

## High antibiotic resistance rate: A difficult issue for *Helicobacter pylori* eradication treatment

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**Author contributions:** This author was the sole contributor to this paper.

**Supported by** Research Fund of Capital Medical Development, No. 2005-1008.

**Conflict-of-interest statement:** No potential conflicts of interest; and no financial support.

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Received: August 25, 2015

Peer-review started: August 26, 2015

First decision: September 29, 2015

Revised: October 17, 2015

Accepted: December 8, 2015

Article in press: December 8, 2015

Published online: December 28, 2015

### Abstract

*Helicobacter pylori* (*H. pylori*) infection is associated with a variety of upper gastrointestinal diseases, including gastric cancer. With the wide application of antibiotics in *H. pylori* eradication treatment, drug-

resistant strains of *H. pylori* are increasing. *H. pylori* eradication treatment failure affects the outcome of a variety of diseases of the upper gastrointestinal tract. Therefore, antibiotic resistance that affects *H. pylori* eradication treatment is a challenging situation for clinicians. The ideal *H. pylori* eradication therapy should be safe, effective, simple, and economical. The eradication rate of triple antibiotic therapy is currently less than 80% in most parts of the world. Antibiotic resistance is the main reason for treatment failure, therefore the standard triple regimen is no longer suitable as a first-line treatment in most regions. *H. pylori* eradication treatment may fail for a number of reasons, including *H. pylori* strain factors, host factors, environmental factors, and inappropriate treatment.

**Key words:** *Helicobacter pylori*; Resistance; Eradication treatment; Triple antibiotic therapy; Gastrointestinal disease

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**Core tip:** *Helicobacter pylori* (*H. pylori*) infection is associated with a variety of upper gastrointestinal diseases, including gastric cancer. *H. pylori* eradication treatment failure affects the outcome of these diseases. The eradication rate of triple antibiotic therapy, the worldwide gold standard, is currently less than 80% in most parts of the world. Antibiotic resistance is the main reason for treatment failure, therefore the standard triple regimen is no longer suitable as a first-line treatment for the majority of the world. *H. pylori* eradication treatment may fail for a number of reasons, including *H. pylori* strain factors, host factors, environmental factors, and inappropriate treatment.

Zhang M. High antibiotic resistance rate: A difficult issue for *Helicobacter pylori* eradication treatment. *World J Gastroenterol* 2015; 21(48): 13432-13437 Available from: URL: <http://www.wjgnet.com>

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection is associated with a variety of upper gastrointestinal diseases, including gastric cancer<sup>[1]</sup>. With the wide application of antibiotics in *H. pylori* eradication treatment, drug-resistant strains of *H. pylori* are increasing. This has attracted the widespread concern of scholars and clinicians throughout the world. *H. pylori* eradication treatment failure affects the outcome of a variety of diseases of the upper gastrointestinal tract. Therefore, antibiotic resistance that affects *H. pylori* eradication treatment is a challenging situation for clinicians. The ideal *H. pylori* eradication therapy should be safe, effective (eradication rate > 90%), simple, and economical. The eradication rate of triple antibiotic therapy, the current worldwide gold standard, is currently less than 80% in most parts of the world<sup>[2]</sup>. Antibiotic resistance is the main reason for treatment failure, therefore the standard triple regimen is no longer suitable as a first-line treatment in most regions<sup>[3]</sup>. *H. pylori* eradication treatment may fail for a number of reasons, including *H. pylori* strain factors, host factors, environmental factors, and inappropriate treatment.

## H. PYLORI STRAIN FACTORS

### Antibiotic resistance and mechanism

Extensive and unreasonable application of antibiotics is the main cause of antibiotic resistance. A European study shows that the resistance rate is related to the dosage of antibiotics used in outpatient wards<sup>[4]</sup>. Several types of antibiotics were used for *H. pylori* eradication therapy, including macrolides, nitromidazole, lactams, aminoglycosides, quinolones, nitrofurans, and tetracycline. An epidemiological investigation showed that the overall prevalence of *H. pylori* in China still remains high; the adult infection rate being 40%-60%<sup>[5]</sup>. For the sixty per cent of antibiotics recommended for eradication treatment, the resistance rates for *H. pylori* are as follows: metronidazole, 60%-70%; clarithromycin, 20%-38%; levofloxacin, 30%-38%; where amoxicillin, furazolidone, and tetracycline resistance rates are still very low (1%-5%). The drug resistance rate significantly influences the eradication rate.

Clarithromycin is a commonly used drug in *H. pylori* eradication treatment. The resistance rate of *H. pylori* to clarithromycin has increased gradually in recent years and the resistance rate is inversely related to the eradication rate. A study of 910 cases in China showed that the clarithromycin-resistance rate was 27.6% in 2005<sup>[6]</sup>. Several studies

showed that the clarithromycin-resistance rates in American and European populations were 29.3% and 11.1%, respectively, in 2009<sup>[7]</sup>. The resistance rate in Turkey was 47.5%<sup>[8]</sup>, and in South America, 17.72%<sup>[9]</sup>. Clarithromycin is a macrolide antibiotic; its pharmacological or antibacterial effect prevents transpeptidation and translocation reactions by binding to domain V of the *H. pylori* 23S ribosomal RNA (23S rRNA), thus inhibiting bacterial protein synthesis. Point mutations in the V functional domain of the 23S rRNA reduce the affinity of clarithromycin for the transpeptidase, inhibiting clarithromycin binding to the 23S ribosomal subunit, resulting in clarithromycin resistance<sup>[10]</sup>. Mutations in the 23S rRNA gene, including A2143G, A2142G, and A2142C, are closely associated with clarithromycin resistance; the most commonly observed of which is A2143G. Mutations in this gene account for 80%-90% of clarithromycin resistance<sup>[11]</sup>.

Metronidazole was the earliest drug used for eradication treatment of *H. pylori*. In the Chinese population, the average *H. pylori* metronidazole-resistance rate is 75.6% and the rate has reached up to 95.4% in some areas<sup>[12]</sup>. In contrast, Japan has a very low metronidazole-resistance rate of around 3.3%-12.9%<sup>[13]</sup>, which may be associated with the restriction of the use of metronidazole. The *H. pylori* metronidazole-resistance mechanism has the following aspects. First, a number of different *H. pylori* rdxA gene mutations are observed<sup>[14]</sup>. Detection of rdxA and frxA mutations can not accurately predict drug resistance to metronidazole<sup>[15]</sup>. Second, the resistance to metronidazole may involve other factors in addition to the nitro-reductase. Finally, most of the research is limited to the detection of mutations at the DNA level, but more studies on the level of transcription and translation are necessary<sup>[16]</sup>. In general, the mechanism of *H. pylori* resistance to metronidazole is relatively complex and needs further research.

With the decreasing eradication rate of classical triple therapy, levofloxacin is becoming widely used in eradication therapy. Although it is a second-line treatment, a high rate of drug resistance has arisen against it. A study in China showed that the levofloxacin-resistance rate was 20.6%<sup>[12]</sup>, and a study in Peru showed the resistance rate at 36.9%<sup>[17]</sup>. Fluoroquinolones act on the DNA gyrase to exert a bactericidal effect. The gyrase enzyme is necessary to maintain the helical structure of DNA. It is a tetrameric enzyme composed of two A subunits encoded by the *gyrA* gene and two B subunits encoded by the *gyrB* gene. Point mutations in the quinolone resistance determining regions can prevent antibiotic binding to gyrase, causing antibiotic resistance<sup>[18]</sup>.

At present, amoxicillin resistance rates are relatively low in China, about 1%-5%<sup>[5]</sup>, and even lower in more developed countries. However, penicillin-allergic patients cannot use amoxicillin. Amoxicillin

resistance can arise by different mechanisms. Among them, mutations in the bacterial penicillin binding protein gene (*PBP1A*) is a common mechanism, which can cause a low or moderate level of drug resistance<sup>[19]</sup>. In recent years, amoxicillin resistance caused by extended spectrum beta-lactamases has also been reported, which can cause high levels of drug resistance<sup>[20]</sup>. Tetracycline and furazolidone resistant rates are still very low<sup>[5,21]</sup>.

Currently, not only has multi-drug resistance become an increasingly severe problem for clinicians, but different regions and groups have different degrees and patterns of resistance. Research shows the *H. pylori* multi-drug resistance rates as high as 34.5%<sup>[22]</sup>, which is a very serious problem. The multi-drug resistance rate of *H. pylori* to levofloxacin and metronidazole was 16.9%, to clarithromycin and metronidazole was 7%, and the resistance rate to all three of the drugs together was nearly 10%. For eradication therapy of *H. pylori*, patients with penicillin allergy have to choose furazolidone or gentamicin, which are drugs with severe adverse reactions, or are left with no treatment alternatives. With the drug-resistance rate peaking, it is difficult to achieve a high eradication rate with the traditional triple therapy. Quadruple therapy can be used as an alternative treatment; however, the effect is limited against multi-drug-resistant strains. An individualized treatment plan is the most effective way to evade the problem of multi-drug-resistant bacteria. In regions with high rates of resistance to clarithromycin, the eradication rate based on culture-guided triple therapy for clarithromycin-sensitive cultures was significantly higher than that for empirical treatment<sup>[23]</sup>. Research shows that sequential therapy and the modified bismuth-containing quadruple therapy has a very high efficacy rate in the Hong Kong area<sup>[24]</sup>. The mechanism of multi-drug resistance in *H. pylori* is closely related to the efflux pump system. Studies on macrolide resistance found that *H. pylori* contains four genes encoding the resistance nodulation cell division (RND) superfamily efflux pump system. Injection of specific efflux pump inhibitors, such as Phe-arg- $\beta$ -naphthylamide (PA $\beta$ N), can inhibit the RND efflux pump system, to reduce the antibiotic minimum inhibitory concentration<sup>[25]</sup>. Proton pump inhibitors (PPIs) and efflux pump inhibitor have a similar structure. In addition to inhibiting gastric acid secretion, PPIs can also inhibit the *H. pylori* RND efflux pump system, which can improve the sensitivity of *H. pylori* to antibiotics<sup>[26]</sup>. A recent comparative analysis of sarcosine-insoluble outer membrane proteins (OMPs) between clarithromycin-resistant and-sensitive strains found that the iron regulation membrane protein, ureaseB, EF-Tu protein complex, and OMPs decreased in resistant strains. At the same time, transmembrane proteins HopT (BabB), HofC, and OMP31 increased in resistant strains. These results were confirmed using

western blot and real-time quantitative polymerase chain reaction analyses. This suggests that changes in the composition of the OMPs may be an additional mechanism of *H. pylori* resistance to clarithromycin<sup>[27]</sup>.

### Genotype and virulence factors

The *H. pylori* genotype is closely related to the efficacy of antibiotic treatment. Data showed that antibiotic sensitivity of the S1/M1 and S1/M2 strains [mostly cytotoxin-associated protein (CagA)+] is higher than that of S2/M2 strains (mostly CagA-)<sup>[28]</sup>. The major *H. pylori* virulence factors, vacuolating cytotoxin A (VacA) and CagA, not only play an important role in the pathogenesis of *H. pylori*, but also have an important effect on the eradication treatment of *H. pylori*. Some studies suggest that the eradication rate of CagA-positive strains is higher than that of CagA-negative strains, but the results have not been confirmed and this requires further study<sup>[29]</sup>.

### Site and density of colonization

*H. pylori* in cells, gastric fundus, gastric antrum, and gastric body junction are usually thought to be difficult to eradicate and colonization in those areas can contribute to treatment failure. *H. pylori* in the gastric antrum and body junction may escape the effects of antibiotics. Owing to the unique structure of the junction, a unique colonizing environment is created; the *H. pylori* colonization in these sites has a different biological behavior, so that they are not sensitive to antibiotics. In addition, protracted use of antacids can make *H. pylori* colonization in the gastric antrum migrate to the gastric body, making eradication treatment even more difficult. More than 10 years after discovery of *H. pylori*, Stark *et al.*<sup>[30]</sup> found that the *H. pylori* NCTC11637 (ATCC43504) strain, when grown in a glass fermenter, can produce a membrane layer structure, insoluble in water and containing polysaccharide, on the surface of a liquid. This confirms that *H. pylori* also has the ability to form bio-films. A large number of *H. pylori* can produce a "bio-film effect" as a self-protection mechanism and also a high *H. pylori* colonization density directly affects the minimum inhibitory concentration. These are both factors that can contribute to treatment failure.

### Conversion to coccoid form

*H. pylori* in unfavorable growth environments are likely to transform into a coccoid form, which is not sensitive to antibiotics. The coccoid form of *H. pylori* exists in two forms: one is dead or degenerated; the second is a non-active stage *H. pylori* which, although alive, are unable to reproduce. *H. pylori* in the coccoid form, upon termination of the use of antibiotics for 2 or more weeks, will restore their activity. This form of *H. pylori* is not only an important reason for eradication failure, but also is infectious<sup>[31]</sup>, which is an important cause of relapse.

## HOST FACTORS

**Patient compliance:** Patients' poor compliance is gradually coming to the attention of clinicians. Poor compliance may be due to a lack of emphasis on eradication therapy, cumbersome events related to drug therapy, and drug-related adverse effects. The drug side effects mostly consist of diarrhea and an appealing taste of the medication. Although the symptoms are relatively mild and do not affect normal life, they can lead to patients' withdrawal owing to the fear of more severe side effects<sup>[32]</sup>. Therefore, physicians should not only strengthen clinical work on the treatment of *H. pylori* patients, but also provide education and reasonable treatment options to the patients. They should stress the need for optimal treatment and the impact of poor compliance on the efficacy of treatment, and explain the side effects of the drugs, thereby encouraging the patients to comply with their treatment regimen and reducing the likelihood of eradication failure because of early withdrawal of medication.

### Gene polymorphisms in patients

PPIs are the most common drugs used for the treatment of digestive diseases. Through efficient and rapid inhibition of gastric acid secretion, PPIs provides a fast cure for gastrointestinal injury, and *H. pylori* eradication regimens established on this basis rely on their potent acid suppression ability. Polymorphisms in the cytochrome P450 (CYP) 2C19 gene affect the efficacy of a PPI-containing regimen, as PPI is mainly metabolized through a CYP2C19 channel. Patients of the strong metabolic type (homozygous wild type, wt/wt) with a high PPI clearance rate, had serum drug concentrations that were significantly lower than in poor metabolizers (homozygous mutants, mt/mt). Therefore, patients with the wild-type allele of CYP2C19 are less likely to be able to eradicate *H. pylori*<sup>[33]</sup>. In addition, polymorphisms in the P-glycoprotein (MDR1) gene also have an effect on the treatment efficacy with PPI regimens<sup>[34,35]</sup>. Studies have shown that for triple eradication therapy based on CYP2C19 metabolic pathway-dependent PPIs such as omeprazole or lansoprazole, the rate of eradication is higher in poor metabolizers than in strong metabolizers<sup>[36]</sup>. Selection of PPIs such as esomeprazole or rabeprazole for use in eradication therapy may help to increase the eradication rate, as the CYP2C19 genotype does not seem to affect the eradication rate when using these PPIs.

### Effect of various types of disease with eradication therapy

A French meta-analysis study of 2751 cases, with an overall eradication failure of 25.8% sought to determine whether eradication therapy failure was associated with particular types of gastrointestinal

diseases. Duodenal ulcer (DU) patients exhibited an *H. pylori* eradication failure rate of 21.9%, which was significantly lower than patients with non-ulcer dyspepsia (NUD) with a failure rate of 33.7% ( $P < 10^{-6}$ ). Drug susceptibility testing implied that the clarithromycin resistance rate of *H. pylori* strains in patients with NUD was significantly higher than DU patients, which also suggests an explanation for the lower *H. pylori* eradication rate in NUD patients<sup>[37]</sup>.

### Smoking

Suzuki *et al*<sup>[38]</sup> suggested that the success rate of *H. pylori* eradication in smokers was lower (8.4%) than that of non-smokers, and among smokers with non-ulcerative dyspepsia, the eradication failure rate was higher, as smoking can reduce gastric mucosal blood flow, can stimulate gastric acid secretion, and also affect the body's metabolism of PPIs.

## ENVIRONMENTAL FACTORS

At least 4 wk after eradication treatment is completed, a follow-up *H. pylori* detection test is performed, to determine whether a relapse or re-infection has occurred. The oro-oral and feco-oral routes are considered to be the most likely routes of *H. pylori* transmission. Studies have found that in patients who have undergone periodontal therapy and an oral cleansing process, the *H. pylori* eradication rate was significantly higher than that of patients who did not, suggesting that *H. pylori* may be spread through saliva<sup>[39]</sup>. In addition to oral *H. pylori* infection, in rural areas and places with poor sanitary conditions, the population has a higher rate of *H. pylori* infection<sup>[40]</sup>.

## OTHER

There is a reduction in the eradication rate if PPIs are used prior to radical *H. pylori* eradication therapy. This may be because protracted use of PPI results in *H. pylori* metastases from the gastric antrum to the body, transforming into the coccoid form. Some studies have also shown that *H. pylori* treatment failure is associated with higher body mass index<sup>[21]</sup>.

## CONCLUSION

In summary, *H. pylori* eradication therapy is influenced by multiple factors. Currently, the mechanisms of resistance in *H. pylori* strains, hosts, and environmental and other factors are not completely understood; therefore, it is a continuing challenge for clinicians to improve the success rate of *H. pylori* eradication. Clinicians should have an in-depth knowledge of *H. pylori* resistance mechanisms and mechanisms of drug action, and raise patients' awareness of their own condition. Depending on the situation in different regions and of different patients, the appropriate individualized treatment

programs should be selected, thereby improving the success rate of *H. pylori* eradication treatment.

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**P- Reviewer:** Pratschke S, Tanimine N    **S- Editor:** Yu J    **L- Editor:** A  
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ISSN 1007-9327

