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Rebamipide and its Application in Clinical Practice (Literature Review, Meta-Analysis and Personal Experience), Part II. Eradication of Helicobacter Pylori and Rebamipide

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ABSTRACT

Introduction: eradication of Helicobacter pylori (HP) is of great importance in faster scarring of ulcers, preventing recurrence of peptic ulcer disease and its complications, including bleeding, histological regression of acute and chronic gastritis, reducing the severity of atrophy of the gastric mucosa or its elimination with timely treatment, reducing the area of intestinal metaplasia, preventing the development of cancer, possible regression of MALT lymphoma in the early stages, positive effect in unexplained iron deficiency anemia, thrombocytopenic purpura and B12 deficiency anemia, to eliminate rosacea, acne and halitosis. In numerous publications in recent years, there has been a decrease in the effectiveness of anti-Helicobacter therapy (anti-H.p.).

A decrease in the effectiveness of anti-H.p. therapy led to a search for methods to optimize such therapy, one of which is the addition of the mucoprotective drug rebamipide.

The Aim: of our work was to evaluate the impact of the effectiveness of adding rebampide to various anti-H.p. dual therapy, triple therapy and quadruple therapy.

Methods: each topic of the drug's use was evaluated from the point of view of evidence-based medicine. 16 studies were included for evaluation: 6 with dual therapy, 8 with triple therapy (the study of Vyalov S.S., 2017 was excluded from the analysis due to the fact that it was presented as an abstract and rebamipide was administered at a dose of 100 mg 2 times a day – off lable), and 2 with quadruple therapy.

Results: of the 6 studies dual PPIs-based anti-H.p. therapy, 4 showed no significant differences in H.p. eradication, with $p>0.05$, while 2 showed significant differences, with $p<0.05$. But with the total addition of all patients in the groups without rebamipide and with rebamipide and the calculation of the average H.p. eradication rate in the corresponding group: out of 251 patients in the group of anti-Hp regimen without rebamipide, 153 achieved eradication - 61.7%, and in the group with rebamipide out of 368 patients 280 – 75.6% (an increase of 13.9%), the differences are statistically significant, at $p<0.01$. The meta-analysis of triple PPIs-based anti-H.p. therapy showed that when comparing the rebamipide groups with the control group, none of the studies showed a significant difference in the effectiveness of H. pylori eradication, $p>0.05$. In the total analysis, the number of patients who participated in the study groups with rebamipide was 254, compared to 159 patients in the control groups without rebamipide. The mean eradication rate of H. pylori in the rebamipide groups was 92.2%, compared to 84.9% in the control groups without rebamipide, with a significant difference at $p<0.05$. The addition of rebampide to quadruple therapy with bismuth tripotassium dicitrate increases the H. pylori eradication rate to more than 90%, promotes earlier relief of the disease symptoms, and eliminates endoscopic changes in the gastric and duodenal mucosa.

Conclusions: thus, the inclusion of rebamipide in the anti-Hp regimen creates a trend towards increased eradication of Helicobacter pylori infection, which is most pronounced when dual anti-Hp therapy is administered. However, the main effect of rebamipide is its influence on the protective abilities of the epithelium of the stomach and duodenum, reducing the severity of chronic gastritis activity, which is very important for further treatment after eradication.

Keywords: Rebamipide, Eradication, Helicobacter Pylori.

Introduction

Eradication of Helicobacter pylori (HP) is of great importance in faster scarring of ulcers, preventing recurrence of peptic ulcer disease and its complications, including bleeding, histological regression of acute and chronic gastritis, reducing the severity of atrophy of the gastric mucosa or its elimination with timely treatment, reducing the area of intestinal metaplasia, preventing the development of cancer, possible regression of MALT lymphoma in the early stages, positive effect in unexplained iron deficiency anemia, thrombocytopenic purpura and B12 deficiency anemia, to eliminate rosacea, acne and halitosis.

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In numerous publications in recent years, there has been a decrease in the effectiveness of anti-Helicobacter therapy (anti-H.p.). Predictors of low effectiveness of anti-H.p. therapy include: low compliance, antibacterial resistance, inadequate acid suppression, polymorphism of the CYP2C19 (*1/*1, *1/*1 + *17, *1/*1 + 17/*17) and MDR1 gene (C3435T) – T/T genotype, polymorphism of the interleukin 1β gene (C-511T) – C/C genotype, high degree of contamination of the gastric mucosa H. pylori, presence of H.p. in the oral cavity, Cag A negative strains and vacA s2 genotype, dup A gene of Helicobacter pylori, hyperacidity, smoking, alcohol consumption, low antioxidant activity, errors in the prescription of anti-H.p. regimen, age over 50 years, use of products that reduce the pH in the stomach (citrus juices).

A decrease in the effectiveness of anti-H.p. therapy led to a search for methods to optimize such therapy: targeted therapy taking into account antibacterial resistance or/and CYP2C19 polymorphism, an increase in the duration of the regimen, an increase in the dose or frequency of administration of anti-H.p. regimen components (proton pump inhibitors - PPIs or antibiotics), the use of new stronger acid-suppressive drugs (Potassium-Competitive Acid Blockers – P-CAB), the use of 3 antibacterial drugs at the same time, the use of new antibacterial drugs, the control of acid production during the anti-H.p. regimen, the combination of anti-H.p. therapy and oral sanitation (elimination of gingivitis, periodontitis, etc.), individualized anti-H.p. therapy, taking into account characteristics of micro- and macroorganisms, adjuvant use of pro- or prebiotics, synbiotics, addition of colloidal bismuth subcitrate, inclusion of rebamipide in the anti-H.p. regimen, effect on the H.p. biofilm, and others.

The Aim of our Work was to Evaluate the Impact of the Effectiveness of Adding Rebamipide to Various Anti-H.P. Dual Therapy, Triple Therapy and Quadruple Therapy

All available sources of information on anti-H.p. therapy with the inclusion of rebamipide were evaluated. Our work was a continuation of the previous article with an assessment of the pleiotropic effects of rebamipide [1]. The first works on the inclusion of rebamipide in the anti-helicobacter regimen were published in 1996. We analyzed data on the use of rebamipide in anti-H.p. treatments (Pubmed/Medline, Cochrane Library, Embase, Scopus, Google Scholar, Web of Science, Russian Science Citation Index – e-library.ru, Russian Gastroenterological Association, AGA, ACG journals, and many others Russian and foreign sources). Each topic of the drug's use was evaluated from the point of view of evidence-based medicine. 16 studies were included for evaluation: 6 with dual therapy, 8 with triple therapy (the study of Vyalov S.S., 2017 was excluded from the analysis due to the fact that it was presented as an abstract and rebamipide was administered at a dose of 100 mg 2 times a day – off lable), and 2 with quadruple therapy (see Table1).

Table 1: Characteristics of included studies of eradication of H. pylori with Rebamipide.

Author	Country	Population, mean age, M/F	Reb+ mode	Slave mode (-)
Saita H., et al. 1996 [2]	Japan	n=60.	Lans 30 мг+ Am 500 mg b.i.d. – 14 days + Reb 100 mg t.i.d. – 8 weeks.	Lans 30 мг+ Am 500 mg b.i.d. – 14 days.
Hahm K.B., et al. 1998 [3]	Korea	n=57. Patients with GU and/or DU. 1-st/2-nd, n=21/36.	Lans 30 mg OD + Am 500 mg t.i.d. – 14 days + Reb 100 mg t.i.d. – 14 days.	Lans 30 mg OD + Am 500 mg t.i.d. – 14 days.
Kato M., et al. 1998 [4]	Japan	n=102. Patients with GU.	Lans 30 mg OD + Am 500 mg t.i.d. – 14 days + Reb 100 mg b.i.d. – 8 weeks.	Lans 30 mg OD + Am 500 mg t.i.d. – 14 days.
Nebiki H., et al. 1998 [5]	Japan	n=120. Patients with GU and DU 1-st group/2-nd, n=60/60.	Om 20 mg b.i.d + Am 500 mg + Reb 100 mg t.i.d..– 14 days.	Om 20 mg b.i.d + Am 500 mg t.i.d. – 14 days.
Fujioka T., et al. 2003 [6]	Japan	n=206. Patients with GU. 1-st group/2-nd: n=104/102. Analyzed 1-st/2-nd groups, n=82/78. 51.5/50.1 years; M – 81/77.	Lans 30 mg b.i.d. + Am 500 mg b.i.d. – 14 days + Reb 100 mg t.i.d. – 8 weeks.	Lans 30 mg b.i.d + Am 500 mg b.i.d. – 14 days, Plaunatol 240 mg/d – 12 weeks.
Bakulina N.V. et al., 2025 [7]	Russia	n=246. Patients with H. pylori. 1 group: AmPPI – n=24. 2 group: RebAmPPI - n=121. 3 group: AmClarPPI – n=101, 44.7/46.6/46.3 years. M – 9/38/35; W - 15/83/66.	Eso 40 mg + Am 1000 mg + Reb 100 mg t.i.d. – 14 days.	Eso 40 mg + Am 1000 mg t.i.d. – 14 days. Eso 20 mg + Am 1000 mg + Clar 500 mg + VTD 240 mg b.i.d. – 14 days.
Kimura M., et al., 1999 [41]	Japan	n-53.	Lans 30 mg OD - 8 weeks. + Am 1500 mg/day + Clar 500 mg/day - 7 days + Reb 300 mg/day – 12 weeks.	Lans 30 mg - 8 weeks. + Am 1500 mg/day + 500 mg/day - 7 days + Plaunatol – 12 weeks.
Lee D.S., et al., 2000 [42]	Korea	n=82. Patients with GU and DU. 1 group: OCAR – n=62. 2: OCA – n-20.	Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. + Reb 100 mg t.i.d. – 14 days.	Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. – 14 days.

Nomura H., et al. 2000 [43]	Japan	n=15. Patients with acute gastritis. Group A – n=5. LACR after 24 hours from onset of the disease. Group B – n=5. Only Lansoprazole. Group C – n=5. LACR afterз 4-6 days from onset of the disease. Average age 35.5 years; Man 11, women 4.	Lans 30 mg + Clar 400 mg + Am 1000 mg + Reb 300 mg/ day – 7 days.	Lans 30 mg OD – 7 days.
Vyalov S.S., 2017 [44]	Russia	n=160. Patients with gastroduodenal pathology. 1-st group: n=80. RebPPIAmC. 2-nd group: n=80. PPIAmClar	Eso 40 mg + Am 1000 am + Clar 500 мг b.i.d. + Reb 100 mg t.i.d. – 14 days.	Eso 40 mg + Am 1000 mg + Clar 500 mg b.i.d. – 14 days.
Dicheva D.T., et al., 2018 [45]	Russia	n=54. Patients with GU or DU. 1-st group – n=23. OA. 2-я: n=31. OCAR. Average age 53 years; M – 32, W – 22.	Om 20 mg + Clar 500 mg + Am 1000 мг b.i.d. + Reb 100 mg t.i.d. – 10 days.	Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. – 10 days.
Andreev D.N., et al., 2018 [46]	Russia	n=94. Patients with GU or DU. A group: n=36. OCA. B group: n=33. OKAP – 10 дней. C group: n=25. OKAP. Average age 41 years; M – 58, W – 36.	B: Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. + Reb 100 mg t.i.d. – 10 days. C: Om 20 mg + Clar 500 mg + Ам 1000 mg b.i.d. + Reb 100 mg t.i.d. – 10 days, then Reb 100 mg t.i.d. – 20 days.	Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. – 10 days.
Korobeynikova E.R, Shkatova E.Yu., 2019 [47]	Russia	n=54. Patients with GEr and DEr. 1-st group – n=36. PAmClarReb. 2-nd group – n=18. PAmClar. Average age 21.0/20.1 years. All man.	Pant 40 mg +Am 1000 mg + Clar 500 mg b.i.d. + Reb 100 mg t.i.d. – 14 days.	Pant 40 mg + Am 1000 mg + Clar 500 mg b.i.d. – 14 days.
Garbuzova OG, Kaiumova ER., 2020. [48]	Russia	n=61. Patients with ErUinjG & Duodenum. 1 group: n=30. RabAmClar. 2-group: n=31. RabAmClarReb. Average age by group: 51/63 years. M/W in 1-st/2-nd groups 10/20 и 15/16.	Rab 20 mg + Am 1000 mg + Clar 500 mg b.i.d. – 14 days.	Rab 20 mg + Am 1000 mg + Clar 500 mg b.i.d. – 14 days + Reb 100 mg t.i.d. – 30 days.
Simanenkov V.I. et al., 2017 [49]	Russia	n=60. Patients with ErUInjG & Duodenum. 1 group: OmClarAm 2 group: OmClarAmBTD 3 group: OmClarAmReb Average age 40.98 years. M - 11, W - 49.	Om 20 mg + Clar 500 mg + Am 1000 mg + b.i.d – 10 days + Reb 100 mg t.i.d. – 30 days.	Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. – 10 days. Om 20 mg + Clar 500 mg + Am 1000 mg + VTD 240 mg b.i.d. – 10 days.
Kim J., et al., 2018 [50]	Korea	n=277. 1 group: ConQuadrother (n=118). 2 group: ConQuadrotherReb (n=85). 3 group: СопKQuadrotherEc (n=74)	Lans 30 mg + Am 1000 mg +Metro 500 mg + Clar 500 mg + Reb 100 mg b.i.d. – 10 дней.	Lans 30 mg + Am 1000 mg + Metro 500 mg + Clar 500 mg b.i.d. – 10 days. Lans 30 mg + Am 1000 mg + Metro 500 mg + Clar 500 mg + Ecabet 1000 mg b.i.d. – 10 days.

Lans – lansoprazole, Am – amoxicillin, Reb – rebamipide, PPI – proton pump inhibitor, Clar – clarithromycin, BTD – bismuth tripotassium dicitrate. UG – ulcer gastric. UD – ulcer duodenum. GEr – Gastric Erosion, DEr – Duodenal Erosion. AmPPI – amoxicillin + proton pump inhibitor. RebAmPPI – rebamipide + amoxicilli + proton pump inhibitor. AmClarPPI – amoxicillin + clarithromycin + proton pump inhibitor. OCAR – omeprazole + clarithromycin + amoxicillin + rebamipide. OCA – omeprazole + clarithromycin + amoxicillin. LACR – lansoprazole + amoxicillin + clarithromycin + rebamipide. RebPPIAmClar – rebamipide + proton pump inhibitor + amoxicillin + clarithromycin. PPIAmClar - proton pump inhibitor + amoxicillin + clarithromycin. PAmClarReb – pantoprazole + amoxicillin + clarithromycin + rebamipide. PAmClar – pantoprazole + amoxicillin + clarithromycin. RabAmClar – rabeprazole + amoxicillin + clarithromycin. RabAmClarReb – rabeprazole + amoxicillin + clarithromycin + rebamipide. OmClarAm - omeprazole

+ clarithromycin + amoxicillin + bismuth tripotassium dicitrate. ConQuadrother – concomitant quadrotherapy. ConQudrother – concomitant quadrotherapy with rebamipide. ConQuadrotherEc – concomitant quadrotherapy with ecabet. M – man, W – women.

The Importance of Rebamipide in Dual PPIS-Based Anti-H.p. Therapy

A meta-analysis of the inclusion of rebamipide in dual anti-H.p. therapy is presented in Table 2. The effectiveness of rebamipide in the eradication of helicobacter pylori in PPIs-based dual anti-Hp therapy was evaluated.

Table 2: Efficacy of dual PPI-based anti-Helicobacter therapy with rebamipide

Study	Groups (n)		Eradication in control group, %	Eradication in group with Rebamipide, %	p
	1-st without Rebamipide	2-nd with Rebamipide			
Saita H., et al. 1996 [2]	27	33	55.6	75.8	NS, >0.05
Hahm K.B., et al. 1998 [3]	21	36	57.1	75.0	NS, >0.05
Kato M., et al. 1998 [4]	45	38	46.7	68.4	S, <0.05
Nebiki H., et al. 1998 [5]	56	58	55.4	75.9	S, <0.05
Fujioka T., et al. 2003 [6]	78	82	67.9	64.6	NS, >0.05
Bakulina N.V., et al. 2025 [7]	24	121	87.5	94.0	0.06
6 studies In total	251	368	MavPP = 61.7	MavPP = 75.6	p<0.01

NS – not significant. The differences were not significant in the three studies. In the group without rebamipide, the eradication rate was 61.7% compared to 75.6% in the group with rebamipide, p<0.01. av – average. PP – per protocolum.

Of the 6 studies, 4 showed no significant differences in H.p. eradication, with p>0.05, while 2 showed significant differences, with p<0.05. But with the total addition of all patients in the groups without rebamipide and with rebamipide and the calculation of the average H.p. eradication rate in the corresponding group: out of 251 patients in the group of anti-Hp regimen without rebamipide, 153 achieved eradication - 61.7%, and in the group with rebamipide out of 368 patients 280 – 75.6% (an increase of 13.9%), the differences are statistically significant, at p<0.01. Is the H. pylori eradication rate with rebamipide optimal when using dual anti-H.p. therapy ? The answer is definitely no, as the target rate should be >90%. Can we recommend this regimen ? Absolutely not, as it would violate ethical standards, as we would be recommending a treatment regimen that does not lead to effective treatment in almost one-third of cases. This would increase the total cost of subsequent treatment courses, consultations, and research, as well as the workload of healthcare professionals and the use of healthcare resources without achieving the desired results. On the other hand, there is a trend towards increasing the rate of H. pylori eradication, which does not reach the optimal value. The rate is 20% lower than the optimal value, and therefore cannot be used in practice. It should also be noted that only one of the six studies presented met the requirements of evidence-based medicine: the randomized, double-blind, placebo-controlled study by Fujioka T. et al. The other studies did not meet these criteria. In the study by Fujioka T. and colleagues, the rate of H. pylori eradication was lower in the group of patients who also took rebumipide [2-6], but it should also be noted that the study used a low dose of amoxicillin, 1000 mg a day (currently, when using dual anti-helicobacter therapy, it is recommended to use a higher dose of amoxicillin, 3 grams a day, divided into 750 mg 4 times a day or 1000 mg 3 times a day).

Our own experience of using rebamipide as part of dual PPIs-based anti-H.p. therapy has revealed the following data. The protocol included: group 1 - 103 patients. 41 women, 62 men. The average age is 47.6 years. Patients in this group took rabeprazole 20 mg rabeprazole 3 times a day and amoxicillin 1000 mg 3 times a day for 14 days plus rebamipid 100 mg 3 times a day for 30 days. There were 51 patients in group 2. 22 Women, 29 men, average age 47.3 years. Group 2 patients took rabeprazole 20 mg 3 times a day and amoxicillin 1000 mg 3 times a day for 14 days. Eradication control was carried out no earlier than 4 weeks after discontinuation of anti-Hp therapy. The comparison groups did not have statistically significant characteristics that could influence the final results of the study. In group 1, 95 out of 103 patients had eradication from all those who entered the protocol 92.2% (Intention to treat - ITT) and 95 out of 102 paients who completed the protocol 93.1% (per protocolum - PP). In group 2, 41 patients out of 52 patients had eradication 78.8% (ITT), 41 patients out of 51 who completed the protocol 80.4% (PP). The differences in eradication rates between groups 1 and 2 are not significant. In each group one patient did not complete the protocol - a pronounced allergic reaction. Our study findings are consistent with data of study Bakuluna N.V., et al. of dual anti-H.p. therapy data. Both studies used high doses of PPIs and amoxicillin. The choice of PPIs was justified by the data of our earlier analysis of the CYP2C19 genotypic polymorphism in patients of our gastroenterology department in St. Petersburg (n=3157) - see Figure 1.

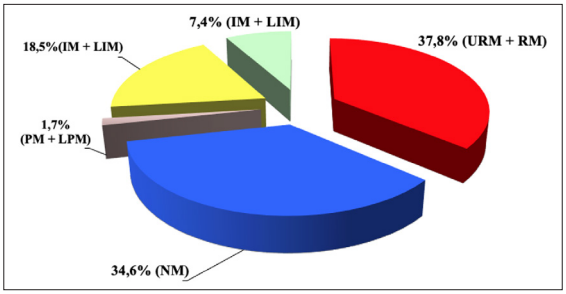

Figure 1: CYP2C19 genotypic polymorphism in St. Petersburg (n=3157).
URM – ultrarapid metabolizer, RM – rapid metabolizer, NM – normal metabolizer, IM – intermediate metabolizer, LIM – likely intermediate metabolizer, PM – poor metabolizer, LPM – likely poor metabolizer, IndM – indeterminate metabolizer.

A previous meta-analysis of dual anti-Helicobacter therapy with the addition of rebamipide was conducted by Nishizawa T et al., 2014 [8]. A distinctive feature of their meta-analysis was the inclusion of both dual and triple anti-Helicobacter therapies. Our meta-analysis included only dual anti-H.p. therapy options and the study by Bakulina N.V. et al. The heterogeneity of these studies should be noted. Only in the study by Bakulina N.V. were doses of amoxicillin 1000 mg 3 times a day used that were adequate for dual anti-H.p. therapy (it is also possible to use 750 mg 4 times a day against the background of adequate acid suppression). In the studies by Saita H., et al., Hahm K.B., et al., Kato M., et al., Nebiki H., et al., the doses of amoxicillin were 2 times lower – 1500 mg a day, in the study by Fujioka T., et al., the dose of amoxicillin was 3 times lower - 1000 mg a day. In the study by Kato M. et al., rebamipide was used at a dose of 100 mg twice daily, which is contrary to the instructions (off-label). Adequate doses of amoxicillin as part of anti-H.p. therapy against the background of adequate acid suppression contributed to a statistically significant increase in the H. pylori eradication rate, which reached the required values of >90% (94.0% - PP). Compared with the other 5 studies, the increase ranged from 18.1% to 29.4% (differences are statistically significant). In this case, dual anti-Helicobacter therapy with adequate doses of acid-suppressive and antibacterial drugs in combination with rebamipide can be recommended both for first-line treatment and for repeated courses of treatment after an unsuccessful eradication attempt.

In the future, it is possible that the introduction of P-competitive acid blockers (P-CAB) into the anti-H. pylori regimen will increase the effectiveness of eradication, and the addition of rebamipide may achieve optimal target values. Currently, several studies have been published that combine vonoprazan 20 mg twice daily with low or high doses of amoxicillin for 7 or 14 days, tegoprazane 50 mg b.i.d and amoxicilline 1000 mg t.i.d. – 14 days [9-39]. In the available literature, P-CAB are represented by the following drugs: vonoprazan, tegoprazan, fexuprazan, keverprazan, and revanprazan. Of these, vonoprazan, tegoprazan, and keverprazan are indicated for the eradication of H. pylori. In a study by Fan Y and co-authors, which examined the effectiveness of dual anti-H.p. therapy with tegoprazane and amoxicillin, it was shown that the 14-day variant of dual therapy with tegoprazane and amoxicillin was not inferior to bismuth-containing quadrotheria (90.3% versus 91.8% per protolum), while the 10-day course did not lose (the optimal values of H. pylori eradication are only 67% - per protocolum) [36].

A meta-analysis of 33 randomized controlled trials revealed fluctuations in H [9-41]. pylori eradication rates during double vonoprazane-based antihelicobacter therapy with a high dose of amoxicillin 3 grams a day from 65.1% to 98.5% (13 RCTs) – (ITT) and from 76.0% to 98.5% - PP (MavPP = 91.6%). The dual vonoprazane-based anti-H.p. therapy regimen with a high amoxicillin (3 grams) content and a duration of 14 days is characterized by fewer adverse events and high compliance than conventional quadrotherapy options with or without bismuth, or triple therapy, therefore rebamipide can be used with this regimen to optimize and obtain even higher rates of H. pylori eradication, reaching optimal taking into account the positive pleiotropic effects of rebamipide on the gastric epithelium, especially in erosive and ulcerative lesions of the gastric mucosa and duodenum. Dual tegopran-based anti-H.p. therapy with amoxicillin 3 grams a day was from 88.2% to 90.3% (2 studies) – MavPP = 89.25%. Dual keverprazan-based anti-H.p. therapy with amoxicillin 3 grams a day was 93.99% - per protocolum, Comparing the average rates of dual PPI-based and vonoprazan-based anti-H.p. therapy the differences between them are statistically significant, respectively 58.1% vs. 91.8% (completed treatment – per protocol). As previously mentioned, the addition of rebampide to double-based PPIs anti-H.p. therapy increased the eradication rate by 12.8% [8].

Metaanalisis of Rokkas T, et al, 2025 compared the efficacy and safety of potassium-competitive acid blockers in dual, triple, and quadruple regimens for first-line anti-Hp therapy and came to the conclusion that dual anti-Hp therapy with P-CAB was ranked first for efficacy with the best-integrated efficacy-safety profile [42]. The addition of rebamipide to dual drug therapy based on proton pump inhibitors or P-competitive acid blockers may not only increase H. pylori eradication, but also have other positive effects of rebamipide (reduction in the severity of inflammation in the gastric mucosa, anticarcinogenic effect, since rebamipide helps to reduce the area of atrophy with long-term use).

The advisability of including P-competitive acid blockers is indicated in such documents as the AGA Clinical Practice Update on Integrating Potassium-Competitive Acid Blockers Into Clinical Practice and Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report [43,44].

Table 3: Efficacy of P-CAB-based dual anti-Helicobacter therapy with rebamipide

Study	n	Eradication H. pylori	Notes
Suzuki S., et al., 2020 [9].	1-st: Von 20 mg + Am 750 mg – b.i.d. – 7 days. (n=168). 2-nd: Von 20 mg + Am 750 mg + Clar 200 mg b.i.d. – 7 days (n=167).	1-st: ITT – 84.5%; PP – 87.1%. 2-nd: ITT – 89.2%; PP – 90.2%. The diffenences are not significant, p=0.372.	Eradication of H.p. in clarithromycin-resistant strains was 92.3% versus 76.2%, p=0.048. There were no significant differences in adverse events.

Furuta T., et al., 2020 [10].	1-st: Von 20 mg b.i.d + Am 500 mg t.i.d. – 7 days. (n=56). 2-nd: Von 20 mg + Am 750 mg + Clar 200 mg b.i.d. – 7 days (n=56).	1-st: ITT – 92.9% 2-nd: ITT – 91.5%. The diffenences are not significant. Double therapy is not less than triple.	AEs did not have significant differences.
Gotoda T., et al., 2020 [11].	1. Von 20 mg + Am 750 mg b.i.d. – 7days (n=60). 2. Von 20 mg + Am 750 mg + Clar 200 mg 2 b.i.d. – 7 days (n=161).	1-st: ITT – 85%. PP – 86.4%. 2-nd: ITT – 82%. PP – 84.1%. The differences not significant..	AEs 6/60 – 10% in 1-st & 19.8% in 2-nd (p=0.108).
Horii T., et al., 2021 [12].	1. Von 20 mg + Am 750 mg b.i.d. – 7 days (n=19). 2. Von 20 mg + Am 750 mg + Clar 200 mg b.i.d. – 7 days (n=24)	1-st: ITT – 84.2%; 84.2%. 2-nd: ITT – 95.8%; 95.8%. The differences not significant, p=0.31.	AEs 7/19 – 36.8% versus 5 from 24 – 20.8% in 2-nd group, The differences not significant.
Chey W.D., et al., 2022 [13].	Efficacy was assessed in 218 patients. 1. Von 20 mg b.i.d + Am 1 gr t.i.d. – 14 days. 2. Lans 30 mg +Am 1 gr + Clar 0.5 gr b.i.d. – 14 days. 3. Von 20 mg + Am 1 gr + Clar 0.5 gr b.i.d. – 14 days.	PP 77.2%/68.5%/80.8% 69.6% и 65.8% in 1 & 3 groups for strains resistant to Clar. versus 31.9%в Lanoprazole-based triple therapy, p<0.001.	In total, diarrhea and dysgeusia were twice as common with lansoprazole-based therapy as with dual vonoprazole-based therapy.
Zuberi B., et al., 2022 [14].	Group A: Om + Am + Clar – 14 days (n=87) Group B: Von 20 mg + Am 1 gr b.i.d. – 14 days (n=92).	A – ITT – 83.9%; PP – 83.9%. B – ITT – 93.5%; PP – 93.5%.	AEs in group B were less often.
Lin Y., et al., 2022 [15].	1-st group: Von 20 mg b.i.d + Am 750 mg 4 times a day – 7 days (n=85). 2-nd group: Von 20 mg b.i.d + Am 500 mg 4 times a day – 7 days. 3-rd group: Von 20 mg b.i.d + Am 750 mg + Clar 500 mg b.i.d. – 7 days.	1-st: ITT – 63.5%; PP – 65.1%. 2-nd: ITT – 58.3%; PP – 66.2%. 3-rd: ITT – 60.7%; PP – 64.9%. Significant differences there were no between groups in eradication.	AEs there are not between groups.
Huangling, L., 2022 [16].	1-st: Von 20 mg + Am 1.0 b.i.d. – 14 days (n=100). 2-nd: Om 20 mg + Ам 1.0 + BTD b.i.d. – 14 дней (n=100)	1-st: ITT – 74.0%; PP – 74.0%. 2-nd: ITT – 54.0%; PP – 54.0%.	AEs significantly less often in 1-st group - 2% versus 9% in 2-nd group.
Chen C., et al., 2022 [17].	1-st: Von 20 mg b.i.d + Am 500 mg t.i.d. – 7 days (n=63) 2-nd: Eso 20 mg + Am 1.0 + Clar 0.5 b.i.d. – 14 days (n=63).	1-я: ITT – 95.2%; PP – 95.2%. 2-я: ITT – 84.1%; PP – 84.1%.	AEs significantly less often in 1-st group than in 2-nd group.
Hu E., et al., et al. 2023 [18].	1-st: Von 20 mg + Am 1.0 b.i.d. – 14 days (n=55). 2-nd: Von 20 mg b.i.d + Am 1.0 t.i.d. – 14 дней (n=55).	ITT – 89.1%. PP – 94.1%. ITT – 87.3%. PP – 95.9%	Low and high doses of amoxicillin did not have significant differences in the eradication of H.p. AEs 29.1% in 1-st group, 20.0% in 2-nd. (differences not significant, p=0.268).
Wang X., et al., 2023 [19].	1-st: Von 20 mg b.i.d + Ам 750 mg 4 times a day – 14 days (n=74). 2-nd: Rab 10 mg + VTD 220 mg, Am 1000 mg + Clar 500 mg b.i.d. – 14 days (n=77)	1-st: ITT – 94.6%; PP – 98.5% 2-nd: ITT – 87.0%; PP – 93.0% DVBT not lower than RBQT.	AEs in 1-st group 39.2% versus 79.2% in 2-nd group, p<0.000.
Li J., et al. 2023 [20].	1-st. Von 20 mg b.i.d + Am 750 mg t.i.d – 14 дней (n=75). 2-nd. Bismuth-containing quadruple therapy – 14 days (n=75). 3-rd. Von 20 mg + Am + Clar – 14 days (n=74)	1-я: ITT – 77.33%; PP – 90.63%. 2-я: ITT – 78.67%; PP – 96.72%. 3-я: ITT – 86.49%; PP – 92.75%. Double therapy is not lower than triple and quadruple therapy.	AEs 9.38% in 1-st group, 22.95% in 2-nd и 1.45% in 3-rd. DVBT had advantages over quadruple therapy in terms of adverse events, compliance and cost. 1:2:3 – 40$:45$:59$.

Meng et al., 2023 [21].	1-st: Von 20 mg b.i.d. + Am 750 mg t.i.d – 14 days (n=58). 2-nd: Eso 40 mg OD + Am 1.0 b.i.d. + Fur 100 mg b.i.d. CB 150 mg t.i.d.. – 14 days (n=57).	1-st: ITT – 84.5%; PP – 90.7%. 2-nd: ITT – 91.8%; PP – 90.6%. The differences between groups are not significant.	AEs significantly less often DVBT 7.4% versus 18.9%.
Yang F., et al., 2023 [22].	A. Von 20 mg b.i.d +Am 1.0 t.i.d. – 14 days (n=200). B. Von 20 mg b.i.d + Ам 1.0 t.i.d. – 10 days (n=200). C. Rab 20 mg + BTD/Tinidazole/Clar 4.2 b.i.d. – 14 days (n=200).	A. ITT – 86.0%; PP – 92.5% B. ITT – 87.0%; PP – 91.6% C. ITT – 70.5%; PP – 80.1%. Groups A & B versus C, p<0.05.	AEs significantly less often in group A 9.5% in B 8.5%, than in C 17%, p=0.003. Mode A has the best price/ performance ratio
Hu J., et al., 2023 [23].	1-st: Von 20 mg b.i.d + Am 1.0 t.i.d. – 14 days (n=97). 2-nd: Eso 20 mg + Am 1.0 b.i.d. + Metro 400 mg 4 times a day – 14 days (n=97).	1-st: ITT – 88.7%; PP – 90.7%. 2-nd: ITT – 91.8%; PP – 96.2%.	AEs significantly less often in 1-st group 16.7% , than in 2-nd group 38.4%.
Gaozhong L., et al., 2023 [24].	1-st: Von 20 mg b.i.d + Am 750 mg 4 times a day – 14 days (n=65). 2-nd: Lev 500 mg OD or Clar 500 mg b.i.d. + Metro 400 mg 4 times a day + CSB 220 mg b.i.d. – 14 days (n=65).	1-st: ITT – 87.7%; PP – 89.2%. 2-nd: ITT – 89.1%; PP – 92.1%. The differences between groups are not significant	AEs significantly less often in 1-st group 17.1% , than in 2-nd group 36.5%.
Peng X., et al., 2023 [25].	1-st: Von 20 mg b.i.d + Am 750 mg 4 times a day – 14 days (n=158) 2-nd: Eso 20 mg + CSB 220 mg + Am 1.0 + Clar 500 mg b.i.d. – 14 days (n=158)	1-st: ITT – 89.9%; PP – 97.9%. 2-nd: ITT – 81.0%; PP – 90.8%.	AEs significantly less often in 1-st group 19.0% , than in 2-nd group 43.0%.
Qian H.-S., et al., 2023 [26].	1-st: Von 20 mg + Am 1000 mg b.i.d. – 10 days (n=125). 2-nd: Eso 20 мg + CSV 200 mg, Am 1.0 + Clar 500 mg b.i.d. – 10 days (n=125)	1-st: ITT – 82.4%; PP – 85.1%. 2-nd: ITT – 88.0%; PP – 90.9%.	AEs significantly less often in 1-st group 8.2% , than in 2-nd group 23.6%.
Ting W., et al., 2023 [27].	1-st: Von 20 mg b.i.d + Am 500 mg t.i.d. – 7 days (n=60). 2-nd: Om 20 mg + Am 1.0 + Clar 500 mg + BTD 220 mg b.i.d. – 14 days (n=60).	1-st: ITT – 88.3%; PP – 91.4%. 2-nd: ITT – 73.3%; PP – 89.6%.	AEs significantly less often in 1-st group 23.7% than in 2-nd group 45.8%.
Ratana-Amornpin S., et al., 2023 [28].	1-st: Von 20 mg b.i.d + Am 500 mg 4 times a day – 14 days (n=21). 2-nd: Von 20 mg + Am 1.0 b.i.d. + Clar 1.0 OD – 14 days (n=27). 3-rd: Von 60 mg OD + Am 1.0 b.i.d. + Clar 1.0 OD – 7 days (n=26). 4-th: Von 20 mg + Am 1.0 b.i.d. + CSB 1048 mg + Clar 1.0 OD (n=26).	1-st: ITT – 66.7%; PP – 96.2%. 2-nd: ITT – 59.3%; PP – 96.2%. 3-rd: ITT – 92.3%; 4-th: ITT – 96.2%; The differences between 1, 2 и 3, 4 groups significant in favor of increasing the dose of vonoprazan or adding CSV.	AEs significantly less often in 1-st group 9.5%, than in others groups 40.7%, 34.6% and 30.8.
Liang X., et al., 2023 [29].	1. Von 20 mg + Am 1000 mg t.i.d. – 14 days (n=42). 2. Eso 20 mg + Am 1.0 + Fur 100 mg b.i.d. + VTD 220 mg t.i.d (n=43).	1-st: ITT – 76.2%; PP – 76.2%. 2-nd: ITT – 72.1% PP – 81.6%.	AEs significantly less often in 1-st group 4.8%, than in 2-nd group 18.4%.
Cheung K.S., et al., 2024 [30].	1. Von 20 mg + Am 1000 mg t.i.d. – 14 days (n=100). 2. Von 20 mg b.i.d + Am 1000 mg + Клар 500 mg b.i.d. - 14 days (n=98). 3. Von 20 mg b.i.d + Tetr 500 mg t.i.d + Metro 500 mg 4 times a day – 14 days (n=100).	1-я: ITT – 96.0%; PP – 96.7%. 2-я: ITT – 95.9% PP – 96.7%. 3-я: ITT – 92.0%; PP – 97.4%. Double therapy is not lower than triple and quadruple therapy.	AEs 39% in 1-st group 56.1% in 2-nd and 71.0% in 3-rd, differences significant, p<0.001. differences significant, in such AEs as dyspepsia, anorexia, nausea, dysgeusia, vomiting - p<0.001.

Yu J., et al., 2024 [31].	1. Von 20 mg b.i.d. + Am 750 mg t.i.d. + Succharamyces. boulardi 250 mg b.i.d. – 14 days (n=63). 2. Von 20 mg + Am 1.0 b.i.d. – 14 days (n=61).	1-я: ITT – 87.3%; PP – 87.3%. 2-я: ITT – 88.9%; PP – 91.8%. The differences between groups are not significant	With dual vonoprazan-based therapy, AEs are significantly less frequent, p=0.04
Chen C., et al., 2024 [32].	1-st: Von 20 mg b.i.d. + Am 1.0 t.i.d. – 14 days (n=45). 2-nd: Von 20 mg b.i.d. + Am 1.0 + Fur 100 mg + CSV 240 mgr b.i.d. – 14 days (n=45). 3-rd: Ilapr 5 mg + Am 1.0 + Fur 100 mg + CSB 240 mg b.i.d. – 14 days (n=45).	1-st: ITT 84.4%; PP 88.4%. 2-nd: ITT 84.4%; PP 92.7%. 3-rd: ITT 84.4%; PP 88.4%. The differences between groups are not significant.	AEs significantly less frequently in group 1 compared to groups 2 and 3, p<0.05.
Guohua L., et al., 2024 [33].	1-st: Von 20 mg b.i.d + Am 1.0 t.i.d. – 14 days (n=100). 2-nd: Eso 20 mg + CSB 220 mg + Am 1.0 + Clar 500 mg b.i.d. – 14 days (n=100).	1-st: ITT 91.0%; PP 94.8%. 2-nd: ITT 84.4%; PP 84.9%.	AES less often in. 1-st group 4.2%,than in 2-nd group 5.4%, differences not significant.
Kong Q., et al., 2024 [34].	n=369. 1-st: TA (n=184) T 50 mg b.i.d. + Am 750 mg 4 times a day – 14 days. 2-nd: EA (n=184) Eso 20 mg + Am 750 mg 4 times a day – 14 days.	1-st: ITT – 85.8%. PP –88.2%. 2-nd: ITT - 84.2%. PP – 88.5%. TA therapy was not inferior to EA therapy.	There are not differences in AEs and compliance between TA and EA therapy.
Yang X-Er., et al., 2025 [35].	A. Eso 20 mg + Am 1.0 4 times a day – 14 days. (n=53). B. Eso 20 mg + Ам 1.0 + Clar 500 mg b.i.d. + CSV 165 mg t.i.d. – 14 days (n=33). C. Von 20 mg b.i.d + Am 1.0 t.i.d. – 14 days (n=183). D: Von 20 mg + Am 1.0 + Clar 500 mg b.i.d. – 14 days (n=184).	A: ITT – 70.59%. PP – 93.94%. B: ITT – 83.49%. PP – 98.38%. C: ITT – 84.15%. PP – 96.75%. D: ITT – 84.15%. PP – 93.75%. DVBT not less than Vonoprazan triple therapy (p<0001).	No differences in AEs or achievement of clinical remission were found between the groups. Course price A – 82.8$: B – 75.2$; C – 40.1$; D – 48.5$.
Fan Y., et al., 2025 [36].	n=228. 1-st: TA (n=76) T 50 mg b.i.d. + Am 1.0 t.i.d. – 14 days. 2-nd: BCQT (n=76) – 14 days. 3-rd: TA (n=76) T 50 mg b.i.d. + Am 1.0 t.i.d. – 10 days.	1-st: 90.3%. PP. 2-nd: 91.8%. PP. 3-rd: 67.2%. PP. Differences between TA 14-day therapy not lower than 1st line and BCQT.	AEs and compliance is similar to BCQT - bismuth-containing quadruple therapy. TA 10-day therapy does not achieve the required effectiveness.
Song Z., et al., 2025 [37].	n=418. 1-st group: Von 20 mg b.i.d. + Am 1.0 t.i.d. – 10 days. 2-nd group: Von 20 mg b.i.d. + Am 1.0 t.i.d. – 14 days.	1-st: ITT - 83.3%. PP - 89.1%. 2-nd: ITT – 88.0%. PP – 95.3%. For first anti-H.p. therapy VA 10 days therapy does not recommended.	Voonoprazan exerted excellent gastric acid suppression during anti-H.p. therapy.
Liu Yu-X., et al., 2025 [38].	n=240. 1-st: Von 50 mg b.i.d. + Am 1000 mg t.i.d – 14 days. 2-nd: DSBIT	VA 14 days not less than DSBIT.	AEs less often in. 1-st group VA than in DSBIT.
Wei S., et al. [39].	n= 394. 1-st: KA. Kev 20 mg b.i.d + Am 1.0 t.i.d. – 14 days. 2-nd: EBQT. Eso 20 mg + Am 1.0 g + Clar 0.5 g + BPC 220 mg b.i.d. – 14 days.	1-st: ITT – 87.88%; PP – 93.99%. 2-nd: ITT – 84.18%; PP – 90.56% Differences between KA 14-day therapy not lower than in EBQT.	AES less often in. 1-st group KA, than in 2-nd group EBQT.

Zhang J-Y.,2026 [40].	n=375. 1-st: Von 20 mg b.i.d. + Am 1.0 g t.i.d. – 10 days. 2-nd:Von 20 mg b.i.d. + Am 1.0 + Clar 0.5 g b.i.d. – 14 days. 3-rd: Von 20 mg b.i.d. + Am 1.0 + Clar 0.5 g + B 240 mg b.i.d. – 14 days.	1-st: ITT – 92.0%; PP – 94.3%. 2-nd: ITT – 89.6%; PP – 94.9%. 3-rd: ITT – 88.8%; PP – 94.1%. The efficacy of dual vonoprazane-based therapy was not lower than VTT and VBQT.	AEs less often in. 1-st group VDT 6.4% than with VTT 36.0% and VBQT 49.6%, p<0.001. Compliance 93% - all groups, p=0.250.
Han Y-Y., et al., 2026 [41].	n=241. 1-st: Von 20 mg b.i.d.+ Am 1.0 g t.i.d – 14 days. 2-nd: Von 20 mg b.i.d. + Am 1.0 g + Min 100 mg + CBP 200 mg b.i.d. – 14 days.	1-st: mITT – 90.7%. PP - 91.4% 2-nd: mITT – 92.5%. PP – 93.7%. Differences are not significant, p>0.05.	AEs less often in group 1 - 8.4% versus 17.9% in group 2, p = 0.033.1000

Von – Vonoprazan, Am –amoxicillin, Clar – Clarithromycin, Lans – Lansoprazole, Om –Omeprazole, VT – bismuth tripotassium dicitrate, Eso – Esomeprazole, Fur – Furazolidon, CB – colloidal bismuth. BCQT– Bismuth-containing quadruple therapy, TA – Tegoprazane + Amoxicillin. Metro – Metronidazole.Tetr – Tetracycline. EBQT – esomeprazole-based bismuth quadruple therapy. BPC – bismuth potassium citrate. DSBIT – Drug sensitivity-based individualized therapy. Kev – keverprazan. B – bismuth. VDT – vonoprazane dual therapy. VTT – vonoprazane. Triple therapy. VBQT – vonoprazane bismuth quadruple therapy. Min – minocycline. CBP – colloidal bismuth pectin.

The Importance of Rebamipide in Triple PPIs-Based Anti-H.P. Therapy.

Eight studies [45-52] were selected for the meta-analysis of triple anti-Helicobacter therapy with rebamipide. None of the included studies were double-blind, placebo-controlled. The Vyalov S.S. study from 2017 was excluded during the sensitivity analysis. The study was presented at the UEGW (United European Gastroenterological Week) as an abstract, and the eradication rate was not specified as to whether it applied to all patients or those who completed the study, as the abstract did not specify the number of patients who completed the study. The dose of rebamipide used in patients off-label group (100 mg twice daily) was not specified. All studies on triple anti-H. pylori therapy are presented in Table 4. The meta-analysis showed that when comparing the rebamipide groups with the control group, none of the studies showed a significant difference in the effectiveness of H. pylori eradication, p>0.05. In the total analysis, the number of patients who participated in the study groups with rebamipide was 254, compared to 159 patients in the control groups without rebamipide. The mean eradication rate of H. pylori in the rebamipide groups was 92.2%, compared to 84.9% in the control groups without rebamipide, with a significant difference at p<0.05. The introduction of rebamipide into the anti-Helicobacter regimen not only creates a trend towards increased eradication rates, but also promotes better scarring of ulcers and healing of erosions, significantly reducing the activity of the inflammatory process in the gastric mucosa, which should be taken into account when conducting anti-Helicobacter therapy. In a study by Lee D.S. and colleagues, the activity of inflammation in the gastric mucosa before and after treatment was lower in patients who took additional rebumipide than in the group without rebumipide, 1.4 ± 0.6 vs. 1.8 ± 0.6, p<0.05 [46]. Similar data were obtained in the study by Andreev D.N. and co-authors: the inflammatory activity in the stomach was statistically significantly lower in the group in which patients took rebampide 6 weeks after the treatment, compared to the group in which the anti-helicobacter regimen was without rebampide, 2 ± 0.63 vs. 1.4 ± 0.52; p=0.0399 [50].

Table 4: Efficacy of triple PPI-based anti-Helicobacter therapy with rebamipide

Study	Quantity (n)	Eradication N.r.	Notes
Kimura M., et al, 1999 [45]	1-st (n=26): L 30 mg/d - 8 weeks. + Am 1500 mg/d + Clar 500mg/d - 7 days+ Reb 300 mg/d – 12 weeks. 2-nd (n=27): L 30 mg/d - 8 weeks. + Am 1500 mg/d + 500 mg/d 7 days + Plautol – 12 weeks.	1-st: ITT – 96.2%; PP – 96.2%. 2-я: ITT – 88.9%; PP – 88.9%. p>0.05.	The differences between the groups are not significant,
Lee D.S., et al., 2000 [46]	1-st (n=62): Om 40 mg + Clar 1.0 + Am 2.0 + Reb 300 mg – 2 weeks. 2-nd (n=20): Om 40 мг + Clar 1.0 + Am 2.0 – 2 weeks.	1-я: ITT – 90%. 2-я: ITT – 80%. the differences are not significant, p>0.05.	Ulcer healing in group 1 was 90% versus 85% in group 2 – NS. Statistically significant inflammation activity in the salivary gland before and after treatment in group 1 was lower than in group 2: 1.4 ± 0.6 versus 1.8 ± 0.6, p < 0.05. AEs between groups were not significant.

Nomura H., et al. 2000 [47]	1-st (n=5): L 30 mg OD + Am 1.0 g + Clar 400 mg b.i.d. + Reb 100 mg t.i.d. – 7 days. 2-nd (n=5) in 1 day after the onset of the disease L 30 mg OD + Am 1.0 g + Clar 400 mg b.i.d. + Reb 100 mg t.i.d. – 7 days, then L 30 mg OD – 3 weeks. 3-rd (n=5) in 4-6 days after the onset of the disease L30 mg OD + Am 1.0 g + Clar 400 mg b.i.d. + Reb 100 mg t.i.d. – 7 days, then L 30 mg – 3 weeks.	1-я: ITT – 100%; PP – 100%. 2-я: ITT – 88.9%; PP – 88.9%. 3-я: ITT – 100%; PP – 100%. The differences between groups 1 & and 3 & 2 are not significant, p>0.05.	There were no differences in AEs between groups. After 4 weeks of treatment, erythema persisted according to endoscopy data in only one patient in Group 2 and one in Group 3.
Vyalov S. S., 2017 [48]	1-st (n=80) E 40 mg + Am 1.0 g + Clar 500 mg + Reb 100 mg b.i.d. – 14 days. 2-nd (n=80) E 40 mg + Am 1.0 g + Clar 500 mg b.i.d. – 14 days.	1-я: 94% 2-я: 82%. Differences are significant, p<0.05.	In the 1st group, a trend towards increased eradication was noted compared to standard triple therapy.
Dicheva D.T., et al., 2018 [49]	1-st: (n=23) Om 20 mg + Am 1.0 g + Clar 0.5 g b.i.d. – 10 days. 2-nd: (n=31) Om 20 mg + Am 1.0 g + Clar 0.5 g b.i.d. + Reb 100 mg t.i.d.– 10 days.	1-я: ITT – 78.2%; PP – 81.8% 2-я: ITT – 83.8%; PP – 86.6%. p>0.05.	No differences in efficacy and safety were found between groups.
Andreev D.N., et al., 2018 [50]	1-st (n=36) Om 20 mg + Am 1.0 g + Clar 500 mg b.i.d. – 10 days. 2-nd (n=33) Om 20 mg + Am 1.0 g + Clar 500 mg b.i.d. + Reb 100 mg 3 t.i.d. – 10 days. 3- rd (n=25) Om 20 mg + Am 1.0 g + Clar 500 mg b.i.d. – 10 days + Reb 100 mgr t.i.d. – 20 days.	1-я: ITT – 77.7%; PP – 82.3% 2-я: ITT – 81.8%; PP – 84.4%. 3-я: ITT – 84.0%; PP – 87.5%. The differences between groups 1 and 3, 1 and 2 are not significant, p>0.05.	Erosive and ulcerative changes in the stomach and duodenum had a more pronounced epithelialization dynamics in the 3rd group. AEs did not have significant differences. In groups 1, 2, and 3, respectively, 22.2%, 24.2%, and 20%. Inflammatory activity in the serum after 6 weeks was statistically significantly lower in group 3 compared to group 1, 2 ± 0.63 versus 1.4 ± 0.52; p=0.0399.
Korobeynikova E.R, Shkatova E.Yu., 2019 [51]	1-я (n=36) Pant 40 mg Am 1.0 g + Clar 500 mg b.i.d. + Reb 100 mg t.i.d. – 14 days. 2-я (n=18) Pant 40 mg Am 1.0 g + Clar 500 mg b.i.d. – 14 days.	1-я: ITT – 91.7%; PP – 91.7% 2-я: ITT – 88.9%; PP – 88.9%. the differences between groups are not significant, p>0.05.	The increase in eradication of H. pylori. with the addition of Reb is 2.8%. Complete relief of pain in groups 1 and 2 was 97.2% and 94.5%. Epithelialization of erosions in groups 1 and 2 was 97.2% and 94.4%, respectively. After treatment, an increase in sialic acid levels was noted, reaching 1.78 in Group 1 versus 1.54 in Group 2. Positive morphological dynamics were noted.
Garbuzova OG, Kaiumova ER., 2020. [52]	1-st (n=30) Rab 20 mg + Am 1.0 g + Clar 500 mg b.i,d. – 14 days. 2-nd (n=31) Rab 20 mg + Am 1.0 g + Clar 500 mg b.i.d. – 14 days + Reb 100 mg t.i.d. – 30 days.	1-st: ITT – 83.3%; PP – 83.3%. 2-nd: ITT – 93.5%; PP – 93.5%. the differences are not significant, p >0.05.	In the 1st group, epithelialization of erosions and ulcers in 24 out of 30 patients was 80%, and in the 2nd group, in 27 out of 31 patients, it was 88%.
7 studies. Study's Vyalov S.S., 2017 was excluded	Total: patients with inclusion of rebamipide n=254; without rebamipide 159.	MavPP with the inclusion of rebamipide 92.2% versus MavPP without rebamipide 84.9%, the differences are significant, p<0.05	The addition of rebamipide to triple anti-H.p. therapy increases the eradication rate to over 90%, making this regimen optimal, accompanied by pronounced dynamics of endoscopic changes, reduced inflammatory activity in the gastric mucosa, and improved speed and quality of scarring.

L – Lansoprazole, Am – Amoxicillin, Clar – Clarithromycin. Reb – Rebamipide. Om – Omeprazole. NS – not significant. AEs – adverse events. MavPP – M average value per protocolum.

This effect of rebamipide is due to the enhancement of the protective properties of the gastric and duodenal mucosal epithelium (increased production of prostaglandin E2, mucus, anti-inflammatory and antioxidant effects of rebamipide, and improved blood circulation in the mucosal epithelium of the gastrointestinal tract).

The Importance of Rebampide in Anti-H.P. Quadruple Therapy [53,54].
The analysis of these studies proves that the addition of rebampide to quadruple therapy with bismuth tripotassium dicitrate increases the H. pylori eradication rate to more than 90%, promotes earlier relief of the disease symptoms, and eliminates endoscopic changes in the gastric and duodenal mucosa.

For all anti-helicobacter regimens with rebampide, increased H. pylori eradication rates are associated with impaired adhesion of H.p. to the gastric mucosa, suppression of H. pylori-induced effects such as tumor necrosis factor alpha (TNF-α) production, β-catenin induction, NF-κB activation, IL-8 production and neutrophil oxidative bursts, inhibition of Helicobacter pylori produced urease, which amplifies the mucosal cytotoxicity caused by the H. pylori.

Thus, the inclusion of rebamipide in the anti-H.p. regimen creates a trend towards increased eradication of Helicobacter pylori infection, which is most pronounced during double anti-H.p. therapy. However, the main effect of rebamipide is its influence on the protective abilities of the gastric and duodenal epithelium, reducing the severity of chronic gastritis, which is crucial for further treatment after eradication.

Despite the general trend in all variants of anti-H.p. rebamipide therapy, as in double, triple or quad therapy with an increase in the rate of eradication, respectively by 15.4% in double therapy (pooled data from the first five studies in Table 2 that did not use optimal doses of PPIs and amoxicillin) and summarized data from studies by Bakulina N.V. and amoxicillin and Starostin B.D. with optimal doses of PPIs and amoxicillin 9.4%, by 7.9% in triple therapy and by 9% in quadruple therapy. The presence of proven significant differences in the overall analysis of studies anti-H.p. therapy with rebamipide of the selected treatment option at $p<0.05$, it should be noted that almost all studies do not there were double-blind, placebo-controlled studies that there were contradictions in the studies, so in the Kim J study, during quadrotherapy with rebamipide, adverse events were statistically significantly more common in the rebamipide group, whereas in the study of Simanenkov V.I. and co-authors, this phenomenon was not noted.

Table 5: Efficacy of anti-Helicobacter quadruple therapy with rebamipide

Study	n	Eradication H. pylori	Notes
Simanenkov V.I., 2017 [53]	1-st (n=20): Om 20 mg + Clar 500 mg + Am 1000 mg b.i.d. - 10 days. 2-nd (n=20): Om 20 mg + Clar 500 mg + Am 1000 mg + BTD 240 mg b.i.d. – 10 days. 3-rd (n=20): Om 20 mg + Clar 500 mg + Am 1000 mg + BTD 240 mg b.i.d. – 10 days + Reb 100 mg t.i.d. – 28 days.	1-я: ITT – 75%; PP – 75%. 2-я: ITT – 85%; PP – 85%. 3-я: ITT – 95%; PP – 95%. Differences between 1 & 2, 2 & 3, 1 & 3 groups were not significant, p>0.05.	Four weeks after the anti-H.r. therapy course symptoms were completely resolved only in the rebamipide group, but persisted in groups 1 and 2, at 30% and 15%, respectively. Four weeks after the end of anti-H.r. therapy, endoscopic changes were absent in 13 of 18 patients in group 1; in 14 of 14 in groups 2 and 3. Duodenal erosions were present in 3 (16.6%) versus 0 (0%) patients. Duodenal ulcers were present in 2 (11.1%) patients in group 1 and 1 in groups 2 and 3 (6.6%) Erosions in the duodenum in 3 (16.6%) in the 1st group versus 0 (0%) in groups 2 and 3, cicatricial and ulcerative deformity duodenum 2 (11.1%) in the 1st group, 1 in groups 2 and 3 (6.6%).
Kim J., et al., 2018 [54]	1-st (n=118): Lans 30 mg + Clar 500 mg + Am 1000 mg + Metro 500 mg b.i.d.– 10 days. 2-nd (n=85): Lans 30 mg + Clar 500 mg + Am 1000 mg + Metro 500 mg + Reb 100 mg b.i.d. – 10 days. 3-rd (n=74): Lans 30 mg + Clar 500 mg + Am 1000 mg + Metro 500 mg + Ecabet 1000 mg b.i.d. – 10 days.	1-st: ITT – 82.8% (97/118). 2-nd: ITT – 90.6% (77/85). 3-rd: ITT – 89.2% (66/74). Differences between 1 & 2, 2 & 3, 1 & 3 groups NS, p>0.05.	AEs were reported in groups 2 and 3 43/85 (50.6%) and 33/74 (44.6%), and in group 1 38/118 (32.2%), p=0.03 (the differences are significant). Compliance had no significant differences between the groups. The risk of eradication insufficiency increased significantly with reduced compliance, p=0.05

2 studies.	Total: patients with rebamipid inclusion n=105; without Reb – 138 (group 1 was not included in the study of Simanenkov V.I. et al. (triple therapy) and the 3rd group in the study of Kim J., et al.(a variant with a mucoprotective drug)	MavITT with the inclusion of rebamipide 92.8% versus MavITT without rebamipide 83.8%, the differences are significant, $p<0.05$	The addition of rebamipide to antihelicobacter therapy (quadrotherapy) exceeds the eradication rate by more than 90%, which makes this regimen optimal, helps to reduce symptoms and eliminate endoscopic changes.

Om – omeprazole, Am – amoxicillin, Clar – clarithromycin, BTD – bismuth tripotassium dicitrate, Rebб – rebamipide, Lans – lansoprazole, Metro – metronidazole. NS –not significant. AEs – adverse events. Doses of rebamipide in study of Kim J., et al were are not optimal (off lable).

Thus, the inclusion of rebamipide in the anti-Hp regimen creates a trend towards increased eradication of Helicobacter pylori infection, which is most pronounced when dual anti-Hp therapy is administered. However, the main effect of rebamipide is its influence on the protective abilities of the epithelium of the stomach and duodenum, reducing the severity of chronic gastritis activity, which is very important for further treatment after eradication.

Rebamipide is the only drug with a proven anti-gastric effect and the ability to eliminate gastric mucosa atrophy, which confirms the expediency of its inclusion in any anti-Helicobacter regimen, as well as its long-term use after an anti-Helicobacter regimen.

A positive effect of rebamipide as a gastroprotector and anti-inflammatory drug during H. pylori eradication therapy on the healing of gastric ulcers was also noted. A randomized, placebo-controlled study showed that the inclusion of rebamipide in the anti-H.p. regimen was accompanied by a higher healing rate in the rebamipide group (104/130) 80.0% compared to placebo (82/124) 66.1% - per protocol; 70.1% (108/154) versus 60.5% (89/147) - intention to treat [55].

The preventive effect of rebamipide is due to the suppression of C11b expression on neutrophils and the production of the pro-inflammatory cytokine IL-8 by gastric epithelial cells, increased levels of prostaglandin E2 in the gastric mucosa [56].

The feasibility and justification for the use of rebamipide in clinical practice as part of an anti-Helicobacter regimen, after the eradication of H. pylori, in order to achieve complete histological remission of chronic gastritis and regression of preneoplastic changes in the gastric mucosa (atrophy and metaplasia) is included in clinical recommendations, consensuses, and guidelines of various gastroenterological communities around the world:
The feasibility and justification for the use of rebamipide in clinical practice as part of an anti-Helicobacter pylori regimen, after the eradication of H. pylori, in order to achieve complete histological remission of chronic gastritis and regression of preneoplastic changes in the gastric mucosa (atrophy and metaplasia) is included in clinical recommendations, consensuses, and guidelines of various gastroenterological communities around the world: Clinical guidelines of the Russian Gastroenterological Association and the Endoscopic Society RENDO for the diagnosis and treatment of gastritis and duodenitis; New possibilities of cytoprotection in the treatment and prevention of diseases of the stomach and intestines (Resolution of the Expert Council and literature review); Asian Pacific Association of Gastroenterology task force recommendations on surveillance for Helicobacter pylori-associated gastric premalignant conditions; Clinical Practice Guidelines for Functional Dyspepsia in Korea and many others, and have also been reviewed in numerous research papers [57-77].

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