

Research Progress of Radical Treatment of Helicobacter Pylori Based on Drug Sensitivity Test as First-Line Treatment

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Abstract

Helicobacter pylori (HP) infection is a global problem that affects about half of the world's population and requires sufficient attention in clinical and scientific work. Due to differences in economic and medical conditions among countries around the world, there is currently no unified treatment plan for anti-HP. In China, empirical quadruple therapy is mainly used. With the abuse of antibiotics, many patients face the problem of secondary eradication after failure, and the resistance rate of HP is gradually increasing. After eradication failure, drug sensitivity cultivation is carried out to choose sensitive antibiotics for treatment. A new strategy is currently needed to address how to improve the eradication rate of HP during the first eradication. This article aims to discuss the first-line treatment plans and research progress for eradicating HP based on drug sensitivity testing before eradication. Compared with traditional empirical therapies, treatment based on drug sensitivity results can effectively improve the eradication rate of HP, and reduce drug resistance rates, and adverse reactions, among other benefits.

Keywords

Drug Susceptibility Test, Helicobacter Pylori (HP) Infection, First-Line Treatment, HP Culture

1. Introduction

Helicobacter pylori HP infection affects more than half of the global population and is associated with the pathogenesis of many diseases, representing a significant burden on public health and healthcare spending. HP is a spiral-shaped,

slightly anaerobic bacteria that is very harsh to growth conditions. It was first successfully isolated from gastric mucosa biopsy tissues of patients with chronic active gastritis in 1983. HP can inhabit human gastric mucosa. This bacterium is characterized by the ability to produce large amounts of urease, which hydrolyzes urea on stomach mucus and synthesizes ammonia to raise the PH around HP [1], so that HP can survive in stomach mucus with a PH below 2. Once HP colonizes in the stomach, the mucosa is affected by bacterial virulence factors and inflammatory responses. Mucosal-induced cytokine activation of neutrophils, local production of reactive oxygen metabolites, epithelial damage and persistent presence of bacteria in the mucosa lead to chronic infection, and the management of HP infection has become a challenge [2].

2. There Is No Consensus on the Treatment of HP Infection

Studies have suggested [3] that HP therapy should aim to eliminate infection in at least 90% of treated patients, and while many clinical trials to eradicate HP infection have been conducted [4], the results have been unsatisfactory over the past decade. In addition, the treatment of HP infection is also complicated by the increase in antimicrobial resistance in different parts of the world [5], including disorders of the gut microbiome, obesity, metabolic syndrome, and autoimmune diseases. The effectiveness of the most commonly recommended regimens has declined, especially the triple regimens containing clarithromycin, proton pump inhibitors (PPI), and amoxicillin, with a corresponding increase in clarithromycin resistance [6]. As a result, many clinicians are faced with the problem of selecting the appropriate protocol to save HP eradication after first-line treatment fails [7].

The prevalence of HP infection varies globally, but increases with age and decreasing socioeconomic status [8] [9]. A large number of studies have shown [10] that it is an important pathogenic factor for digestive diseases such as chronic atrophic gastritis, gastric ulcer, gastric cancer and pancreatic disease. For most ulcer patients unrelated to the use of NSAIDs, eradication of HP infection can cure recurrent duodenal ulcer and gastric ulcer. In addition, the eradication of HP can also reduce the occurrence of atrophic gastritis and the risk of gastric malignant lesions progressing to gastric cancer, and can also lead to the regression of most localized gastric MALT lymphomas [11]. Recent studies have suggested that [12] HP infection is also closely related to other systemic diseases, such as serum vitamin B12 and iron deficiency, hepatocellular carcinoma, coronary heart disease, metabolic syndrome, Parkinson's disease, neurodegenerative disorders, etc. The eradication of HP is an important link in the prevention and treatment of these diseases.

Current European studies [13] [14] suggest the adoption of detection and treatment strategies in countries where HP prevalence is at least 20% and where patients have a high risk of gastric disease. Since HP infection is closely related to ulcer, gastric cancer and MALT lymphoma, HP detection and treatment are

recommended for all patients with digestive tract-related symptoms (**Figure 1**). An Irish study [15] pointed out that since antibiotics are more stable in a less acidic environment, PPI inhibits gastric acid secretion, so PPI can improve the eradication rate of HP. Increasing the frequency of PPI administration from once daily to twice daily has been shown [16] to have a positive effect on eradication rates. In addition, compared with the first-generation PPIs (omeprazole, Lansoprazole and Pantoprazole), the overall HP eradication rate of the new-generation PPIs is higher, and 40 mg of esomeprazole has the most obvious clinical benefit [17], and the recommended duration of HP eradication is 10 - 14 days.



Figure 1. *Helicobacter pylori* infection, Duodenal ulcer.

Most treatment methods for HP infection in China are as follows: If the urea breath test is positive, bismuth quadruple therapy for 14 days is used as the main treatment plan for the empirical treatment of HP [18] (**Figure 2**). There are many factors for treatment failure, including high bacterial load in the stomach, low pH in the stomach and impaired gastric immunity. However, treatment failure is largely associated with the emergence of drug-resistant HP and poor patient compliance [19] [20]. China's fifth National Consensus Report on the Treatment of *Helicobacter pylori* infection [21] proposed that with the increase of clarithromycin resistance rate, the following two protocols (PPI + bismuth + amoxicillin + metronidazole, PPI + bismuth + amoxicillin + tetracycline) could be used, and it was recommended to increase the dosage of metronidazole to 1600 mg/d to improve its clinical efficacy. However, higher doses of antibiotics lead to more adverse events and require better tolerability, thus complicating treatment decisions, especially for those who are older or have other systemic diseases that are accompanied by other medications, and reducing drug use is necessary [11].

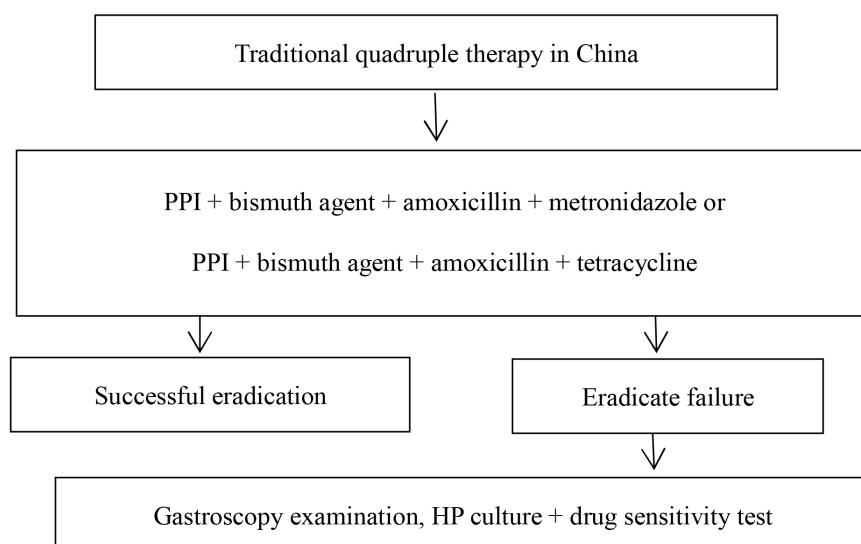


Figure 2. Traditional quadruple therapy.

In Japan [21], the eradication rate of HP is slowly declining, while the number of drug-resistant bacteria is also increasing accordingly. A study retrospectively evaluated the resistance rate and therapeutic effect of clarithromycin and metronidazole in HP infected patients, and the results showed that the resistance to clarithromycin was increasing every year, with higher resistance in women and young patients (<30 years old), and the resistance rate of metronidazole was stable. But it declines with age. Even triple therapy with Vonazan (P-CAB), metronidazole, and clarithromycin did not achieve satisfactory eradication rates, even in clarithromycin sensitive groups [22].

At present, HP drug sensitivity test is not put before treatment at home and abroad. Due to differences in geographical location or race, antibiotic selection is also different in different places [23]. After empirical treatment fails, it is not recommended to use antibiotics of the same compound again. Increase the likelihood of successful eradication [15].

3. At Present, a Common Diagnostic Method for HP Infection Is Used in Our Country

At present, the diagnosis of HP infection is mainly divided into non-invasive methods and invasive methods, and the classification depends on whether endoscopy is required. The non-invasive methods mainly include [24] fecal antigen detection method, urea breath test, serological antibody detection method, etc. Which have the advantages of simple operation, safety and convenience, rapid detection and low cost. Disadvantages: If a patient has taken a proton pump inhibitor, bismuth, or antibiotic in the two weeks prior to the test, the sensitivity of the test will be affected, and the serological antibody test has a poor positive predictive value when there is an active HP infection, making it difficult to distinguish between past and current infection. Invasive detection can be performed by the following methods [25] [26]: Histopathological staining, culture method,

rapid urease test, PCR method, etc. The advantages of such detection methods are high sensitivity and specificity, and can be used for drug sensitivity tests and bacteriological research, which can effectively reduce the occurrence of drug resistance events [27]. The main disadvantages are the high cost of traumatic examination, the need for professionally trained operators, high-quality biopsy tissue samples, and the need to take biopsies from multiple places. Sample sampling has a great impact on the results and the test cycle is long [28].

To maximize a patient's potential benefit from HP treatment, physicians must choose options that increase eradication rates by even just 1%. Globally, successful treatment options can be achieved, and mandatory eradication rates of 90% or more are also strongly recommended [29]-[31]. However the more failures to eradicate HP, the lower the chance of eventual treatment success; Therefore, after initial failure, all eradication efforts are focused on second-line protocols to avoid further antibiotic resistance. When second-line treatment fails, antibiotic sensitivity testing in all areas is recommended. In countries where upper gastrointestinal endoscopy is convenient and low-cost, post-endoscopy treatment for primary gastrointestinal diseases [32], such as dyspepsia, is generally considered to be superior to empirical drug treatment, because it is more reassuring to exclude organic diseases through endoscopy, thus improving patient satisfaction. In addition, a significant proportion of patients whose symptoms do not improve after empirical treatment will eventually undergo endoscopy.

4. HP Culture + Drug Sensitivity Test

Although the current international consensus report recommends [33] tailored treatment for patients with refractory *Helicobacter pylori* infection, the number of studies is small and, ideally, treatment should be adjusted by sensitivity testing whenever possible. In fact, a Polish trial [34] showed that first-line culture-guided triple therapy had a success rate of 95.5% and 96.6%, respectively, based on protocol and intention-to-treat analyses. A foreign study also showed [35] that continuous monitoring of antimicrobial resistance is indeed feasible and necessary for clinicians to understand the management of HP infection, and the evidence from a large number of studies provides a basis for personalized treatment based on antibiotic susceptibility testing to improve the eradication rate of primary and subsequent anti-HP.

HP culture + drug sensitivity test (**Figure 3**): It refers to taking stomach tissue through gastroscope for HP culture, and evaluating the resistance of antibiotic drugs through drug sensitivity test for positive samples of HP culture, so as to provide a basis for clinical drug use. Positive culture is regarded as the gold standard of HP infection and evidence of active infection. The specificity of test results is high, and drug susceptibility tests and bacteriological studies can be conducted to effectively reduce the occurrence of drug resistance events [25]. In particular, strain sensitivity testing should be performed in patients with treatment failure, because culture-directed therapy can provide better eradication rates and reduce side effects compared to empirical therapy.

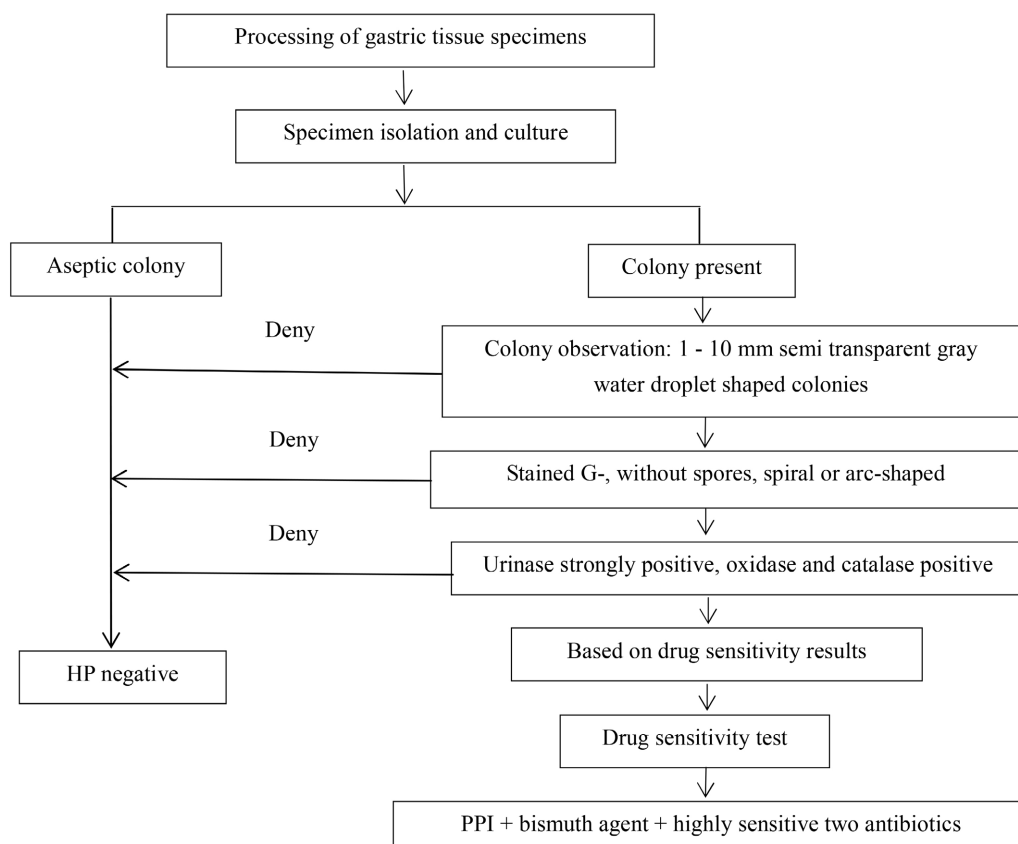


Figure 3. HP cultivation process diagram.

5. Discuss

Cultivation-based eradication therapy has been used as a method of treatment failure related to drug resistance, and of course, histopathological examination is the gold standard for diagnosing HP related gastritis. The reliability of detecting HP related gastritis depends on the location, quantity, and size of the specimens taken. The cultivation conditions for HP are relatively strict, and it is necessary to consider whether the HP infection site was not taken during sampling or whether the sample was contaminated during transportation; If the sampling is incorrect, it can lead to pathological omissions. Identifying the site of HP related gastritis in the stomach during gastroscopy reduces the testing error and excessive workload of pathologists, and requires more detailed examination of the entire stomach, improving the detection rate of early cancer. High resolution magnifying endoscopy clearly has advantages [36], however, magnifying endoscopy is not only expensive and takes a long time to examine, but also requires special preparation from the examinee and a doctor who is proficient in this examination. In daily work, examining the physician's understanding of the morphology of HP infection in the stomach may improve the success rate of HP cultivation. In addition, has the patient previously eradicated HP; Long term oral administration of probiotics leads to changes in the gastric microbiota, resulting in negative culture [37]. This type of problem requires us to continuously explore

and improve in our future work. Regarding whether probiotics can improve the eradication rate of HP, the conclusions reported so far are inconsistent due to the different types, dosages, timing, and combined use of probiotics in various studies [37].

6. Summary and Prospect

Studies [38] have shown that there is a risk of recurrence after HP infection per year, and the rate of re-infection seems to have a significant impact on cost-effectiveness. In a study in Taiwan Region [39], the rate of reinfection increased from 1% to 2.5%, and the annual cost of testing and treatment per person increased by 76%. In cost-benefit analyses, the efficacy of HP eradication was estimated to be between 80% and 92%. In conclusion, in the asymptomatic general population, a single HP screening and eradication treatment appears to be cost-effective for people who test positive for HP, and retreatment for patients who have failed treatment does not appear to be a satisfactory treatment based on limited evidence.

Therefore, it is necessary to further study whether the drug sensitivity test should be used to cure HP as the first-line treatment, and HP culture + drug sensitivity test should be conducted before the first treatment, and sensitive antibiotics should be selected to eradicate HP according to the drug sensitivity results. In the era of increasing antibiotic resistance, compared with traditional empirical therapy, individualized treatment based on drug sensitivity results may effectively improve the eradication rate of HP [40], reduce the time and cost of repeated treatment, reduce antibiotic resistance rate and adverse reactions, avoid secondary multiple drug resistance caused by eradication failure, and obtain greater economic benefit ratio.

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Conflicts of Interest

There are no statements of interest or controversy in the article.

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