

## Antibiotic treatment for *Helicobacter pylori*: Is the end coming?

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### Abstract

Infection with the Gram-negative pathogen *Helicobacter pylori* (*H. pylori*) has been associated with gastro-duodenal disease and the importance of *H. pylori* eradication is underscored by its designation as a group

I carcinogen. The standard triple therapy consists of a proton pump inhibitor, amoxicillin and clarithromycin, although many other regimens are used, including quadruple, sequential and concomitant therapy regimens supplemented with metronidazole, clarithromycin and levofloxacin. Despite these efforts, current therapeutic regimens lack efficacy in eradication due to antibiotic resistance, drug compliance and antibiotic degradation by the acidic stomach environment. Antibiotic resistance to clarithromycin and metronidazole is particularly problematic and several approaches have been proposed to overcome this issue, such as complementary probiotic therapy with *Lactobacillus*. Other studies have identified novel molecules with an anti-*H. pylori* effect, as well as tailored therapy and nanotechnology as viable alternative eradication strategies. This review discusses current antibiotic therapy for *H. pylori* infections, limitations of this type of therapy and predicts the availability of newly developed therapies for *H. pylori* eradication.

**Key words:** *Helicobacter pylori*; Treatment; Antibiotic resistance; Therapeutic regimens; Novel agents

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**Core tip:** This article reviews the recent literature describing antibiotic resistance and trends in *Helicobacter pylori* (*H. pylori*) treatment. As there is no effective conventional therapy, new treatments are being developed and bismuth quadruple, sequential, concomitant therapies are recommended as a first-line regimen in regions with high levels of clarithromycin resistance. Quinolones have also been used for *H. pylori* treatment, although the cure rate has gradually reduced with this approach. New therapeutic directions include probiotic supplementation, tailored therapy, novel agents, and nanotechnology.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a Gram-negative, flagellated, spiral shaped microaerophilic bacterium first identified by Marshall and Warren<sup>[1-3]</sup>. These bacteria have morphological characteristics penetrate the mucosa and colonize the stomach and duodenum<sup>[4]</sup>. *H. pylori* are responsible for the pathogenesis that leads to gastritis, peptic ulcer disease (PUD), gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma<sup>[3,5,6]</sup>. The World Health Organization has classified *H. pylori* as a group I carcinogen with a risk of stomach cancer<sup>[7,8]</sup>. *H. pylori*-related stomach cancer represents 5.5% of all cancers worldwide and 25% of all infection-associated malignancies. Socioeconomically, *H. pylori* infection increases the risk of malignancy and the expense of *H. pylori*-associated morbidity<sup>[9]</sup>. *H. pylori* infection has also been related to non-digestive conditions such as ischemic heart disease, stroke, Alzheimer's disease, Parkinson's disease, and iron deficient anemia<sup>[4,10]</sup>. In other report, some patients with gastritis resolved *H. pylori* infection without using antibiotic treatment<sup>[11]</sup>. Although the prevalence of *H. pylori* infection has been reduced in developed countries, it has remained prevalent in developing countries<sup>[12,13]</sup> with rates of infection varying according to nation, patient age, and socioeconomic states<sup>[14]</sup>. Eradication of *H. pylori* is an effective treatment for PUD, gastric MALT lymphoma, and preventing the recurrence of stomach cancer after endoscopic treatment<sup>[15-17]</sup>.

A standard triple therapy (STT), consisting of a proton pump inhibitor (PPI), clarithromycin and amoxicillin, was established in clinical practice for the eradication of *H. pylori* infection<sup>[18,19]</sup>. However, in recent years, the efficacy of STT has been critically altered in many regions of the world as eradication rates have diminished to inadequately low levels<sup>[18,20]</sup>. The causes for this decline may involve patient compliance, bacterial factors, obesity, smoking, reinfection, and genetic polymorphisms in CYP2C19. However, antibiotic resistance may be the primary reason for reduced eradication of *H. pylori* infection worldwide<sup>[20-22]</sup>. In addition, the eradication rates differ by region, even in the same country. In South Korea, one study reported that the eradication rates of first-line therapy decreased from 81.3% to 77.5% from 2001-2007<sup>[23]</sup>, while another showed that no definite evidence of a significant change in the eradication rate during 2000-2010<sup>[24]</sup>. This may be due to geographical differences in antibiotic resistance and the methods used to confirm eradication. In a region with high rates of clarithromycin resistance, sequential or concomitant therapy is recommended as the first-line *H. pylori* eradication treatment<sup>[25]</sup>. The primary reason for the growth in antibiotic resistance is the emergence of point mutations in the *H. pylori* genome<sup>[26]</sup>. Thus, the development of novel treatment methods to increase

eradication rates and reduce antibiotic resistance is needed. The focus of this review will be on current *H. pylori* therapies and limitations, as well as alternative anti-*H. pylori* regimens.

## CURRENT ANTIBIOTIC RESISTANCE IN WORLDWIDE

The most important antibiotics in *H. pylori* treatment are clarithromycin, metronidazole, and amoxicillin. Figure 1 illustrates recently reported clarithromycin and metronidazole resistance rates worldwide. Resistance to these antibiotics is thought to be the main cause of eradication failure<sup>[27-29]</sup>. Antibiotic resistance is discovered by bacterial culture-based techniques (*E*-test, modified disk diffusion, agar dilution method, and breakpoint susceptibility test) and molecular methods [polymerase chain reaction (PCR), real-time PCR, allele-specific PCR, sequencing, and fluorescent *in situ* hybridization]<sup>[30]</sup>. Although these methods are useful for examining antibiotic resistance, their implementation at the early stages of *H. pylori* remains impractical due to the time required to obtain results and the high cost of the tests.

Clarithromycin is a macrolide antibiotic that inhibits protein synthesis by binding to and slowing the actions of the bacterial ribosome<sup>[30]</sup>. Clarithromycin resistance is due to three point mutations at A2142C, A2142G, and A2143G in the 23s *rRNA* gene<sup>[31]</sup>. In particular, the A2143G mutation has been related to a very low eradication rate<sup>[32]</sup>. In contrast, the A2143G mutation occurs in only 23% of resistant strains in Eastern countries<sup>[31]</sup>. This suggests that clarithromycin point mutations may be geographically distinct between Eastern and Western countries and new point mutations have appeared in South America<sup>[33]</sup>. Clarithromycin resistance is also different depending on the area. In Brazil, stomach biopsy specimens positive for *H. pylori* were analyzed by PCR to detect the point mutation associated with clarithromycin resistance<sup>[34]</sup>. The results uncovered primary clarithromycin resistance in 16.5% patients. Recently, the clarithromycin resistance rate in South Korea was reported to range from 17.2% to 23.7%<sup>[35]</sup>. In a study published in Japan, the clarithromycin resistance rate in 2002 was 18.9%; however, the clarithromycin resistance rate in 2006 increased to 27.2%<sup>[36]</sup>. Even with third-line eradication therapy, clarithromycin resistance rates in Japan were reported as 86.4%<sup>[37]</sup>. Several studies in China have reported increased resistance rates Shanghai<sup>[38]</sup>, 21.5% resistance in the southeast coastal region<sup>[39]</sup>, and a relatively high rate of 33% in Vietnam, which is near Southeast China<sup>[40]</sup>. In Western Asia, resistance to clarithromycin has been reported to be > 10% in Iran and > 20% in Turkey<sup>[13]</sup>. In one study, clarithromycin resistance was reported in 47.5% of patients with dyspepsia in Turkey<sup>[41]</sup>. In sharp contrast to other Asian countries, no resistance to clarithromycin has been reported in Malaysia<sup>[42]</sup> and the prevalence of resistance to clarithromycin in Gambia and Senegal also remains

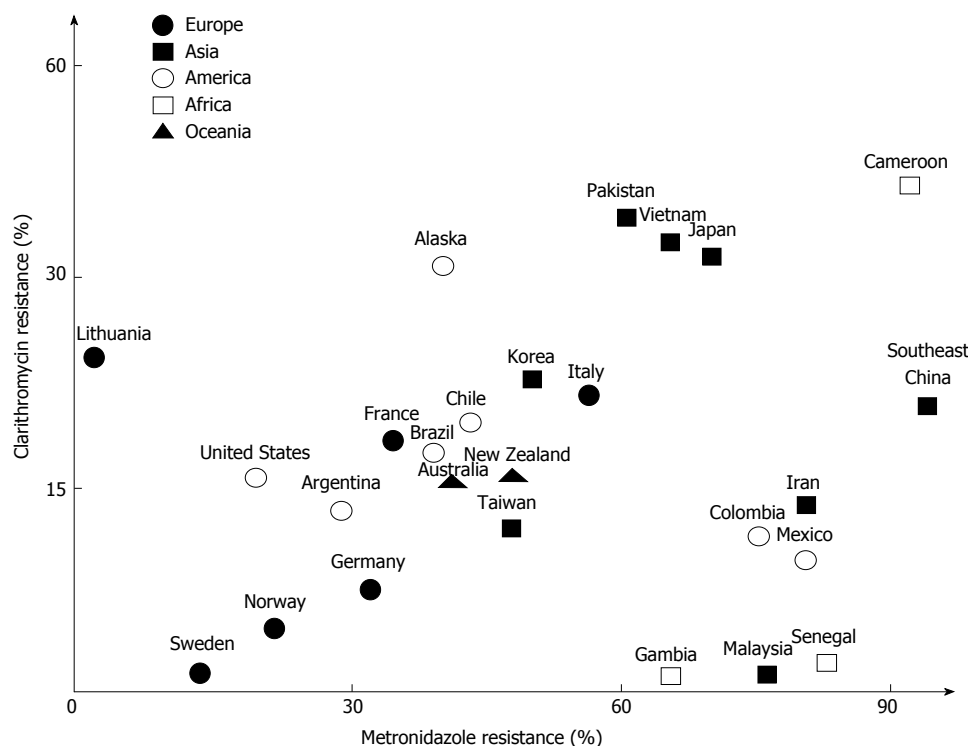


Figure 1 Worldwide rates of resistance to clarithromycin and metronidazole.

very low<sup>[43,44]</sup>. Resistance to clarithromycin has also risen by > 20% in Southern Europe, although in Northern Europe the resistance rate is less than 10%<sup>[45]</sup> compared to 1.5% in a random adult Swedish population<sup>[46]</sup> and 7.5% in central Germany<sup>[47]</sup>. During the last 15 years, a twofold increase in clarithromycin resistance was reported in Italy<sup>[48]</sup> and in Spain, where the mean clarithromycin resistance rate was 18.3% in 1709 patients<sup>[49]</sup>, and 34.7% in Portuguese children<sup>[50]</sup>. In contrast to the general trend, the rate of *H. pylori* strains resistant to clarithromycin decreased from 34% to 22% during 6 years in Southern Poland<sup>[51]</sup>. Despite these variations, the overall frequency of clarithromycin resistance has risen from 10.2% to 21.3% worldwide, and A2143G is the most frequently reported point mutation. Present European guidelines recommend 7 d of STT in regions in which the rate of clarithromycin resistance is < 20%, and 14 d in regions with clarithromycin resistance rates of > 20%<sup>[25,45]</sup>.

The mechanism mediating resistance to metronidazole is complex. Modifications in the *rdxA* gene, assumed to be point mutations, are considered a primary cause<sup>[30]</sup>. Metronidazole resistance may also influence the treatment outcome, although it is generally considered less clinically important than clarithromycin resistance<sup>[52,53]</sup>. Overall, the Eastern Asian region has higher metronidazole resistance rates with 95.4% in the southeast coastal region of China<sup>[39]</sup> and 71.3% in Japan<sup>[37]</sup>. In Vietnam, the resistance rate was 69.9% among 103 strains<sup>[40]</sup>. Unlike the clarithromycin resistance rate, there was a high prevalence of resistance to metronidazole (75.5%) in Malaysia<sup>[42]</sup>, a 76.8% rate in Iran<sup>[54]</sup> and a high resistance rate in Africa<sup>[43,44]</sup>. Another

study showed that 80% of strains in Mexico were resistant to metronidazole<sup>[55]</sup>. Overall, metronidazole resistance is > 50% in much of the world but there are reports that metronidazole resistance has declined in Northern Europe<sup>[9,30]</sup>, while in the United States and Europe, the metronidazole resistance rate was reported to be < 40%<sup>[30,56]</sup>, and 22.5% in 102 isolates from Norway<sup>[57]</sup>. However, in Central and Southern Europe, resistance rates remain markedly higher—34.9% in France and 32.7% in Germany<sup>[47,58]</sup>.

Amoxicillin is a beta-lactam antibiotic that was first used for *H. pylori* therapy<sup>[25]</sup>. Unlike clarithromycin and metronidazole, amoxicillin resistance rates are low worldwide<sup>[30]</sup>: 0% or < 1% in Europe<sup>[30]</sup>. However, other studies revealed high amoxicillin resistance rates in Iran, Japan, and Cameroon<sup>[37,45,54]</sup>.

Fluoroquinolones are the sole class of antibiotics for treatment of *H. pylori* that directly inhibit bacterial DNA synthesis. Resistance to fluoroquinolones occurs primarily by mutation in the genes for topoisomerase IV and gyrase<sup>[59]</sup>. Levofloxacin is currently recommended as a second-line *H. pylori* treatment when first-line therapy containing clarithromycin has failed, although levofloxacin resistance has been predicted to increase in the near future<sup>[25]</sup>. Levofloxacin resistance rates in Asia differ from region to region with rates of 20.6% in the southeast coastal region of China and 18.4% in Vietnam<sup>[39,40]</sup>. Fluoroquinolone resistance was noted as 62.3% in Pakistan<sup>[60]</sup>, while Japan and Malaysia had low resistance rates of 8.2% and 0%, respectively<sup>[37,42]</sup>. Primary *H. pylori* resistance to ciprofloxacin occurred at a high frequency (15.7%) in South Korea<sup>[61]</sup>. A study by Mégraud<sup>[62]</sup> of more than 2000 patients with *H.*

**Table 1** Decline in rates of *Helicobacter pylori* eradication following first-line standard triple therapy

Country	Ref.	Publication	Treatment duration	Patients	Therapy regimen	Eradication rate (ITT)	Eradication rate (PP)
South Korea	Na <i>et al</i> <sup>[177]</sup>	2007	7 d	3267	Standard PPI Cla 500 mg bid Amo 1 g bid	NA	84.3%
	Chung <i>et al</i> <sup>[178]</sup>	2012	10 d	80	Lan 30 mg bid Cla 500 mg bid Amo 1 g bid	58.7%	67.6%
Japan	Asaka <i>et al</i> <sup>[179]</sup>	2001	7 d	96	Lan 30 mg bid Cla 200 mg bid	NA	90.7%
	Fujioka <i>et al</i> <sup>[180]</sup>	2012	7 d	3162	Amo 750 mg bid Rab 10 mg bid Amo 750 mg bid Cla 200 mg bid	80.7%	NA
	Nishizawa <i>et al</i> <sup>[27]</sup>	2012	7 d	55	Lan 30 mg bid Cla 400 mg bid Amo 750 mg bid	74.5%	80.4%
	Nishida <i>et al</i> <sup>[181]</sup>	2014	7 d	134/134	Eso 20 mg bid Cla 400 mg bid Amo 750 mg bid Lan 30 mg bid Cla 400 mg bid Amo 750 mg bid	69.4%/73.9%	76.9%/79.8%
Taiwan	Sheu <i>et al</i> <sup>[182]</sup>	2000	7 d or 2 wk	286	Ome 20 mg bid Amo 1 g bid Cla or Met bid	NA	87.8%
	Chen <i>et al</i> <sup>[117]</sup>	2014	7 d	73	Rab 20 mg bid Cla 500 mg bid Amo 1 g bid	57.5%	61.8%
Turkey	Ozçay <i>et al</i> <sup>[183]</sup>	2004	4 wk: PPI 2 wk: Cla, Amo	102	Ome or Lan Cla 7.5 mg/kg bid Amo 20 mg/kg bid	NA	75.7%
	Kutluk <i>et al</i> <sup>[184]</sup>	2014	10 d	74	Lan 1 mg/kg per day Cla 20 mg/kg per day Amo 50 mg/kg per day	52.7%	55.7%
Italy	Catalano <i>et al</i> <sup>[185]</sup>	1999	10 d	84	Ome 20 mg bid Cla 500 mg bid Amo 1 g bid	NA	94.0%
	Paoluzi <i>et al</i> <sup>[186]</sup>	2010	7 d	90	Eso 20 mg bid Cla 500 mg bid Amo 1 g bid	66.0%	75.0%
Latin America	Greenberg <i>et al</i> <sup>[106]</sup>	2011	14 d	488	Lan 30 mg bid Cla 500 mg bid Amo 1 g bid	82.2%	87.1%

ITT: Intention to treat; PP: Per protocol; PPI: Proton pump inhibitor; NA: Not available; Cla: Clarithromycin; Amo: Amoxicillin; Lan: Lansoprazole; Rab: Rabeprazole; Eso: Esomeprazole; Ome: Omeprazole; Met: Metronidazole.

*pylori* infection showed resistance rates of 14.1% for levofloxacin, with significantly higher fluoroquinolone resistance in Western/Southern Europe than in Northern Europe<sup>[62]</sup>. O'Connor *et al*<sup>[63]</sup> reported that 11.7% of patients had strains resistant to levofloxacin in Ireland and there was a 29.1% resistance rate in 2011 in Germany<sup>[64]</sup>, 15% in Senegal<sup>[44]</sup> and 23% in Brazil<sup>[65]</sup>.

## THE EFFICACY OF STT AND BISMUTH QUADRUPLE THERAPY ARE DECREASING

The first-line regimen for the eradication of *H. pylori* infection consists of STT using a PPI, amoxicillin and clarithromycin and was first introduced by Dr. Bazzoli. In studies conducted during the 1990s, STT yielded > 80%

treatment success with reports of > 90% possible<sup>[66,67]</sup>. However, the increased prevalence of clarithromycin resistance has accounted for the diminished efficacy of STT. Table 1 shows eradication rates from recent studies using STT. Generally, STT is not recommended as a first-line regimen when the clarithromycin resistance rate is > 15%-20%, and other therapies such as quadruple therapy or sequential therapy are suggested<sup>[25]</sup>. Thus, a steady increase in *H. pylori* resistance to amoxicillin and metronidazole has also resulted in reduced treatment success of STT<sup>[27,68,69]</sup>. The ideal outcome of *H. pylori* eradication is > 80% by intention to treat (ITT) analysis and > 90% by per protocol (PP) analysis. According to a recent study, the eradication rate was unacceptably low for treatment success, with only 18% exceeding 85% and approximately 60% failing to attain 80% eradication by ITT analysis<sup>[20]</sup>. Over the past 20 years, the efficacy

of STT has decreased, with eradication rates < 80% by ITT analysis<sup>[41]</sup>. According to the present formula by Dr. Graham<sup>[70]</sup>, if clarithromycin resistance rate of 20%, the outcome of clarithromycin containing triple therapy is reduced to 77.2% by PP analysis. Already in some countries the eradication rates have been reported to be < 50% and if this trend continues for another 20 years, the efficacy of STT will be negligible.

Various methods have been considered to circumvent the STT eradication rate decrease. The first method suggested that increasing the STT duration would improve treatment efficacy. In an early meta-analysis, a 14-d STT regimen raised the eradication rate compared to a 7-d regimen<sup>[71]</sup>. Another meta-analysis supported this result by showing that extending STT over 7 d improved the eradication rate<sup>[72]</sup>. However, other reports determined that extending STT was not cost-effective and increased adverse events and decreased compliance, resulting in no significant difference between the eradication rate and extended treatment duration<sup>[73]</sup>. Another means of addressing the decrease in STT eradication rate is to increase the dose of PPI, which has a positive effect on treatment success. PPIs delay gastric emptying and increase gastric pH, which improves the effect of antibiotics by preventing acid-related degradation<sup>[74]</sup>. A meta-analysis reported increased eradication rates from STT involving PPI administration twice per day compared with once per day<sup>[75]</sup>. Another systematic review reported that utilizing a high dose of PPI increased the *H. pylori* treatment rate<sup>[76]</sup> and the use of high-dose PPI increased the effectiveness of STT compared with a single does PPI<sup>[77]</sup>. In spite of these positive outcomes, STT is now regarded as an outdated therapy.

Bismuth quadruple therapy (bismuth subcitrate potassium, metronidazole, tetracycline, PPI) has been suggested as a first-line treatment option for regions with a high (> 20%) incidence of clarithromycin resistance<sup>[53]</sup>. In a meta-analysis of nine randomized controlled trials (RCTs), bismuth quadruple therapy and STT resulted in similar compliance rates, side effects, and eradication rates as a primary therapy for *H. pylori* infection<sup>[78]</sup>. For example, the ITT eradication rate with modified bismuth quadruple therapy was 92.7% in a recent randomized study in Chinese patients<sup>[79]</sup>. A pilot study in United States Hispanics showed that 14-d bismuth quadruple anti-*H. pylori* therapy achieved a > 95% eradication rate<sup>[80]</sup>. However, in some studies the eradication rate of bismuth quadruple therapy was < 80%<sup>[81-83]</sup>. A decrease in the bismuth quadruple therapy eradication rate was highly associated with metronidazole resistance<sup>[20]</sup>.

## ARE THERE SUITABLE SEQUENTIAL AND CONCOMITANT THERAPY ALTERNATIVES?

Sequential therapy was introduced by Zullo *et al.*<sup>[84]</sup> in Italy in 2000. This regimen includes a PPI and amoxicillin

for 5 d, followed by a PPI, clarithromycin, and tinidazole triple therapy for another 5 d. Several studies have indicated that the eradication rate of sequential therapy was significantly higher than that of STT<sup>[85-87]</sup>. The reason that sequential therapy has a higher eradication rate than STT is that amoxicillin and PPI administered during the first 5 d decreases *H. pylori* density in the stomach, which increases clarithromycin and metronidazole efficacy<sup>[32,88-90]</sup>. In addition, amoxicillin damages the bacterial cell wall and limits production of an efflux channel underlying drug resistance. However, it is uncertain whether improvement in the eradication rate is due to sequential therapy or additional use of antibiotics such as tinidazole. Recent data from South Korea, showed a lower *H. pylori* eradication rate with sequential therapy with eradication rates by ITT analysis of 79.0% and by PP analysis of 84.9%<sup>[91]</sup>. Another study showed that the eradication rates by ITT were 72.1% and 80.2% in 10-d and 15-d sequential groups, respectively<sup>[92]</sup>. Although the 15-d sequential therapy group cure rate was higher than that of the 10-d sequential therapy group, the eradication rate remains low. In the study by Zhou *et al.*<sup>[93]</sup>, there was no significant difference between the eradication rates achieved with STT (66.4%) and sequential therapy (72.1%) by ITT analysis. Moreover, the sequential therapy group with dual clarithromycin resistance and metronidazole resistance had a lower eradication rate (43.9%) compared to the rate seen with only clarithromycin resistance (88.9%)<sup>[93]</sup>. In a 2015 study from India that compared sequential therapy to ciprofloxacin-containing sequential therapy, the ITT cure rate in the sequential therapy group was 66% and only 73.5% in the ciprofloxacin group<sup>[94]</sup>. Thus, the sequential therapy efficacy in Asia was lower than reported by earlier European studies. Another meta-analysis showed that the overall eradication rate of sequential therapy was 84.3% (95%CI: 82.1%-86.4%), although this was not superior to 14-d STT<sup>[86]</sup>. However, sequential therapy was able to eradicate 72.8% of the *H. pylori* resistant to clarithromycin<sup>[86]</sup>. In addition to the problem of sequential therapy eradication rate reduction, treatment compliance can be reduced due to medication changes during treatment. Furthermore, if eradication fails, no second-line treatment regimen has been established<sup>[95]</sup>.

Concomitant therapy, also known as non-bismuth quadruple therapy, consists of PPI and all three antibiotics (clarithromycin, amoxicillin, metronidazole) administered concomitantly to provide a simpler treatment regimen compared to sequential therapy<sup>[96]</sup>. Recently, several studies have compared concomitant therapy to STT and sequential therapy. In one study, 10-d concomitant therapy resulted in a better eradication rate in settings with antibiotic-resistant *H. pylori* strains<sup>[97]</sup>. Eradication rates for concomitant and sequential therapies were 100% vs 75% for clarithromycin-resistant strains and 75% vs 60% for clarithromycin-resistant/metronidazole-resistant strains<sup>[97]</sup>. A meta-analysis of 15 studies showed a mean *H. pylori* eradication rate of 90% by ITT analysis

for concomitant therapy and reported that longer treatment improved the outcomes compared to STT<sup>[98]</sup>. Another meta-analysis showed that concomitant therapy was superior to STT<sup>[99]</sup>. In studies published in South Korea, the eradication rate for concomitant therapy was considerably higher than that for sequential therapy<sup>[100,101]</sup>. However, several other studies have reported no difference in eradication rates between sequential and the concomitant therapy<sup>[102-104]</sup>. In a randomized open-label study, ITT eradication rates were 75.6% (95%CI: 66.3%-84.9%) in the sequential therapy group and 80.8% (95%CI: 71.8%-88.5%) in the concomitant therapy group<sup>[104]</sup>. In both groups, there was no difference in eradication rates and the treatment rate was lower than expected<sup>[104]</sup>. Furthermore, in some studies, concomitant therapy had a lower eradication rate than other regimens<sup>[83,105,106]</sup>. A total of 200 patients were randomized and the ITT eradication rates were 79% (95%CI: 71.0%-87.0%) in the bismuth group and 74% (95%CI: 68%-81%) in the concomitant group, although this was not statistically significant<sup>[83]</sup>. Another study compared the eradication rate between 10-d sequential therapy, 5-d concomitant therapy, 14-d concomitant therapy and 14-d hybrid therapy<sup>[105]</sup>. In ITT analysis, sequential therapy showed the highest eradication rate, which was higher than even 5-d concomitant therapy<sup>[105]</sup>. This is supported by an RCT of 1463 patients in seven Latin American sites (Chile, Colombia, Costa Rica, Honduras, Nicaragua, Mexico) that reported the eradication rate with 14-d standard therapy was 82.2%, compared to 73.6% with 5-d concomitant therapy and 76.5% with 10-d sequential therapy<sup>[106]</sup>. Currently, concomitant therapy has several limitations. First, side effects were reported to occur more frequently than with sequential therapy<sup>[107]</sup>. Second, there are few data describing the effect of metronidazole resistance in concomitant therapy. Moreover if dual-resistance to clarithromycin and metronidazole was > 15%, the eradication rate decreased<sup>[108,109]</sup>. Finally, as with sequential therapy, when first-line treatment fails no second-line treatment for concomitant therapy has been established. Tables 2 and 3 indicate that current trends of *H. pylori* eradication for sequential and concomitant therapy.

## ADDING LEVOFLOXACIN AND OTHER QUINOLONES TO EXISTING TREATMENT

Levofloxacin has a large spectrum of activity against diverse Gram-positive and -negative bacteria<sup>[110]</sup> though inhibition of bacterial topoisomerase II<sup>[111]</sup>. There have been several studies of levofloxacin use as a first-line treatment<sup>[112]</sup>. To overcome increasing clarithromycin resistance, levofloxacin has been used as an alternative to clarithromycin in either STT or sequential therapy<sup>[53]</sup>. Table 4 shows *H. pylori* eradication rates following levofloxacin-containing therapy. According to a meta-analysis, 10-d of levofloxacin triple therapy is more

efficacious than 7-d bismuth-based quadruple therapy (RR = 1.41, 95%CI: 1.25-1.59) in the eradication of *H. pylori* infection<sup>[113]</sup>. In another study, levofloxacin-based triple therapy (ITT, 80.8%; 95%CI: 73%-88%) was more effective than STT (ITT: 64%, 95%CI: 55%-73%) and there were no differences in compliance or side effects<sup>[114]</sup>. However, other studies reported that levofloxacin-containing regimens did not have superior eradication rates compared to other treatments. Meta-analyses and a recent study in 2014 have shown that the outcome of levofloxacin-based first-line therapy was similar to STT<sup>[115,116]</sup> with an overall crude eradication rate of 79.1% in the levofloxacin group compared to 81.4% in the STT group<sup>[116]</sup>. A recent RCT in Taiwan with over 153 patients determined there was an advantage to levofloxacin-amoxicillin/clavulanate-PPI therapy over STT, although there was a low eradication rate (ITT analysis: 78.1% vs 57.5%)<sup>[117]</sup>. Unsatisfactory results were reported in an Asian meta-analysis, which showed that 7-d STT was more effective than 7-d levofloxacin-based therapy<sup>[118]</sup>. However, in European countries, levofloxacin-based therapy was more effective than STT<sup>[118]</sup>. Regional differences in *H. pylori* resistance to antibiotics might account for these results. Although levofloxacin has been suggested as a replacement for clarithromycin in *H. pylori* treatment, increasing quinolone resistance is a larger problem. According to Graham *et al.*<sup>[119]</sup>, in the presence of fluoroquinolone resistance treatment success with quinolone-containing therapy decreases and these results can be predicted using a formula. A report published in United States in 2015 determined that the prevalence of levofloxacin resistance was 31.3% (95%CI: 23.1%-39.4%)<sup>[120]</sup> and another study showed a high rate of quinolone resistance (50%) in Congo<sup>[121]</sup>. We calculated the effect of quinolone resistance on treatment success using the proposed formula, which indicated success rates of 87.6% and 73.5%, respectively<sup>[119,122]</sup>. The levofloxacin resistance rate is also relatively high in East Asia, where there is also a higher prevalence of stomach cancer compared to other regions<sup>[122,123]</sup>. Sifloxacin, which has lower minimum inhibitory concentration for *H. pylori*, and levofloxacin triple therapy combined with bismuth quadruple therapy have been suggested as solutions to this problem, although further evidence is required to establish this approach<sup>[122,124]</sup>.

## PROBIOTICS AS ANOTHER APPROACH TO IMPROVE ERADICATION RATES

Many studies have demonstrated that probiotics have an inhibitory effect on *H. pylori*. Although some studies have reported that probiotics alone have limited efficacy<sup>[125,126]</sup>, they can be useful when used as a supplemental drug. In a study by Lv *et al.*<sup>[127]</sup>, the cure rates in the probiotic supplementation group were superior to those in the group that did not receive probiotics (RR, 1.12; 95%CI: 1.06-1.19), and probiotics reduced the risk of *H. pylori* therapy related side effects (RR, 0.60; 95%CI:

**Table 2** *Helicobacter pylori* eradication rates following first-line sequential therapy

Country	Ref.	Publication	Treatment duration	Patients	Therapy regimen	Eradication rate (ITT)	Eradication rate (PP)
South Korea	Lee <i>et al</i> <sup>[92]</sup>	2014	10 d	111	1 <sup>st</sup> 5 d: Eso + Amo 2 <sup>nd</sup> 5 d: Eso + Cla + Met	72.1%	78.4%
	Lee <i>et al</i> <sup>[91]</sup>	2015	10 d	100	1 <sup>st</sup> 5 d: Rab + Amo 2 <sup>nd</sup> 5 d: Rab + Cla + Met	79.0%	84.9%
China	Zhou <i>et al</i> <sup>[93]</sup>	2014	10 d	140	1 <sup>st</sup> 5 d: Eso + Amo 2 <sup>nd</sup> 5 d: Eso + Cla + Tin	72.1%	76.5%
Qatar	Ben Chaabane <i>et al</i> <sup>[94]</sup>	2015	14 d	106	1 <sup>st</sup> 7 d: Rab + Amo 2 <sup>nd</sup> 7 d: Rab + Cla + Met	66.0%	76.0%
Italy	Pontone <i>et al</i> <sup>[187]</sup>	2010	10 d	84	1 <sup>st</sup> 5 d: Lan + Amo 2 <sup>nd</sup> 5 d: Lan + Cla + Met	83.3%	90.9%
Spain	Molina-Infante <i>et al</i> <sup>[114]</sup>	2010	10 d	115	1 <sup>st</sup> 5 d: Ome + Amo 2 <sup>nd</sup> 5 d: Ome + Cla + Met	76.5%	80.8%

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Ome: Omeprazole; Eso: Esomeprazole; Tin: Tinidazole; Rab: Rabeprazole.

**Table 3** *Helicobacter pylori* eradication rates following first-line concomitant therapy

Country	Ref.	Publication	Treatment duration	Patients	Therapy regimen	Eradication rate (ITT)	Eradication rate (PP)
South Korea	Lim <i>et al</i> <sup>[104]</sup>	2013	14 d	78	Rab 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	80.8%	81.3%
	Lee <i>et al</i> <sup>[100]</sup>	2015	7 d	170	Rab 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg tid	79.4%	94.4%
Thailand	Kongchayanun <i>et al</i> <sup>[188]</sup>	2012	5 d/10 d	55/55	Rab 20 mg bid Amo 1 g bid Met 400 mg tid Cla 1 g qd	89.1%/96.4%	NA
Singapore	Ang <i>et al</i> <sup>[102]</sup>	2015	10 d	153	PPI standard does Amo 1 g bid Cla 500 mg bid Met 400 mg bid	81.7%	95.4%
Spain	Molina-Infante <i>et al</i> <sup>[97]</sup>	2012	10 d	209	PPI standard does Amo 1 g bid Cla 500 mg bid Met 500 mg bid	87.0%	89.0%
	McNicholl <i>et al</i> <sup>[103]</sup>	2014	10 d	168	Ome 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	87.0%	91.0%
Latin America	Greenberg <i>et al</i> <sup>[106]</sup>	2011	5 d	489	Lan 30 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	73.6%	NA

ITT: Intention to treat; PP: Per protocol; NA: Not available; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; PPI: Proton pump inhibitor; Rab: Rabeprazole; Ome: Omeprazole.

0.40-0.91). In another meta-analysis, the pooled odd ratios (ORs) for the eradication rate were higher in the probiotic group than the control group (OR = 1.67; 95%CI: 1.38-2.02) by ITT, and adverse effects were lower in the probiotic group (OR = 0.49, 95%CI: 0.26-0.94)<sup>[128]</sup>. This study also showed racial differences

in the sensitivity to probiotics, with greater differences in Asian populations compared to Caucasians. Adults, as well as children, have reported that probiotics positively affect eradication rates<sup>[129]</sup>. *Saccharomyces boulardii* is a type of probiotic gaining attention as a supplement for *H. pylori*. Recent reports have suggested that STT combined

**Table 4** *Helicobacter pylori* eradication rates following first-line levofloxacin-containing therapy

Country	Ref.	Publication	Treatment duration	Patients	Therapy regimen	Eradication rate (ITT)	Eradication rate (PP)
South Korea	Choi <i>et al</i> <sup>[189]</sup>	2011	7 d	98	Ome 20 mg bid Lev 200 mg bid	65.3%	73.6%
China	Liao <i>et al</i> <sup>[122]</sup>	2013	14 d	81	Amo 1 g bid Lan 30 mg bid Lev 500 mg qd	82.7%	85.9%
Taiwan	Liou <i>et al</i> <sup>[190]</sup>	2010	7 d	217	Amo 1 g bid Lan 30 mg bid Lev 750 mg qd	74.2%	80.1%
	Chen <i>et al</i> <sup>[117]</sup>	2014	7 d	73	Amo 1 g bid Rab 20 mg bid Lev 500 mg bid	78.1%	80.9%
Spain	Molina-Infante <i>et al</i> <sup>[114]</sup>	2010	10 d	115	Amo 1 g bid Ome 20 mg bid Lev 500 mg bid	80.8%	82.6%

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Lev: Levofloxacin; Amo: Amoxicillin; Rab: Rabeprazole; Eso: Esomeprazole; Cla: Clarithromycin; Ome: Omeprazole.

with *S. boulardii* could be effective for enhancing *H. pylori* eradication rates<sup>[130]</sup>. Compared with no intervention, *S. boulardii*-including regimens significantly increased treatment success (RR, 1.13; 95%CI: 1.05-1.21) and reduced *H. pylori* therapy-related adverse effects (RR, 0.46; 95%CI: 0.3-0.7)<sup>[131]</sup>. Furthermore, *Lactobacillus* and *Bifidobacterium* species also have an anti-*H. pylori* effect. A meta-analysis of 10 studies on *Lactobacillus*-containing and *Bifidobacterium*-containing probiotics use as a supplementation to *H. pylori* eradication therapy found that the pooled ORs by ITT analysis and PP analysis were 2.066 (95%CI: 1.398-3.055) and 2.321 (95%CI: 1.715-3.142), respectively<sup>[132]</sup>. In addition to the above references, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* supplementation to STT is effective for *H. pylori* eradication and dynamic changes in intestinal flora<sup>[133]</sup>. In recent RCT study, *Lactobacillus reuteri* was identified as a new probiotic proposed for the treatment of *H. pylori* infection. A combination that includes *L. reuteri* was able to reduce antibiotic-associated adverse events and to increase the *H. pylori* eradication rate<sup>[134]</sup>. Although more research into these probiotics is needed, it is important to note that there are reduced drug complications and treatment is comparatively free from resistance. Therefore, probiotics will be considered important future therapeutics for *H. pylori* eradication.

## IS TAILORED THERAPY ON THE HORIZON FOR *H. PYLORI* TREATMENT?

It is well known that clarithromycin sensitivity of the *H. pylori* infection contributes to the success of the STT eradication rate<sup>[52,135]</sup>. Generally in infectious disease treatment, bacterial culture is carried out prior to determine the antibiotic selection of the organism. However, *H. pylori* bacterial culture is difficult and time-consuming, with various protocols for evaluating resistance. Thus, *H. pylori* treatment has depended on empirical antibiotic treatment<sup>[109]</sup>. In their study, Gerrits

*et al*<sup>[136]</sup> determined that the A2142G, A2143G mutations were highly related to resistance using PCR, which was partially used to identify resistance to clarithromycin in *H. pylori*<sup>[137]</sup>. There are several advantages to this method because it is relatively simple and efficient with a cost similar to a rapid urease test<sup>[135]</sup>. In a recent study of 1232 patients, the eradication rate by selective treatment in the tailored group was 91.2%, which was significantly higher than control groups (amoxicillin, rabeprazole, clarithromycin; 75.9% and amoxicillin, rabeprazole, metronidazole; 79.1%)<sup>[138]</sup>.

Appropriate stomach acid suppression, as well as resistant strains of *H. pylori*, remains a problem for successful eradication. PPI plays an important role in *H. pylori* eradication and the main enzyme involved in PPI metabolism is CYP2C19<sup>[139]</sup> and CYP2C19 genotypes can influence PPI efficacy<sup>[140]</sup>. Homozygous extensive metabolizer (HomEM) results in the highest rates of PPI metabolism, heterozygous extensive metabolizer (HetEM) results in moderate rates of PPI metabolism, while poor metabolizers (PM) exhibit the lowest rates of PPI metabolism<sup>[139]</sup>. The frequency of CYP2C19 polymorphism differs depending on ethnicity. Asians have a higher proportion of PM compared with Western populations, particularly Caucasians and African-Americans<sup>[139,141]</sup>. In contrast, Caucasians have a higher prevalence rate of HomEM compared with Asians<sup>[142]</sup>. Accordingly, geographic differences should be considered in selecting doses or types of PPIs for *H. pylori* treatment since there is a significant difference between HetEM and HomEM (OR = 1.90; 95%CI: 1.38-2.60) in *H. pylori* eradication rate<sup>[143]</sup>. In additional subanalysis of individual PPIs revealed that omeprazole was influenced by the CYP2C19 genotype<sup>[143]</sup>. In another meta-analysis, successful eradication rates differed considerably between PM and HetEM (OR = 1.73, *P* = 0.002) and between PM and HomEM (OR = 2.79, *P* < 0.0001) and even between HetEM and HomEM (OR = 2.00, *P* < 0.0001)<sup>[144]</sup>. This study showed that



a regimen including rabeprazole was not affected by CYP2C19 genotype status<sup>[144]</sup>. According to a meta-analysis of a RCT in 2013, regardless of the PPI being taken, the eradication rates of PM were higher than HetEM and HomEM<sup>[145]</sup>. In addition, results of the sub-analysis of the PPI type, omeprazole and lansoprazole were affected by CYP2C19 genotype. Unlike above, esomeprazole and rabeprazole were not affected by CYP2C19 genotype<sup>[145]</sup>. In studies published in Japan, esomeprazole and rabeprazole are less influenced by CYP2C19 genotype compared with another PPIs<sup>[146,147]</sup>. The efficacy of tailored *H. pylori* eradication treatment was demonstrated by Sugimoto *et al.*<sup>[148]</sup>. In a tailored regimen, *H. pylori* patients with clarithromycin-sensitivity were treated with clarithromycin, amoxicillin, rabeprazole, while clarithromycin-resistant patients were treated with metronidazole, amoxicillin, rabeprazole for 1 wk. As a result, the overall eradication rate was 96.7% (95%CI: 92.5%-98.9%) by ITT analysis and 97.4% (95%CI: 93.4%-99.3%) by PP analysis<sup>[148]</sup>. The method achieved high eradication rates of 94.3% in CYP2C19 rapid metabolizers<sup>[148]</sup>. Although CYP2C19 genotyping remains difficult clinically, tailored therapy may be useful in overcoming decreased eradication rates.

## NEWER AGENTS AND NONTRADITIONAL THERAPIES FOR *H. PYLORI* ERADICATION: HOPE IS COMING?

In the last decade, many researchers have argued that new classes of antimicrobials with novel mechanisms of action are necessary to overcome increasing drug resistance. Some agents have shown an antibacterial effect against *H. pylori in vitro* regardless of drug resistance and are effective even at low pH. Among them, pyloricidin A, B, and C have a strong and selective anti-*H. pylori* effect which an MIC<sub>90</sub> value of 0.013 mg/L<sup>[149]</sup>. Benzimidazole derivatives (MIC<sub>90</sub> = 0.025), polycyclic compound (MIC<sub>90</sub> = 0.2-0.39), arylthiazole derivative 44 (MIC<sub>90</sub> = 0.0065) also were highly effective against *H. pylori*<sup>[149]</sup>.

Cathelicidins and defensins are examples of human antimicrobial peptides (AMPs) native to the innate immune system of many eukaryotes that have activity against *H. pylori*<sup>[150]</sup>. LL-37 is a cathelicidin with an anti-*H. pylori* effect<sup>[151]</sup>, and a recent study demonstrated that cathelicidin limited *H. pylori* colonization and related gastritis in mouse models<sup>[152]</sup>. Defensin peptides have also been indicated to impede *H. pylori*<sup>[153]</sup>. Human beta defensin 2 and 3 are differentially expressed in gastric mucosa during *H. pylori* infection<sup>[154]</sup>. Oligo-acyl-lysyl (OAK) peptides, which have a structure and function similar to those of natural AMPs, have broad-spectrum antibacterial activity and anti-*H. pylori* effect *in vivo*<sup>[155]</sup>. Unlike the natural AMPs, OAK peptides are without known proteolytic cleavage sites and thus, resistant to enzymatic cleavage.

SQ109 was developed as a tuberculosis treatment

and known to be safe and tolerated in human trials<sup>[150]</sup>. In an *in vitro* study, SQ109 had anti-*H. pylori* activity and a low *H. pylori* resistance rate<sup>[156]</sup>. Pyridodiazepines are potent and selective molecules that target the *H. pylori* MurI inhibitor not effective against other bacteria<sup>[157]</sup>. Sulfonamides and sulfamates were potent anti-beta-carbonic anhydrase molecules<sup>[150]</sup>. *H. pylori* beta-carbonic anhydrase catalyzes the hydration of carbon dioxide to proton and bicarbonate to facilitate *H. pylori* metabolism of urea and bicarbonate and survive in low pH. Sulfonamides and sulfamates, inhibit the enzyme and are effective against *H. pylori*<sup>[158]</sup>.

Phytotherapy is expected to be another promising therapy for *H. pylori* eradication. Ginger rhizome extract has been demonstrated to have defensive activity in the stomach, increase stomach mucin regeneration, reinforce antioxidant enzymes, and suppress *H. pylori* growth<sup>[159]</sup>. Capsaicin has an anti-inflammatory effect and inhibited *H. pylori*-induced interleukin (IL)-8 production by gastric epithelial cells<sup>[160]</sup>. Sulphoraphane has also been indicated to suppress colonization and inhibit gastritis in *H. pylori*-infected mice and humans<sup>[161]</sup>. Red ginseng extract has inhibitory 5-LOX enzyme activity and LOX-inhibiting action that suppresses inflammation of *H. pylori*-infected gastric epithelial cells<sup>[162]</sup>. Epigallocatechin gallate, one of the green tea catechins, showed significant cytoprotective effects against *H. pylori* associated gastric cytotoxicity<sup>[163]</sup>. Red wine and resveratrol have also been shown to inhibit the growth of *H. pylori cagA+* strains *in vitro*<sup>[164]</sup>. In an open-label RCT, adding vitamin C and E to antibiotic regimens showed excellent *H. pylori* eradication rates. Compared to the group that did not contain vitamin, the group that combined vitamin C and E to lansoprazole, amoxicillin, clarithromycin, and bismuth citrate treatment had significantly higher eradication rates of 91.3% by ITT analysis and 93.5% by PP analysis<sup>[165]</sup>. Thus, vitamin supplementation may be a future treatment option for *H. pylori*-related disease.

## MICRO- AND NANO-TECHNOLOGY: IS THE ROAD TO *H. PYLORI* ERADICATION IN THE FUTURE?

Recently, several studies have determined the antibacterial activity of micro- and nano-technology against *H. pylori*. Liposomes are spherical vesicles that contain amphiphilic lipids in a bi- or multi-layer with an aqueous core used to encapsulate several compounds<sup>[4]</sup>. This material contains biocompatible and biodegradable constituents without significant toxicity<sup>[4]</sup>. According to Obonyo *et al.*<sup>[166]</sup>, a liposomal nanoformulation of linolenic acid is a favorable nanotherapeutic with bactericidal activity against resistant strains of *H. pylori*. Another study suggested that an epitope-based therapeutic *H. pylori* vaccine may be beneficial in eradicating *H. pylori*<sup>[167]</sup> and a double liposome-based dual drug system may be helpful for treatment of *H. pylori* infection<sup>[168]</sup>.

Polymeric particles have a number of advantages for use as an antibiotic delivery factor with an anti-*H. pylori* effect. It is possible to manipulate their shape to affect biodistribution to increase interactions with the target cell. They also have mucoadhesive properties and protects drugs from proteolytic enzyme. Importantly polymeric particles possess several mechanisms to overpower microbes<sup>[4]</sup>. Encapsulation of clarithromycin and omeprazole using gliadin nanoparticles as a mucoadhesive component has been reported for the treatment of *H. pylori*<sup>[169]</sup>. Another study also showed that positively charged gelatin microspheres could be a feasible applicant delivery system for eradication of *H. pylori*<sup>[170]</sup>. The amoxicillin-loaded chitosan mucoadhesive microspheres could increase gastrointestinal residence time and enhance amoxicillin stability to contribute to *H. pylori* treatment<sup>[171]</sup>. In addition, chitosan nanoparticles improved the anti-*H. pylori* effect of chitosan<sup>[172]</sup>. Genipin-cross-linked fucose-chitosan/heparin nanoparticles diminished drug release in stomach acid and then released amoxicillin in an *H. pylori* survival situation to inhibit *H. pylori* proliferation. In addition, amoxicillin-loaded nanoparticles increased *H. pylori* eradication and decreased *H. pylori*-associated gastric inflammation in an animal model<sup>[173]</sup>. The metronidazole-loaded porous microparticles that exhibit sustained release of metronidazole could assist *H. pylori* eradication and healing from mucosal damage<sup>[174]</sup>. Silver nanoparticles may also be safer bactericidal agents for the treatment of *H. pylori*-induced gastritis<sup>[175]</sup>. Berberine-loaded targeted nanoparticles stimulated *H. pylori* clearance and suppressed stomach inflammation in *H. pylori* infection<sup>[176]</sup>.

## CONCLUSION

Many studies have determined that novel agents and treatment regimens can improve eradication of *H. pylori*. With STT, high doses of PPI and prolonged therapy duration can increase eradication rates; indeed, in Europe and some regions of Asia these results are improved further with concomitant therapy. Concomitant therapy is less affected by antibiotic resistance, which adds value as an alternative treatment. Nevertheless, the eradication rates following concomitant therapy will gradually decrease due to the rapidly emerging antibiotic resistance of *H. pylori* worldwide.

In this review, we highlighted new and promising directions in *H. pylori* eradication. Although there are some practical limitations in applying probiotics and tailored therapy, they could of assistance in fighting *H. pylori*. Newer agents, nontraditional therapy, and microtechnology are also expected to play a major role in *H. pylori* eradication. However, several issues need to be solved to apply these treatments to the clinic. First, novel agents must be devoid of known proteolytic cleavage sites and thus, resistant to human digestive enzymatic cleavage. Second, these agents must be effective in an acidic environment. Third, these novel

agents should be free from antibiotic resistance such as OAK. OAK have multiple nonspecific actions, so it would be hard to occur antibiotic resistance of *H. pylori*. Fourth, further studies are necessary to assess micro- and nano-toxicity, *in vitro* as well as *in vivo*. The safety and pharmacokinetic properties of novel treatments for *H. pylori* in humans also need to be evaluated. Finally, although novel treatments have many advantages, clinical studies are required to determine whether these findings can be applied to humans. In order to improve the eradication rate for *H. pylori* infection, further studies must be required.

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