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**OPINION REVIEW**

- 5017 Reducing anastomotic leak in colorectal surgery: The old dogmas and the new challenges  
*Meyer J, Naiken S, Christou N, Liot E, Toso C, Buchs NC, Ris F*

**REVIEW**

- 5026 Diagnostic and prognostic potential of tissue and circulating long non-coding RNAs in colorectal tumors  
*Galamb O, Barták BK, Kalmár A, Nagy ZB, Szigeti KA, Tulassay Z, Igaz P, Molnár B*
- 5049 Autoantibodies: Potential clinical applications in early detection of esophageal squamous cell carcinoma and esophagogastric junction adenocarcinoma  
*Xu YW, Peng YH, Xu LY, Xie JJ, Li EM*

**MINIREVIEWS**

- 5082 Role of endoscopic ultrasound in the screening and follow-up of high-risk individuals for familial pancreatic cancer  
*Lorenzo D, Rebours V, Maire F, Palazzo M, Gonzalez JM, Vullierme MP, Aubert A, Hammel P, Lévy P, Mestier LD*
- 5097 Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: Old and new tricks to improve effectiveness  
*Ierardi E, Losurdo G, Fortezza RFL, Principi M, Barone M, Leo AD*

**ORIGINAL ARTICLE****Basic Study**

- 5105 Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease  
*Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH*
- 5120 Allyl isothiocyanate ameliorates lipid accumulation and inflammation in nonalcoholic fatty liver disease via the Sirt1/AMPK and NF- $\kappa$ B signaling pathways  
*Li CX, Gao JG, Wan XY, Chen Y, Xu CF, Feng ZM, Zeng H, Lin YM, Ma H, Xu P, Yu CH, Li YM*
- 5134 Effect of Tong Xie Yao Fang on endogenous metabolites in urine of irritable bowel syndrome model rats  
*Zhao XY, Wang JW, Yin Y, Li K, Zhang M, Yan FP*

**Case Control Study**

- 5152 Association of XPG rs2094258 polymorphism with gastric cancer prognosis  
*Wang XQ, Terry PD, Li Y, Zhang Y, Kou WJ, Wang MX*

**Retrospective Study**

- 5162 Timing, distribution, and microbiology of infectious complications after necrotizing pancreatitis  
*Lu JD, Cao F, Ding YX, Wu YD, Guo YL, Li F*

- 5174 Risk factors for Mallory-Weiss Tear during endoscopic submucosal dissection of superficial esophageal neoplasms  
*Chen W, Zhu XN, Wang J, Zhu LL, Gan T, Yang JL*

**Clinical Trials Study**

- 5185 Overlay of a sponge soaked with ropivacaine and multisite infiltration analgesia result in faster recovery after laparoscopic hepatectomy  
*Zhang H, Du G, Liu YF, Yang JH, A-Niu MG, Zhai XY, Jin B*

**Observational Study**

- 5197 Analysis of 72 patients with colorectal high-grade neuroendocrine neoplasms from three Chinese hospitals  
*Wang ZJ, An K, Li R, Shen W, Bao MD, Tao JH, Chen JN, Mei SW, Shen HY, Ma YB, Zhao FQ, Wei FZ, Liu Q*

**META-ANALYSIS**

- 5210 Bilateral *vs* unilateral placement of metal stents for inoperable high-grade hilar biliary strictures: A systemic review and meta-analysis  
*Ashat M, Arora S, Klair JS, Childs CA, Murali AR, Johlin FC*

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

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### 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<sup>+</sup>/K<sup>+</sup>-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

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**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.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a microaerophilic Gram-negative bacterium that colonizes the human stomach thus causing gastritis, peptic ulcer and malignant diseases (gastric cancer and mucosa associated lymphoid tissue lymphoma)<sup>[1]</sup>. 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<sup>[2]</sup>. 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<sup>[3]</sup>. 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<sup>[4-7]</sup>. *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<sup>[4-9]</sup>. 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<sup>[8]</sup>. 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<sup>[10,11]</sup>. Finally, an additional demonstration in favor of PPI role in *H. pylori* treatment was suggested by Figura *et al*<sup>[12]</sup>, 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<sup>[13]</sup> 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<sup>[14]</sup>. 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<sup>[15,16]</sup>. In the OPTRICON trial<sup>[15]</sup>, 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.*<sup>[16]</sup> 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%)<sup>[17]</sup>. At this regard, very high PPI doses have been frequently proposed in the context of dual therapy: A meta-analysis<sup>[18]</sup> 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%<sup>[19]</sup>. Additionally, the same high-dose PPI-amoxicillin dual therapy achieved a very satisfactory eradication rate (96.1%) in China<sup>[20]</sup>. These recent evidences suggest that increasing PPI doses may have the power to reach an effectiveness similar to that obtained by adding further antibiotics<sup>[21]</sup>. 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<sup>[22]</sup> 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<sup>[16,23-28]</sup>. As shown, in most cases the dose escalation allowed to gain a small increment in eradication rate without changes in adverse events<sup>[18]</sup>. 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<sup>[29]</sup>. Finally, the utility of dose doubling has been underlined in a study by Ormeci *et al.*<sup>[30]</sup> 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%)<sup>[31]</sup>. 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<sup>[32-34]</sup>. 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)<sup>[32]</sup>. A similar result was observed in a retrospective study by Tokoro *et al.*<sup>[33]</sup>. 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<sup>[34]</sup>.

## 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.*<sup>[35]</sup> 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

**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 <i>et al</i> <sup>[16]</sup> , 2016	Esomeprazole 20 mg vs 40 mg bid	14-d triple therapy (CLA+AMO)	59/72 (81.9)	54/73 (73.9)
Gisbert <i>et al</i> <sup>[23]</sup> , 2005	Esomeprazole 20 mg vs 40 mg bid	7-d triple therapy (CLA+AMO)	117/150 (78)	111/150 (74)
Anagnostopoulos <i>et al</i> <sup>[24]</sup> , 2004	Omeprazole 20 mg vs esomeprazole 40mg bid	7-d triple therapy (CLA+AMO)	50/52 (96.1)	37/52 (71.1)
Sheu <i>et al</i> <sup>[25]</sup> , 2005	Omeprazole 20 mg vs esomeprazole 40 mg bid	7-d triple therapy (CLA+AMO)	86/100 (86)	79/100 (79)
Manes <i>et al</i> <sup>[26]</sup> , 2005	Omeprazole 20 mg vs omeprazole 40 mg bid	7-d triple therapy (CLA+TNZ)	132/161 (82)	135/162 (83.3)
Choi <i>et al</i> <sup>[27]</sup> , 2007	Omeprazole 20 mg vs esomeprazole 40 mg bid	7-d triple therapy (CLA+AMO)	104/148 (70.3)	290/428 (67.7)
Hu <i>et al</i> <sup>[28]</sup> , 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.

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<sup>[36]</sup>. 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<sup>[37]</sup>. 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<sup>[38]</sup> and esomeprazole has only a minimal first pass metabolism characterized by poor hydroxylation via CYP2C19<sup>[39]</sup>.

A meta-analysis by Padol *et al*<sup>[40]</sup> 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,  $P = 0.25$ )<sup>[40]</sup>. An additional meta-analysis of sixteen randomized clinical trials by Tang *et al*<sup>[41]</sup> 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<sup>[41]</sup>.

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<sup>[42]</sup>.

## 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<sup>[43]</sup>. VPZ is a competitive inhibitor of H<sup>+</sup>/K<sup>+</sup>-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<sup>[44,45]</sup>. 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<sup>[46]</sup>. 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<sup>[47,48]</sup>, VPZ induces a fast, powerful and long-lasting gastric acid inhibition<sup>[49]</sup>. 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<sup>[50]</sup>.

VPZ is given at a dose of 20 mg bid in eradication regimens. A meta-analysis of ten studies<sup>[51]</sup>, 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<sup>[52]</sup>, however even randomized controlled trials, which are summarized in Table 2<sup>[53-55]</sup>, 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<sup>[56]</sup> 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<sup>[50]</sup>.

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## CONCLUSION

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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<sup>[57]</sup>. 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)<sup>[58-61]</sup>. 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<sup>[62-64]</sup>. 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.

**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 <i>et al.</i> <sup>[53]</sup> , 2016	Vonoprazan 20 mg bid AMO 750 mg bid CLA 400 mg bid	LAN 30 mg AMO 750 mg bid CLA 400 mg bid	299/329 (90.9%)	241/321 (75.1%)
Maruyama <i>et al.</i> <sup>[54]</sup> , 2017	Vonoprazan 20 mg bid AMO 750 mg bid CLA 400 mg bid	LAN 30 mg or RAB 20 mg bid AMO 750 mg bid CLA 400 mg bid	69/72 (95.8%)	48/69 (69.6%)
Sue <i>et al.</i> <sup>[55]</sup> , 2018	Vonoprazan 20 mg bid AMO 750 mg bid CLA 400 mg bid	LAN 30 mg or RAB 10 mg or ESO 20 mg bid AMO 750 mg bid CLA 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.

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