**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 49445

**Manuscript Type:** MINIREVIEWS

**Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: Old and new tricks to improve effectiveness**

Ierardi E *et al*. PPI and *H. pylori* eradication

Enzo Ierardi, Giuseppe Losurdo, Rosa Federica La Fortezza, Mariabeatrice Principi, Michele Barone, Alfredo Di Leo

**Enzo Ierardi, Giuseppe Losurdo, Rosa Federica La Fortezza, Mariabeatrice Principi, Michele Barone, Alfredo Di Leo,** Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Bari 70124, Italy

**ORCID number:** Enzo Ierardi (0000-0001-7275-5080); Giuseppe Losurdo (0000-0001-7038-3287); Rosa Federica La Fortezza (0000-0003-2587-097X); Mariabeatrice Principi (0000-0003-0545-5656); Michele Barone (0000-0001-8284-5127); Alfredo Di Leo (0000-0003-2026-1200).

**Author contributions**: Ierardi E, Losurdo G and Di Leo A planned the study; La Fortezza RF, Principi M and Barone M collected the data; Ierardi E, Losurdo G and La Fortezza RF wrote the first draft; all authors read and approved the final version; Ierardi E and Losurdo G contributed equally and are co-first authors.

**Conflict-of-interest statement:** none declared.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Corresponding author:** **Enzo Ierardi, MD, Academic Fellow, Associate Professor, Doctor,** Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio Cesare 11, Bari 70124, Italy. e.ierardi@virgilio.it

**Telephone:** +39-80-5593452

**Fax:** +39-80-5593088

**Received:** May 28, 2019

**Peer-review started:** May 28, 2019

**First decision:** July 21, 2019

**Revised:** July 26, 2019

**Accepted:** August 7, 2019

**Article in press:** August 7, 2019

**Published online:** September 14, 2019

**Abstract**

The survival and replication cycle of *Helicobacter pylori* (*H. pylori*) is strictly dependant on intragastric pH, since *H. pylori* enters replicative phase at an almost neutral pH (6-7), while at acid pH (3-6) it turns into its coccoid form, which is resistant to antibiotics. On these bases, it is crucial to increase intragastric pH by proton pump inhibitors (PPIs) when an antibiotic-based eradicating therapy needs to be administered. Therefore, several tricks need to be used to optimize eradication rate of different regimens. The administration of the highest dose as possible of PPI, by doubling or increasing the number of pills/day, has shown to be able to improve therapeutic outcome and has often proposed in rescue therapies, even if specific trials have not been performed. A pre-treatment with PPI before starting antibiotics does not seem to be effective, therefore it is discouraged. However, the choice of PPI molecule could have a certain weight, since second-generation substances (esomeprazole, rabeprazole) are likely more effective than those of first generation (omeprazole, lansoprazole). A possible explanation is due to their metabolism, which has been proven to be less dependent on cytochrome P450 (CYP) 2C19 genetic variables. Finally, vonoprazan, a competitive inhibitor of H+/K+-ATPase present on luminal membrane of gastric parietal cells has shown the highest efficacy, due to both its highest acid inhibition power and rapid pharmacologic effect. However current data come only from Eastern Asia, therefore its strong power needs to be confirmed outside this geographic area in Western countries as well as related to the local different antibiotic resistance rates.

**Key words:** *Helicobacter pylori*; Proton pump inhibitors; Eradication; Cytochrome P450; Optimization

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The most adequate acid suppression by proton pump inhibitors (PPIs) is fundamental to optimize antibiotic therapies for *Helicobacter pylori* eradication. Herein, we summarize data from literature in order to ascertain the most effective strategies in this topic. Increasing PPI dose showed a real benefit on eradication rate even in the absence of dedicated trials. Second-generation PPIs, as demonstrated in some meta-analyses, may be more effective than old PPI molecules. Finally, vonoprazan, a novel molecule, has shown promising results but, currently, data come from Asian countries, therefore its strong power needs to be confirmed outside this geographic area.

Ierardi E, Losurdo G, La Fortezza RF, Principi M, Barone M, Di Leo A. Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: Old and new tricks to improve effectiveness. *World J Gastroenterol* 2019; 25(34): 5097-5104

**URL:** https://www.wjgnet.com/1007-9327/full/v25/i34/5097.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v25.i34.5097

**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) is a microaerofilic Gram-negative bacterium that colonizes the human stomach thus causing gastritis, peptic ulcer and malignant diseases (gastric cancer and mucosa associated lymphoid tissue lymphoma)[1]. Therefore, a prompt eradication of *H. pylori* may heal non-malignant conditions and stop the development of neoplastic diseases.

Until few decades ago, the human stomach was considered as a “sterile” organ where the acidic pH hampered the growth of any germ. However, the discovery of *H. pylori* has disavowed this axiom[2]. Urease is the most important enzyme of this bacterium, since it allows *H. pylori* stomach colonization by degrading urea into carbon dioxide and ammonia, an alkaline molecule able to counteract acidic environment below the layer of neutral mucins that cover the gastric wall[3]. Thus, the survival and growth of *H. pylori* is strictly dependant on urease effect on intragastric pH at this site. Indeed, it has been observed that only bacteria in replicative vegetative phase are susceptible to antibiotics[4-7]. *H. pylori* enters replicative phase at an almost neutral pH (6-7), while at acid pH (3-6) it turns into the coccoid form that is resistant to antibiotics[4-9]. On these bases, it is crucial to increase intragastric pH by proton pump inhibitors (PPIs) when an antibiotic-based eradicating therapy needs to be administered, since an inadequate acid suppression may keep some bacteria in non replicative forms, not susceptible to antibiotics. On the other hand, this mechanism explains some cases of treatment failure, not linked to bacterial genotypic resistance[8]. A further relevant property of PPIs is the ability to reduce intragastric bacterial load, thus making more likely the success of antibiotics. This relevant aspect is supported by the observation that patients with very high bacterial load are the most resistant ones to therapeutic approaches[10,11]. Finally, an additional demonstration in favor of PPI role in *H. pylori* treatment was suggested by Figura *et al*[12], who showed that lansoprazole reduces minimal inhibitory concentration of cultured *H. pylori* strains through a possible direct inhibitory effect on bacterial replication. The evidence of the pivotal usefulness of a correct use of PPIs in the eradication of *H. pylori* led us to perform a narrative review aimed to explore some poorly considered aspects of PPI management in this context.

**THE OPTIMAL DOSE**

Current Maastricht V guidelines[13] recommend high PPI dose, which is equivalent to omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg, all twice daily, while low doses are discouraged since they are ineffective, as clearly highlighted in 2015 Italian guidelines[14]. Therefore, a very high dose is defined by both doubling usual amount (*e.g*., lansoprazole 60 mg bid) or multiple administration (*e.g*., lansoprazole 30 mg tid or qid). At this regard, there is no unanimous consent for the definition of the very high dose of esomeprazole, since some Authors suggest 20 mg bid and others 40 mg bid[15,16]. In the OPTRICON trial[15], esomeprazole 40 mg bid was given with a 14-d triple therapy in 402 naïve patients, with an eradication rate at intention to treat of 81.3%. Unfortunately, in this trial the alternative arm was represented by concomitant therapy, therefore it was inadequate to give useful information about the PPI dose effectiveness. On the other hand, De Francesco *et al*[16] showed that esomeprazole 40 mg bid with 14-d triple therapy showed eradication rate of 81.9% compared to 73.9% of esomeprazole 20 mg bid. Interestingly, in a Thai study, lansoprazole 60 mg bid within a 10-d triple therapy showed a similar effectiveness of 10-d sequential therapy with lansoprazole at standard dose (80% *vs* 85%)[17]. At this regard, very high PPI doses have been frequently proposed in the context of dual therapy: A meta-analysis[18] demonstrated that such regimen, when used in rescue line, was equivalent to those recommended by guidelines (pooled eradication rate of 81.3% *vs* 81.5%, risk ratio = 1). In Taiwan, an optimized dual therapy with esomeprazole 40 mg tid plus amoxicillin 750 mg qid showed an effectiveness of the 91.7%, higher, even if not significantly (*P* = 0.21), than that of concomitant regimen, which displayed an outcome of the 86.7%[19]. Additionally, the same high-dose PPI-amoxicillin dual therapy achieved a very satisfactory eradication rate (96.1%) in China[20]. These recent evidences suggest that increasing PPI doses may have the power to reach an effectiveness similar to that obtained by adding further antibiotics[21]. Nevertheless, the real “test bed” of very high PPI dose is represented by the comparison with standard dose within the same eradication regimen. A meta-analysis[22] of seven studies, enrolling articles in which 7-d triple therapy was associated to either standard or very high dose, showed that the last one had a significantly higher eradication rate (82% versus 74%, with a risk ratio = 1.09, *P* = 0.03). Other similar head-to-head trials are summarized in Table 1[16,23-28]. As shown, in most cases the dose escalation allowed to gain a small increment in eradication rate without changes in adverse events[18]. Only one study, performed with dexlansoprazole, a new molecule, did not achieve a satisfactory eradication rate (53.8%) for dual therapy, but in this case only 13 patients were enrolled[29]. Finally, the utility of dose doubling has been underlined in a study by Ormeci *et al*[30] demonstrating that, in extensive metabolizers, triple therapy with standard dose of rabeprazole or pantoprazole failed in 12/75 and 13/81 patients respectively. Conversely, the re-administration of the same regimen with very high PPI dose in patients who failed therapy surprisingly allowed eradication in 10/12 for rabeprazole and 10/13 for pantoprazole. It is, therefore presumable, that in these cases treatment failure was not due to antibiotic resistance, but to an inadequate acid suppression.

**PRE-TREATMENT WITH PPI**

There is conflicting evidence whether a pretreatment with PPI may affect the efficacy of *H. pylori* eradicating regimens. Based on the assumption that PPIs slowly achieve the steady state and the optimal blood concentrations, it has been hypothesized that a pretreatment with these drugs before starting antibiotics may improve therapy effectiveness. Janssen et al. have reported that three-day pretreatment with a PPI (lansoprazole 30 mg twice daily) before quadruple eradication therapy paradoxically decreased eradication rate (66% *vs* 84%)[31]. The authors theorized that PPIs might induce coccoid-persistent forms of *H. pylori*, less vulnerable to the antibiotics. Other studies have reported that pretreatment did not affect treatment outcome[32-34]. Inoue et al. have reported that there was no statistically significant difference in the eradication rate with the regimen of lansoprazole, amoxicillin and clarithromycin between patients with and without pretreatment (lansoprazole 30 mg, once daily)[32]. A similar result was observed in a retrospective study by Tokoro *et al*[33]. The same Author investigated as well the influence of a pretreatment with histamine 2 receptor antagonist on *H. pylori* eradication; results indicated that bacterium eradication was not changed by this approach[34].

**HAVE ALL PPI THE SAME EFFECTIVENESS?**

The effectiveness of a PPI is related to the dose, formulation, relative power, frequency of administration and genetic differences in the activity of cytochrome P450 (CYP) enzymes of the subjects assuming the drug. A meta-analysis by McNicholl *et al*[35] compared first-generation (omeprazole, lansoprazole and pantoprazole) with second-generation PPIs (rabeprazole and esomeprazole). Thirty-five studies and 5998 patients were analyzed; the main ﬁnding of the meta-analysis was that the second-generation PPIs appeared to have a small superiority in eradication rate, because of their higher acid inhibition power. The eradication rates for esomeprazole was higher than for ﬁrst-generation PPIs: 82.3% *vs* 77.6%; odd ratio (OR) = 1.32 [95% confidence interval (CI): 1.01-1.73]; also rabeprazole showed better results than ﬁrst-generation PPIs: 80.5% *vs* 76.2%; OR = 1.21 (95%CI: 1.02-1.42). The new generation PPIs, esomeprazole and rabeprazole, had similar eradication rates: 78.7% *vs* 76.7%; OR = 0.90 (95%CI: 0.70-1.17).

Liver metabolism of PPIs is a relevant parameter since PPIs are prodrugs and, therefore, they are rapidly metabolized. The main enzymes involved in the metabolism of PPIs are CYP2C19 and CYP3A4. There are genetic differences in the activity of CYP2C19. Patients producing the largest amount of this enzyme are called “homozygous extensive metabolizer” (HomEM); “Heterozygous extensive metabolizer” (HetEM) are carriers of one wild-type and one mutation-type allele. Finally “poor metabolizer” (PM) patients have two “loss of function” variant alleles[36]. The pharmacokinetics properties of PPIs have significant difference between PM and HomEM. Indeed, in PM patients, a tendency towards a better eradication rate was found when treatment contained ﬁrst-generation PPIs, whereas EM patients obtained higher eradication rates with therapy regimens based on new-generation PPIs[37]. Possible explanations may be that the CYP2C19 has no significant effect on the rabeprazole-based or esomeprazole-based triple therapies. Indeed, rabeprazole is metabolized through a non-enzymatic pathway, with scanty involvement of CYP2C19[38] and esomeprazole has only a minimal first pass metabolism characterized by poor hydroxylation via CYP2C19[39].

A meta-analysis by Padol *et al*[40] showed a significant difference between HetEM and HomEMs (OR = 1.90, 95%CI: 1.38-2.60, *P* < 0.0001) in favor of HetEM. A higher *H. pylori* eradication rates, in dual and triple omeprazole therapies, was recorded in PM over both HomEM (OR = 4.03, 95%CI: 1.97-8.28, *P* = 0.0001), and HetEM (OR = 2.24, 95%CI: 1.09-4.61, *P* = 0.03). Dual and triple rabeprazole and triple lansoprazole therapies were not significantly different between PM and HomEM (OR = 1.04, 95%CI: 0.44-2.46, *P* = 0.25)[40]. An additional meta-analysis of sixteen randomized clinical trials by Tang *et al*[41]. investigated the differences in eradication rate between HomEMs, HetEMs and PMs and confirmed the trend of a better eradication rate for PMs over HomEMs and HetEMs. The sub-analysis of individual PPIs showed a significant low eradication rate in both HomEMs versus HetEMs and HomEMs *vs* PMs with either omeprazole (OR 0.329; 95%CI: 0.195-0.553 and OR 0.232; 95%CI: 0.105-0.515, respectively) or lansoprazole (OR 0.692; 95%CI: 0.485-0.988 and OR 0.441; 95%CI: 0.252-0.771, respectively), while no significant difference was seen between HetEMs and PMs[41].

Additionally, some novel formulations of PPIs, such as modified release-dexlansoprazole, and instant release-omeprazole or tenatoprazole, which may increase the control of intragastric pH especially at night, are under investigation. However, they have not been tested yet for *H. pylori* despite they represent an excellent starting point for future investigations[42].

**NOVEL DRUGS: A FOCUS ON VONOPRAZAN**

Vonoprazan (VPZ) is a molecule that has been recently introduced in Japan for the treatment of acid-related diseases, and it is currently available only in Japanese market[43]. VPZ is a competitive inhibitor of H+/K+-ATPase present on luminal membrane of gastric parietal cells. The binding power is much more powerful than conventional PPIs, i.e. its biological activity is 300 times greater than lansoprazole[44,45]. VPZ has two further pharmacological benefits over other PPIs: it does not require pharmacological activation by gastric acid to inhibit acid secretion, and has a longer half-life, due to its slow dissociation kinetics from proton pump[46]. Another peculiarity consists in the rapid onset of the effect: while PPIs usually require more than 75-100 h to achieve the maximal gastric acid inhibitory effect[47,48], VPZ induces a fast, powerful and long-lasting gastric acid inhibition[49]. Therefore, in conclusion, VPZ seems to be better than conventional PPIs for five reasons: (1) It is more potent in acid secretion blockade; (2) it has a fast onset of action; (3) it is less prone to metabolization variables due to cytochrome polymorphisms; (4) greater safety; and (5) better tolerability[50].

VPZ is given at a dose of 20 mg bid in eradication regimens. A meta-analysis of ten studies[51], enrolling 10644 patients overall, demonstrated that triple therapy with VPZ in first line eradicated *H. pylori* in the 87.9%, while the eradication rate with traditional PPIs was 72.8% (risk ratio = 1.19, *P* < 0.001). Most of such studies were retrospective[52], however even randomized controlled trials, which are summarized in Table 2[53-55], confirmed that VPZ was better than conventional PPIs for *H. pylori* treatment in any case. However, the most interesting result comes from studies performed on clarithromycin resistant strains. A meta-analysis of 5 studies[56] showed that the eradication rate in clarithromycin susceptible patients did not differ from that of other PPIs (95.4% *vs* 92.8%), while VPZ was clearly superior in clarithromycin resistant strains (82% *vs* 40%, *P* < 0.001). Authors explained this finding with the following reasons: (1) VPZ prevents nocturnal acid breakthrough, which is linked to therapy failure; and (2) VPZ is not influenced by CYP2C19 polymorphisms. Finally, it seems that the effectiveness of this drug could be explained by its best suppression of acid secretion. Nevertheless, these enthusiastic results require to be confirmed by forthcoming studies outside Japan[50].

**CONCLUSION**

Evidence in literature clearly shows that a strong inhibition of gastric acid secretion is crucial for *H. pylori* eradication. Therefore, several tricks have to be used to optimize eradication rate of different regimens. The administration of the highest dose as possible seems to be able to improve therapeutic outcome even if specific trials are necessary. Pre-treatment does not seem to be effective, therefore it is discouraged. However, the choice of PPI molecule could have a certain weight, since second-generation substances are likely more effective because their metabolism is less dependent on CYP2C19 genetic variables. VPZ has shown the highest efficacy, but current data come from Eastern Asia, therefore its strong power needs to be confirmed outside this geographic area in Western countries. In the era of antibiotic resistance, the strategies to improve eradication rate are decreasing[57]. Until novel antibiotics will be discovered, a wise choice of antibiotic combination, may be guided by a tailored approach based on the knowledge of antibiotic susceptibility (preferably with non-invasive modality)[58-61]. Nevertheless, approaches which bypass the problem of antibiotic resistance, such as PPI optimization, vaccine, probiotics or phytochemistry, could be an useful ace up your sleeve[62-64]. In particular, the creation of novel and more effective and powerful PPIs could be an additional weapon against *H. pylori*. Finally, the marketing of VPZ in Western countries is expected to confirm its stunning results in the far East countries.

**REFERENCES**

1 **Ierardi E**, Goni E, Losurdo G, Di Mario F. Helicobacter pylori and nonmalignant diseases. *Helicobacter* 2014; **19 Suppl 1**: 27-31 [PMID: 25167942 DOI: 10.1111/hel.12157]

2 **Waldum HL**, Kleveland PM, Sørdal ØF. Helicobacter pylori and gastric acid: An intimate and reciprocal relationship. *Therap Adv Gastroenterol* 2016; **9**: 836-844 [PMID: 27803738 DOI: 10.1177/1756283X16663395]

3 **Marshall BJ**. Virulence and pathogenicity of Helicobacter pylori. *J Gastroenterol Hepatol* 1991; **6**: 121-124 [PMID: 1912416 DOI: 10.1111/j.1440-1746.1991.tb01450.x]

4 **Keren I**, Kaldalu N, Spoering A, Wang Y, Lewis K. Persister cells and tolerance to antimicrobials. *FEMS Microbiol Lett* 2004; **230**: 13-18 [PMID: 14734160 DOI: 10.1016/S0378-1097(03)00856-5]

5 **Graham DY**, Shiotani A. New concepts of resistance in the treatment of Helicobacter pylori infections. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 321-331 [PMID: 18446147 DOI: 10.1038/ncpgasthep1138]

6 **Mizoguchi H**, Fujioka T, Nasu M. Evidence for viability of coccoid forms of Helicobacter pylori. *J Gastroenterol* 1999; **34 Suppl 11**: 32-36 [PMID: 10616763 DOI: 10.1097/00004836-199912000-00014]

7 **Reshetnyak VI**, Reshetnyak TM. Significance of dormant forms of Helicobacter pylori in ulcerogenesis. *World J Gastroenterol* 2017; **23**: 4867-4878 [PMID: 28785141 DOI: 10.3748/wjg.v23.i27.4867]

8 **Graham DY**, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153 [PMID: 20525969 DOI: 10.1136/gut.2009.192757]

9 **Scott D**, Weeks D, Melchers K, Sachs G. The life and death of Helicobacter pylori. *Gut* 1998; **43 Suppl 1**: S56-S60 [PMID: 9764042 DOI: 10.1136/gut.43.2008.S56]

10 **De Francesco V**, Zullo A, Perna F, Giorgio F, Hassan C, Vannella L, Cristofari F, Panella C, Vaira D, Ierardi E. Helicobacter pylori antibiotic resistance and [13C]urea breath test values. *J Med Microbiol* 2010; **59**: 588-591 [PMID: 20093375 DOI: 10.1099/jmm.0.018077-0]

11 **Maconi G**, Parente F, Russo A, Vago L, Imbesi V, Bianchi Porro G. Do some patients with Helicobacter pylori infection benefit from an extension to 2 weeks of a proton pump inhibitor-based triple eradication therapy? *Am J Gastroenterol* 2001; **96**: 359-366 [PMID: 11232676 DOI: 10.1111/j.1572-0241.2001.03519.x]

12 **Figura N**, Crabtree JE, Dattilo M. In-vitro activity of lansoprazole against Helicobacter pylori. *J Antimicrob Chemother* 1997; **39**: 585-590 [PMID: 9184356 DOI: 10.1093/jac/39.5.585]

13 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

14 **Zagari RM**, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B, Farinati F, Ierardi E, Maconi G, Rugge M, Calabrese C, Di Mario F, Luzza F, Pretolani S, Savio A, Gasbarrini G, Caselli M. Guidelines for the management of Helicobacter pylori infection in Italy: The III Working Group Consensus Report 2015. *Dig Liver Dis* 2015; **47**: 903-912 [PMID: 26253555 DOI: 10.1016/j.dld.2015.06.010]

15 **Molina-Infante J**, Lucendo AJ, Angueira T, Rodriguez-Tellez M, Perez-Aisa A, Balboa A, Barrio J, Martin-Noguerol E, Gomez-Rodriguez BJ, Botargues-Bote JM, Gomez-Camarero J, Huerta A, Modolell I, Ariño I, Herranz-Bachiller MT, Bermejo F, McNicholl AG, O'Morain C, Gisbert JP; European Registry on H. pylori management (Hp‐EuReg). Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: The OPTRICON study. *Aliment Pharmacol Ther* 2015; **41**: 581-589 [PMID: 25776067 DOI: 10.1111/apt.13069]

16 **De Francesco V**, Ridola L, Hassan C, Bellesia A, Alvaro D, Vaira D, Zullo A. Two-week Triple Therapy with either Standard or High-dose Esomeprazole for First-line H. pylori Eradication. *J Gastrointestin Liver Dis* 2016; **25**: 147-150 [PMID: 27308644 DOI: 10.15403/jgld.2014.1121.252.2w3]

17 **Auesomwang C**, Maneerattanaporn M, Chey WD, Kiratisin P, Leelakusolwong S, Tanwandee T. Ten-day high-dose proton pump inhibitor triple therapy versus sequential therapy for Helicobacter pylori eradication. *J Gastroenterol Hepatol* 2018; **33**: 1822-1828 [PMID: 29804294 DOI: 10.1111/jgh.14292]

18 **Gao CP**, Zhou Z, Wang JZ, Han SX, Li LP, Lu H. Efficacy and safety of high-dose dual therapy for Helicobacter pylori rescue therapy: A systematic review and meta-analysis. *J Dig Dis* 2016; **17**: 811-819 [PMID: 27977071 DOI: 10.1111/1751-2980.12432]

19 **Tai WC**, Liang CM, Kuo CM, Huang PY, Wu CK, Yang SC, Kuo YH, Lin MT, Lee CH, Hsu CN, Wu KL, Hu TH, Chuah SK. A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-Helicobacter pylori treatment in Taiwan: A prospective randomized trial. *J Antimicrob Chemother* 2019; **74**: 1718-1724 [PMID: 30768161 DOI: 10.1093/jac/dkz046]

20 **Yu L**, Luo L, Long X, Liang X, Ji Y, Graham DY, Lu H. High-dose PPI-amoxicillin dual therapy with or without bismuth for first-line Helicobacter pylori therapy: A randomized trial. *Helicobacter* 2019; **24**: e12596 [PMID: 31111580 DOI: 10.1111/hel.12596]

21 **Gisbert JP**, McNicholl AG. Optimization strategies aimed to increase the efficacy of H. pylori eradication therapies. *Helicobacter* 2017; **22** [PMID: 28464347 DOI: 10.1111/hel.12392]

22 **Villoria A**, Garcia P, Calvet X, Gisbert JP, Vergara M. Meta-analysis: High-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2008; **28**: 868-877 [PMID: 18644011 DOI: 10.1111/j.1365-2036.2008.03807.x]

23 **Gisbert JP**, Domínguez-Muñoz A, Domínguez-Martín A, Gisbert JL, Marcos S. Esomeprazole-based therapy in Helicobacter pylori eradication: Any effect by increasing the dose of esomeprazole or prolonging the treatment? *Am J Gastroenterol* 2005; **100**: 1935-1940 [PMID: 16128936 DOI: 10.1111/j.1572-0241.2005.00178.x]

24 **Anagnostopoulos GK**, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Esomeprazole versus omeprazole for the eradication of Helicobacter pylori infection: Results of a randomized controlled study. *J Clin Gastroenterol* 2004; **38**: 503-506 [PMID: 15220685 DOI: 10.1097/01.mcg.0000129061.54277.c6]

25 **Sheu BS**, Kao AW, Cheng HC, Hunag SF, Chen TW, Lu CC, Wu JJ. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. *Aliment Pharmacol Ther* 2005; **21**: 283-288 [PMID: 15691303 DOI: 10.1111/j.1365-2036.2005.02281.x]

26 **Manes G**, Pieramico O, Perri F, Vaira D, Giardullo N, Romano M, Nardone G, Balzano A. Twice-daily standard dose of omeprazole achieves the necessary level of acid inhibition for Helicobacter pylori eradication. A randomized controlled trial using standard and double doses of omeprazole in triple therapy. *Dig Dis Sci* 2005; **50**: 443-448 [PMID: 15810623 DOI: 10.1007/s10620-005-2455-6]

27 **Choi HS**, Park DI, Hwang SJ, Park JS, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI. Double-dose, new-generation proton pump inhibitors do not improve Helicobacter pylori eradication rate. *Helicobacter* 2007; **12**: 638-642 [PMID: 18001407 DOI: 10.1111/j.1523-5378.2007.00556.x]

28 **Hu JL**, Yang J, Zhou YB, Li P, Han R, Fang DC. Optimized high-dose amoxicillin-proton-pump inhibitor dual therapies fail to achieve high cure rates in China. *Saudi J Gastroenterol* 2017; **23**: 275-280 [PMID: 28937021 DOI: 10.4103/sjg.SJG\_91\_17]

29 **Attumi TA**, Graham DY. High-dose extended-release lansoprazole (dexlansoprazole) and amoxicillin dual therapy for Helicobacter pylori infections. *Helicobacter* 2014; **19**: 319-322 [PMID: 24698653 DOI: 10.1111/hel.12126]

30 **Ormeci A**, Emrence Z, Baran B, Soyer OM, Gokturk S, Evirgen S, Akyuz F, Karaca C, Besisik F, Kaymakoglu S, Ustek D, Demir K. Can Helicobacter pylori be eradicated with high-dose proton pump inhibitor in extensive metabolizers with the CYP2C19 genotypic polymorphism? *Eur Rev Med Pharmacol Sci* 2016; **20**: 1795-1797 [PMID: 27212172]

31 **Janssen MJ**, Laheij RJ, Jansen JB, de Boer WA. The influence of pretreatment on cure rates of Helicobacter pylori eradication. *Neth J Med* 2004; **62**: 192-196 [PMID: 15460498 DOI: 10.1089/1540999041281052]

32 **Inoue M**, Okada H, Hori S, Kawahara Y, Kawano S, Takenaka R, Toyokawa T, Onishi Y, Shiratori Y, Yamamoto K. Does pretreatment with lansoprazole influence Helicobacter pylori eradication rate and quality of life? *Digestion* 2010; **81**: 218-222 [PMID: 20090337 DOI: 10.1159/000260416]

33 **Tokoro C**, Inamori M, Koide T, Iida H, Sakamoto Y, Endo H, Hosono K, Takahashi H, Yoneda M, Yasuzaki H, Ogawa M, Abe Y, Kubota K, Saitou S, Kawana I, Matsuda R, Takahashi D, Nakajima A. Does pretreatment with proton pump inhibitors influence the eradication rate of Helicobacter pylori? *Hepatogastroenterology* 2010; **57**: 1645-1649 [PMID: 21443136 DOI: 10.1007/s11999-010-1543-x]

34 **Tokoro C**, Inamori M, Koide T, Sekino Y, Iida H, Sakamoto Y, Endo H, Hosono K, Takahashi H, Yoneda M, Yasuzaki H, Ogawa M, Abe Y, Kubota K, Saito S, Kawana I, Nakajima A, Maeda S, Matsuda R, Takahashi D. Influence of pretreatment with H2 receptor antagonists on the cure rates of Helicobacter pylori eradication. *Med Sci Monit* 2011; **17**: CR235-CR240 [PMID: 21525804 DOI: 10.12659/MSM.881762]

35 **McNicholl AG**, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: Esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2012; **36**: 414-425 [PMID: 22803691 DOI: 10.1111/j.1365-2036.2012.05211.x]

36 **Tomalik-Scharte D**, Lazar A, Fuhr U, Kirchheiner J. The clinical role of genetic polymorphisms in drug-metabolizing enzymes. *Pharmacogenomics J* 2008; **8**: 4-15 [PMID: 17549068 DOI: 10.1038/sj.tpj.6500462]

37 **Kuo CH**, Lu CY, Shih HY, Liu CJ, Wu MC, Hu HM, Hsu WH, Yu FJ, Wu DC, Kuo FC. CYP2C19 polymorphism influences Helicobacter pylori eradication. *World J Gastroenterol* 2014; **20**: 16029-16036 [PMID: 25473155 DOI: 10.3748/wjg.v20.i43.16029]

38 **Adachi K**, Katsube T, Kawamura A, Takashima T, Yuki M, Amano K, Ishihara S, Fukuda R, Watanabe M, Kinoshita Y. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. *Aliment Pharmacol Ther* 2000; **14**: 1259-1266 [PMID: 11012469 DOI: 10.1046/j.1365-2036.2000.00840.x]

39 **Andersson T**, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40**: 411-426 [PMID: 11475467 DOI: 10.2165/00003088-200140060-00003]

40 **Padol S**, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: A meta-analysis. *Am J Gastroenterol* 2006; **101**: 1467-1475 [PMID: 16863547 DOI: 10.1111/j.1572-0241.2006.00717.x]

41 **Tang HL**, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: A meta-analysis of randomized clinical trials. *PLoS One* 2013; **8**: e62162 [PMID: 23646118 DOI: 10.1371/journal.pone.0062162]

42 **Hunt RH**, Scarpignato C. Potent Acid Suppression with PPIs and P-CABs: What's New? *Curr Treat Options Gastroenterol* 2018; **16**: 570-590 [PMID: 30361857 DOI: 10.1371/journal.pone.0062162]

43 **Mori H**, Suzuki H. Role of Acid Suppression in Acid-related Diseases: Proton Pump Inhibitor and Potassium-competitive Acid Blocker. *J Neurogastroenterol Motil* 2019; **25**: 6-14 [PMID: 30504527 DOI: 10.5056/jnm18139]

44 **Parsons ME**, Keeling DJ. Novel approaches to the pharmacological blockade of gastric acid secretion. *Expert Opin Investig Drugs* 2005; **14**: 411-421 [PMID: 15882117 DOI: 10.1517/13543784.14.4.411]

45 **Ashida K**, Sakurai Y, Hori T, Kudou K, Nishimura A, Hiramatsu N, Umegaki E, Iwakiri K. Randomised clinical trial: Vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther* 2016; **43**: 240-251 [PMID: 26559637 DOI: 10.1111/apt.13461]

46 **Scott DR**, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+ -ATPase. *Aliment Pharmacol Ther* 2015; **42**: 1315-1326 [PMID: 26423447 DOI: 10.1111/apt.13414]

47 **Saitoh T**, Fukushima Y, Otsuka H, Hirakawa J, Mori H, Asano T, Ishikawa T, Katsube T, Ogawa K, Ohkawa S. Effects of rabeprazole, lansoprazole and omeprazole on intragastric pH in CYP2C19 extensive metabolizers. *Aliment Pharmacol Ther* 2002; **16**: 1811-1817 [PMID: 12269976 DOI: 10.1046/j.1365-2036.2002.01348.x]

48 **Sugimoto M**, Furuta T, Shirai N, Ikuma M, Hishida A, Ishizaki T. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther* 2006; **80**: 539-548 [PMID: 17112810 DOI: 10.1016/j.clpt.2006.08.010]

49 **Jenkins H**, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, Yoneyama T, Ashida K, Ogama Y, Warrington S. Randomised clinical trial: Safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 2015; **41**: 636-648 [PMID: 25707624 DOI: 10.1111/apt.13121]

50 **Abadi ATB**, Ierardi E. Vonoprazan and Helicobacter pylori Treatment: A Lesson From Japan or a Limited Geographic Phenomenon? *Front Pharmacol* 2019; **10**: 316 [PMID: 31024299 DOI: 10.3389/fphar.2019.00316]

51 **Jung YS**, Kim EH, Park CH. Systematic review with meta-analysis: The efficacy of vonoprazan-based triple therapy on Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2017; **46**: 106-114 [PMID: 28497487 DOI: 10.1111/apt.14130]

52 **Sugimoto M**, Yamaoka Y. Role of Vonoprazan in Helicobacter pylori Eradication Therapy in Japan. *Front Pharmacol* 2019; **9**: 1560 [PMID: 30697158 DOI: 10.3389/fphar.2018.01560]

53 **Murakami K**, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: A phase III, randomised, double-blind study. *Gut* 2016; **65**: 1439-1446 [PMID: 26935876 DOI: 10.1136/gutjnl-2015-311304]

54 **Maruyama M**, Tanaka N, Kubota D, Miyajima M, Kimura T, Tokutake K, Imai R, Fujisawa T, Mori H, Matsuda Y, Wada S, Horiuchi A, Kiyosawa K. Vonoprazan-Based Regimen Is More Useful than PPI-Based One as a First-Line Helicobacter pylori Eradication: A Randomized Controlled Trial. *Can J Gastroenterol Hepatol* 2017; **2017**: 4385161 [PMID: 28349044 DOI: 10.1155/2017/4385161]

55 **Sue S**, Ogushi M, Arima I, Kuwashima H, Nakao S, Naito M, Komatsu K, Kaneko H, Tamura T, Sasaki T, Kondo M, Shibata W, Maeda S. Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-susceptible Helicobacter pylori: A multicenter, prospective, randomized trial. *Helicobacter* 2018; **23**: e12456 [PMID: 29271026 DOI: 10.1111/hel.12456]

56 **Li M**, Oshima T, Horikawa T, Tozawa K, Tomita T, Fukui H, Watari J, Miwa H. Systematic review with meta-analysis: Vonoprazan, a potent acid blocker, is superior to proton-pump inhibitors for eradication of clarithromycin-resistant strains of Helicobacter pylori. *Helicobacter* 2018; **23**: e12495 [PMID: 29873436 DOI: 10.1111/hel.12495]

57 **Ierardi E**, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change Helicobacter pylori treatment: A matter of geography? *World J Gastroenterol* 2013; **19**: 8168-8180 [PMID: 24363506 DOI: 10.3748/wjg.v19.i45.8168]

58 **Iannone A**, Giorgio F, Russo F, Riezzo G, Girardi B, Pricci M, Palmer SC, Barone M, Principi M, Strippoli GF, Di Leo A, Ierardi E. New fecal test for non-invasive Helicobacter pylori detection: A diagnostic accuracy study. *World J Gastroenterol* 2018; **24**: 3021-3029 [PMID: 30038469 DOI: 10.3748/wjg.v24.i27.3021]

59 **Ierardi E**, Giorgio F, Iannone A, Losurdo G, Principi M, Barone M, Pisani A, Di Leo A. Noninvasive molecular analysis of Helicobacter pylori: Is it time for tailored first-line therapy? *World J Gastroenterol* 2017; **23**: 2453-2458 [PMID: 28465629 DOI: 10.3748/wjg.v23.i14.2453]

60 **Giorgio F**, Ierardi E, Sorrentino C, Principi M, Barone M, Losurdo G, Iannone A, Giangaspero A, Monno R, Di Leo A. Helicobacter pylori DNA isolation in the stool: An essential pre-requisite for bacterial noninvasive molecular analysis. *Scand J Gastroenterol* 2016; **51**: 1429-1432 [PMID: 27687850 DOI: 10.1080/00365521.2016.1216592]

61 **Cammarota G**, Ianiro G, Bibbò S, Di Rienzo TA, Masucci L, Sanguinetti M, Gasbarrini A. Culture-guided treatment approach for Helicobacter pylori infection: Review of the literature. *World J Gastroenterol* 2014; **20**: 5205-5211 [PMID: 24833850 DOI: 10.3748/wjg.v20.i18.5205]

62 **Talebi Bezmin Abadi A**. Vaccine against Helicobacter pylori: Inevitable approach. *World J Gastroenterol* 2016; **22**: 3150-3157 [PMID: 27003991 DOI: 10.3748/wjg.v22.i11.3150]

63 **Losurdo G**, Cubisino R, Barone M, Principi M, Leandro G, Ierardi E, Di Leo A. Probiotic monotherapy and Helicobacter pylori eradication: A systematic review with pooled-data analysis. *World J Gastroenterol* 2018; **24**: 139-149 [PMID: 29358890 DOI: 10.3748/wjg.v24.i1.139]

64 **Vale FF**, Oleastro M. Overview of the phytomedicine approaches against Helicobacter pylori. *World J Gastroenterol* 2014; **20**: 5594-5609 [PMID: 24914319 DOI: 10.3748/wjg.v20.i19.5594]

**P-Reviewer:** Chiba T, Ding SZ **S-Editor:** Yan JP

**L-Editor:** A **E-Editor:** Zhang YL

**Specialty type:** Gastroenterology and hepatology
**Country of origin:** Italy
**Peer-review report classification**
**Grade A (Excellent):** 0
**Grade B (Very good):** B, B
**Grade C (Good):** 0
**Grade D (Fair):** 0 **Grade E (Poor):** 0

**Table 1 Main studies exploring very high dose *vs* standard proton pump inhibitors dose in *Helicobacter pylori* eradication regimens**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **PPI comparison** | **Antibiotic regimen** | **Very high dose eradication rate (%)** | **Standard dose eradication rate (%)** |
| De Francesco *et al*[16], 2016  | Esomeprazole 20 mg *vs* 40 mg bid | 14-d triple therapy (CLA+AMO) | 59/72 (81.9) | 54/73 (73.9) |
| Gisbert *et al*[23], 2005  | Esomeprazole 20 mg *vs* 40 mg bid | 7-d triple therapy (CLA+AMO) | 117/150 (78) | 111/150 (74) |
| Anagnostopoulos *et al*[24], 2004 | Omeprazole 20 mg *vs* esomeprazole 40mg bid | 7-d triple therapy (CLA+AMO) | 50/52 (96.1) | 37/52 (71.1) |
| Sheu *et al*[25], 2005 | Omeprazole 20 mg *vs* esomeprazole 40 mg bid | 7-d triple therapy (CLA+AMO) | 86/100 (86) | 79/100 (79) |
| Manes *et al*[26], 2005 | Omeprazole 20 mg *vs* omeprazole 40 mg bid | 7-d triple therapy (CLA+TNZ) | 132/161 (82) | 135/162 (83.3) |
| Choi *et al*[27], 2007 | Omeprazole 20 mg *vs* esomeprazole 40 mg bid | 7-d triple therapy (CLA+AMO) | 104/148 (70.3) | 290/428 (67.7) |
| Hu *et al*[28], 2017 | Rabeprazole 10 mg *vs* 20 mg qid | 14-d dual therapy (AMO) | 71/87 (81.6) | 68/87 (78.1) |

All percentages are expressed as intention to treat. AMO: Amoxicillin; CLA: Clarithromycin; TNZ: Tinidazole; PPI: Proton pump inhibitors.

**Table 2 Randomized controlled trials comparing vonoprazan *vs* proton pump inhibitors for *Helicobacter pylori* eradication regimens**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Protocol in vonoprazan group** | **Protocol in PPI group** | **Eradication rate in vonoprazan group** | **Eradication rate in PPI group** |
| Murakami *et al*[53], 2016  | Vonoprazan 20 mg bidAMO 750 mg bidCLA 400 mg bid | LAN 30 mg AMO 750 mg bidCLA 400 mg bid | 299/329 (90.9%) | 241/321 (75.1%) |
| Maruyama *et al*[54], 2017  | Vonoprazan 20 mg bidAMO 750 mg bidCLA 400 mg bid | LAN 30 mg or RAB 20 mg bidAMO 750 mg bidCLA 400 mg bid | 69/72 (95.8%) | 48/69 (69.6%) |
| Sue *et al*[55], 2018  | Vonoprazan 20 mg bidAMO 750 mg bidCLA 400 mg bid | LAN 30 mg or RAB 10 mg or ESO 20 mgbidAMO 750 mg bidCLA 400 mg bid | 48/55 (87.3%) | 39/51 (76.5%) |

All percentages are expressed as intention to treat. AMO: Amoxicillin; CLA: Clarithromycin; ESO: Esomeprazole; LAN: Lansoprazole; RAB: Rabeprazole; PPI: Proton pump inhibitors.