was observed in Colombia. In the US and all Europe countries, resistance rates of 20–30% and 28.6–3.8% were reported, respectively [15,23,24]. High resistance rates have also been reported in Asia, in particular in China and Korea (63.9% and 49.6%, respectively) [17,25].

Fluoroquinolones have been the leading choice to solve *H. pylori* antibiotic resistance [18,26,27]. The resistance rate of *H. pylori* strains to this antibiotic is low compared to the two above-mentioned drugs. However, fluoroquinolone-containing regimens cannot replace all eradication therapies or first line therapies, because resistance rates differ by region [28].

The key factor to achieve successful eradication is assessing antibiotic susceptibility. Regional differences in antibiotic susceptibility have been reported. As the prescriptions of

antibiotics differ by area, age, country, and background, resistant bacteria strains also differ. The use of inappropriate antibiotics contributes to the creation of novel resistant pathogens. Thus, the best way to achieve effective eradication is to select an appropriate drug by checking the presence or absence of resistant bacteria in individual patients. If this is not possible, the antibiotic should be selected in consideration of the resistance characteristics in the patient's region of residence.

2.2 Virulence factors

Characterizing the pathogenesis of *H. pylori* infections, in particular, the interaction between virulence factors in the organism and host genetics, is crucial. Although gastric cancer and duodenal ulcer are at the opposite ends of the disease spectrum, *H. pylori* infection promotes the development of both diseases. A clearer understanding of how *H. pylori* infection remains latent in the majority of infected patients and why only the minority ever develops a severe disease might lead to the development of new preventive approaches and novel therapeutic targets.

2.2.1 Cytotoxin-associated gene A product (CagA)—*CagA* is located at one end of the *cag* pathogenicity island (PAI) and encodes CagA, a 120–145-kDa immunodominant protein [29]. CagA is injected into gastric epithelial cells through the type IV secretion system (T4SS), which is an extracellular structure for transferring nucleic acids and proteins that is encoded by the *cag* PAI. CagA mimics a host cell protein and binds and activates multiple signaling factors [30]. Tyrosine phosphorylation by Src family kinases, which undergoes translocated CagA, is characterized by the presence of a Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Different tyrosine phosphorylation motifs are associated with different binding abilities of the Src homology 2 domain of the Src homology 2-containing protein-tyrosine phosphatase (SHP-2) and induced morphological changes in epithelial cells [31].

Based on proprietary *cagA* gene, *H. pylori* can be categorized as *cagA*-positive or -negative. In transgenic mice, wild-type CagA induced gastric epithelial hyperplasia, gastric polyps, and adenocarcinoma [32]. Similarly, Mongolian gerbils infected with wild-type CagA developed inflammation, gastric dysplasia, and gastric cancer [33]. CagA expression in *cagA*-positive *H. pylori* strains has shown to be associated with the host inflammatory response and an increased risk for clinical outcomes [34]. Recently, a meta-analysis of 16 studies showed that patients infected with *cagA*-positive strains were at increased risk for non-cardiac gastric cancer (OR 2.01, 95%CI 1.21–3.32) [35].

The key between *cagA* and eradication is gastric mucosal inflammation. Increased blood flow caused by severe mucosal inflammation is thought to improve the flow of antibiotics [36]. In 1997, it was first reported that the presence of *cagA* gene caused a difference in cure rates (Table 1). The study indicated that the cure rate of patients infected with *cagA*-positive strains was significantly higher than that of patients infected with *cagA*-negative strains (*cagA*-positive, 73%; *cagA*-negative, 52%; p = 0.017). However, several important issues are pointed out in Table 1: 1) Sample sizes were small in several studies; 2) Different regions were studied; 3) Different treatment regimens were used or the duration of treatment was different; and 4) The background was different. However, even when these issues are taken

into account and based on the data presented in the Table, the cure rates in patients infected with *cagA*-negative *H. pylori* strains were still lower than that of patients infected with *cagA*-positive strains (*cagA*-positive, 83%; *cagA*-negative, 69%; p < 0.01) (Table 1).

2.2.2 Vacuolating cytotoxin A (VacA)—VacA is a cytotoxin secreted by bacteria. It enters host cells through endocytosis, thereby inducing multiple cellular activities such as the alteration of membrane permeability, ultimately resulting in apoptosis with vacuolation via autophagy [37]. All *H. pylori* strains possess the *vacA* gene, but vacuolating activity differs among strains. The gene encoding *vacA* displays allelic diversity, including signal (s) regions s1 and s2 and middle (m) regions m1 and m2. Based on *in vitro* experiments, s1m1 strains are the most cytotoxic strains as they consistently induce cell vacuolation. They are followed by s1m2 strains (cell vacuolation not consistently induced) and s2m2 strains that have no cytotoxic activity because they fail to induce cell vacuolation [38]. In agreement with *in vitro* data, significant associations between *vacA* s1 and *vacA* m1 genotypes and peptic ulcer or gastric carcinoma prevalence was shown in several countries [39].

VacA s1 strains have a significant correlation with the presence of *cagA* (r = 0.87) [40]. In spite of the concordance a theory that a high cure rate is related with highly virulence factors, several studies indicated that *H. pylori vacA* s2 strains were difficult to cure with significant differences (Table 2). Based on all the data reported in Table 2, the overall cure rate of patients infected with s2 strains was significantly lower than that of those infected with s1 strains (s2, 81%; s1; 72%; P = 0.02). On the other hand, there was no significant difference in the cure rate of patients infected with m1 and m2 strains. Table 2 includes a list of previous studies based on the *vacA* status and *H. pylori* eradication success.

It was recently shown that multi component vaccines consisting CagA, VacA and neutrophil-activating protein (NAP) with aluminum hydroxide, administered intramuscularly or parenterally induced antibody responses and interferon-γ (IFN-γ) production in almost all individuals, and still detectable several months after the last immunization. Preliminary data show that this vaccine is equally safe and highly immunogenic in *H. pylori*-infected individuals [41].

2.2.3 Outer inflammatory protein A (OipA), duodenal ulcer promoting gene A product (DupA), and blood group antigen-binding adhesion (BabA)—OipA, an outer membrane protein that is involved in *IL-8* production in the gastric mucosa, is independent of the *cag* PAI, and leads actin dynamics via the phosphorylation from multiple pathways [42]. Variations in the number of CT repeats lead to an altered functional status of OipA (switch "on" and "off" states). Strains with an *oipA* "on" status have been more frequently found in patients with gastric cancer than in those with gastritis [33]. The *oipA* "on" status is strongly correlated with the presence of *cagA* (r = 0.82) and is an independent predictor of duodenal ulcer (OR 5.0, 95% CI 2.1–11.9) [40]. Although we expected *oipA* "off" be less exposed with antibiotic due to the less ability to attach, a study reported that the *oipA* "off" status showed a higher cure rate in patients treated with short-term quadruple therapy than the *oipA* "on" status (94.6% *vs.* 86.8%. respectively; P = 0.02) [43]. Further studies between *oipA* and eradication are expected in the near future.

DupA is an *H. pylori* virulence factor that is located in the plasticity region of the *H. pylori* genome. It has been shown to be associated with an increased risk for duodenal ulcer but was protective against gastric atrophy, intestinal metaplasia, and gastric cancer [44]. The *dupA* gene is classified as either *dupA1* (long-type, 1884 bp) or *dupA2* (the truncated version by the mutations) [45]. An *in vitro* study of *dupA* mutants showed that *dupA* substantially increased *H. pylori*-induced IL-12p40 and IL-12p70 production by CD14+ mononuclear cells [46]. *DupA1* (without frameshift mutations) was significantly correlated with gastric ulcer and gastric cancer than gastritis (OR 3.35, 95% CI1.55–7.24 and OR 4.14, 95% CI 1.23–13.94, respectively), even after adjusting for age, sex, and *cagA* [47]. It was reported that the secretion of gastric acid in *dupA*-positive patients was significantly higher than that in *dupA*-negative patients [48]. The authors concluded that *dupA* might affect intragastric pH. The presence of *dupA* might render *H. pylori* eradication difficult. The cure rate in patients infected with *dupA*-positive *H. pylori* strains was significantly lower than that infected with *dupA*-negative strains with clarithromycin resistance (28.6% *vs.* 69%, respectively; P = 0.04) [49]. In the study's multivariate analysis, *dupA* presence was independent risk factor for eradication failure (OR 3.71, 95% CI 1.07–12.83). High gastric secretion might be become the reason the difficulty of eradication in the patients with *dupA*-positive strain.

BabA was detected on the bacterial cell outer membrane of the CCUG17875 strain, which contains one silent *babA1* and one expressed *babA2* gene [50]. The sequences of these two genes differ only by the presence of a 10 bp deletion in the signal peptide sequence of *babA1* which eliminates its translational initiation codon [51]. A recent study reported that the *babA* mutant was less capable of inducing DNA double-strand breaks (DSBs) in primary and transformed murine and human epithelial and mesenchymal cells, suggesting that bacterial adhesion via *babA* is required to induce DSBs. The induction of DSBs contributes to the genetic instability and frequent chromosomal aberrations that are the hallmarks of gastric cancer [52]. Moreover, BabA expression is a major determinant of the density of *H. pylori* colonization. The absence of Lewis b expression was shown to be inversely proportional with the density of colonization and Lewis x or Lewis a expression [53]. Colonization density might adversely affect the efficacy of eradication and ulcer healing [54]. Eradication and ulcer cure rates decrease from 88% for low-density colonization to 69% and 63%, respectively, for high-density colonization. Thus, although the role of BabA in eradication has only been indirectly shown right now, this bacterial adherence factor could provide the basis for vaccine therapy and might be become a future target for therapeutic interventions.

3. Host factors

3.1 Impact of acid inhibition on H. pylori eradication

It is well known that acid inhibition affects the cure rate of *H. pylori* and that inadequate usage of acid inhibitors leads to eradication failure. There are several reasons why acid inhibitors required for eradication therapy are. 1) Acid inhibitors create an optimal environment for antibiotics such as macrolides or quinolones as they maintain a pH 7.4 in the gastric submucosal layer [55]; 2) A higher pH increases the benefits of amoxicillin by

more than 10 times [56]; 3) *H. pylori* changes from a non-dividing to a growth state, the latter of which is effective for antibiotics such as clarithromycin or amoxicillin by elevating the pH of the gastric surface [57]. Thus, PPIs, which rapidly and potently neutralize intragastric pH, are needed for successful eradication. Several studies showed the importance of a high intragastric pH for eradication success. The median 24-hour intragastric pH was significantly higher in the group with successful eradication than in the group with failure eradication (pH 6.4, range 5.0–7.6 *vs.* pH 5.2, range 2.2–6.2; p = 0.013) [58]. In a meta-analysis comparing high-dose with standard-dose PPI, cure rates of 82% and 74% were achieved, respectively (RR 1.09; 95% CI 1.01–1.17) [59]. Maintaining an intragastric pH > 6 is important for eradication therapy [60]. The one of the successful key to eradicate the patients infected with clarithromycin-resistant *H. pylori* strains may maintain high pH levels [58].

Drug metabolizing enzymes (for example, CYP), drug resistance genes (for example, *MDR1*), and inflammation-related cytokine genes (for example, *IL-1* and *TNF-α*) contribute to gastric acid secretion. Eradication could target these genes since their activities depend on genetic polymorphisms. PPIs are the most popular acid inhibitors. They are mainly metabolized by *CYP2C19* (Figure 1). Inflammatory cells infiltrating the gastric mucosa in patients with *H. pylori* infection induce several proinflammatory cytokines. *IL-1* and *TNF-α* are well known as inhibitors of gastric acid secretion, on another hand, *MDR1* is one of the most important transporters for drug disposition in humans.

3.2 Cytochrome P 2C19 (CYP2C19)

PPI has prominent role to inhibit gastric acid suppression against upper gastrointestinal diseases, such as gastroesophageal reflux disease (GERD), gastroduodenal ulcers, and Zollinger-Ellison syndrome. The prophylactic use of PPIs is recommended in patients taking drugs that potentially induce peptic ulcers (e.g., non-steroidal anti-inflammatory drugs and anti-platelet drugs such as low-dose aspirin) [61,62]. In addition, PPIs are indispensable drugs for *H. pylori* eradication therapy, as the rapid and potent neutralization of gastric acid improves the cure rate of *H. pylori* [63]. Moreover, PPIs increase the intragastric concentration of amoxicillin by strongly inhibiting acid secretion [56]. Since omeprazole (OPZ), a substituted benzimidazoles, was found to inhibit gastric acid secretion by blocking H^+/K^+-ATPase (a proton pump), a number of PPIs have been developed later. PPIs are mainly metabolized by CYP in the liver, and *CYP2C19* is the most essential metabolize enzyme [10] (Figure 1). *CYP2C19* polymorphisms involved on the largest part of interindividual variability in pharmacokinetics and pharmacodynamics. The principal *CYP2C19* genotypes are classified as extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM) based on the combination of two SNPs in *CYP2C19*2* in exon 5 and *CYP2C19*3* in exon 4 [64]. Racial differences in the proportion of genotypes have been identified. The incidences of EMs are 98% in black American [65], 68.8% in Caucasian [66], and 34.9% in Asian [67]. It was also reported that acid inhibition by OPZ is associated with the *CYP2C19* genotype [68]. EMs eliminate PPIs from systemic circulation faster than IMs or PMs. Thus, PPI plasma levels of EMs are the lowest in *CYP2C19* genotypes. The 24-hour intragastric pH is also lower in EMs than IMs or PMs. Different host *CYP2C19* genotypes are associated with different cure rates of *H. pylori*

infection. In a study using standard therapy, the cure rate of EMs was significantly lower than that of IMs and PMs (72.2%, 92.1%, and 97.8%, respectively). Moreover, 70% of patients who failed eradication were EMs [69]. To overcome the problem for EM, a high intragastric pH should be maintained for 24 hours. Since the key factor is that PPI inhibits gastric acid secretion in a dose-dependent manner, high-dose multiple-dividing PPI therapy was developed. When PPIs were administered 4 times rather than once daily, maintaining a 24-hour high intragastric pH could achieve sufficient acid inhibition through maintaining appropriate PPI plasma levels, even in patients with EMs [70]. Changing the dosing schedules in consideration of *CYP2C19* polymorphism was also found to be important. Using specific dosing schedules (for example, once daily for PMs, twice daily for IMs, and 4 times daily for Ems) was successful at maintaining a pH of at least 4 [71]. High-dose multiple-dividing PPI therapy could achieve eradication rates over 90%, even in EM patients [72].

3.3 Interleukin 1 (IL-1)

IL-1β is a member of the inflammatory cytokines that were identified as chemoattractants for neutrophils, lymphocytes, and monocytes. Mucosal IL-1β expression and production is upregulated during *H. pylori* infection and plays an important role in initiating and amplifying the inflammatory response to the infection [73,74]. In an animal model, increasing IL-1β levels in the gastric mucosa suppressed gastric acid secretion. For example, IL-1β reduced gastric acid secretion by 80% in a rat model that was intravenously infused with pentagastrin. IL-1β was 100 times more potent than PPIs and 6,000 time more potent than H2 receptor antagonist (H2RA) [75]. It is thought that IL-1β in the gastric mucosa of *H. pylori*-infected individuals is one of the mediators for the inhibition of gastric acid secretion and induces inflammation [76]. In a Mongolian gerbil model of *H. pylori* infection, gastric inflammation and IL-1β levels were significantly increased in the gastric mucosa [77].

In humans, the *IL-1B* gene contains three polymorphisms (located −511, −31, and +3954 bp from the transcriptional start site) [78]. The IL-1 receptor antagonist gene (*IL-RN*) has a variable number of identical 86 bp tandem repeats in intron 2 [79]. The ratio of gastric atrophy, gastritis, peptic ulcer, and gastric cancer is associated with these polymorphisms [76,80]. Mucosal IL-1β levels in the *IL-1B*-511 T/T g or *IL-1RN**2 genotypes were significantly higher than in carriers of the *IL-1B*-511C or *IL-1RN**1 alleles (*IL-1β 511*: antrum p <0.05, corpus p <0.01; *IL-1RN*: antrum p = 0.01, corpus p = 0.056) [81]. Furthermore, the *IL-1B*-511 T/T genotype exhibited an increased histological score, such as inflammatory cell infiltration atrophy, more frequency than C allele carriers, but not the difference in *IL-1RN* polymorphism [80,81]. *IL-1*β polymorphisms have also shown to be associated with the risk of gastric cancer (OR for gastric cancer 2.6, 95% CI 1.7–3.9 for the *IL-1*β −511 T/T genotype when compared with the C/C genotype; OR 2.5, 95% CI 1.6–3.8 for the *IL-1*β −31 T/T genotype when compared with the C/C genotype, and OR 3.7, 95 % CI 2.4–5.7 for the *IL-1RN**2 genotype when compared with the *1 genotype) [76]. This, the polymorphism in the *IL-B*-511T/T and *IL-RN**2 genotypes increase IL-1β levels, suppress gastric acid secretion, induce histological inflammatory cell infiltration, and cause the development of gastroduodenal diseases such as gastric atrophy and gastric cancer.

The cure rate in individuals harboring the *IL-1B*-511 T/T genotype was significantly higher than that of individuals harboring the C/C genotype (T/T genotype: 94.7%, C/C genotype: 77.3%; P = 0.002) (Table 3). In particular, the cure rate of individuals with the T/T genotype was higher than that of carriers of the C genotype infected with clarithromycin-resistant *H. pylori* strains (T/T genotype: 78%, C/T genotype: 50%, C/C genotype: 35%). Another study reported that the *IL-1β* −511 T/T and C/T genotypes showed very similar eradication rates (88.2% and 87.2%, respectively), whereas the C/C genotype had a much lower eradication rate (72.2%) (Table 3) [82]. In contrast, no difference in cure rates has been observed for the *IL-1B*-31, +3954, and *IL-1RN* polymorphisms (Table 3).

3.4 Multi-drug resistance gene 1 (MDR1)

MDR1 is one of the most important transporters for drug disposition in humans. *MDR1* , more commonly referred to as P-glycoprotein (P-gp), which is an integral membrane protein weighing 170 kDa [83]. The drug is usually influenced by ATP-dependent efflux transporter; P-gp [84]. PPIs are substrates for and inhibitors of P-gp [85]. Although the majority of single nucleotide polymorphisms (SNPs) have no effect on humans, it was reported that the *MDR1* 3435 T/T genotype in exon 26 was associated with significantly lower intestinal P-gp expression and increased bioavailability of some drugs after oral administration [86].

The involvement of the *MDR1* 3435 T/T exon 26 SNP for eradication is controversial (Table 4). In Japan, it was reported that 82% and 81% of patients with the *MDR1* 3435 C/C and C/T genotypes, respectively, showed successful *H. pylori* eradication. In contrast, only 67% of patients with the T/T genotype showed successful eradication (P = 0.001 for all) (Table 4). Two reports from Korea and Poland reported that the cure rate was independent of the *MDR1* genotype (Table 4).

3.5 Tumor necrosis factor-α (TNF-α) and other cytokines

TNF-α encoded by *TNF-A* on chromosome 6 is a proinflammatory cytokine that is involved in several pathways of gastric acid inhibition. For example, TNF-α inhibits basal acid and stimulates acid through histamine and gastrin [87]. It is produced by macrophages, monocytes, neutrophils, T cells, and NK cell after stimulation. *H. pylori* infection elevates TNF-α in tissue, inducing cytotoxicity and apoptosis of gastric epithelial cells [88]. *TNF-α* has five biallelic SNPs in its promotor region; -G238A, -G308A, -C857T, -C863A, and T1031C. Some polymorphism in *TNF-A* are thought to be related to its expression. For example, *TNF-A*-308A has been shown to increase TNF-α production [89]. The *TNF-A*-G238A and -G308A polymorphisms are relevant to different transcriptional intra-individual activities and are associated with an increased risk for gastric cancer and gastric and duodenal ulcer [90,91]. Furthermore, the *TNF-A*-308A polymorphism was more strongly associated with *H. pylori cagA*-positive strains when compared with *cagA*-negative strains or controls (p = 0.019 and p = 0.011, respectively) [92]. However, no significant associations were shown between the *TNF-A* (−1031, −857, and −863 polymorphisms and and eradication (Table 4).

IL-8 and IL-10 are important mediators in gastric physiology and are thought to have important roles in the etiology of gastric cancer. For example, IL-8 stimulates the

proliferation of endothelial cells, and IL-10 downregulates cytotoxic responses. In spite of some studies, only one report showed a significant correlation between the *H. pylori* eradication rate and these factors [93].

4. Other factors implicated in *H. pylori* eradication

Several factors such as smoking, food, economic status, treatment compliance, treatment duration, dosages, and methods of treatment (e.g., concomitant, hybrid, or sequential therapy) have been shown to be associated with the cure rate of *H. pylori* infection. However, a discussion of these factors is not within the main scope of this review.

5. Future aspects of *H. pylori* eradication therapy

Multi-dividing therapy for 7 days after assessing clarithromycin resistance resulted in an overall cure rate of 97.4% (148/152 study participants; 95% CI 93.4–99.3%) in the PP analysis and 96.7% (148/153 study participants; 95% CI 92.5–98.9%) in the ITT analysis [21]. The cure rates for patients infected with clarithromycin-resistant strains were 98.4% and 98.4% in the PP and ITT analysis, respectively.

Recently, new system that can simultaneously analyze *CYP2C19* and clarithromycin susceptibility within 30 min was developed [94]. The susceptibility targets the A2142G and A2143G point mutations in the *H. pylori* 23S rRNA and the fully automated DNA analyzer measures the polymorphisms in gastric juice sample collected by aspiration during gastroduodenoscopy. Although this automated machine is rapid and effective for increase eradication rate, the procedure is costly (around 150 US dollars), need a special automated machine and requires patients to undergo an upper endoscopy [94].

6. Conclusion

In this review, we discuss the treatment of *H. pylori* infection in relation to therapeutic targets. We mention the increase in antibiotic-resistant strains and provide a list of virulence factors. Antibiotic-resistant *H. pylori* strains are difficult to cure, and developing a treatment strategy targeting these strains is crucial. Virulence factors not only involved in the progression of gastroduodenal disease but might be also related to cure therapy. In the section on host factors, we describe the importance of acid inhibition, the appropriate usage of PPIs, and list several polymorphisms. *CYP2C19* must be useful in eradication therapy. We expect that the most suitable eradication therapy will use these targets in near future.

7. Expert opinion

In summary, there are three main targets to achieve effective eradication therapy for *H. pylori* infection.

The first therapeutic target is to identify counter measures for antibiotic-resistant *H. pylori* strains. Susceptibility to antibiotics should be assessed in all patients, ideally, before the start of eradication treatment so that physicians can prescribe the appropriate antibiotics. Physicians should also know the resistance rates of *H. pylori* in their country of residence as

the ratio of resistant strains differ by country (e.g., Southern *vs.* Northern European countries). The number of clarithromycin- and metronidazole-resistant *H. pylori* strains have increased recently. Thus far, the resistance rate to fluoroquinolones has been relatively low, but it has seen a rapid increase in some countries. Although fluoroquinolone-containing regimens or novel antibiotics might become important options of treatment, these do not adapt in all countries. Susceptibility to antibiotics should be checked to enable the administration of effective antibiotics and to avoid the development of novel resistant pathogens. Moreover, effective eradication can be achieved if each patient is checked for the absence or presence of resistant bacteria.

The second therapeutic target is inhibiting acid suppression since insufficient acid inhibition leads to eradication failure. Maintaining a high intragastric pH for 24 hours increases the effectiveness of some antibiotics and makes *H. pylori* easier to cure. Thus, physicians should maintain a high intragastric pH (pH 6) to achieve successful eradication. Intragastric pH levels are associated with the PPI dose and regimen. Hence, a high-dose and multiple-dividing PPI therapy should be selected for effective eradication. This will not change until the development of more powerful and long-acting acid inhibitors.

Although until now we could not modify the patient's genotypes, identifying high-risk groups is very important to become the third therapeutic target. Candidates for one of the most significant risk factors are EMs on *CYP2C19* polymorphisms. As EMs metabolize PPIs quickly, it is difficult to elevate intragastric pH in patients with this compared to other genotypes. So, EMs may need to increase dosage and frequency of PPI. Fortunately, as some studies showed the frequency of EMs, it may not need to measure *CYP2C19* genotypes if the countries, area or race have the high frequency of EMs. In these cases, special PPI therapy (e.g. high-dose multiple therapy) should be applied without measuring *CYP2C19*. On the other hand, it may be needed to know the genotypes for saving cost and solution of troublesome for patients in low frequency of EMs. Some studies showed that the presence of *cagA* and *vacA* s2 could be risk factors for eradication. Moreover, the cure rate in individuals with the *IL-1B*-511 C/C genotype was significantly lower than in those having other genotypes. In summary, the *CYP2C19, IL-1*β, *and cagA* polymorphisms are relevant to clinical practice. By analyzing these polymorphisms before eradication, high-risk groups can be identified, and effective eradication can be achieved in these patients. Novel markers that are more sensitive and effective for eradication will likely be identified in future studies.

We herein described *H. pylori* eradication therapy utilizing the three targets antibiotic resistance, adequate acid inhibition, and the identification of high-risk groups. Our ultimate goal is to achieve a cure rate of nearly 100%. To achieve this aim, it is necessary to administer precise care for each patient, including assessments of antibiotic resistance and/or genetic polymorphisms. However, the usefulness of utilizing several targets (e.g., virulence factors and genetic polymorphisms except *CYP2C19*) for increasing the eradication rate still needs to be confirmed in clinical practice. Furthermore, as examining both antibiotic resistance and gene polymorphisms requires specialized laboratories and equipment (e.g., PCR machines), it might be difficult to apply this approaches in clinical practice worldwide. To get a gastric mucosal sample, an upper endoscopy is also sometimes required. Therefore, these evidence-based medicines are necessary for some condition including their cost.

However, we believe that personalized medicine will increase the *H. pylori* cure rate, and that the costs can be offset by achieving a higher cure rate. At least, physicians should know the local peculiarity in susceptibility to antibiotics or the frequency of some genotypes. Further studies are required to establish a complete eradication therapy utilizing these or new targets.

Acknowledgments

Abbreviations

BabA	blood group antigen binding adhesion
bp	base pair
CagA	cytotoxin-associated gene A product
CYP2C19	cytochrome P450 2C19
DSB	double strand break
DupA	duodenal ulcer promoting gene A product
EM	extensive metabolizer
GERD	gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
H2RA	H2 receptor antagonist
IFN	interferon
IL	interleukin
IL-RN	IL-1 receptor antagonist gene
IM	intermediate metabolizer
ITT	intention-to-treat
MDR1	multidrug-resistant transporter 1
NSAID	non-steroidal anti-inflammatory drug
OipA	outer inflammatory protein
OPZ	omeprazole
Rpl22	ribosomal protein L 22

rRNA	ribosomal RNA
PAI	pathogenicity island
PM	poor metabolizer
PP	per-protocol
PPI	protein pump inhibitor
SHP2	Src homology 2-containing protein-tyrosine phosphatase
SNP	single nucleotide polymorphism
T4SS	type IV secretion system
VacA	vaculating cytotoxin A

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Highlights Box

- Ideally susceptibility to antibiotics resistance should be assessed in all patients before the start of eradication treatment to avoid the development of novel resistant pathogens and to obtain more effective *H. pylori* eradication. At least, physicians should know the resistance rates of *H. pylori* in their region.

- Physicians should maintain a high intragastric pH to achieve successful *H. pylori* eradication with a high-dose and multiple-dividing PPI therapies.

- The extensive metabolizers on *CYP2C19* polymorphisms may need increasing dosage and frequency of PPI. Particular methods of PPI therapy should be apply without measuring *CYP2C19*.

- The presence of *cagA* and *vacA* s2 genotype could be risk factors for eradication. Moreover, the cure rate in individuals with the *IL-1B*-511 C/C genotype was significantly lower than in those having other genotypes.

- By identifying high-risk groups before eradication, an effective eradication could be achieved.

Omeprazole

CYP2C19 → CYP3A4

5-Hydroxy omeprazole/ 5-O-Desmethyl omeprazole

Omeprazole sulphone/ 3-Hydroxy omeprazole

CYP3A4 → CYP2C19 →

Omeprazole hydroxysulphone

Esomeprazole

CYP2C19 → CYP3A4

5-Hydroxy Esomeprazole/ 5-O-Desmethyl Esomeprazole

Esomeprazole sulphone/ 3-Hydroxy Esomeprazole

CYP3A4 → CYP2C19 →

Esomeprazole hydroxysulphone

Pantoprazole

CYP2C19 → CYP3A4

Demethylated-pantoprazole

Pantoprazole sulphone

Sulfotransferase

Pantoprazole sulfate

Lansoprazole

CYP2C19 → CYP3A4

5-Hydroxy-lansoprazole

Lansoprazole sulphone

Rabeprazole

CYP2C19 → CYP3A4

Dimethylated--Rabeprazole

Rabeprazole sulphone
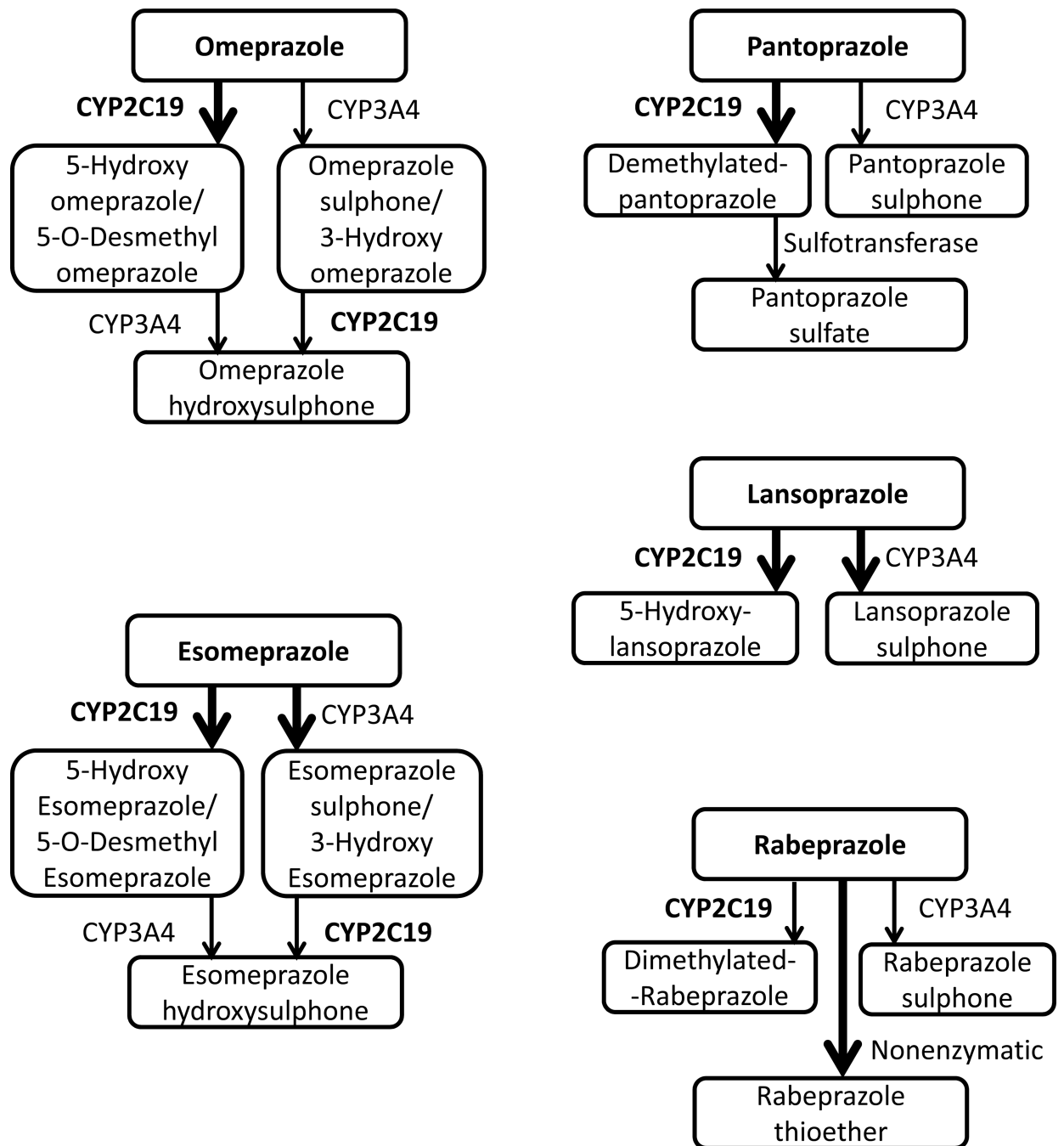
Nonenzymatic

Rabeprazole thioether

Figure 1. All proton pump inhibitors are metabolized by cytochrome P 2C19
Esomeprazole, omeprazole, pantoprazole, lansoprazole, and rabepazole depend on CYP2C19 polymorphisms.

Table 1

Cure rates for *H. pylori* infections by *cagA* status

Authors	Year	Country	cagA diagnosis	Regimen, duration (d)	Cure rate cagA+ (n)	Cure rate cagA− (n)	P value
van der Hulst et al.	1997	Netherlands	PCR	OA, 14	73% (89/122)	52% (17/33)	0.02 *
Greenberg et al.	1999	USA	WB	OC, 14	65% (22/34)	100% (10/10)	0.08
Lopez-Brea et al.	1999	Spain	PCR	BAM	75% (6/8)	75% (18/24)	>0.05
van Doorn et al.	2000	Netherlands	PCR	LBTM, 4 or 5	81% (48/59)	50% (19/38)	<0.01 *
Broutet et al.	2001	France	PCR	PAC	76% (64/84)	63% (45/72)	0.07
Sarc et al.	2001	Turkey	IgG	LAC, 7	87% (111/127)	72% (41/57)	0.02 *
Rudi et al.	2002	Germany	PCR	PPI+AC or CM, 7	89% (73/82)	79% (26/33)	0.15
Queiroz et al.	2002	Brazil	PCR	PCF, 7	One arm	75% (17/20)	One arm
Scholte et al.	2002	Netherland	PCR	OAC, 7	100% (10/10)	81% (13/16)	0.15
Treiber et al.	2002	Germany	PCR	PPI+ACM, 3 or 5	91% (147/161)	87% (61/70)	0.33
De Francesco et al.	2002	Italy	PCR	RA+RCT, 10	87% (27/31)	86% (24/28)	>0.05
Chaudhuri et al.	2003	India	PCR	OAC, 10	60% (25/42)	60% (3/5)	>0.05
Russo et al.	2003	Italy	PCR	LAC, 7	76% (69/91)	42% (8/19)	<0.01 *
Xia et al.	2003	Australia	IgG	OAC, 7	88% (63/72)	One arm	One arm
De Francesco et al.	2004	Italy	PCR	RA+RCT or RAC, 10	93% (68/73)	77% (12/22)	<0.05 *
Zhao et al.	2007	China	PCR	EAC	93% (54/58)	38% (3/8)	<0.01 *
Total					83% (813/982)	69% (300/435)	<0.01 *

Data are based on per-protocol (PP) analyses.

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Significantly different

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Total: Excluding single-arm study

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Eradication duration were not shown

P >0.05: No detailed data were available; the author described the results as not significant.

A, amoxicillin; AC, amoxicillin and clarithromycin; ACM, bismuth, clarithromycin, and metronidazole; BAM, bismuth, amoxicillin, and metronidazole; CM, clarithromycin and metronidazole; CT, clarithromycin and tinidazole; EAC, esomeprazole, amoxicillin, and clarithromycin; LAC, lansoprazole, amoxicillin, and clarithromycin; LBTM, lansoprazole, bismuth, tetracycline, and metronidazole; OA, omeprazole and amoxicillin; OAC, omeprazole, amoxicillin, and clarithromycin; OC, omeprazole and clarithromycin; PAC, pantoprazole, amoxicillin, and clarithromycin; PAM,

pantoprazole, amoxicillin, and metronidazole; PFC, pantoprazole, furazolidone, and clarithromycin; PPI, proton pump inhibitor; RA, rabeprazole amoxicillin; RAC, rabeprazole, amoxicillin, and clarithromycin; RCT, rabeprazole, clarithromycin, and tinidazole

Table 2

H. pylori cure rates by *vacA*

Authors	Year	Country	vacA Diagnosis	Regimen, duration (d)	vacAtype	Cure rate (n)	P value
Lopez-Brea et al.	1999	Spain	PCR	BAM**	s1 vs. s2	50% (3/6) vs. 80% (21/26)	>0.05
van Doorn et al.	2000	Netherlands	PCR	LBTM, 4 or 5	s1 vs. s2	75% (56/75) vs. 50% (11/22)	0.03*
Rudi et al.	2002	Germany	PCR	PPI+AC or CM, 7	s1 vs. s2	87% (80/92) vs. 83% (19/23)	0.59
Scholte et al.	2002	Netherland	PCR	OAC, 7	s1 vs. s2	100% (11/11) vs. 85% (11/13)	0.17
Chaudhuri et al.	2003	India	PCR	OAC, 10	s1 vs. s2	62% (26/42) vs. 40% (2/5)	>0.05
Russo et al.	2003	Italy	PCR	LAC, 7	s1 vs. s2	77% (67/87) vs. 43% (9/21)	<0.01*
De Francesco et al.	2004	Italy	PCR	RA+RCT or RAC, 10	s1 vs. s2	91% (40/44) vs. 90% (46/51)	>0.05
Zhao et al.	2007	China	PCR	EAC**	s1 vs. s2	93% (53/57) vs. 44% (4/9)	<0.05*
Rudi et al.	2002	Germany	PCR	PPI+AC or CM,7	m1 vs. m2	90% (44/49) vs. 83% (55/66)	0.32
Scholte et al.	2002	Netherland	PCR	OAC,7	m1 vs. m2	100% (5/5) vs. 83% (16/19)	0.34
Chaudhuri et al.	2003	India	PCR	OAC, 10	m1 vs. m2	46% (11/24) vs. 74% (17/23)	<0.05*
De Francesco et al.	2004	Italy	PCR	RA+RCT or RAC, 10	m1 vs. m2	89% (33/37) vs. 90% (52/58)	>0.05
Zhao et al.	2007	China	PCR	EAC**	m1 vs. m2	94% (17/18) vs. 83% (40/48)	<0.05*
Total					s1 vs. s2	81% (336/414) vs. 72% (123/170)	0.02*
					m1 vs. m2	83% (110/133) vs. 84% (180/214)	0.73

Data are based on per-protocol (PP) analyses.

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Significantly different

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Eradication duration were not shown

P >0.05: No detailed data were available; the author described the results as not significant.

A, amoxicillin; R, rabeprazole; AC, amoxicillin and clarithromycin; ACM, bismuth, clarithromycin, amoxicillin, and metronidazole; BAM, bismuth, amoxicillin, amoxicillin, and metronidazole; CM, clarithromycin and metronidazole; CT, clarithromycin and tinidazole; EAC, esomeprazole, amoxicillin, and clarithromycin; LAC, lansoprazole, amoxicillin, and clarithromycin; LBTM, lansoprazole, bismuth, tetracycline, and metronidazole; OA, omeprazole and amoxicillin; OAC, omeprazole, amoxicillin, and clarithromycin; OC, omeprazole and clarithromycin; PAC, pantoprazole, amoxicillin, and clarithromycin; PAM, pantoprazole, amoxicillin, and metronidazole; PFC, pantoprazole, furazolidone, and clarithromycin; PPI, proton pump inhibitor; RA, rabeprazole and amoxicillin; RAC, rabeprazole, amoxicillin, and clarithromycin; RCT, rabeprazole, clarithromycin, and tinidazole

Table 3

H. pylori cure rates and *IL-1*

Gene	Authors	Year	Country	Patients (n)	Regimen	Genotype	Cure rates (n)	P value
IL-1B −511	Take et al.	2003	Japan	231	OAC, LAC, RAC	C/T + T/T *vs.* C/C	80% (138/172) *vs.* 80% (47/59)	0.25
	Furuta et al	2004	Japan	336	OAC, LAC	C/C *vs.* C/T *vs.* T/T	77% (75/97) *vs.* 90% (147/164) *vs.* 95% (71/75)	0.05 * (C/C *vs.* C/T) <0.01 * (C/C *vs.* T/T)
	Sugimoto et al.	2006	Japan	360	OAC, LAC, RAC	C/C *vs.* C/T *vs.* TT	72% (70/97) *vs.* 88% (164/187) *vs.* 88% (67/76)	<0.01 * (C/C *vs.* C/T) <0.01 * (C/C *vs.* T/T)
	Zhang et al.	2010	China	224	OAC, RAC	C/C *vs.* C/T *vs.* TT	87% (39/45) *vs.* 88% (68/77) *vs.* 89% (91/102)	0.91
IL-1B +3954	Zhang et al.	2010	China	224	OAC, RAC	C/C *vs.* C/T *vs.* TT	89% (183/206) *vs.* 83% (15/18) *vs.* none	0.45
	Gawronska-Szklarz et al.	2010	Poland	139	PAM	C/C *vs.* C/T *vs.* TT	75% (9/12) *vs.* 81% (38/47) *vs.* 70% (56/80)	0.40
IL-1B −31	Ishida et al.	2006	Japan	67	LAC	C/C *vs.* C/T *vs.* TT	100% (14/14) *vs.* 83% (30/36) *vs.* 77% (13/17)	>0.05
	Zhang et al.	2010	China	224	OAC, RAC	C/C *vs.* C/T *vs.* TT	92% (22/24) *vs.* 92% (57/62) *vs.* 86% (119/138)	0.44
IL-1B-RN	Sugimoto et al.	2006	Japan	360	OAC, LAC, RAC	*2 carrier *vs.* non-carrier	76% *vs.* 85% **	>0.05
	Zhang et al.	2010	China	224	OAC, RAC	1/1 *vs.* 1/2 *vs.* 1/4 *vs.* 2/2	87% (143/164) *vs.* 92% (45/49) *vs.* 100% (1/1) *vs.* 90% (9/10)	0.67

Treatment duration was 7 days in all studies.

Data are based on per-protocol (PP) analyses.

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Significantly different

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Raw data were not shown.

P >0.05: No detailed data were available; the author described the results as not significant.

Zambon et al showed that there was no difference between eradication rate and *IL-Iβ* −31, *IL-IRN*; however, no detailed data were provided.

IL, interleukin; LAC, lansoprazole, amoxicillin, and clarithromycin; OAC, omeprazole, amoxicillin, and clarithromycin; PAM, pantoprazole, amoxicillin, and clarithromycin; RAC, rabeprazole, amoxicillin, and clarithromycin

Table 4

H. pylori cure rates *MDR1* and *TNF-α*.

Gene	Authors	Year	Country	Patients (n)	Regimen	Genotype	Cure rates (n)	P value
MDR1 3435	Gawronska-Szklarz et al.	2005	Poland	70	OAC, PAM	C allele carrier *vs* T/T	40% (21/52) *vs* 72.2% (13/18)	<0.05 *
	Gawronska-Szklarz et al.	2005	Poland	70	OAC, PAM	C/C *vs* C/T *vs* T/T	41% (11/27) *vs* 40% (10/25) *vs* 72% (13/18)	<0.05 *
	Furuta et al.	2007	Japan	314	LAC	C/C *vs* C/T *vs* T/T	82% (83/101) *vs* 81% (112/139) *vs* 67% (44/73)	<0.01 * (T/T *vs.* C/T) <0.01 * (T/T *vs.* C/C)
	Oh et al.	2009	Korea	210	PAC	C/C *vs.* C/T *vs.* T/T	83% (62/75) *vs* 84% (92/102) *vs.*77% (20/26)	0.66
	Gawronska-Szklarz, et al.	2010	Poland	139	PAM	C/C *vs.* C/T *vs.* T/T	75% (33/44) *vs* 74% (45/61) *vs* 74% (25/34)	0.99
TNF-α 1031	Sugimoto et al.	2006	Japan	360	OAC, LAC, RAC	C allele carrier *vs* T/T	84% *vs.* 83% **	>0.05
	Ishida et al.	2006	Japan	67	LAC	C/C *vs* C/T *vs.* T/T	100% (2/2) *** *vs.* 71% (10/14) *vs.* 85% (45/51)	>0.05
TNF-α 857	Sugimoto et al.	2006	Japan	360	OAC, LAC, RAC	T allele carrier *vs.* C/C	82% *vs.* 84% **	>0.05
TNF-α 863	Sugimoto et al.	2006	Japan	360	OAC, LAC, RAC	A allele carrier *vs* C/C	85% *vs.* 83% **	>0.05

Treatment duration was 7 days in all studies.

Data are based on per-protocol (PP) analyses.

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Significantly different

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Raw data were not shown.

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n = 2

IL, interleukin; LAC, lansoprazole, amoxicillin, and clarithromycin; MDR1, multidrug-resistant transporter-1; OAC, omeprazole, amoxicillin, and clarithromycin; PAC, pantoprazole, amoxicillin, and clarithromycin; PAM, pantoprazole, amoxicillin, and clarithromycin; RAC, rabeprazole, amoxicillin, and clarithromycin; TNF, tumor necrosis factor