



Helicobacter pylori Eradication Therapy: Current Regimens



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Abstract

At the moment, 7 regimens of *Helicobacter pylori* (*H. pylori*) eradication therapy (ET) are used in clinical practice: triple therapy with clarithromycin, triple therapy with metronidazole, bismuth-containing quadrotherapy, bismuth-free quadrotherapy (concomitant therapy), sequential therapy, fluoroquinolone-containing triple therapy (triple therapy with levofloxacin) and hybrid therapy. According to the latest meta-analyses, the most effective regimens of ET are sequential therapy, concomitant therapy and hybrid therapy. The highest incidence of adverse events is observed with the use of hybrid therapy.

Keywords: *Helicobacter pylori*; Eradication therapy; Triple therapy; Bismuth-containing quadrotherapy; Sequential therapy; Concomitant therapy; Hybrid therapy

Abbreviation: ET: Eradication Therapy; PPI: Proton Pump Inhibitor

Introduction

Helicobacter pylori (*H. pylori*) is the leading etiopathogenetic factor in the development of a number of gastroduodenal diseases, including chronic gastritis, gastric and duodenal ulcer, gastric MALT-lymphoma, and gastric adenocarcinoma of both intestinal and diffuse types [1-3]. In addition, to date, there is evidence of association of *H. pylori* infection with the development of several extragastroduodenal pathologies represented by iron deficiency anemia of unspecified etiology, idiopathic thrombocytopenic purpura and vitamin B12 deficiency [3-5].

To date, a large number of eradication therapy (ET) regimens are used in the treatment of *H. pylori*-associated

diseases (Table 1). The current stage of the study of *H. pylori* infection is associated with a negative trend in the decline in the effectiveness of classical ET regimes, which correlates with the growth of antibiotic resistant strains of bacteria in the population [1,3,6]. Based on these data, modern recommendations, including the consensus of Maastricht V (2015), the Toronto Consensus (2016) and the consensus of the American College of Gastroenterologists (2017) regulate a differentiated approach to the appointment of a specific ET regimen depending on the level of regional resistance of the microorganism and local data on the effectiveness of various modes of ET [3,7,8].

Table 1: Regimens of *H. pylori* eradication therapy.

Regimen	Contents
Triple therapy with clarithromycin	PPI+amoxicillin+clarithromycin
Triple therapy with metronidazole	PPI+ amoxicillin+metronidazole
Bismuth-containing quadrotherapy	PPI+ metronidazole+tetracycline+bismuth preparation
Quadruple therapy without bismuth preparations (concomitant therapy)	PPI+ amoxicillin+clarithromycin+metronidazole
Sequential therapy	PPI+amoxicillin (first 5 days) and PPI+clarithromycin+metronidazole (next 5 days)
Fluoroquinolone - containing triple therapy (triple therapy with levofloxacin)	PPI+amoxicillin+levofloxacin
Hybrid therapy	PPI+amoxicillin (first 5-7 days) and PPI+amoxicillin+clarithromycin+metronidazole (next 5-7 days)

Eradication Therapy Regimens

Triple therapy with clarithromycin

Triple therapy with clarithromycin remains the most popular mode of ET in most regions of the world. At the same time, in recent years, the effectiveness of the above regime has significantly decreased [9,10]. According to the latest meta-analyses, the effectiveness of triple ET is about 69-77% [11-13]. Given this negative trend, consensus Maastricht V and Toronto consensus recommend the use of this protocol only in regions with low resistance to clarithromycin [3,7,8]. In addition, the use of this regimen in persons previously treated with macrolides in the treatment of other diseases is not recommended [8]. The incidence of side effects with the use of triple therapy with clarithromycin reaches 24% with 14 days of therapy [14]. The most common side effects that develop in patients are dysgeusia (impaired taste perception), nausea and diarrhea.

Triple therapy with metronidazole

The use of triple therapy with metronidazole is in demand in regions with high resistance to clarithromycin, but low resistance to metronidazole [3]. According to the latest meta-analysis, the effectiveness of this treatment protocol is 70.1% [13]. Prolongation of treatment and use of higher doses of metronidazole allows to increase the effectiveness of treatment to 80%. Adverse events with the use of triple therapy with metronidazole develop in 30% of patients [13]. In this case, severe side effects that require the termination of the course of ET, are observed only in 1.4% of patients.

Bismuth-containing quadrotherapy

Bismuth-containing quadruple therapy, along with triple therapy with clarithromycin, is the most common protocol for the eradication of *H. pylori* worldwide [15]. In general, it is believed that the effectiveness of quadrotherapy with bismuth preparations slightly exceeds 80% threshold [1]. In two independent meta-analyses, it was shown that the effectiveness of this treatment protocol as a first-line regimen is at the level of 77.6-78.3%, and this is quite comparable with the effectiveness of classical triple therapy [12,16]. One of the limiting factors to the wide use of this therapy is the inaccessibility of bismuth and tetracycline preparations in a number of countries [17].

The incidence of side effects in the context of 10-day and 14-day courses of bismuth-containing quadrotherapy is 23% [14]. The use of this mode of ET leads to the risk of developing side effects such as headache, nausea, discoloration of teeth and metallic taste in the mouth.

Quadrotherapy without bismuth preparations (concomitant therapy)

A number of researchers consider concomitant therapy as one of the most promising modes of ET in the era of growth of antibiotic resistance [17-19]. Within the framework of this ET, three antibacterial drugs are applied at once, causing a different

altering effect on *H. pylori*. The meta-analysis, which included 19 studies involving 2090 patients, demonstrated high efficacy of the treatment regime, equal to 88% [19]. An updated meta-analysis of 2015 confirms the high level of *H. pylori* eradication (86.7%) [20]. According to North American consensus, concomitant therapy on a par with bismuth-containing quadrotherapy are priority protocols for the first-line ET [7,8].

The use of concomitant therapy is usually characterized by a moderate incidence of side effects, averaging 24% [14]. Patients may experience nausea, dysgeusia, metallic taste in the mouth, dry mouth, diarrhea, headache and increased AST and ALT in the serum.

Sequential therapy

Sequential therapy remains one of the most studied modes of ET throughout the world, despite the fact that the resistance to clarithromycin has a significant effect on its effectiveness [3]. Interest in sequential therapy is due to its complex mechanism of action on the microorganism. During the first phase of the protocol, clarithromycin-resistant strains of *H. pylori* and most of the bacteria on the surface of the mucosa are eliminated, and during the second stage -others, including in the depth of the gastric pits and adhered to the epithelium [21,22]. In addition, amoxicillin during the first stage of the application of this protocol leads to a significant reduction in bacterial load and a reduction in the formation of transmembrane efflux channels in the bacterial cell for the removal of antibiotics, which significantly increases the effectiveness of subsequent use of clarithromycin and metronidazole/tinidazole [23,24]. According to the results of two meta-analyses, the effectiveness of sequential therapy is about 84% [11,25].

With the use of sequential therapy, the risk of side effects, in spite of the presence of three antibacterial drugs in its composition, is somewhat lower in comparison with the classical regimens, since each of these drugs is used no more than 5 days. The total incidence of adverse events is 22% [14]. In this case, to the most frequent side effects in the application of this regime can be attributed dysgeusia, metallic taste in the mouth, nausea and headache.

Triple therapy with levofloxacin

Triple therapy with levofloxacin is quite effective in the framework of ET both in the first line and in the second line, but the rapidly progressing pattern of resistance of the microorganism to fluoroquinolones limits the wide use of this protocol [3,8]. According to the latest meta-analysis, the effectiveness of this mode of ET as first-line therapy is 80.7% [26].

The use of triple therapy with levofloxacin is characterized by a good safety profile. With 7-day courses of therapy, adverse events develop in only 15% of patients [14]. The most common side effects when using this mode of ET include nausea, diarrhea, headache, insomnia, as well as an increase in AST and ALT in the serum.

Hybrid therapy

Hybrid ET is considered as one of the most effective regimens along with concomitant therapy. The mechanism of complex antihelicobacter action of hybrid therapy is similar to sequential therapy and is determined simultaneously by three antibacterial drugs [27]. According to several meta-analyzes, the effectiveness of hybrid therapy is 88.5-91.2% [28-30]. However, this indicator has significant regional differences and requires further validation in different populations.

Despite the high efficiency, hybrid therapy has a suboptimal safety profile. The incidence of adverse events with this mode of ET varies from 26 to 32.9%, depending on the duration of the course of treatment [14,28-30]. However, only 2.5% of cases require discontinuation of the course of ET due to the development of severe side effects [28]. Typically, patients

Table 2: Efficacy and safety of ET regimens.

Regimen	Efficacy	Incidence of Adverse Events
Triple therapy with clarithromycin	68,9%-77,1%	21-24%
Triple therapy with metronidazole	70,1%	30%
Bismuth-containing quadrotherapy	77,6-78,3%	23%
Quadruple therapy without bismuth preparations (concomitant therapy)	86,7-88%	24%
Sequential therapy	84,1-84,3%	22%
Fluoroquinolone - containing triple therapy (triple therapy with levofloxacin)	80,7%	15-27%
Hybrid therapy	88,5-91,2%	26-32,9%

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have nausea, dysgeusia, metallic taste or dry mouth, as well as diarrhea.

Conclusion

At present, 7 regimens of *H. pylori* ET are used in clinical practice: triple therapy with clarithromycin, triple therapy with metronidazole, bismuth-containing quadrotherapy, quadruple therapy without bismuth preparations (concomitant therapy), sequential therapy, fluoroquinolone - containing triple therapy (triple therapy with levofloxacin), and hybrid therapy. According to the latest meta-analyzes, the most effective regimens of ET are sequential therapy, quadruple therapy without bismuth preparations ("simultaneous therapy") and hybrid therapy. The highest incidence of adverse events is observed with the use of hybrid therapy. Summary data on the effectiveness and safety of ET regimes are given in Table 2.

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