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Eradication of *Helicobacter Pylori* Infection: Past, Present, and Future

Baryshnikova NV[1]*, Uspenskiy YP[1] and Suvorov AN[2]

[1]Department of internal diseases, Pavlov First St-Petersburg State Medical University, Russian Federation

[2]Department of molocular microbiology, Science research Institute of Experimental Medicine, Russian Federation

***Corresponding author:** Natalia Baryshnikova, MD, PhD, Department of internal diseases, Pavlov First St-Petersburg State Medical University, 14, Vavilovykh Str, 195257 St-Petersburg, Russian Federation, Tel: +7-921-301-33-77, E-mail: baryshnikova_nv@mail.ru*

Abstract

This review is a comprehensive summary of different variants of anti-*Helicobacter pylori* therapy from past strategies to the current state of the art. Nowadays we see a progressive decreasing of eradication rate in many countries in case of use standard triple therapy. It can be associated with high clarithromycin resistance of *Helicobacter pylori*. Gradual increase in number of the used antibiotics, the increase in duration of treatment, use of new antibacterial compounds and schemes of treatment do not lead to a long-term positive effect on eradication rate and on preservation of risk of development of side reactions. It is necessary to pay active attention to new approaches to treatment and alternative options of therapy of an *Helicobacter pylori* infection. One of the most perspective methods of improving the efficacy of eradication can be the usage of probiotics, especially in addition to standard therapy. Probiotics have some mechanisms to influence on *Helicobacter pylori*: lactic acid production, synthesis of bacteriocins and antimicrobial metabolites, concurrence for adhesion sites, the reparation of the barrier function of the stomach mucosa, a decrease of inflammation and increase of immunity of infected humans. Bismuth subcitrate is very effective in eradication, cytoprotection, and atrophic changes regression and can be recommended for eradication schemes as classic quadrotherapy also as a 4th additional component in classic triple therapy.

Keywords

Helicobacter pylori, Eradication, Antibiotic resistance, Probiotics, Bismuth

Introduction

For last three decades, researchers consider *Helicobacter pylori* to be the hot topic and keep a strong focus on it. There are numerous lines of anti-*H. pylori* therapy. Since 80s up until now eradication therapy was constantly changing. It is being altered nowadays as well. Several lines of therapy didn't establish appropriate efficacy when others remain to be highly effective up until now. Along with old methods, there are active discussions on implementing new compounds and alternative methods to impair on this infection.

The stages of development of eradication therapy could be divided into two sub-periods: before Maastricht and after Maastricht, between which Fourth Maastricht Consensus era is a real state of the art. We see the high probability for new methods of treatment to take a turn, many of which are under development nowadays.

Past Treatment Strategies

Before maastricht consensus period

B.J. Marshall and J.R. Warren were the first who could isolate a microorganism in human stomach mucosa and the first who could cultivate it in 1982 [1]. After that, these scientists made several additional experiments confirm an important role of *Helicobacter pylori* (*Campylobacter pyloridis*) in the pathogenesis of chronic gastritis and ulcer disease. The main experiment was performed by B.J. Marshall who drank liquid with pure culture of this microorganism and after 10 days he have a symptoms, endoscopic and morphological evidence of acute gastritis and *H. pylori (C. pyloridis)* in stomach mucosa [2]. After that B.J. Marshall eradicated *H. pylori (C. pyloridis)*-associated gastritis using bismuth and metronidazole [3]. J.R. Warren и B.J. Marshall could show that antibiotics are effective in majority of cases of chronic gastritis and duodenal ulcer [3,4].

So in was an onset of an active investigation of the efficacy of different antimicrobial drugs in *H. pylori* eradication with detection of antibiotic resistance of microorganism (Table 1).

Table 1. Primary *H. pylori* resistance to antibiotics [5].

The main cause for formation of the secondary resistance to antibiotics is a genetic factor: e.g. change of level of an expression

Table 1: Primary *H. pylori* resistance to antibiotics [5].

Non-resistance	Resistance
B-lactams: penicillins (e.g. amoxicillin)	Cephalosporins (e.g. cephalexin, cephsulodin)
Macrolides	Polimixin
Tetracyclines	Sulfanilamides
Nitromidasols	Trimethoprim
Nitrofurans	Vancomycin
Fluoroquinolones	Non- ftor-quinolons
Rifamycins	Aminoglycosides
Bismuth	Antifungal

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of own genes due to the high genetic variability of *H. pylori*. Genetic changes of microbe can be associated with uncontrolled usage of antibiotics due to other diseases (e.g. usage of macrolides in patients with urogenital infections). Resistance to antibiotics is the important factor of low eradication rate. Already in B.J. Marshall work [4] it was revealed that all samples of a microorganism were sensitive to penicillin, erythromycin, tetracycline, cephalosporins, gentamicin and bismuth citrate and only 80% of the studied samples were sensitive to metronidazole or tinidazole [4]. At the time practitioners and researchers saw ways to overcome resistance to antibiotics by means of bismuth addition in schemes of treatment [6], which is actual method also nowadays.

Eradication therapy started as a monotherapy or double-antibiotic therapy.

Bismuth salts, especially colloid bismuth subcitrate, one of the first drugs which began to be used in *H. pylori* eradication [7,8]. Bismuth subsalicylate also have certain efficacy against this microbe: results of placebo-controlled trial shown that this drug suppressed growth of *H. pylori* in of 65% of patients and eradicated it in one patient [9].

The schemes which are containing bismuth and nitroimidazoles have shown significant clinical success. So, when comparing efficacy of different variants of an anti-Helicobacter therapy, it was shown that efficacy of *H. pylori (C pyloridis)* eradication scheme with colloidal bismuth subcitrate and tinidazole is more that 70% [10]. Schemes with omeprazole and bismuth also were in use at that time [11].

One of the first schemes of triple therapy included colloidal bismuth subcitrate, tetracycline and metronidazole with application period of 2-4 weeks. It was effective in 91-96% of patients [12,13]. Efficacy of triple therapy with bismuth, amoxicillin and metronidazole was higher than 80% [14].

Standard triple therapy: proton pump inhibitor (PPI), amoxicillin, and clarithromycin began to use in the middle of 90th in XX century [15]. Due to high efficacy this scheme was claimed as a gold standard for the treatment of *H. pylori* and became a worldwide recommended for first-line eradication [16]. In studies conducted during that time, standard triple therapy (7-14 days) was shown > 80% and even > 90% eradication success [17,18]. However, the subsequent efficiency of this treatment scheme decreased progressively. The core reason for such decrease is growth of *H. pylori* resistance to clarithromycin [16,19]. This research reflected the need for controlling level of *H. pylori* resistance to clarithromycin. It was recommended to avoid usage of this antibiotic if regional resistance level higher than 15-20% [20,21].

In the course of evolution of eradication therapy H_2-blockers were replaced with the PPI which are possessing higher anti-acid activity and not having so expressed withdrawal syndrome that allowed them to have a primary position in different anti-*H. pylori* schemes [22].

Maastricht consensus period

Since today, there were four Maastricht Consensus: postulates of First Maastricht Consensus have been published in 1997, Second - in 2000, Third - in 2007 and Fourth - in 2012.

According to First Maastricht Consensus [17] for the therapy of *H. pylori* infection the triple therapy is recommended, consisting of a PPI, and two of the following: clarithromycin, a nitroimidazole (metronidazole or tinidazole) and amoxicillin. In various combinations it scheme was recommended to use as a first-line therapy. At that moment, triple therapy (bismuth tripotassium dicitrate plus metronidazole and tetracycline) have lower efficacy than PPI, clarithromycin, and amoxicillin therapy. It can be explained by two important mechanisms of PPI-antibiotic combination: anti-acid and antibacterial effects. It was recommended to use a standard dose of PPI (e.g. omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg [23]), twice a day and antibiotic combinations during 7 days such as:

a. metronidazole 400 mg twice daily (or tinidazole 500 mg twice daily) plus clarithromycin 250 mg twice daily;

b. amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily (advisable when metronidazole resistance is likely)

c. amoxicillin 500 mg three times daily plus metronidazole 400 mg three times daily (advisable when clarithromycin resistance is likely).

In case of no efficacy of first-line therapy, a second-line therapy should be selected after consideration of previous treatment and microbial sensitivities.

According to Second Maastricht Consensus [20] for the first-line therapy of *H. pylori* infection it was recommended triple therapy using a PPI or ranitidine bismuth citrate in standard dose (e.g. esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg, ranitidine bismuth citrate 400 mg) with clarithromycin (500 mg twice a day) and amoxicillin (1000 mg twice a day) or metronidazole (500 mg twice a day) for 7 days or longer (10-14 days). An H_2-blocker ranitidine bismuth citrate was included in eradication scheme because numerous studies demonstrating similar efficacy of ranitidine and PPIs [24,25]. Second-line therapy should use quadruple therapy with a PPI in standard dose, bismuth (120 mg four times a day), metronidazole (500 mg twice a day) and tetracycline (500 mg four times a day). Where bismuth is not available, second-line therapy should be performed by PPI triple therapy [20].

It is interesting that already in this period spoke about possibilities of probiotics and vaccines against *H. pylori* infection. Also at that time it was postulated about the importance of *H. pylori* resistance to clarithromycin as a factor of low eradication rate [26]. In case of high metronidazole resistance, it was recommended to use furazolidone [27].

According to Third Maastricht Consensus [21] for the therapy of *H. pylori* infection it was still recommended PPI-clarithromycin - amoxicillin – or metronidazole regimen, but only if the primary resistance to clarithromycin in the area is lower than 15% to 20% and prevalence of metronidazole resistance is lower than 40%. Several researchers have revealed that a 14-day rather than a seven-day treatment had a slight advantage in terms of treatment success [21]. Bismuth-based quadruple therapies (when available) are acceptable as alternative first-line therapy. For second-line therapy, bismuth-based quadruple therapies or PPI-amoxicillin or tetracycline and metronidazole are recommended. Third line therapy or rescue therapy is used after the determination of sensitivity of *H. pylori* to antibiotics.

Present treatment strategies

According to Fourth Maastricht Consensus [28] the following variants of eradication therapy showed the efficiency in large-scale, placebo-controlled researches (duration 7-14 days) and are recommended for clinical application:

1. The triple therapy including PPI plus clarithromycin and amoxicillin or metronidazole are still in use. The most recent data shows this combination has lost some efficacy and often allows the cure less than the 80% of patients [29].

2. Sequential treatment includes a 5-day period with PPI and amoxicillin, followed by a 5-day period with PPI plus clarithromycin and metronidazole (or tinidazole) in standard doses [30].

3. Three antibiotics (e.g. amoxicillin, calrithromycin and metronidazole) together with a PPI (non-bismuth quadruple therapy or concomitant therapy) [31,32].

4. The bismuth-containing quadruple therapy including PPI , bismuth salts, tetracycline and metronidazole esspessially in the same pill [33].

5. It is possible to use the triple therapy on the base of a

Table 2: The level of *H. pylori* resistance to clarithromycin (According recent Workshop of European Helicobacter Study) [37].

Country, number of patients (n)	Resistance to antibiotics, %						
	AMO	CLA	MTX	TETR	FTOR	RIF	FURAZ
Thailand [38], n = 400	5.2	3.7	3.6	1.7	7.7 - CIPRO 7.2 - LEVO	-	-
Laos [38], n = 119	-	1.6	-	-	13.4	-	-
Bhutan [38], n = 111	0	0	82.9	0	2.7	-	-
Myanmar [38], n = 52	0	0	36.5	0	5.8	-	-
Spain [39], n = 254	-	53.8	34.9	-	6.9 - LEVO	-	-
Greece [40], n = 77	3.9	47.7	21.5	-	6.2 - LEVO	-	-
Brasil [41], n = 72	-	12.5	-	-	11.1	-	-
Mongolia [42], n = 152	33	35	68.4	-	-	-	-
Iran [43], n = 58	27.21	30.37	81.64	42.4	-	-	-
Latin America [44]	4	12	53	6	15	-	3
New Zeeland [45]	-	16.4	49.3	0	9.5	-	-
Korea [46]	2.1	16	56.3	0	22.3	0	0
Korea [47]	14.9	23.7	-	-	28.4	-	-
Belgium [48]	0.8	13.3	26.1	-	23.8	-	-
Germany [49]	0	7.5	32.5	Менее 5	11.7	5	-
Ireland [50]	-	-	-	0	11.7	-	-
China [51]	0.1	21.5	95.4	-	20.6	0,1	-
De Francesco V et al. A systematic review of studies from many countries [52]	11.s2	17.2	26.7	5.9	16.2 - LEVO	1,4	-

Comment to table 2: AMO – amoxicillin, CLA – clarithromycin, MTX – methotrexate, TETRA – tetracyclin, FTOR – fluoroquinolone (CIP – ciprofloxacin, LEVO – levofloxacin), RIF – rifabutin, FURAZ – furazolidone.

levofloxacin (IPP, amoxicillin, levofloxacin) as an alternative scheme of treatment of rescue therapy [28].

Modern approach also suggests hybrid therapy: a 5-7-days dual therapy with a PPI (standard dose, twice a day) and amoxicillin (1000 mg, twice a day) followed by a 5-7-days quadruple therapy with a PPI (standard dose, twice a day), amoxicillin (1000 mg, twice a day), clarithromycin (500 mg, twice a day) and metronidazole (500 mg, twice a day) [34].

As one can see over the time the number of antibiotics and duration of treatment are progressively increasing. This can be a reason of raise in frequency of side effects of eradication such as colon dysbiosis and decrease of eradication rate due to formation of antibiotic resistance.

There are several problems that can reduce the efficacy of anti-*H. pylori* therapy (e.g. resistance to antibiotics, low patients compliance, usage of generics, etc.). One of the main factors of lower eradication success is a progressive growth of microorganism resistance to antibiotic especially to clarithromycin. It is revealed that high resistance of *H. pylori* to clarithromycin leads to catastrophic decrease of eradication therapy efficacy from 80-90% to 30-60% [35]. Summarized results of 20 European studies about efficacy of first-line therapy (PPI, amoxicillin and clarithromycin) in 2751 patients show that in case of clarithromycin resistance eradication rate decrease to 18,3% (in compare with 87,8% in case of infect of non-resistance *H. pylori* strains [36]. Nowadays we see worldwide tendency to growth *H. pylori* clarithromycin resistance (Table 2).

Table 2. The level of *H. pylori* resistance to clarithromycin (According recent Workshop of European Helicobacter Study) [37].

Significantly different results of *H. pylori* clarithromycin resistance are a way to differ treatment in various regions. For optimization of eradication schemes, Fourth Maastricht Consensus recommended different therapy strategies in regions with high and low clarithromycin resistance [28].

Progressive decreasing of standard triple therapy efficacy in many countries all around the world is a reason to find possible ways to improve the efficacy of anti-*H. pylori* therapy. These ways can be [28,53]:

1. Usage of high dosage of PPI

2. Prolonged eradication therapy

3. High dosage of traditional used antibiotics

4. Change of antibiotics with known high *H. pylori* resistance to new antibacterial drug or drugs with low *H. pylori* resistance.

5. Sequential treatment, concomitant and hybrid therapy

6. Additional usage of probiotics

High dosage of proton pump inhibitors application

Increasing the dosage of PPI causes concentration rise of active component in the blood stream, as well as an antisecretory effect. It can increase an eradication rate of 6-10% [54]. Serious side effects while the high dosage of PPI for eradication therapy does not get developed. The reason is a very limited time of high dosage application. However, increased dosage of antisecretory therapeutics is not commonly approved. The reasons are non-optimal price/quality ratio and lack of effect on complications decrease, i.e. bleeding/hemorrhage [55].

Prolonged of eradication therapy

This is the most widely spread and best-adopted option of increasing efficacy of eradication therapy. As a part of Standards, the method provides legal reliability for practical physicians for cases of fail and patient objections, complications manifestations, and other situations. Currently, according to Fourth Maastricht Consensus, an extension of anti-*H. pylori* therapy up to 10-14 days increases the efficacy of eradication by 5% (in comparison to 7 days treatment) [28]. The study by a research group in Italy provided evidence on the higher efficacy of 14 day combined therapy (proton pump inhibitors, amoxicillin, clarithromycin) compared to 7-day treatment length (70% and 57% accordingly) [56]. Research group from Croatia provided a comparison of 7-, 10- and 14-day treatment schemes. Results indicated proven efficacy over 80% for combination of proton pump inhibitors, amoxicillin, clarithromycin only for 10 and 14 days length. In case of combination proton pump inhibitors, amoxicillin and metronidazole efficacy of 80% was reached only with 14-day length of therapy [57].

The meta-analysis comparison for 2-week and 1-week eradication therapy research for non-Russia practices confirms that the extension of therapy length allows to reach better eradication results [58]. Russian studies also confirm the necessity of length extension of anti-Helicobacter therapy because according to the modern state of the art seven-day three-component scheme is not effective enough [59].

Increasing the dosage of traditional antibacterial medicaments

The dynamics of dosage increasing for eradication therapy of *H. pylori* could be observed through the development of Maastricht

protocols/consensus. Through the period between First and Third Maastricht consensus the doses of Metronidazole were increased from 400 mg 2 times a day up to 500 mg 3 times a day, amoxicillin from 500 mg 3 times a day to 1000 mg 2 times a day, clarithromycin from 250 mg 2 times a day to 500 mg 2 times a day [21].

Unfortunately, this way of increasing of eradication rate can lead to developing of complications, in particular, a colon dysbiosis but doesn't allow increasing the percent of a successful eradication significantly.

Usage of new antibacterial medicaments

Levofloxacin-based therapy is an effective in *H. pylori* eradication [60]. In the majority of studies use a scheme: PPI in standard dose, amoxicillin 1000 mg, levofloxacin 500 mg twice a day 10-14 days as a first-line, second-line or third-line therapy. Unfortunately in some countries there is data indicating that usage of levofloxacin leads to the progressive growth of *H. pylori* resistance to fluoroquinolones. It is limited of levofloxacin-based therapy. There are data revealing efficacy of other fluoroquinolones in eradication schemes, e.g. moxifloxacin [61] sitafloxacin [62].

Some macrolides other than clarithromycine demonstrate high efficacy in eradication schemes, e.g. azithromycin and josamycin. In some studies it was shown that scheme with azithromycin has eradication rate around 78% - 86.3%, with josamycin - в 85.6%, with josamycin and bismuth – more than 90% [63].

Nowadays some scientists use anti –TB-antibiotic rifabutin [60] in the scheme: PPI, amoxicillin 1000 mg, rifabutin 150 mg twice a day 10-14 days. Efficacy of this treatment is around 79%-95% as a second-line therapy and 61%-68% as a third-line therapy [60]. However, often side reactions of rifabutin, e.g. myelotoxicity, thrombocytopenia, disorders of vision, can limited usage of this scheme [60]. Moreover wide use of rifabutin can lead to increase the percent of rifabutin-resistant strains *Mycobacterium tuberculosis*, which significantly worsen treatment of patients with tuberculosis.

Nitrofurans are also effective in eradication schemes because *H. pylori* resistance to this group of antimicrobial medicaments is low. Usually they use in case of methronidazole-resistant (nitromidazole-resistant) strains of *H. pylori*. Furazolidone-based schemes were offer for recommendation in China gastroenterological society due to its high efficacy in China [64]. However, usage of furazolidone has some restrictions. Important of these restrictions are side effects, e.g. gepatotoxity, neurotoxity, gematotoxity that limited an administration of furazolidone. In some works scientists use eradication scheme with another nitrofuran – nifuroxazide. Efficacy of these schemes is around [53]. Nowadays an optimal nitrofuran for treatment of *H. pylori*-associated diseases is nufuratel. Efficacy of nifuratel-contain eradication schemes is around 82-100% [65]. Additional positive feature of nifuratel is correction of colon microflora with decrease content of semi-pathogenic microorganism and increase of *Bifidobacteria spp.* and *Lactobacillus spp*. level [65].

Rifaximin also used in the second line of eradication therapy in dose 400 mg 2-3 times a day. Scientists from Italy used PPI, clarithromycin and rifaximin in treatment of 24 patients and see eradication rate 58% [66].

Some groups attempted to use doxycycline in schemes of an eradication therapy [67,68].

Usage of bismuth salt

Due to the increasing resistance of *H. pylori* to clarithromycin and other antibiotics in eradication schemes include salt of bismuth because of absence of primary and secondary resistance of *H. pylori* to bismuth. Also usage of bismuth can protect patients against side effects of treatment such as antibiotic-associated diarrhea and colon dysbiosis. Moreover, there are data that bismuth tripotassium dicitrate have a beneficial effect on a content of an intestinal microflora (as an intestinal antiseptic) [69]. In some cases (e.g. at elderly people of allergic patients) it is possible to use a double therapy (PPI and bismuth threepotassium dicitrate) or monotherapy with bismuth [70].

In a number of research works it scientists obtained data that addition of a bismuth tripotassium dicitrate to triple standard therapy promotes reliable increase in percent of an effective eradication [71-73]. In this case monitoring of the growing resistance to a clarithromycin isn't required and bismuth-containing therapy can compensate the lack of new, alternative antibiotics.

Cytoprotective properties of bismuth provide effective protection for stomach mucosa against the damaging action of products of an inflammation for the purpose of prevention of progressing of gastritis [74]. It is shown, that usage of bismuth salt (e.g. tripotassium dicitratobismuthate) leads to regression of atrophic changes of a stomach [75].

Sequential therapy

Sequential therapy is an alternative for classic triple standard therapy [76]. The main goal of this variant of treatment is overcoming of the increasing resistance of *H. pylori* to a clarithromycin. Therefore, this concept in the treatment of an *H. pylori* infection can be recognized by the new standard, especially in the countries and regions with the high resistance of a microorganism to macrolides. Sequential therapy includes two parts: 1st part – usage of PPI and amoxicillin in standard doses for five days, 2nd part – usage of PPI, clarithromycin and metronidazole (or tinidazole) also for five days. It is possible to add salt of bismuth to this therapy. All mechanisms of high efficiency of sequential therapy aren't clear yet. Possibly, usage of amoxicillin leads to 1. "weakening" of a cellular wall of bacteria that interferes with formation of the channels blocking action of a clarithromycin and causing resistance of a bacterium to it and 2. promotes development of most expressed pharmacological effect of the antibiotics accepted in the 2nd phase. Perhaps one of the reasons of higher efficiency of sequential therapy, is combination of medication with an additional antibacterial drugs (tinidazole or metronidazole) [76]. According to results of some studies, efficiency of sequential therapy doesn't depend on properties of a microbe (cagA+status, bacterial loading) and the human (associated diseases, smoking, etc.) [77].

Concomitant therapy

Concomitant therapy includes four compounds: 20-40 mg of PPI twice daily and 1000 mg of amoxicillin twice daily, 500 mg of clarithromycin twice daily 500 mg of metronidazole every eight hours for 10-14 days. This scheme of therapy is recommended in case of high clarithromycin resistance. The efficacy of this treatment method is confirmed by results of meta-analysis. Seven studies provided data on 2412 adult patients shown that there are no significant differences between concomitant therapy and sequential therapy. Also, there was no difference in the rate of adverse events [78]. Other meta-analysis and clinical trials show that concomitant therapy is more effective that sequential or hydrid therapy, e.g. 10-day concomitant therapy showed better eradication rate than sequential therapy (94.4% v.s. 82.2%, $p = 0.002$) [79]. In other study was revealed that triple therapy eradication rates were 76.2%-84.2%; 84.4% - in sequential therapy and 94.4% in the concomitant group ($P = 0.0002$) [80].

Hybrid therapy

Hybrid therapy is the therapy consisting of PPI in standard dose, amoxicillin 1000 mg both twice daily for 10-14 days; plus clarithromycin, 500 mg and tinidazole 500 mg both twice daily just during the last 5-7 days [81,82]. This type of eradication scheme has lower efficacy in compare with sequential and concomitant therapy. But some studies showed similar efficacy [83,84].

Usage of probiotics

One of the most perspective ways for optimization and improving eradication therapy is the usage of probiotics in addition to standard schemes. Several years ago it was only an interesting idea but nowadays it often use and has promising results in the majority of

Table 3: A meta-analysises that assessed the impact of different probiotics in addition to *H. pylori* eradication therapy [87].

Probiotics	Eradication rate	Frequency of side effects
Lactobacillus and bifidobacterium [90,91]	Statistically significant increase	Statistically significant reduce
Lactoferrin [92,93]	Statistically significant increase	Statistically significant reduce
Fermented milk [94]	Statistically significant increase	No data
Lactobacillus spp. [95]	Statistically significant increase	Statistically significant reduce
Saccharomyces boulardii [86,96]	Statistically significant increase	Statistically significant reduce

studies. In Fourth Maastricht Consensus, it is postulated that certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects [28].

Probiotics have some mechanisms to influence on *H. pylori*: lactic acid production, synthesis of bacteriocins and antimicrobial metabolites [85]. Other possible mechanisms of probiotics are concurrence for adhesion sites, the reparation of the barrier function of the stomach mucosa, a decrease of inflammation and increase of immunity of infected humans [53,86].

There are promising results for evidence that probiotics decrease of *H. pylori* colonization of the gastric mucosa. Results of meta-analysis showed that usage of probiotics in addition to standard eradication therapy lead to an increase of eradication rate and decrease of side effects frequency (Table 3) [87-89].

In some studies is shown that standard triple therapy with bismuth and probiotics is very effective. For example, usage of 30 mg lansoprazole twice daily, 1 g amoxicillin twice daily, 1 g clarithromycin once daily and 1,048 mg bismuth subsalicylate twice daily for 7 or 14 days and probiotic bacteria composed of Bifidobacterium lactis, Lactobacillus acidophilus and Lactobacillus paracasei have 100% efficacy against *H. pylori* [97].

In work of Turkey scientists was no statistically significant efficacy of probiotics against *H. pylori* in comparison with placebo [98].

A meta-analysis from China shows that usage of probiotics for *H. pylori* eradication can increase eradication rates and reduce side effects of antibiotics. Probiotic administration prior and subsequent to the therapy and for a duration of > 2 weeks may increase the eradication efficacy. According to this meta-analysis, the most effective probiotics are *Lactobacillus* or multiple probiotic strains [99].

In Russian practice there is also use of different variants of probiotics therapy: pre-eradication therapy – 3-4 weeks before eradication to improve immunity of patients and increase of predictability of an eradication success; co-eradication therapy – at the same time with eradication to increase of eradication rate and decrease of side effects frequency; post-eradication therapy – 3-4 weeks after eradication for intestinal microflora correction and decrease of probability of *H. pylori* reinfection (recolonization) [53].

Probiotic monotherapy

This method of treatment of *H. pylori* infection can be recommended for some categories of patients: patients with non-atrophic chronic gastritis and/or duodenal ulcer in remission; patients infected with low virulent strains of *H. pylori*; patients who have allergic reaction to antibiotics; patients who refuse to take antibiotics; persons who infected with *H. pylori* but haven't any clinical symptoms of dyspepsia; for family members of *H. pylori* infected patient for prophylaxis against microbe invasion. There are many studies confirming the efficacy of probiotics monotherapy for *H. pylori* eradication. This therapy demonstrates lower efficacy that standard schemes but it have a very low frequency of side effects. Also in the era of increasing of *H. pylori* antibiotic resistance probiotic therapy can be a good alternative to classic treatment. For better effect, the duration of probiotic therapy can be 3-4 weeks or longer.

Usage of probiotic which contain lacto-acid bacteria in the treatment of chronic *H. pylori* associated gastritis patients eradication rate was 48% in one study [100] and 41% in another study [101]. Eradication was successful in 6 from 14 patients who used L. acidophilus [102]. In other study it was shown that 29 patients with *H. pylori* associated ulcer disease who used *Enterococcus faecium* strain L-3 10^{6-7} cfu/g 3 dragee 3 times a day during one month have success of eradication 38% [103]. These results were significantly higher than level of spontaneous *H. pylori* eradication (approximately 5%) and can be explained by improving of colon microbiota balance, positive influence of probiotic on the human immune system or by the direct inhibition of *H. pylori* by bacteriocins of probiotic strain. In this study in case of 7-days standard triple therapy (control group) eradication rate was 60% [103].

There are several pieces of evidence of the role of probiotics against the carcinogens of *H. pylori*. It is possible that probiotics may act as antineoplastic agents in the stomach by affecting the polyamine content and functions [104].

The results of in vitro studies demonstrated that probiotics can directly inhibit *H. pylori* [105,106]. This is very important for future probiotics usage as anti-*H. pylori* agents. It was shown that 14 strains of Helicobacter pylori were successfully cultivated from dyspeptic patients. Incubation was made in standard conditions for *H. pylori*. Two variants of probiotic medications were used: 1st contain *Enterococcus faecium* strain L-3, 2nd – lyophilisate cultural fluid of *Bacillus subtilis*. The studied probiotic medications were dissolved in distilled water in part 1:100 and were added in a cup with an agar with different *H. pylori* strains. The assessment of growth of *H. pylori* was analyzed after 6-7 days. Inhibition of grow of *H. pylori* was in 50% cases with *Bacillus subtilis* and in 78.6% with *Enterococcus faecium* strain L-3 [106].

Despite the rather large number of the research works confirming the efficiency of probiotics in eradication, larger randomized controlled investigations are needed to understand clearly the effects of probiotics on *H. pylori* eradication.

Future Treatment Strategies

Metabiotics

Recent researches shown innovative and a very actual approach is the usage of probiotic metabiotics - medicaments on base of products of a metabolism or structural components of probiotic microorganisms [107].

Very promising application as a way of elimination of *H. pylori* from a human organism is use of a medicament on a base of the inactivated cells of pro-biotic bacteria of Lactobacillus reuteri DSMZ 17648 (Pylopass™) allocated and processed in the biotechnological way. *Lactobacillus reuteri DSMZ 17648* – special strain of lactobacilli possessing unique ability: specific contact cells of *H. pylori* and to form co-aggregans without influencing other bacteria and normal intestinal flora. This specific co-aggregation decrease of *H. pylori* mobility. Also co-aggregants of microbe aggregants of pathogens cease to communicate with mucous a digestive tract and "are washed away" from a stomach that as a result leads to reduction of colonization of *H. pylori* in a stomach mucosa, reducing risk of development of gastritis and ulcer disease [108,109].

Bacteriophages

Bacteriophages are in a focus of interest of a great number of scientists: they in compare with probiotic microorganisms possess the highest degree of specificity concerning certain microorganisms. But also it is a negative side: high variability of microorganism leads to loss of specificity of bacteriophages, and, therefore, and their "uselessness" in this case. In addition there are difficulties of selection and reproduction of phages, and the immune system can react to this

type of treatment also negatively.

Bacteriocins

Bacteriocins (bacterial proteins or peptides with antimicrobial action) is one of the most interesting for investigation due to presence in bacteriocins specify of bacteriophages and safety of probiotics [110]. Nowadays bacteriophages are the factors of microbial antagonism. They provide the regulation of bacterial population a colonization resistance of humans and animals to pathogens. Almost all bacteria from lactic acid bacteria can made bacteriocins. For example, In Korean study antimicrobial activity of seven bacteriocins (nisin A; lacticin A164, BH5, JW3, and NK24; pediocin PO2; and leucocin K) produced by lactic acid bacteria against *H. pylori* strains was investigated in vitro using a broth microdilution assay. Lacticins A164 and BH5 showed the strongest antibacterial activity against *H. pylori* strains [111].

Vaccines

Another method to fight with this microorganism is attempted to create a vaccine against *H. pylori*. Allegedly, process of increasing of content of immunocompetent cells in a stomach mucosa at early stages of pathogenesis of *H. pylori*-associated diseases leads to exhaustion of mechanisms of protection and dictates need to stimulate development of protection factors by immunization [112]. After vaccination, a specific immune answer develops due to the synthesis of antibodies, and the combined cellular, molecular and humoral answer also develop that have to provide full protection against *H. pylori*. The most effective ways of vaccination are intramuscular and intranasal, but intragastric and rectal are less effective [113].

As antigens for immunization against *H. pylori* can be used several factors of pathogenesis of *H pylori*-associated diseases: VacA, CagA, NapA, BabA, SabA and urease [114]. The majority of research works is conducted on animals, mainly on mice, however, optimum strategy of creation of vaccines against a *H. pylori* infection is strategy of possibility of use of the developed vaccines at people [115]. Promising research is the study of Malfertheiner P. in which studied safety and an immunogenetics of the vaccine for intramuscular vaccination with recombinant VacA, CagA and NapA on aluminum hydroxide at 57 healthy *H. pylori*-negative volunteers in randomized blind research of the first phase with various terms and dosages of a vaccine. All persons who were vaccinated have been examined in 5 and 36 months after vaccination, in 18 and 24 months after the first vaccination. As a result, it was established that in all variants of immunization there was a development of specific IgG and activation of the cellular answer concerning one or two proteins and in 86% of cases – all three anti-genes. Thus, the number of side effects was little [116].

Xu C et al. created a recombinant strain of Salmonella, which express *H. pylori* urease and interleucin-2. At immunized mice were a more significant decrease of results of rapid urease test in comparison with mice, which were immunized with the vaccine, expressing only urease [117]. The level of interferon-γ and defensine-1 in stomach increase after immunization. It can be an protect factor against *H. pylori* aggression [112].

Also promising results show the usage by upon oral immunization of recombinant Bacillus subtilis sporeswith express of UreB protein of Helicobacter acinonychis [118]. In another study is revealed that the recombinant L. lactic expressing UreB can be potentially used as an edible vaccine for controlling *H. pylori* infection [119,120].

Efficacy of DNA-vaccines also confirmed in mice (vaccination on base of urease B) [121]. Potential advantages of DNA vaccines are simplicity of preparation and use (can be used together with food), temperature stability and stimulation of the cytotoxic T-cellular answer that is important for treatment and prevention of a *H. pylori*-associated diseases [122]. Mechanisms of activity of DNA vaccines are studied insufficiently. Theoretically, they are safe, but it isn't necessary to forget that the integration of DNA into cages of a macroorganism can promote development of anti-DNA - autoimmune reaction.

Unfortunately, the vaccine, which could be recommended for use at the person, doesn't exist yet, despite more than 20-year history of their creation and a large number of examples of efficiency of vaccines at animals. Mechanisms of action of vaccines at animals and the person are clear insufficiently and need further specification. It isn't necessary to forget that side effects of vaccination against *H. pylori* aren't completely studied that also demands improvement of methods of creation of vaccines.

New acid blockers

New acid blocker Vonoprazan - potassium-competitive acid blocker (P-CAB) comes in gastroenterology around one year ago [123]. Now this medicine is approved in Japan for the treatment of acid-related diseases and *H. pylori* eradication. Vonoprazan is very strong acid secretion inhibitor and shows promising results of *H. pylori* eradication with vonoprazan-based triple therapy after failure of proton pump inhibitor-based triple therapy [124].

Alternative methods of *H. pylori* eradication

The main alternative ways of *H. pylori* eradication are usage of new medicaments and biologically active substances, ozonetherapy, laserotherapy. Eradication rate in case of using propolis can be around 60% [125,126]. In is shown good efficacy by melatonin for increase of eradication rate [127]. Ozone seems to be effective in treatment f *H. pylori*-associated gastritis and ulcer disease due to bactericide properties, anti-inflammatory effect (oxidation of arachidonic acid - predecessor of prostaglandin E starting inflammatory process); immunomodulatory action, and also analgesic effect [128,129].

Treatment with use of the laser can increase the effect of antibacterial medicaments that leads to high efficacy of *H. pylori* eradication (86.7% in case of use antibiotics and laser in comparison with 66.7% in case of use antibiotic only) [130]. After exposure of helium-neonic laser contours of an external and internal membrane of *H. pylori* lost the clearness, and on separate sites were faltering or completely disappeared. It confirm the direct properties action of laser on this microorganism [131]. Using laserotherapy it is possible to decrease inflammatory and destruction (ulcerate) lesions and increase eradication rate. After using laserotherapy (endocscopic) for three times negative result of rapid urease test was 85.8% in antrum and 88.5% in stomach corpus. Histological data shown that after treatment with laserotherapy *H. pylori* absences in 71.4% in antrum and 77.4% in stomach corpus [132].

Role of genetic features of *H. pylori*

Genetic properties of *H. pylori* can play an important role in the efficacy of eradication. It is established that cagA-positive strains are more susceptibility to antibiotics in comparison with cagA-negative strains. Presence of allele VacA s1m1 also increases the susceptibility of microorganism in comparison with allele VacA s2m2 [133]. Only the minor part of *H. pylori*-infected people (less than 10-20%) has *H. pylori*-associated diseases [134]. This supervision is explained by the fact that population of *H. pylori* possesses high heterogeneity, and its' strains considerably differ in a virulence. Based on mentioned clinical manifestations of diseases are capable to cause not all of *H.pylori* strains [135]. Since nineties of XX century it was known *H. pylori* strains were different on the genome and called "ulcerogenic" (synthesis cytotoxins, are associated with stomach ulcer, active or atrophic gastritis) and "non-ulcerogenic" (don't synthesis cytotoxins, are associated with simple gastritis) [136,137]. It will become possible to choose the type of treatment on the basis of such important factor as genetic features of strains of *H. pylori*. Thus, it is necessary to notice that in a case of infection of the patient with low virulent strains also possibly monotherapy use by a probiotics or metabiotics as an alternative to antibiotics and PPI.

Role of genetic properties of human

There are an additional factor that influence on eradication efficacy is human genetic features especially polymorphism of CYP2C19. The CYP2C19 genotype is an important factor of *H. pylori* eradication

in patients taking omeprazole-based or lansoprazole-based triple therapies and levofloxacin-based triple therapy but no so significant in case of rabeprazole-based or esomeprazole-based triple therapies [138,139]. Mutations in CYP2C19 influence on metabolism of different drugs and divided on three types: without mutations – rapid metabolizers, a mutation in one allele – intermediate metabolizers, mutations in two alleles – slow metabolizers. Eradication rate is the highest in slow metabolizers [140]. The CYP2C19 and IL-1B-31CC genotype can be predictors of success of treatment [141]. Also polymorphism of IL-1β-511 significantly influence on eradication rate: in T-allele (IL-1β-511 C/T or IL-1β-511 T/T) presence eradication have better results than in case of IL-1β-511 C/C allele [142].

Expression and functional activity of polyspecific ATP-dependent efflux transporter – P-glycoprotein (P-gp) influence of adsorption of many medicaments also play a role in the pathogenesis of *H. pylori* infection [143]. This expression and functional activity encoding by MDR1 (ABCB1) gene [144]. It is considered that genotypes of MDR1 3435 C/T and C/C are characterized by the high and moderate level of an expression of P-gp on apical poles of membranes of intestinal enterocytes. In turn, the genotype of MDR1 3435 T/T is associated with the low level of an expression of P-gp that causes higher level of absorption of medicinal substance in a system blood-groove in comparison with genotypes of C/T and C/C [145]. Unfortunately the current usage of genetic analysis in *H. pylori* infected patients is not common in clinical practice. It can be explained by high cost of the analysis and absence of diagnostic standards.

In the conclusion, it is necessary to notice that today anti-*H. pylori* therapy with different antibiotics using at the same time cannot be dogmatic. It is important to investigate genetic features of microorganism and human. It is possible that increase of treatment duration, an increase of doses of antibiotics, usage of new antibiotics none enough effective. A large number of researches in the different countries of the world will help to develop optimum ways of an eradication of *H. pylori*. Considering that gradual increase in number of the used antibiotics, the increase in duration of treatment, use of new compounds and schemes of treatment do not lead to a long-term positive effect on preservation of risk of development of side reactions, it is necessary to pay active attention to new approaches to treatment and alternative options of therapy of an *H. pylori* infection.

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