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REVIEW ARTICLE

Eradication of *Helicobacter pylori* infection

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Abstract Eradication of *Helicobacter pylori* infection has become an important issue recently, because this bacterial species cluster can cause many gastrointestinal diseases. Elevated antibiotic resistance is related to an increasing failure rate of *H. pylori* eradication. Standard triple therapy is still the first-line therapy; however, according to the Maastricht IV Consensus Report, it should be abandoned in areas of high clarithromycin resistance. Alternative first-line therapies include bismuth-containing quadruple therapy, sequential, concomitant, and hybrid therapies. Quinolone-based triple therapy may be considered as first-line therapy in areas of clarithromycin resistance >15–20% and quinolone resistance <10%. Unique second-line therapy is still unclear, and bismuth-containing quadruple therapy or levofloxacin-based triple therapy can be used as rescue treatment. Third-line therapy should be under culture guidance to select the most effective regimens (such as levofloxacin-based, rifabutin-based, or furazolidone-based therapies). Antibiotics resistance, patient compliance, and CYP 2C19 genotypes could influence the outcome. Clinicians should use antibiotics according to local reports.

Introduction

Helicobacter pylori, a Gram-negative bacterium found in the stomach, has been shown to be the pathogen connected to many gastrointestinal diseases, such as peptic ulcer disease and gastric mucosa-associated lymphoid tissue lymphoma [1]. Thus, successful eradication of *H. pylori*

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is an important part of the treatment. According to the recommendations from the Maastricht IV Consensus Report, the first-line regimen for *H. pylori* eradication includes proton pump inhibitor (PPI), clarithromycin (CAM), and amoxicillin (AMX) or metronidazole (MET) [2]. However, it also recommends that this regimen should be abandoned when the CAM-resistance rate in the region is >15—20%, because many studies published recently have demonstrated that the intention to treatment (ITT) eradication rate is falling short of 80% [3—5], which is defined as the acceptable level in the Maastricht guidelines [2]. Among the factors [antibiotic resistance, poor compliance, high gastric acidity, high bacterial load, and cytochrome P450 2C19 (CYP2C19) polymorphism] that contribute to the decline of *H. pylori* eradication rate [6], antibiotic resistance is thought to play a cardinal role [7—9]. Alternative strategies have been developed aiming to overcome treatment failure. This article reviews recent novel and acceptable regimens and the factors influencing the efficacy of eradication.

The challenge of *H. pylori* eradication

Generally speaking, the optimized therapy for microbial infection depends on the appropriate selection of antimicrobial regimens to which the infected microbes are susceptible. However, the susceptibility of *H. pylori* to the antibiotics that are commonly used is changing. Within the antibiotics in the *H. pylori* eradication regimens, CAM and MET resistance is the most important, because this cannot be overcome by increasing dosage or duration [10]. The prevalence of the resistant strains is variable in different geographic areas. For example, in the study from De Francesco et al. [11], the prevalence of CAM-resistant strains in America was 29.3%, which was higher than that in Asia (18.9%) and Europe (11.1%). Furthermore, the existence of the CAM-resistance strain was low in The Netherlands (1%) compared with other European countries. Therefore, it is suggested that the antibiotic selection for the eradication regimen should be based on local resistance reports [10].

Another issue that influences the efficacy of *H. pylori* eradication is the intragastric acidity. The low pH level of the gastric environment might affect the stabilization of acid-labile antibiotics, such as CAM [12]. The PPI in the eradication regimen is responsible for the elevation of intragastric pH level, and its effect depends on the different genotypes of CYP2C19, which results in different degrees of PPI metabolism individually. The distribution of the three genotypes, extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM), is variable in different regions. The proportion of individuals with PM genotype is higher in Asia (20%) than in Western countries (5%) [13,14]. The PM genotype is connected with higher intragastric pH level, better transportation of antibiotics from plasma to gastric juice with increasing luminal concentrations, and higher effectiveness in eradication of *H. pylori* [12]. Within all the PPIs, rabeprazole and esomeprazole appear relatively less influenced by CYP2C19 [12,14]. One study has mentioned that increasing the dosage of omeprazole (from 20 mg to 40 mg) might improve the efficacy of eradication [15]; however, this observation is still questionable [16,17].

It is still uncertain as to whether genotyping of CYP2C19 should be performed prior to starting second-line *H. pylori* therapy. According to the Second Asia—Pacific consensus, it is not necessary because of the cost and low availability [18].

First-line therapy

Standard triple therapy

Recently, it was suggested that the standard triple therapy should now be avoided owing to increasing resistance [2,10]. The reason is the increasing CAM- or MET-resistant strains of *H. pylori* [10]. A study from Japan reporting the change in the standard triple therapy eradication rate in the 12-year observation period between 1997 and 2008 disclosed that the prevalence of CAM-resistant strains increased from 8.7% to 34.5%, in opposition to the trend in the eradication rate from 90.6% to 74.8% [5]. A meta-analysis showed that the CAM- or MET-resistant strains increased globally, and was considered to be responsible for the decline in the eradication rate [9]. When the prevalence of resistant strain reaches >15—20%, the eradication rate often decreases to <85% in per-protocol (PP) analysis and 80% in ITT analysis respectively [9,19,20]. This observation raises a question whether the regimen is still suitable for the choice of first-line therapy. When comparing the eradication rates between CAM-sensitive and CAM-resistant strains, the standard triple therapy has a drastically different performance between the two groups (88% vs. 18%) [9]. This finding gives the traditional regimen promise in areas where the CAM or MET resistance is relatively low (1% in The Netherlands) [11]. Therefore, whether the triple therapy remains the standard first-line regimen depends on the local prevalence of the antibiotic-resistant strain of *H. pylori*.

Several issues have been mentioned for the improvement of the eradication rate [2]. One of them is the extended duration of the standard triple therapy. One study reporting from seven Latin American sites revealed that 14-day triple therapy still could reach an 82.2% eradication rate (ITT) [21], demonstrating that prolonged duration may be an alternative method in improving the performance of standard triple therapy regimen, especially for regions where bismuth therapy is not available.

Alternative first-line eradication regimens

Bismuth-containing therapy has been mentioned as a successful therapy since the 1990s [22]. The original 14-day regimen contained bismuth and two antibiotics (MET and tetracycline). Later, the alternative version with added PPI (bismuth-containing quadruple therapy) showed its ability to overcome MET resistance [22]. However, this regimen has not been widely used because of the administration of a large number of pills, high cost, poor compliance, severe side effects, and unavailability of bismuth. Currently, this quadruple therapy with 10-day duration is advocated as an alternative first-line regimen for *H. pylori* eradication