***Helicobacter Pylori*: a comprehensive review for primary care providers**

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Helicobacter pylori is the most prevalent bacteria infecting humans resulting in a variety of gastrointestinal and extra gastrointestinal complications. Although most of the infected adults are asymptomatic, the prevalence varies in different parts of the world it is higher in Eastern and Southern Europe. Eradication of *Helicobacter pylori* is necessary to prevent precancerous conditions like gastric atrophy, gastric intestinal metaplasia and gastric dysplasia. This comprehensive review addresses briefly on: whom and how to test and treat including recommended first line therapies, salvage therapies, testing for eradication and strategy to be used in primary care clinics.

Key words: eradication, atrophy, metaplasia, dysplasia and salvage.

Abbreviations:

HP = *Helicobacter pylori*

PUD = Peptic Ulcer Disease

MALT = Low-grade gastric marginal zone B-cell lymphoma

UBT = Urea Breath Test

RCT = Randomized Controlled Trial

INTRODUCTION

Helicobacter pylori (HP) is a Gram-negative microaerophilic bacteria which was discovered more than 3 decades ago by pathologist Robin Warren who first reported curved bacteria colonizing the gastric mucosa and suggested the possibility of causing gastric inflammation [1]. With an estimated 4.4 billion infected individuals, the prevalence of HP varies in different parts of the world, highest in developing countries in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia (54.7%). In the USA and Western European countries the prevalence is decreasing [2] but varies by race, highest in Alaskan Natives 75.0% [3], followed by non-whites (34.5% to 61.6%) [4, 5] and whites (18.4% to 26.2%). In Europe, prevalence is higher in Eastern (62.8%) and Southern Europe (55.0%) and lower in Northern (41.6%) and Western Europe (34.3%). The country with the highest prevalence is Portugal 86.4%. In Eastern Europe, the prevalence is highest in Russia (78.5%). Romania has a prevalence of 68.5%, and the Czech Republic has the lowest prevalence (41.2%) [2].

The exact means of acquisition of the infection is not always clear, but the most common risk factors are low socioeconomic status, infected parents, the number of siblings and community water supplies in some developing countries [6–8]. *H. Pylori* has been associated with numerous gastrointestinal complications like chronic gastritis, gastric ulcer, duodenal ulcer, chronic uninvestigated dyspepsia, functional dyspepsia, gastric cancer, and low-grade gastric marginal zone B-cell lymphoma (formerly known as gastric mucosa-associated lymphoid tissue B-cell lymphoma) [9]. Other extra-gastric complications, less common and with less evidence of association, include hematological disorders (iron deficiency anemia, Vitamin B12 deficiency, immune thrombocytopenic purpura, ischemic heart disease and neurodegenerative diseases [10–11]. HP was declared a class I human carcinogen by the International Agency for Research on Cancer [12]. Eradication therapy of HP before the onset of precancerous lesions (gastric atrophy, gastric intestinal metaplasia, and gastric dysplasia) had significantly decreased the risk of developing gastric cancer [13]. Since most of the HP infections in adults are

asymptomatic, the eradication for HP is offered to symptomatic individuals and those at risk for developing complications from HP infection. [14].

This is a practical and comprehensive guide to be used in primary care clinics for screening, testing and treating HP.

Whom to test

1. All patients with active gastric and duodenal peptic ulcer disease (PUD) [14], previous history of PUD (not treated or no documented cure), low-grade gastric marginal zone B-cell lymphoma [15], a history of early gastric cancer or gastrointestinal metaplasia resection [16, dyspepsia under the age of 60 years with no alarm features {Ford, 2008 #17}, long term low dose aspirin, chronic treatment with a non-steroidal anti-inflammatory drug (NSAID), unexplained iron deficiency anemia after extensive evaluation, and adults with idiopathic thrombocytopenic purpura (ITP)[14].

2. If endoscopy is obtained in dyspepsia, obtain biopsies for HP testing [14].

3. Do not test patients with typical symptoms of gastroesophageal reflux disease (GERD) without a history of PUD [17].

4. There is inadequate evidence to test and treat HP in asymptomatic individuals with a family history of gastric cancer, hyperplastic gastric polyps and hyperemesis gravidarum [14].

How to test

The diagnosis of HP can be broadly classified into non-invasive and invasive methods. Non-invasive methods are preferred since they are easier to obtain, with less risk of harm and at a lower cost than endoscopy-based invasive methods (Table 1).

¹³C or radioactive ¹⁴C-urea breath test (UBT), stool antigen test, and serum antibody testing are the most common non-invasive methods. ¹³C-UBT has a high sensitivity (88%-95%) and specificity (95%-100%) [18]. The basis of UBT is hydrolysis of urea with a carbon isotope being converted by HP to produce CO² and ammonia [19, 20]. Stool antigen testing using laboratory-based monoclonal enzyme immunoassay has high sensitivity and specificity (94 and 97% respectively) [21, 22]. ELISA based serological testing to detect IgG antibodies is inexpensive but fails to distinguish between active and past infection [23, 24].

Table 1

Methods of testing for HP

Testing	Method	Pros	Cons	Comments
Non-invasive	Urea breath testing (UBT)	Simple and safe Easy to perform High sensitivity and specificity High diagnostic accuracy	False positive results due to urease producing organisms; Radiation if ¹⁴ C is used	Most commonly used False-negative results with PPIs or antibiotics use or in active UGIB (low specificity).
	Stool antigen testing	High sensitivity and specificity No special skill required	Sample collection	Most commonly used False-positive results with PPIs or antibiotics use High sensitivity after UGIB.
	Serology	Simple blood test Not affected by UGIB	Cannot distinguish past or active infection	Rarely used but a negative test has high negative predictive value during active UGIB. No false negatives with PPI use.
Invasive	Rapid biopsy urease testing	Rapid and cheap High specificity (99%)	Low sensitivity (80%)	Most commonly used False-negative results with PPIs or antibiotics use. Low sensitivity with UGIB*.
	Histology	Gold standard Cheap and universally used	Florescent microscopy use for detection Might require addition biopsy sample	Most commonly used.
	Culture	Data about antibiotic resistance is obtained High specificity	Time consuming Ideal incubation conditions/transport medium needed Low sensitivity	False-negative results with PPIs or antibiotics use. NOT commonly used.
	PCR	Data about antibiotic resistance is obtained Rapid test High specificity Used in low bacterial load	Low sensitivity Higher cost Time consuming process Risk	NOT commonly used.

*UGIB = Upper Gastrointestinal bleed.

When endoscopy is indicated (dyspepsia with alarm symptoms, gastrointestinal bleeding, concerns for malignancy), HP can be detected with any of the following methods: biopsy for rapid urease test (BRUT), histology, polymerase chain reaction and less commonly by bacterial culture [25]. BRUT is cheap, fast and highly specific test but sensitivity is affected by the number of bacteria in the biopsy and other urease producing bacteria which lead to false positive test results [26]. The sensitivity and specificity of histological diagnosis of HP depends on colonization in the mucosa, location of the biopsy and pathologist expertise with special stains [27, 28]. PCR testing is used to detect low bacterial loads and specific type of mutations with antimicrobial resistance [29]. Culture is cumbersome but has the highest specificity with variable sensitivity due to quality of biopsies, transport conditions and very slow growth of HP [30].

Whom to treat

Everyone with a positive HP test should be offered treatment [14].

How to treat

Selection of the treatment regimen is based on a combination of factors:

- 1) Allergy to penicillin
- 2) Local resistance to clarithromycin
- 3) History of macrolide use
- 4) History of quinolone use

Treatment regimens include PPI twice daily and a combination of antibiotics (2 antibiotics in triple therapy or 3 antibiotics in quadruple therapy) for 10 to 14 days. These regimens are recommended by specialty groups (American College of Gastroenterology, Toronto Consensus and Maastricht V/Florence Consensus) (Tables 2 and 3).

Treatment efficacy is decreased with decreased compliance, high gastric acidity, high bacterial load and especially sensitivity of bacteria to antibiotics, most importantly to clarithromycin [24]. Nitroimidazole (metronidazole or tinidazole) resistance is less important and 14-day treatment regimen seems to overcome this resistance [24].

It is imperative to know the resistance of clarithromycin or local eradication rate with clarithromycin triple therapy regimen before choosing it as a first line regimen.

Recommended first line therapies:

1) PAC, PMC Clarithromycin triple therapy (PPI, amoxicillin or metronidazole plus clarithromycin)

is recommended in areas where clarithromycin resistance is <15%. Higher eradication rates are achieved with 14 days [31].

2) PBMT Bismuth quadruple therapy (PPI, bismuth, metronidazole, tetracycline) is the preferred therapy in areas of high resistance to clarithromycin and metronidazole, and in patients who were previously treated with macrolides [14, 23, 33]. Ten to 14 days of this therapy is superior to 7 days of clarithromycin triple therapy (85% vs 73%). If bismuth is not available, consider regimens with rifampin, levofloxacin or high dose amoxicillin [24].

3) PAMC Concomitant therapy (PAMC-PPI, amoxicillin, metronidazole, clarithromycin) is recommended in areas of only clarithromycin resistance and in patients without prior macrolide use [24]. The cure rates are 90% with concomitant therapy compared to 78% with clarithromycin triple therapy [34]. The duration of proven efficacy of this treatment is 10 days and the consensus group recommendation is for 14 days [14].

4) Probiotics: There is increasing evidence to the benefit of probiotics as adjuncts to antibiotics and PPI [14]. *Lactobacillus reuteri* when supplemented with the triple therapy reduced side effects of treatment, increased eradication rate and improved the histological features of *H. pylori* infection when compared to placebo [32].

Salvage therapies:

Levofloxacin is recommended as first line treatment only by American College of Gastroenterology (ACG) and not by the other consensus groups due to concerns for increasing levofloxacin resistance and decreased efficacy [14, 23, 33]. Sequential and hybrid therapies are given for 5–7 days followed by another 5–7 days with a different antibiotic combination.

1) PAL Levofloxacin triple therapy (PPI, levofloxacin, amoxicillin) has a pooled eradication rate of 84% (range 73–92%) with 10-day therapy [35–37]. After 2 failed other treatments (clarithromycin triple therapy and bismuth quadruple therapy), the pooled eradication rate with levofloxacin-based therapy is 73% (188). Fourteen days is more effective and has higher efficacy in eradication of HP [38].

2) Levofloxacin sequential therapy consisting of first 5–7 days of PPI and amoxicillin followed by 5–7 days of a PPI, levofloxacin, and nitroimidazole. It has superior eradication compared to clarithromycin triple therapy (83.6% vs. 64%) or standard sequential therapy (87.4% vs. 78.9%) with clinical significance [39].

3) LOAD (PPI, levofloxacin, doxycycline, nitazoxanide) 10-day therapy provides an eradication rate of 90% compared to 73% of clarithromycin triple therapy [14].

4) Sequential therapy (PPI and amoxicillin for 5 days followed by PPI, clarithromycin, metronidazole for an additional 5 days) has an overall eradication rate of 84.3%. The efficacy of this regimen varies geographically, with higher eradication rates seen in Italy when compared to United States and Latin American countries [34, 40] (Table 2). This regimen is not superior to 14 days of clarithromycin triple therapy [20].

5) HDDT High dose dual regimen (PPI, amoxicillin high dose) has an eradication rate of 71% and there is no significant difference when compared to rifabutin triple therapy [41]. The efficacy is due to a combination of factors: HP does not develop resistance to amoxicillin and efficacy of amoxicillin is increased with elevated pH [42, 43].

6) PAR Rifabutin triple therapy (PPI, amoxicillin, rifabutin) is recommended as salvage therapy due to concern for myelosuppression and drug interactions with prolonged use. A 10-day regimen has an eradication of 87% [44].

Table 2

Treatment regimens for HP recommended by the consensus groups (ACG, Toronto and Maastricht V/Florence)

Drug Regimen	Dosing	Duration (days)	Recommendation
Bismuth quadruple (PBMT)	PPI bid Bismuth qid *Metronidazole 400 mg qid or 500 mg tid–qid Tetracycline 500 mg qid	14	First line Areas of high resistance to both clarithromycin and metronidazole Salvage therapy if not tried before.
Concomitant non-bismuth quadruple (PAMC)	PPI bid Amoxicillin 1000 mg bid *Metronidazole 500 mg bid Clarithromycin 500 mg bid	14	First line Areas of high resistance to only clarithromycin Salvage therapy if not tried before.
Clarithromycin triple (PAC, PMC)	PPI bid Amoxicillin 1000 mg or metronidazole 500 mg bid Clarithromycin 500 mg bid	14	First line Use only if the clarithromycin resistance is <15%
Levofloxacin triple (PAL)	PPI bid Amoxicillin 1000 mg bid Levofloxacin 500 mg once daily or 250 mg bid	14	Salvage
Levofloxacin Sequential	PPI bid Amoxicillin 1000 mg bid for 5–7 days PPI bid, Amoxicillin 1000 mg bid, Levofloxacin 500 mg once daily, metronidazole 500 mg bid for 5–7 days	10–14	Salvage
LOAD	PPI bid Doxycycline 100 mg daily Levofloxacin 500 mg once daily Nitazoxanide 500 mg Bid	7–10	Salvage
Sequential non-bismuth Quadruple (Sequential)	PPI bid Amoxicillin 1000 mg bid for 5–7 days followed by *Metronidazole 500 mg + clarithromycin 500 mg bid for 5–7 days more	10–14	Salvage Do not use in areas of clarithromycin resistance is high Rarely used
Hybrid non-bismuth Quadruple (Hybrid)	PPI bid Amoxicillin 1000 mg bid *Metronidazole 500 mg for 7 days + clarithromycin 500 mg bid for 7 days	14	Salvage Rarely used
High-dose dual therapy (HDDT)	Rabeprazole 20 mg qid Amoxicillin 750 mg qid	14	Salvage
Rifabutin-containing therapy (PAR)	PPI bid Amoxicillin 1000 mg bid Rifabutin 150 mg bid or 300 mg qd	10	Salvage
Vonoprazan based therapies	Vonoprazan 20 mg bid Amoxicillin 750 mg bid	7–10	Approved only in Japan

*Nitroimidazole: Metronidazole or tinidazole

Table 3

Simplified treatment algorithm

	Prior macrolide use or high resistance NO	Prior macrolide use or high resistance YES
Penicillin allergy NO	Any treatment may be used	
Recommended first line	Bismuth quadruple	Bismuth quadruple
	Concomitant	Levofloxacin triple
	Clarithromycin triple	Levofloxacin sequential
Other	Levofloxacin triple	Concomitant
	Levofloxacin sequential	LOAD
	LOAD	Hybrid
	Hybrid	
	Sequential	
Penicillin allergy YES	Clarithromycin triple	Bismuth quadruple
	Bismuth quadruple	

Who should be tested for cure and how to confirm eradication?

Test for confirmation of eradication should be offered to any patient treated for HP 4 weeks after the treatment, and can be done by any non-invasive testing (UBT, stool antigen testing) or any of the endoscopy-based testing [20]. Before testing, PPIs should be stopped for 2 weeks and antibiotics or bismuth stopped for 4 weeks to prevent decreased test sensitivity. Gastrointestinal bleeding due to PUD also lowers sensitivity of the test and a negative test result needs to be repeated ideally by urea breath test [45, 46].

Strategies to treat refractory HP

1. Do not use clarithromycin or levofloxacin regimens if the resistance is >15% locally.

2. Use bismuth quadruple therapy if not previously used. HP RCTs in Europe and Asia showed an eradication rate of 80% for a 14 day treatment with bismuth quadruple therapy in patients with a history of treatment failure [47, 48]

3. In penicillin allergic patients, test for penicillin allergy after first treatment failure since HP rarely develops resistance to amoxicillin.

4. Ensure treatment is for 14 days.

5. Obtain susceptibility testing for antibiotics if possible.

6. Use rifabutin-based therapies or amoxicillin high dose therapy.

7. Vonoprazan-based therapy with amoxicillin is effective with eradication 85–89%. Vonoprazan is only approved in Japan as both first and second line therapies [49].

8. It is important to know the local rate of resistance when considering a quinolone-based regimen.

Strategy to be used in primary care clinics

Test for HP patients with gastric and peptic ulcers, gastric cancer, on long term NSAIDs and on low dose ASA. Test using urea breath test or stool antigen. Treat all patients positive for HP. Treat with twice daily PPI and a combination of antibiotics for 10–14 days. The preferred regimen is bismuth based. Do not use clarithromycin-containing treatments if resistance is >15% unless you use 2 other antibiotics in the regimen. Levofloxacin-based therapy should be reserved for treatment failure. Test for penicillin allergy if considering amoxicillin in patients with penicillin allergy history. Know your local antibiotic resistance. Test for cure 4 weeks after antibiotic treatment and 2 weeks after PPI.

CONCLUSION

Primary care providers are essential in detecting and treating patients with HP. We believe this concise review facilitates understanding of this disease and leads to better patient care.

Helicobacter pylori reprezintă o infecție frecventă ce poate asocia un număr însemnat de complicații gastrointestinale. Deși majoritatea adulților sunt asimptomatici, prevalența infecției variază în lume și este mai mare în estul și sudul Europei.

Eradicarea infecției este necesară pentru a preveni dezvoltarea afectărilor precanceroase cum ar fi atrofia gastrică, metaplasia intestinală și displazia gastrică. Acest articol prezintă pe cine trebuie să testăm și cum trebuie să testăm, precum și indicațiile terapeutice de primă linie, terapia de salvare, eradicarea infecției și strategia de avut în vedere în cabinetele medicilor de familie.

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REFERENCES

- PINCOCK S. Nobel Prize winners Robin Warren and Barry Marshall. *Lancet*. 2005; **366**(9495):1429.
- HOOI JKY., LAI WY., Ng WK., SUEN MMY., UNDERWOOD FE., TANYINGOH D., et al. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. *Gastroenterology*. 2017; **153**(2):420–9.
- PARKINSON AJ., GOLD BD., BULKOW L., WAINWRIGHT RB., SWAMINATHAN B., KHANNA B., et al. High prevalence of *Helicobacter pylori* in the Alaska native population and association with low serum ferritin levels in young adults. *Clin Diagn Lab Immunol*. 2000; **7**(6):885–8.
- EVERHART JE., KRUSZON-MORAN D., PEREZ-PEREZ GI., TRALKA TS., MCQUILAN G. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis*. 2000; **181**(4):1359–63.
- CARDENAL VM., MULLA ZD., ORTIZ M., GRAHAM DY. Iron deficiency and *Helicobacter pylori* infection in the United States. *Am J Epidemiol*. 2006; **163**(2):127–34.
- SCHWARZ S., MORELLI G., KUSECEK B., MANICA A., BALLOUX F., OWEN RJ., et al. Horizontal versus familial transmission of *Helicobacter pylori*. *PLoS Pathog*. 2008; **4**(10):e1000180.
- FORD AC., FORMAN D., BAILEY AG., GOODMAN KJ., AXON AT., MOAYYEDI P. Effect of sibling number in the household and birth order on prevalence of *Helicobacter pylori*: a cross-sectional study. *Int J Epidemiol*. 2007; **36**(6):1327–33.
- WEYERMANN M., ROTHENBACHER D., BRENNER H. Acquisition of *Helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. *Am J Gastroenterol*. 2009; **104**(1):182–9.
- JIANG J., CHEN Y., SHI J., SONG C., ZHANG J., WANG K. Population attributable burden of *Helicobacter pylori*-related gastric cancer, coronary heart disease, and ischemic stroke in China. *Eur J Clin Microbiol Infect Dis*. 2017; **36**(2):199–212.
- GONI E., FRANCESCHI F. *Helicobacter pylori* and extragastric diseases. *Helicobacter*. 2016; **21** Suppl 1:45–8.
- LIU J., WANG F., SHI S. *Helicobacter pylori* Infection Increase the Risk of Myocardial Infarction: A Meta-Analysis of 26 Studies Involving more than 20,000 Participants. *Helicobacter*. 2015; **20**(3):176–83.
- Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994; **61**:1–241.
- KOSUNEN TU., PUKKALA E., SARNA S., SEPPALA K., AROMAA A., KNEKT P., et al. Gastric cancers in Finnish patients after cure of *Helicobacter pylori* infection: A cohort study. *Int J Cancer*. 2011; **128**(2):433–9.
- CHEY WD., LEONITIADIS GI., HOWDEN CW., MOSS SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol*. 2017; **112**(2):212–39.
- NAKAMURA S., SUGIYAMA T., MATSUMOTO T., IJIMA K., ONO S., TAJIKA M., et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. *Gut*. 2012; **61**(4):507–13.
- YOON SB., PARK JM., LIM CH., CHO YK., CHOI MG. Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. *Helicobacter*. 2014; **19**(4):243–8.
- RAGHUNATH AS., HUNGIN AP., WOOFF D., CHILDS S. Systematic review: the effect of *Helicobacter pylori* and its eradication on gastro-oesophageal reflux disease in patients with duodenal ulcers or reflux oesophagitis. *Aliment Pharmacol Ther*. 2004; **20**(7):733–44.
- HOWDEN CW., HUNT RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol*. 1998; **93**(12):2330–8.
- GRAHAM DY., MIFTAHUSSURUR M. *Helicobacter pylori* urease for diagnosis of *Helicobacter pylori* infection: A mini review. *J Adv Res*. 2018; **13**:51–7.
- CHEY WD., WONG BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007; **102**(8):1808–25.
- TREVISANI L., SARTORI S., GALVANI F., ROSSI MR., RUINA M., CHIAMENTI C., et al. Evaluation of a new enzyme immunoassay for detecting *Helicobacter pylori* in feces: a prospective pilot study. *Am J Gastroenterol*. 1999; **94**(7):1830–3.
- VAIRA D., MALFERHEINER P., MEGRAUD F., AXON AT., DELTENRE M., HIRSCHL AM., et al. Diagnosis of *Helicobacter pylori* infection with a new non-invasive antigen-based assay. HpSA European study group. *Lancet*. 1999; **354**(9172):30–3.
- MALFERHEINER P., MEGRAUD F., O'MORAIN CA., ATHERTON J., AXON AT., BAZZOLI F., et al. Management of *Helicobacter pylori* infection – the Maastricht IV/ Florence Consensus Report. *Gut*. 2012; **61**(5):646–64.

24. MALFERHEINER P., MEGRAUD F., MORAIN CA., GISBERT JP., KUIPERS EJ., AXON AT., *et al.* Management of *Helicobacter pylori* infection – the Maastricht V/Florence Consensus Report. *Gut*. 2017; **66**(1):6.
25. YANEZ P., LA GARZA AM., PEREZ-PEREZ G., CABRERA L., MUNOZ O., TORRES J. Comparison of invasive and noninvasive methods for the diagnosis and evaluation of eradication of *Helicobacter pylori* infection in children. *Arch Med Res*. 2000; **31**(4):415–21.
26. BRANDI G., BIAVATI B., CALABRESE C., GRANATA M., NANNETTI A., MATTARELLI P., *et al.* Urease-positive bacteria other than *Helicobacter pylori* in human gastric juice and mucosa. *Am J Gastroenterol*. 2006; **101**(8):1756–61.
27. WRIGHT CL., KELLY JK. The use of routine special stains for upper gastrointestinal biopsies. *Am J Surg Pathol*. 2006; **30**(3):357–61.
28. GENTA RM., GRAHAM DY. Comparison of biopsy sites for the histopathologic diagnosis of *Helicobacter pylori*: a topographic study of *H. pylori* density and distribution. *Gastrointest Endosc*. 1994; **40**(3):342–5.
29. TAYLOR DE., GE Z., PURYCH D., LO T., HIRATSUKA K. Cloning and sequence analysis of two copies of a 23S rRNA gene from *Helicobacter pylori* and association of clarithromycin resistance with 23S rRNA mutations. *Antimicrob Agents Chemother*. 1997; **41**(12):2621–8.
30. HIRSCHL AM., MAKRIATHIS A. Methods to detect *Helicobacter pylori*: from culture to molecular biology. *Helicobacter*. 2007; **12** Suppl 2:6–11.
31. YUAN Y., FORD AC., KHAN KJ., GISBERT JP., FORMAN D., LEONTIADIS GI., *et al.* Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database Syst Rev*. 2013; **(12)**:Cd008337.
32. FALLONE CA., CHIBA N., VAN ZANTEN SV., FISCHBACH L., GISBERT JP., HUNT RH., *et al.* The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults. *Gastroenterology*. 2016; **151**(1):51–69.e14.
33. LI BZ., THREAPLETON DE., WANG JY., XU JM., YUAN JQ., ZHANG C., *et al.* Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network meta-analysis. *Bmj*. 2015; **351**:h4052.
34. NISTA EC., CANDELLI M., CREMONINI F., CAZZATO IA., DI CAROA S., GABRIELLI M., *et al.* Levofloxacin-based triple therapy vs. quadruple therapy in second-line *Helicobacter pylori* treatment: a randomized trial. *Aliment Pharmacol Ther*. 2003; **18**(6):627–33.
35. BILARDI C., DULBECCO P., ZENTILIN P., REGLIONI S., IIRITANO E., PARODI A., *et al.* A 10-day levofloxacin-based therapy in patients with resistant *Helicobacter pylori* infection: a controlled trial. *Clin Gastroenterol Hepatol*. 2004; **2**(11):997–1002.
36. SAAD RJ., SCHOENFELD P., KIM HM., CHEY WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol*. 2006; **101**(3):488–96.
37. ERCIN CN., UYGUN A., TOROS AB., KANTARCIOGLU M., KILCILER G., POLAT Z., *et al.* Comparison of 7- and 14-day first-line therapies including levofloxacin in patients with *Helicobacter pylori* positive non-ulcer dyspepsia. *Turk J Gastroenterol*. 2010; **21**(1):12–6.
38. BASU PP., RAYAPUDI K., PACANA T., SHAH NJ., KRISHNASWAMY N., FLYNN M. A randomized study comparing levofloxacin, omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of *Helicobacter pylori*. *Am J Gastroenterol*. 2011; **106**(11):1970–5.
39. KALE-PRADHAN PB., MIHAESCU A., WILHELM SM. Fluoroquinolone Sequential Therapy for *Helicobacter pylori*: A Meta-analysis. *Pharmacotherapy*. 2015; **35**(8):719–30.
40. GREENBERG ER., ANDERSON GL., MORGAN DR., TORRES J., CHEY WD., BRAVO LE., *et al.* 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. *Lancet*. 2011; **378**(9790):507–14.
41. MIEHLKE S., HHANSKY K., SCHNEIDER-BRACHERT W., KIRSCH C., MORGANER A., MADISCH A., *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther*. 2006; **24**(2):395–403.
42. LABENZ J. Current role of acid suppressants in *Helicobacter pylori* eradication therapy. *Best Pract Res Clin Gastroenterol*. 2001; **15**(3):413–31.
43. SHIOTA S., REDDY R., ALSARRAJ A., EL-SSERAG HB., GRAHAM DY. Antibiotic Resistance of *Helicobacter pylori* Among Male United States Veterans. *Clin Gastroenterol Hepatol*. 2015; **13**(9):1616–24.
44. PERRI F., FESTA V., CLEMENTE R., VILLANI MR., QUITADAMO M., CARUSO N., *et al.* Randomized study of two “rescue” therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am J Gastroenterol*. 2001; **96**(1):58–62.
45. GISBERT JP., ABRAIRA V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol*. 2006; **101**(4):848–63.
46. GISBERT JP., ESTEBAN C., JIMENEZ I., MORENO-OTERO R. 13C-urea breath test during hospitalization for the diagnosis of *Helicobacter pylori* infection in peptic ulcer bleeding. *Helicobacter*. 2007; **12**(3):231–7.
47. MIEHLKE S., KIRSCH C., SCHNEIDER-BRACHERT W., HHAERLAND C., NEUMEYER M., BASTLEIN E., *et al.* A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter*. 2003; **8**(4):310–9.
48. CAO Z., CCHEN Q., ZHANG W., LIANG X., LIAO J., LIU W., *et al.* Fourteen-day optimized levofloxacin-based therapy versus classical quadruple therapy for *Helicobacter pylori* treatment failures: a randomized clinical trial. *Scand J Gastroenterol*. 2015; **50**(10):1185–90.
49. DONG SQ., SINGH TP., WEI X., YAO H., WANG HL. Review: A Japanese population-based meta-analysis of vonoprazan versus PPI for *Helicobacter pylori* eradication therapy: Is superiority an illusion? *Helicobacter*. 2017; **22**(6):e12438.