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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 (a 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 definitely 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 isoform [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].

Among all PPI agents, rabeprazole and esomeprazole differ in minimum dependence on phenotypically determined variants of hepatic metabolism. Rabeprazole is metabolized mainly non-enzymatically and there by less dependent on the *CYP2C19* gene polymorphism [15, 17].

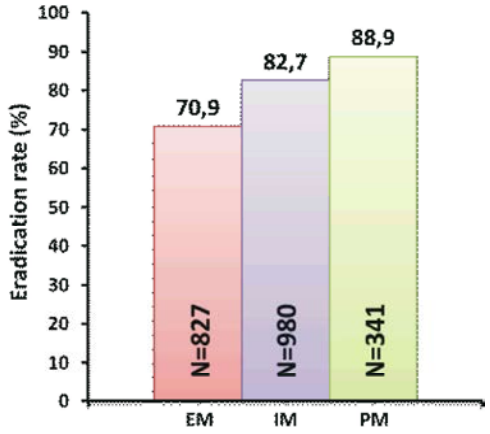

Fig. 1: Influence of various CYP2C19 phenotypes on the AHT effectiveness (acc. to S. Padol, *et al*. [16])
EM - «extensive» metabolizers, IM - «intermediate» metabolizers, PM - «poor» metabolizers

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. Furata *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-producingIL-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].

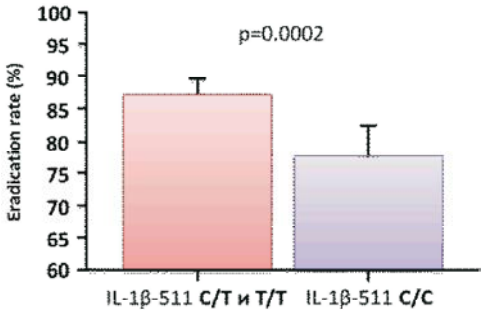

Fig. 2: Influence of the IL-1β-511 gene polymorphism on the AHT effectiveness (acc. to M. Sugimoto, *et al*. [40])

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 <of 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

1. Peura, D.A. and S.E. Crowe, 2010. Helicobacter pylori. In: Feldman M., Friedman L.S., Brandt L.J., eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th ed. Philadelphia, Pa: Saunders Elsevier, pp: 50.
2. Maev, I.V., A.A. Samsonov and D.N. Andreev, *et al*., 2012. Modern aspects of diagnosis and treatment of infection Helicobacter pylori (based on consensus Maastricht-IV, Florence 2010). Meditsinskiy Sovet, 8: 10-9 (in Russian).
3. Maev I.V., A.A. Samsonov and D.N. Andreev, *et al*., 2013. Clinical significance of Helicobacter pylori infection. Klin Med. (Mosk). 8: 4-12 (in Russian).
4. Huang X., X. Qu and W. Yan, *et al*., 2010. Iron deficiency anaemia can be improved after eradication of Helicobacter pylori. Postgrad Med J. 86(1015): 272-8.
5. Stasi, R., A. Sarpatwari and J.B. Segal, *et al*., 2009. Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review. Blood, 113(6): 1231-40.
6. Mayev, I.V., Yu.A. Kucheryavy and D.N. Andreyev 2013. The causes for inefficacy of antihelicobacter therapy. Ross. zhurn. gastroenterol., gepatol., Koloproktol, 6: 62-72 (in Russian).
7. Georgopoulos, S.D., V. Papastergiou and S. Karatapanis, 2012. Helicobacter pylori eradication therapies in the era of increasing antibiotic resistance: A paradigm shift to improved efficacy. Gastroenterol. Res. Pract., 757926.

8. De Francesco V., E. Ierardi, C. Hassan and A. Zullo, 2012. Helicobacter pylori therapy: Present and future. World J. Gastrointest Pharmacol Ther, 3(4): 68-73.
9. Scott D., D. Weeks, K. Melchers and G. Sachs, 1998. The life and death of Helicobacter pylori. Gut, 43(1): 56-60.
10. Erah P.O., A.F. Goddard and D.A. Barrett, *et al*., 1997. The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection. J. Antimicrob Chemother, 39(1): 5-12.
11. Chang, C.S., C.Y. Yang and F.N. Wong, *et al*., 1999. The effect of intragastric acidity on Helicobacter pylori eradication with bismuth-metronidazole-amoxicillin. Hepatogastroenterology, 46(28): 2713-7.
12. Hirschowitz, B.I. and M.M. Haber, 2001. Helicobacter pylori effects on gastritis, gastrin and enterochromaffin-like cells in Zollinger-Ellison syndrome and non-Zollinger-Ellison syndrome acid hypersecretors treated long-term with lansoprazole. Aliment Pharmacol Ther, 15: 87-103.
13. Osefo, N., T. Ito and R.T. Jensen, 2009. Gastric acid hypersecretory states: recent insights and advances. Curr Gastroenterol Rep., 11(6): 433-41.
14. Chaudhry, A.S., R. Kochhar and K.K. Kohli, 2008. Genetic polymorphism of CYP2C19 & therapeutic response to proton pump inhibitors. Indian J. Med Res., 127(6): 521-30.
15. Maev IV, T.S. Oganesian, K.T. Momynaliev and I.U.A. Kucheriavyi, 2008. Cytochrome-P-4502C19 gene polymorphism and Helicobacter pylori infection treatment. Eksp Klin Gastroenterol., 3: 78-85. (in Russian).
16. Padol, S., Y. Yuan and M. Thabane, *et al*., 2006. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J. Gastroenterol, 101(7): 1467-75.
17. Shi, S. and U. Klotz, 2008. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J. Clin Pharmacol, 64(10): 935–951.
18. Yang J.C., H.L. Wang and H.D. Chern, *et al*., 2011. Role of omeprazole dosage and cytochrome P450 2C19 genotype in patients receiving omeprazole-amoxicillin dual therapy for Helicobacter pylori eradication. Pharmacotherapy, 31(3): 227-38.
19. Pan X., Y. Li and Y. Qiu, *et al*., 2010. Efficacy and tolerability of first-line triple therapy with levofloxacin and amoxicillin plus esomeprazole or rabeprazole for the eradication of Helicobacter pylori infection and the effect of CYP2C19 genotype: a 1-week, randomized, open-label study in Chinese adults. Clin Ther., 32(12): 2003-11.
20. Lee J.H., H.Y. Jung and K.D. Choi, *et al*., 2010. The Influence of CYP2C19 Polymorphism on Eradication of Helicobacter pylori: A Prospective Randomized Study of Lansoprazole and Rabeprazole. Gut Liver, 4(2): 201-6.
21. Higgins, C.F., 1992. ABC transporters: from microorganisms to man. Annu Rev Cell Biol, 8: 67-113.
22. Leonard, G.D., T. Fojo and S.E. Bates, 2003. The role of ABC transporters in clinical practice. Oncologist, 8(5): 411-24.
23. Pauli-Magnus, C., S. Rekersbrink and U. Klotz, 2001. Fromm M.F. Interaction of omeprazole, lansoprazole and pantoprazole with P glycoprotein. Naunyn Schmiedebergs Arch Pharmacol, 364: 551-7.
24. Hoffmeyer S., O. Burk and O. Von Richter, *et al*., 2000. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci USA, 97: 3473-8.
25. Cascorbi, I., T. Gerloff and A. Johne, *et al*., 2001. Frequency of single nucleotide polymorphisms in the P-glycoprotein drug transporter MDR1 gene in white subjects. Clin Pharmacol. Ther., 69: 169-74.
26. Siegmund, W., K. Ludwig and T. Giessmann, *et al*., 2002. The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. Clin Pharmacol Ther., 72: 572-83.
27. Brinkmann, U., I. Roots and M. Eichelbaum, *et al*., 2001. Pharmacogenetics of the human drug-transporter gene MDR1: impact of polymorphisms on pharmacotherapy. Drug Discov Today, 6(16): 835-839.
28. Gawronska-Szklarz, B., J. Wrzesniewska and T. Starzynska, *et al*., 2005. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection. Eur. J. Clin Pharmacol, 61: 375-9.

29. Furuta T., M. Sugimoto and N. Shirai, *et al*., 2007. Effect of MDR1 C3435T polymorphism on cure rates of Helicobacter pylori infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP 2C19 genotypes and 23S rRNA genotypes of H. pylori. Aliment Pharmacol Ther, 26(5): 693-703.
30. Komoto, C., T. Nakamura and T. Sakaeda, *et al*., 2006. MDR1 haplotype frequencies in Japanese and Caucasian and in Japanese patients with colorectal cancer and esophageal cancer. Drug Metab Pharmacokinet, 21: 126-32.
31. Chowbay, B., H. Li and M. David, *et al*., 2005. Meta-analysis of the influence of MDR1 C3435T polymorphism on digoxin pharmacokinetics and MDR1 gene expression. Br J. Clin Pharmacol, 60: 159-71.
32. Wang, M., T. Furuta and M. Takashima, *et al*., 1999. Relation between interleukin-1beta messenger RNA in gastric fundic mucosa and gastric juice pH in patients infected with Helicobacter pylori. J Gastroenterol, 34(11): 10-17.
33. Wallace, J.L., M. Cucala, K. Mugridge and L. Parente 1991. Secretagogue-specific effects of interleukin-1 on gastric acid secretion. Am J. Physiol, 261: G559-G564
34. Beales, I.L. and J. Calam, 1998. Interleukin 1 beta and tumour necrosis factor alpha inhibit acid secretion in cultured rabbit parietal cells by multiple pathways. Gut., 42: 227-234.
35. Hwang, I.R., T. Kodama and S. Kikuchi, *et al*., 2002. Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in Helicobacter pylori infection. Gastroenterology, 123: 1793-803.
36. Furuta, T., N. Shirai and M. Takashima, *et al*., 2002. Effect of genotypic differences in interleukin-1 beta on gastric acid secretion in Japanese patients infected with Helicobacter pylori. Am J. Med. 112:141-3.
37. Take, S., M. Mizuno and K. Ishiki, *et al*., 2003. Interleukin-1beta genetic polymorphism influences the effect of cytochrome P 2C19 genotype on the cure rate of 1-week triple therapy for Helicobacter pylori infection. Am J.Gastroenterol, 98: 2403-8.
38. Furuta, T., N. Shirai and F. Xiao, *et al*., 2004. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol, 2: 22-30.
39. Sugimoto, M., T. Furuta and N. Shirai, *et al*., 2006. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther., 80: 41-50.
40. Sugimoto, M., T. Furuta and Y. Yamaoka, 2009. Influence of inflammatory cytokine polymorphisms on eradication rates of Helicobacter pylori. J. Gastroenterol Hepatol, 24(11): 1725-32.
41. O'Connor, J.P., I. Taneike and C. O'Morain, 2009. Improving compliance with helicobacter pylori eradication therapy: when and how? Therap Adv Gastroenterol, 2(5): 273-9.
42. Graham, D.Y., G.M. Lew and H.M. Malaty, *et al*.,, 1992. Factors influencing the eradication of Helicobacter pylori with triple therapy. Gastroenterology, 102: 493-496.
43. Hudson, N., W.G. Brydon and M.A. Eastwood, *et al*., 1995. Successful H. pylori eradication incorporating a one-week antibiotic regimen. Aliment Pharmacol Ther., 9: 47-50.
44. Peura, D.A., 2006. Treatment of Helicobacter pylori infection. In: Wolfe MM, ed. Therapy of digestive disorders, Philadelphia: Elsevier, pp: 277.
45. Camargo, M.C., M.B. Piazuelo and R.M. Mera, *et al*., 2007. Effect of smoking on failure of H. pylori therapy and gastric histology in a high gastric cancer risk area of Colombia. Acta Gastroenterol Latinoam, 37(4): 238-45.
46. Suzuki, T., K. Matsuo and H. Ito, *et al*., 2006. Smoking increases the treatment failure for Helicobacter pylori eradication. Am J. Med., 119: 217-224.
47. Suzuki, T., K. Matsuo and A. Sawaki, *et al*., 2007. Influence of smoking and CYP2C19 genotypes on H. pylori eradication success. Epidemiol Infect, 135(1): 171-6.
48. Labenz, J., M. Stolte and A.L. Blum, *et al*., 1995. Intragastric acidity as a predictor of the success of Helicobacter pylori eradication: a study in peptic ulcer patients with omeprazole and amoxicillin. Gut., 37: 39-43.
49. Abdullahi, M., B. Annibale and D. Capoccia, *et al*., 2008. The eradication of Helicobacter pylori is affected by body mass index (BMI). Obes Surg., 18(11): 1450-4.
50. Pai, M.P. and D.T. Bearden, 2007. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy, 27(8): 1081-91.

51. Gasbarrini, A, V. Ojetti and D. Pitocco, *et al*., 1999. Insulin-dependent diabetes mellitus affects eradication rate of Helicobacter pylori infection. Eur J. Gastroenterol. Hepatol., 11(7): 713-6.
52. Gasbarrini, A., V. Ojetti and D. Pitocco, *et al*., 2000. Efficacy of different Helicobacter pylori eradication regimens in patients affected by insulin-dependent diabetes mellitus. Scand J.Gastroenterol, 35(3): 260-3.
53. Sargýn, M., O. Uygur-Bayramicli and H. Sargýn, *et al*., 2003. Type 2 diabetes mellitus affects eradication rate of Helicobacter pylori. World J. Gastroenterol, 9(5): 1126-8.