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Review Article

Emphasizing the importance of successful eradication of *Helicobacter pylori* on initial treatment

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Abstract: *Helicobacter pylori* (*H. pylori*) infection is the most important risk factor for gastric cancer and plays an initiating role in the development of intestinal-type gastric cancer. Eradication of *H. pylori* significantly reduces the incidence and mortality of gastric cancer. International expert consensus recommends eradication treatment for all infected individuals unless competing considerations. However, large-scale *H. pylori* eradication treatments have led to increasing rates of resistance to multiple antibiotics, together with factors such as coccoid transformation, host CYP2C19 gene polymorphisms, and inappropriate treatment regimens, resulting in a gradual decline in *H. pylori* eradication rates. Currently, empirical and repeated eradication of *H. pylori* treatment is common in clinical practice, which will certainly lead to a further increase in antibiotic resistance, resulting in a great waste of medical resources and an increased psychological burden on patients and their relatives. Therefore, successful eradication of *H. pylori* on initial treatment should be given high priority, and the implementation of personalized treatment is essential.

Keywords: *Helicobacter pylori*, personalized treatment, eradication on initial treatment

Introduction

Helicobacter pylori (*H. pylori*) infection is the most important risk factor for gastric cancer with a prevalence of up to 50% in the world population [1]. The pathogenesis of most intestinal-type gastric cancers follows the Correa pattern of "normal gastric mucosa - non-atrophic gastritis - atrophic gastritis - intestinal metaplasia - dysplasia - gastric cancer", and *H. pylori* plays an initiating role in this process [2]. The International Agency for Research on Cancer (IARC) and the U.S. Department of Health and Human Services both list *H. pylori* as a definite carcinogen [3, 4]. Several large cohort studies have shown that the eradication of *H. pylori* significantly reduces the incidence and mortality of gastric cancer [5, 6]. In addition to its role in gastric cancer prevention, *H. pylori* eradication can cure *H. pylori*-associated peptic ulcers as well as reduce their recurrence. The risk of NSAID-associated gastric complications and the chance for transmission are also decreased. These all minimized the cost for prevention, diagnosis, management, and outcome of *H. pylori*-associated disease [7]. Therefore, the Kyoto Global Consensus Report on *H. pylori* gastritis recommends eradication treatment when *H. pylori* infection is confirmed by testing, regardless of whether the infected patient has symptoms or complications unless competing considerations [7]. However, large-scale *H. pylori* eradication treatments have led to increasing resistance rates to multiple antibiotics, together with factors such as coccoid transformation, host CYP2C19 gene polymorphisms, and inappropriate treatment regimens, resulting in a gradual decline in *H. pylori* eradication rates. If this trend is not reversed, it will certainly further aggravate the burden of gastric cancer. Therefore, the idea of successful eradication of *H. pylori* on initial treatment and the adoption of personalized treatment guided by antibiotic phenotypic or

genotypic resistance testing should be highly valued.

"Three highs and one low" with declining eradication rate

Despite several international or national expert consensuses on the importance of *H. pylori* eradication, in recent years, *H. pylori* have shown a "three highs and one low" situation in many regions, with high infection rates, high pathogenicity, high antibiotic resistance, and low eradication rates. Large-scale and inappropriate eradication treatments are occurring in many countries and regions, while *H. pylori* resistance (antibiotic-resistant mutations) is increasing, with rates of metronidazole resistance of around 80% and levofloxacin and clarithromycin resistance of >60% in some regions [8, 9]. The resistance rate of antibiotics used to be low in resistance rates, such as amoxicillin and tetracycline, is gradually increased with more frequent use. The rate of dual and multiple antibiotic resistance is also rising, which requires great attention [10-12]. Together with the effects of *H. pylori* coccoid transformation and host CYP2C19 gene polymorphisms, the eradication rate of *H. pylori* has been declining (from nearly 90% to around 70%) [13-15]. "Antibiotic resistance" is currently the biggest problem in *H. pylori* infection treatment. Repeated eradication failures not only result in a huge waste of medical resources, but will also further burden antibiotic resistance. The speed of discovery and development of antibacterial drugs is far from keeping up with the growth of antibiotic resistance. In the long run, if action is not taken now to give high priority to the importance of successful eradication of *H. pylori* on initial treatment, we may face a situation where there are no effective antibiotics to treat *H. pylori* infection in the future. For patients, the adverse drug reactions (gastrointestinal reactions, liver damage, dysbiosis, etc.) derived from triple or quadruple eradication therapy cannot be ignored [16-18].

Repeated treatment failures will undoubtedly cause physical and psychological harm to patients and their families. In clinical practice, we often encounter patients with *H. pylori* infection seeking medical treatment due to "fear of gastric cancer". The interaction of repeated treatment failure, adverse drug reactions, and high mental stress enabled patients to have difficulty in living and working normally. Therefore, the importance of successful eradication of *H. pylori* on initial treatment should be highly valued both in the long term and at present.

The key elements for improving the successful initial eradication rate of H. pylori

The main determinant of initial eradication success is pretreatment antibiotic resistance [19]. First, overall standardized management of antibiotics use is critical and patients should be educated for adverse consequences of antibiotic abuse. Second, gastroenterologists must know the patient's antibiotic medication history and local antibiotic resistance (reliable knowledge of antibiotic resistance is still lacking in many regions) before prescribing the initial eradication treatment for *H. pylori*, to avoid administering potentially resistant antibiotics. The ideal solution to improve the initial eradication rate of *H. pylori* is to personalize the treatment based on antibiotic resistance (phenotypic and genotypic resistance) and coccoid transformation before treatment [20, 21]. Meanwhile, a proton pump inhibitor can inhibit gastric acid secretion and increase gastric pH, thus enhancing the effect of antibiotics and playing an important role in eradication treatment. Therefore, choosing the appropriate PPI according to the patient's CYP2C19 genotype can further improve the eradication rate [13].

Currently, an increasing number of gastroenterologists are advocating tailored treatment of *H. pylori* based on antibiotic resistance, coccoid transformation (for patients who have failed eradication), and individual PPI metabolic genotype obtained before treatment. Therefore, large-scale, multicentre epidemiological studies on *H. pylori* infection, antibiotic-resistant phenotypes and genotypes are necessary to meet the needs of personalized clinical care.

In the past, personalized treatment of *H. pylori* required solving the challenge of isolating and culturing the strain. The three-gas incubator provides a good microaerobic environment, which greatly improves the success rate of *H. pylori* culture. Antibiotic susceptibility testing can be performed by Kirby-Bauer or E-test method, which evaluates antibiotic susceptibility by the diameter of the inhibition ring.

Today, *H. pylori* antibiotic resistance gene mutation testing achieves higher sensitivity than culture-based antibiotic susceptibility testing, solving the challenge of culture failure for antibiotic susceptibility testing and providing insight into resistance at the molecular biological level. Molecular *H. pylori* antibiotic susceptibility testing is endorsed by the latest expert consensus and clinical practice guidelines, particularly for clarithromycin resistance, where the resistance genotype is highly concordant with the resistance phenotype and has a higher sensitivity and specificity [22-25]. A comparison of culture-based antibiotic susceptibility testing and antibiotic resistance gene mutation testing is described in **Table 1**. Nowadays, the commercial *H. pylori* 23S rRNA mutation test kit has been approved in some countries for rapid and sensitive detection of *H. pylori* infection and clarithromycin genotype resistance, providing rapid and accurate guidance for *H. pylori* infection treatment, and effectively increasing the initial eradication rate of *H. pylori*. This may change clinical practice in the management of *H. pylori* infection and individual treatment choices, as well as facilitate the surveillance of trends in resistance [19]. In China, the China Centre for *Helicobacter pylori* Molecular Medicine (CCHpMM), advocated by the late gastroenterologist Professor Xiao Shudong, not only conducts *H. pylori* culture and antibiotic susceptibility testing, but also antibiotic resistance gene research and testing. Based on the research foundation of CCHpMM, a kit for the detection of *H. pylori* 23S rRNA gene mutations (RT-PCR technology) was approved in China, bringing personalized eradication therapy derived from rapid resistance gene testing available.

The host CYP2C19 gene polymorphism test can understand the metabolic genotype (extensive, intermediate, and poor metabolizer) of PPI in the population. Studies reported that the extensive metabolizer accounts for 26.4% of the population in China [26] while more than 40% of the patients were extensive metabolizers in CCHpMM database. Therefore, the type and dose of PPI should be selected appropriately to improve the eradication rate of *H. pylori*.

Coccoid transformation is the self-protective mechanism of *H. pylori* strain under the effect of sublethal doses of antibiotics leading to a significant decrease in the susceptibility of the strain to antibiotics and the consequence of treatment failure. When coccoid transformation occurs, it is difficult to achieve successful treatment with continued antibiotics administration, so it is recommended to stop the medication for 3 to 6 months before eradication. The coccoid transformation detection is performed by immunohistochemical staining to observe the morphology and number of *H. pylori* in the gastric mucosa and has significant advantages in the diagnosis of *H. pylori* coccoid transformation.

If applicable, the best procedure for initial treatment patients should be the testing for clarithromycin resistance genes (23S rRNA gene mutations), which identifies *H. pylori* infection and clarithromycin resistance at the same time. If clarithromycin-sensitive, clarithromycin-containing triple or quadruple therapy can achieve satisfactory efficacy. If clarithromycin-resistant, furazolidone-containing bismuth quadruple therapy regimen may be applied following the Chinese experience [27, 28]. If initial treatment is failed, an advanced personalized treatment process, including culture-based antibiotic susceptibility testing, resistance gene testing, CYP2C19 gene polymorphism testing, and coccoid transformation testing, and the treatment referring to the personalized treatment decision-making process in Taipei global consensus should be applied [29]. The application process of *H. pylori* personalized treatment is shown in **Figure 1**.

Studies showed that empirical treatment from experienced clinicians also achieved a high eradication rate, which indicated the necessity of strengthening the 'consensus' education and quality training of physicians and promoted the organic integration of standardized empirical treatment and personalized treatment to effectively elevate the eradication rate of *H. pylori* [28, 30]. CCHpMM has now developed a map of antibiotic-resistant phenotypes and genotypes of *H. pylori* in China, providing an important reference for the rational selection of *H. pylori* eradication treatment regimens in China [12].

Emphasis on the importance of successful eradication of *H. pylori* on initial treatment

Increasing rates of *H. pylori* antibiotic resistance (antibiotic-resistant gene mutations) due to large-scale eradication therapy, as well as

Table 1. Comparison of culture-based antibiotic susceptibility testing and antibiotic resistance gene mutation testing

	Culture-based antibiotic susceptibility testing	Antibiotic resistance gene mutation testing	
		DNA sequencing	Polymerase chain reaction (PCR)
Specimens	Gastric mucosal biopsy specimens	Gastric mucosal biopsy specimen/paraffin-embedded specimen/fecal specimens	Gastric mucosal biopsy specimen/paraffin-embedded specimen/fecal specimens
Testing time	About 14 days	About 3 days	2-3 hours
Transfer conditions	Strict transfer requirements, requiring special preservation solution, low temperature	Simple transfer requirements, low temperature	Simple transfer requirements, low temperature
Testing operation and instrument requirements	Complex operation, requiring specialized operators and three-gas incubation conditions	Simple operation, requires sequencing instrument, not available in most hospitals	Relatively simple operation, only requires PCR instrument, available in most hospitals
Sensitivity and specificity	Low sensitivity, high specificity	High sensitivity, high specificity	High sensitivity, high specificity
Applications	Mostly applied for antibiotic susceptibility testing in patients with refractory infections and scientific research, not suitable for large-scale application	Rapid diagnosis of H. pylori infection and understanding of antibiotic susceptibility, detection of heterogeneous antibiotic resistance, and identification of reinfection and recurrence	

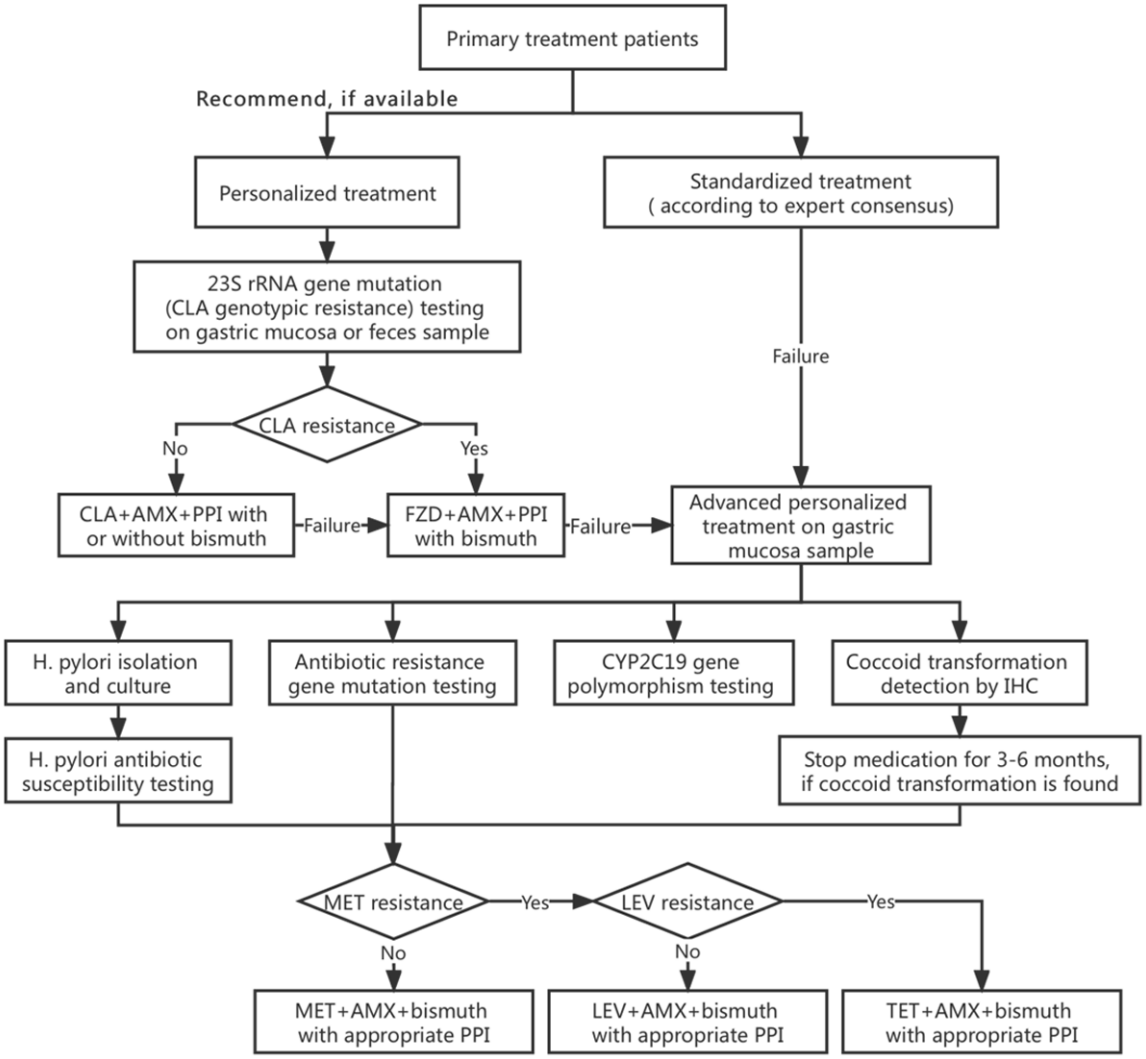

Figure 1. Application process for personalized treatment of *H. pylori*. CLA: clarithromycin, AMX: amoxicillin, FZD: furazolidone, MET: metronidazole, LEV: levofloxacin, TET: tetracycline, PPI: proton pump inhibitor, IHC: immunohistochemical stain.

coccoid transformation, host CYP2C19 gene polymorphisms, and inappropriate treatment regimens, have contributed to a significant decline in *H. pylori* eradication rates. Despite the increasing variety of combinations of eradication regimens and longer treatment courses or higher doses recommended by consensus, the overall trend in initial eradication rates has not been effectively controlled. The negative impact of repeated treatment failures on antibiotic resistance is far-reaching, and it is important to improve the initial treatment eradication rate. Therefore, personalized treatment of *H. pylori* is imperative, especially guided by antibiotic susceptibility testing in the first treatment. The awareness for successful eradication on initial treatment and personalized treatment strategies should be integrated into pre, during, and post-treatment of *H. pylori* infection. In addition, natural medicines (e.g. Traditional Chinese Medicine) are a treasure trove of new antibacterial drugs whose effects deserve further standardized research.

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Disclosure of conflict of interest

None.

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