Host Factors Influencing the Eradication Rate of Helicobacter Pylori

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Abstract: Currently, the resistance of Helicobacter pylori to antibacterial is considered as a major factor negatively affecting the effectiveness of anti-Helicobacter therapy (AHT). However, treatment success may depend on a series of host (patient) factors alongside with the antibiotic resistance. This paper summarizes and analyzes the main host factors, affecting the efficiency of modern AHT regimens: conditions caused by hypersecretion of hydrochloric acid; polymorphisms in the genes (CYP2C19, MDR1, IL-1β); low compliance; smoking; overweight/obesity and diabetes mellitus.

Key words: Helicobacter Pylori • Eradication • Treatment • Antibiotic Resistance • Polymorphism • Cyp2c19 • Mdr1 • Il-1β • Compliance • Smoking • Obesity • Diabetes Mellitus

INTRODUCTION

Today, the Helicobacter pylori infection (H. pylori) is considered to be the most important etiopathogenetic factor of the pathogenic mechanism of chronic gastritis, gastroduodenal ulcer, MALT-lymphoma and gastric adenocarcinoma [1-3]. In addition, the past few decades have offered us a number of studies demonstrating the possible direct or indirect association of H. pylori with the development of idiopathic iron deficiency anemia as well as idiopathic thrombocytopenic purpura [4, 5].

It is almost 20 years to the day since U.S. National Institutes of Health (US NIH) have adopted the first recommendations for H. pylori treatment. Since that time, anti-Helicobacter therapy (AHT), which includes a combination of antibacterial drugs along with a proton pump inhibitor (PPI), is considered to be non-alternative treatment of H. pylori-associated diseases [3]. However, the passed period of AHT practical application for the purpose of eradication of the microorganism as well as hundreds of clinical studies definitively give us evidence of the absence of guaranteed success, regardless of the regimen chosen. Studies of recent decades have shown that a large number of heterogeneous factors may affect the effectiveness of AHT. Certainly, the resistance of Helicobacter pylori to antibacterial is considered as a major factor negatively affecting the effectiveness of various AHT regimens [3, 6, 7]. However, the efficiency of microorganism eradication may also depend on series of host (patient) factors: conditions caused by hypersecretion of hydrochloric acid; polymorphisms in the genes (CYP2C19, MDR1, IL-1β); low compliance; smoking; overweight/obesity and diabetes mellitus [6, 8].

Hypersecretion of hydrochloric acid. PPIs are a necessary component of AHT regimens, which is largely depends on sharp fall or full leveling of the activity of different antibiotics at very low values of gastric juice pH [8]. At the same time, it is known that H. pylori may become non-replicating but stays viable (i.e. becomes phenotypically resistant), when its ambient pH is from 3 to 6 [9]. Increasing pH above 6 enables bacteria to pass to a replicative state, when becoming sensitive to amoxicillin and clarithromycin. In addition, the highest resistance (maximum half-life period) of amoxicillin and clarithromycin is shown while the same pH values [10]. A 5.4% advantage in AHT effectiveness in patients with normacidity at the time of beginning the eradication regimen over the patients with initial hyperacidity should be regarded as an evidence in favor of the above observations [11]. Thus, the patients suffering from

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diseases associated with hypersecretion of hydrochloric acid (Zollinger-Ellison syndrome, idiopathic hydrochloric acid hypersecretion, systemic mastocytosis), typically have more poor response to standard AHT regimens [6, 8, 12, 13].

The CYP2C19 gene polymorphism. Given the importance of PPI in AHT regimens, the principal question is phenotypic differences in the metabolism of this class of drugs. The main method of PPI metabolism is a cytochrome P450 enzyme system in the liver, with the participation of its two isoforms -CYP2C19 (mainly) and CYP3A4. Metabolic rate as well as PPI effectiveness is determined primarily by polymorphism of the gene encoding the CYP2C19 isofrom [14, 15]. Depending on the types of mutations, the CYP2C19 population can be classified into three phenotypic groups [15]:

- Extensive metabolizers (homozygote, no mutation):
  wt/wt (CYP2C19*1/*1);
- Intermediate metabolizers (heterozygote, mutation in one allele):
  wt/m1 (CYP2C19*1/*2),
  wt/m2 (CYP2C19*1/*3);
- Poor metabolizers (mutation in both alleles):
  m1/m1 (CYP2C19*2/*2),
  m1/m2 (CYP2C19*2/*3),
  m2/m2 (CYP2C19*3/*3).

Patients with the extensive metabolizer phenotype have extensive PPI metabolism, therefore, they have lesser intensity of antisecretory effect of PPI rather than the patients with intermediate and poor metabolizer phenotypes. In the context of AHT the difference in antisecretory effect may determine a lower level of eradication of H. pylori in extensive metabolizers [6, 14, 15]. Thus, a meta-analysis by S. Padol et al. (2006) has demonstrated a more higher effectiveness of AHT in the patients with poor (88.9%) and intermediate (82.7%) metabolizer phenotypes compared with the extensive metabolizer phenotype (70.9%) (Fig. 1) [16].

![Fig. 1: Influence of various CYP2C19 phenotypes on the AHT effectiveness (acc. to S. Padol, et al. [16])](image)

EM - «extensive» metabolizers, IM - «intermediate» metabolizers, PM - «poor» metabolizers

Esomeprazole is S-enantiomer of omeprazole and this property causes its slower P450 cytochrome biotransformation in contrast to the racemate (Omeprazole) within the phenomenon of stereoselectivity [6, 17].

Due to the fact that molecular genetic studies are hardly accessible to the practitioner it is possible to identify extensive metabolizers in clinical practice by focusing on the preservation of abdominal pain syndrome on the 3rd-4th day after starting PPI therapy, as well as the slow endoscopic dynamics during epithelialization of erosions and scarring of ulcers in patient. In turn, the lack of antisecretory effect of PPI therapy can be verified by the 24-hour intragastric pH-metry [6].

It should be noted that the use of a double dose of PPI for extensive metabolizers not always allows achieving therapeutic success [8, 14, 17]. Thus, the study by J.C. Yang et al. (2011) [18] has shown that an increase in the dose of omeprazole (20 mg to 40 mg) increases the effectiveness of AHT in extensive metabolizers, however, other studies didn’t give the analogous results [19, 20].

The MDR1 Gene Polymorphism: It is known that ATP-dependent polyspecific efflux transporter-P-glycoprotein (P-gp) [21, 22], can affect the absorption of many oral drugs. The latter is an important component of cell homeostasis, which carries out efflux of xenobiotics from the cytosol into the extracellular space through the plasma membrane [22]. PPIs are P-gp substrates, due to which the activity of the latter may affect the effectiveness of the antisecretory therapy and, therefore, the success of AHT [23].
Expression and functional activity of P-gp gene is determined by the MDR1 gene polymorphism (ABCB1), which encodes the said protein [22, 24]. The most studied variation of this gene is a single-nucleotide polymorphism at position 3435 of exon 26 [24, 25]. It is assumed that the MDR1 3435 C/T and C/C genotypes are characterized by high and moderate levels of expression of P-gp at the apical pole of intestinal enterocytes. The MDR1 3435 T/T genotype, in turn, is associated with low P-gp expression, which causes a higher level of drug absorption into the systemic blood circulation compared with C/T and C/C genotype [26, 27].

There are not so many studies evaluating the impact of the MDR1 gene polymorphism on the AHT effectiveness. The paper by B. Gawronska-Szklarze et al. (2005) has presented MDR1 3435 T/T genotype associated with a higher level of H. pylori eradication, than C/C genotype [28]. However, the study by T. Furuta et al. (2007) had the opposite results. Thus, MDR1 3435 T/T genotype was characterized by a lower frequency of H. pylori eradication (67%) compared with C/T (81%) and C/C (82%) genotypes [29]. Probably, the heterogeneity of the results obtained may be caused by different influence of the MDR1 gene polymorphism on the drugs pharmacokinetics in Europoids and Asians [30]. Furthermore, it is possible that the expression of P-gp may be affected by parallel nucleotide polymorphisms at other loci of MDR1 gene [29, 31].

The IL-1β Gene Polymorphism: The interest in the proinflammatory IL-1β cytokine in the context of efficiency is caused by wide variability of the biological activity of this cytokine and in particular its ability to inhibit the production of hydrochloric acid by the parietal cells of the stomach [32]. Numerous studies have shown that IL-1β is the strongest of the known inhibitors of acid production [32, 33, 34]. Thus, the IL-1β gene polymorphism can determine a various antisecretory effect of this cytokine. Currently, the biallelic polymorphism of IL-1β gene at the position -511 is the most studied one, which is represented by replacement of cytosine to thymine (C→T). It has been proved that the polymorphic variants of the IL-1β gene are high-producing IL-1β [35]. Individuals, either homozygous (T/T) or heterozygous (C/T) for the high-producing IL-1β allele, produce 4 and 2 times more this cytokine respectively than individuals homozygous for a wild-type allele (C/C) of this gene [35, 36].

Earlier studies by foreign authors state that the polymorphism of IL-1β-511 gene affects significantly the effectiveness of AHT: the eradication percentage is higher in the presence of the T-allele [37-39]. According to a survey by M. Sugimoto et al. (2009) the effectiveness of AHT in relation to IL-1β-511 C/C genotype is 77.4% (95% CI: 71.9-92.3), which is considerably lower compared with C/T and T/T genotypes (87.2%; 95% CI: 84.5-89.5, p=0.0002) (Fig. 2) [40].

Low Patient Compliance: Failure to comply with the AHT requirements by the patient often results in treatment failure [6, 8, 41]. 20 years ago, Graham D.Y. et al. demonstrated that patients with good compliance have a higher AHT effectiveness (96%) than patients with low compliance (69%) [42]. In this case, the major reason for the reduction of compliance is the development of side effects during the course of AHT [6]. The relevance of this issue is determined not only by the fact that all first-line AHT regimens include two antibacterial drugs in high doses at once, but the duration of the treatment, which can continue up to 14 days [8, 41].

The frequency of side effects is very variable when using different AHT regimens. The studies with a seven-day AHT regimen prescribed have shown 41% frequency of side effects, which provoked cessation of therapy in 3-10% of the patients [43]. However, the prolongation of AHT regimen up to 10-14 days is usually accompanied by the development of side effects in more than half of the cases [1, 44].

Smoking: Accumulated data shows that smoking has negative influence on the AHT effectiveness [46-48]. Particularly, the meta-analysis by T. Suzuki et al., (2006)
demonstrated that the AHT effectiveness is 8.4% higher (95% CI: 3.3-13.5%, p <0.01) for non-smokers. Moreover, the odds ratio of eradication therapy failure for smokers was 1.95 (95% CI: 1.55-2.45, p <0.01) [47].

The real reason of decrease in AHT effectiveness for this category of patients is undefined. It is believed that smoking may result in decreased gastric blood flow and mucus secretion, thereby reducing the delivery of antibiotics in the gastric mucosa [8, 47]. In addition there is an assumption that smoking can modulate the activity of CYP2C19, thereby changing the PPI pharmacokinetics [48]. Another possible explanation for the negative effects of smoking on the AHT effectiveness may be that smoking leads to hypersecretion of hydrochloric acid, which, in turn, degrades the activity and stability of antibiotics [49].

Overweight/Obesity: The study by M. Abdullahi et al. (2008) showed a reliable association between the low AHT effectiveness and the overweight or obesity in patients without diabetes mellitus. Thus, the AHT effectiveness for these patients was 55.0% compared with 85.4% for those with a BMI <25 kg/m2 (OR: 4.77, 95% CI: 1.64-13.87, p <0.005) [49]. Mechanisms of the influence of overweight and obesity on the AHT effectiveness are the subject of discussion and, probably, similar relationship can be explained by the change in pharmacokinetic parameters (increase in distribution volume) of drugs and primarily antibiotics [6, 50].

Diabetes Mellitus: Several studies have found a negative effect of concomitant diabetes mellitus (both type 1 and 2) on the effectiveness of AHT. Thus, the AHT effectiveness for this category of patients is generally 30% less than for the control groups [51-53]. Probably, this is due to diabetic angiopathy of the mucous membranes of the gastrointestinal tract, leading to malabsorption of antibacterial drugs [53]. In addition, patients with diabetes mellitus are more prone to bacterial infections and hence, use antibiotics more often, causing the formation of resistant strains of H. pylori [52, 53].

CONCLUSION

Thus, the AHT effectiveness depends on quite wide range of heterogeneous factors. Given that molecular genetic studies are hardly accessible to the practitioner, the priority task of the clinician to ensure optimum level of the AHT effectiveness for the individual patient is to achieve a high compliance of treatment in combination with correct prescription of AHT. Moreover, it is advisable to identify patients at risk of AHT failure: smokers, patients with overweight or concomitant diabetes mellitus and diseases associated with hypersecretion of hydrochloric acid. To achieve the highest AHT effectiveness for these categories of patients, tactics of maximum treatment optimization has been approved: prolongation of AHT protocol up to 14 days, the use of PPI double-dose and the addition of bismuth-containing drugs in drug regimen.

REFERENCES


