H.Pylori Related Peptic Ulcer Disease–Overview

Divya Sanganabhatla, R. Shyam Sunder

Abstract: ***H. pylori are spiral-shaped bacteria that grow in the digestive tract and have a tendency to attack the stomach lining. H. pylori infections are usually harmless, but they're responsible for the majority of ulcers in the stomach and small intestine. H. pylori are adapted to live in the harsh, acidic environment of the stomach. These bacteria can change the environment around them and reduce its acidity so they can survive. The shape of H. pylori allows them to penetrate your stomach lining, where they're protected by mucus and your body's immune cells are not able to reach them. The bacteria can interfere with your immune response and ensure that they're not destroyed. This can lead to stomach problems .These are diagnosed by various tests clinically. After H. pylori is identified in patients with gastritis or a peptic ulcer, the standard procedure is to eradicate the bacterial infection and allow the ulcer to heal. The typical therapy is a one week "triple therapy" consisting of a proton pump inhibitor such as omeprazole and the antibiotics clarithromycin and amoxicillin. There have been different varieties of the "triple therapy" that have been developed. Some varieties may use a different proton pump inhibitor such as pantoprazole or rabeprazole. They may also replace the amoxicillin with metronidazole for people who are allergic to penicillin. The new revolutions in therapy have made the treatment of peptic ulcers easier and have made it possible to cure the disease. In prior times only the symptoms were treated using antacids, H2-antagonists or proton pump inhibitors alone. Now further advancements have allowed for the treatment process to even decrease from 14 days to a possible 7-10 day treatment period. With advances in the efficacy of proton pump inhibitors a change in the patients diet is not even necessary.***

Keywords: Quadruple therapy; Stool test; Triple therapy; Urea breathe test.

I. INTRODUCTION

Since the introduction of Helicobacter pylori to the medical community by Marshall and Warren almost two decades ago, Helicobacter pylori has been the focus of basic biochemical and clinical research and debate. Its relevance to human disease, specifically to peptic ulcer disease, gastritis, and gastric malignancy, is indisputable. Many questions, however, still remain concerning the optimal diagnostic and therapeutic regimens with which to approach the organism Helicobacter pylori is a gram negative, microaerophilic bacterium that can inhabit various areas of the stomach, particularly the antrum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. Over 80% of individuals infected with the bacteria are asymptomatic. The bacterium was initially named Campylobacter pyloridis, then renamed C. pylori (pylori = genitive of pylorus) to correct a Latin grammar error.

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When 16S rRNA gene sequencing and other research showed in 1989 that the bacterium did not belong in the genus Campylobacter, it was placed in its own genus, Helicobacter. The genus derived from the ancient Greek "spiral" or "coil". The specific epithet pylōri means "of the pylorus" or pyloric valve (the circular opening leading from the stomach into the duodenum), from the Ancient Greek word πυλωρός, which means gatekeeper. More than 50% of the world's population harbor Helicobacter pylori in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries [1]

II. PATHOGENESIS

The earliest descriptions of the organism classified it as predominately extracellular, gramnegative, flagellated, and motile. With the advancement of biochemical techniques, new information about the pathogenicity and virulence factors of Helicobacter pylori has emerged, indicating that infection by Helicobacter pylori requires a complex interaction of both bacterial and host factors. Investigators have identified several bacterial proteins necessary for colonization of the gastric mucosa by Helicobacter pylori, including proteins active in the transport of the organism to the surface of the mucosa (eg, flagellin, which is encoded on genes flaA and flaB). Once in the presence of the gastric mucosa, bacteria induce a transient hypochlorhydria by an unknown mechanism . The urease enzyme produced by the bacteria alters the microenvironment of the organism to facilitate colonization. Adherence then occurs via interaction between cell-surface glycolipids and adhesins specific to Helicobacter pylori. There also appears to be a role played by proteins called cecropins, which are produced by Helicobacter pylori and inhibit the growth of competing organisms, as well as by a P-type adenosine triphosphatase, which helps prevent excessive alkalinization of the microenvironment by urease. Once attached to gastric mucosa, Helicobacter pylori causes tissue injury by a complex cascade of events that depends on both the organism and the host. Helicobacter pylori, like all gram negative bacteria, has in its cell wall lipopolysaccharide, which acts to disrupt mucosal integrity. Furthermore, Helicobacter pylori release several pathogenic proteins that induce cell injury. For example, the CagA protein, produced by cytotoxic-associated gene A (cagA), is a highly immunogenic protein that may be associated with more severe clinical syndromes, such as duodenal ulcer and gastric adenocarcinoma (although this question is far from settled). There is increasing evidence that CagA positivity is associated with an increased risk for distal, but not proximal, gastric adenocarcinoma. In addition, protein products of the vacuolating cytotoxin A gene (vacA) and the A gene induced.

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By contact with epithelium (iceA) are known to be associated with mucosal injury. Once colonization of the gastric mucosa has taken place, the immunogenic properties of Helicobacter pylori induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestations of the infection. This process is mediated by host factors, including interleukins 1, 2, 6, 8, and 12; interferon gamma, tumor necrosis factor, T and B lymphocytes and phagocytic cells. These factors mediate injury through release of reactive oxygen species and inflammatory cytokines. Helicobacter pylori additionally appear to increase the rate of mucosal-programmed cell death (also known as apoptosis) (Tandon R et al., 2000).

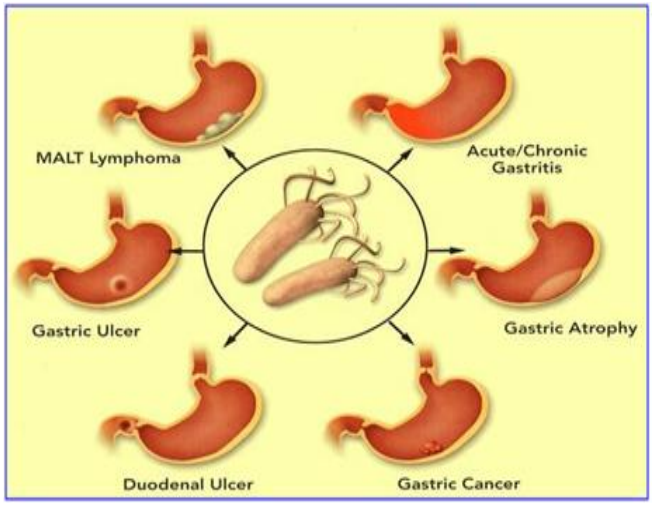

Fig1: H.Pylori Disease profile Diagnosis

A. Urea Breath Tests

Urea breath tests require the ingestion of urea labeled with the nonradioactive isotope carbon 13 or carbon 14. Specificity and sensitivity approach 100%. Urea breath testing is one option for test of cure and should be performed four to six weeks after completion of eradication therapy. Proton pump inhibitors (PPIs) must be stopped for at least two weeks before the test, and accuracy is lower in patients who have had distal gastrectomy. Cost and inconvenience are disadvantages of this test (Moayyedi P et *al*.,2006)

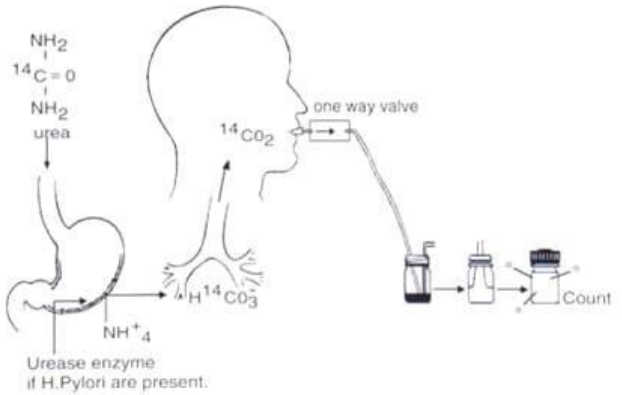

Fig 2: Urea Breathe test

B. Stool Monoclonal Antigen Tests

Stool antigen tests using monoclonal antibodies are as accurate as urea breath tests if a validated laboratory-based monoclonal test is used (Talley NJ et *al*.,2005, Malfertheiner P et al.,2012)They are cheaper and require less equipment than urea breath tests. Like urea breath tests, stool antigen tests detect only active infection and can be used as a test of cure. PPIs should be stopped for two weeks before testing, but stool antigen tests are not as affected by PPI use as are urea breath tests.

C. Serologic Tests

Serologic antibody testing detects immunoglobulin G specific to *H. pylori* in serum and cannot distinguish between an active infection and a past infection. Serologic tests may be most useful in mass population surveys and in patients who cannot stop taking PPIs (e.g., those with gastrointestinal bleeding or continuous NSAID use) because the tests are not affected by PPI or antibiotic use (Chey WD et *al*.,2007).

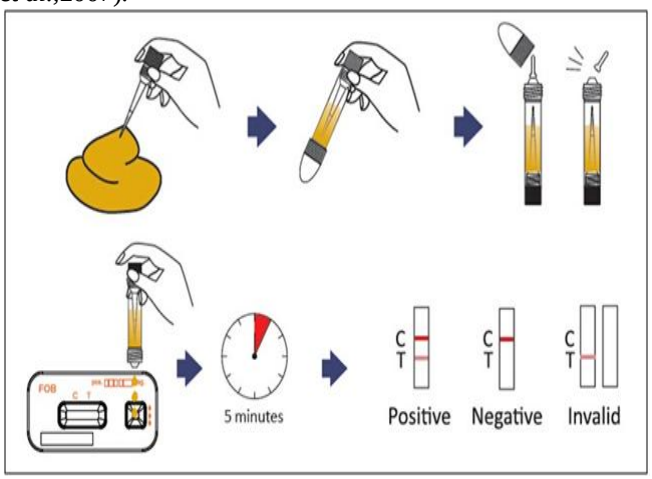

Fig 3: Stool test and Blood test

D. Endoscopy with Biopsy

Endoscopy with biopsy is recommended to rule out cancer and other serious causes in patients 55 years or older, or with one or more alarm symptoms. In patients who have not been taking a PPI within one to two weeks of endoscopy, or bismuth or an antibiotic within four weeks, the rapid urease test performed on the biopsy specimen provides an accurate, inexpensive means of diagnosing *H. pylori* infection (Chey WD et *al*.,2007). Patients who have been on these medications will require histology, with or without rapid urease testing. Culture and polymerase chain reaction allow for susceptibility testing but are not readily available for clinical use in the United States.

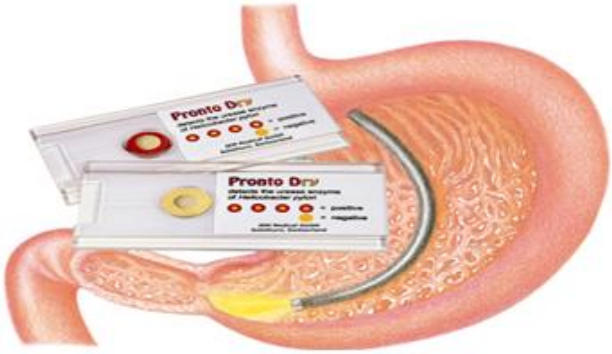

Figure 4: Biopsy Test

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III. TREATMENT

Eradication of *H. pylori* is recommended in all patients with PUD. First-line therapy should have an eradication rate of more than 80%.[4] Because pretreatment susceptibility is rarely known to the primary care physician, therapy must be chosen empirically based on regional bacterial resistance patterns, local recommendations, and drug availability. *Table 1* includes treatment options; standard triple therapy is a reasonable initial therapy where clarithromycin resistance is low (Ford AC et *al*.,2006 , Gisbert JP et *al*.,2010, Wu DC et *al*.,2010).

Table 1: Treatment Regimens for *Helicobacter pylori* Infection

TYPE	REGIMEN	DURATION	ERADICATION RATE	COMMENTS
First line				
Standard triple therapy	PPI, amoxicillin 1 g, and clarithromycin 500 mg (Biaxin) twice daily	7 to 10 days (up to 14 days)	70% to 85%	Preferred
	PPI, clarithromycin 500 mg, and metronidazole 500 mg (Flagyl) twice daily	10 to 14 days	70% to 85%	
Sequential therapy	PPI and amoxicillin 1 g twice daily, followed by PPI, clarithromycin 500 mg, and tinidazole 500 mg (Tindamax) or metronidazole 500 mg twice daily	10 days (5 days for each regimen)	> 84%	Needs validation in the United States
Second line				
Non–bismuth-based quadruple therapy (concomitant therapy)	PPI, amoxicillin 1 g, clarithromycin 500 mg, and tinidazole 500 mg or metronidazole 500 mg twice daily	10 days	90%	Less complex than sequential therapy with similar eradication rates
Bismuth-based quadruple therapy	Bismuth subsalicylate 525 mg or subcitrate 300 mg, metronidazole 250 mg, and tetracycline 500 mg, four times daily; and PPI twice daily	10 to 14 days	75% to 90%	May also be used if first-line therapy fails
Levofloxacin-based triple therapy	PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg (Levaquin) once daily	10 days		Needs validation in United States; should be used as salvage therapy only

PPI = proton pump inhibitor.

Eradication heals most duodenal ulcers and greatly diminishes the risk of recurrent bleeding. A systematic review found that treatment of *H. pylori* infection is more effective than antisecretory noneradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. Current data suggest that increasing the duration of therapy to 14 days significantly increases the eradication rate.

A. Standard Triple Therapy

A seven- to 10-day triple drug regimen consisting of a PPI, amoxicillin 1 g, and clarithromycin 500 mg (Biaxin) twice daily has long been the first-line therapy to eradicate *H. pylori*. However, increasing resistance to clarithromycin is associated with declining eradication rates, now well below 80% (Houben MH et *al*.,1999) .Therefore, this regimen is not recommended where the prevalence of clarithromycin-resistant strains of *H. pylori* exceeds 15% to 20%.[1] An alternative triple drug regimen substitutes metronidazole 500 mg twice daily for amoxicillin. Adding probiotics to triple therapy, specifically *Saccharomyces boulardii* and *Lactobacillus*, has been shown to increase eradication rates (absolute increase of 9% and 5%, respectively) and decrease adverse effects of treatment, particularly diarrhea (absolute decrease of 14% and 7%, respectively) (Szajewska H et *al.*,2010 , Zou J, et al 2009).

B. Sequential Therapy

Sequential therapy consists of a five-day course of a PPI and amoxicillin 1 g taken twice daily, followed by a five-day course of a PPI, clarithromycin 500 mg, and metronidazole 500 mg (Flagyl).

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Or tinidazole 500 mg (Tindamax) taken twice daily. The overall eradication rate is 84%, with an eradication rate of 73% for clarithromycin-resistant strains. A recent meta-analysis of available global data revealed that sequential therapy is superior to seven-day triple therapy, but it is not superior to 14-day triple therapy, bismuth-based quadruple therapy, or non–bismuth-based quadruple therapy (Gisbert JP et *al.*, 2011)

Compliance and tolerance rates of sequential therapy are similar to those of triple therapy but cost is lower, especially when the cost of failure of first-line therapy is considered. However, most studies were performed in Italy, and the ACG guideline states that sequential therapy requires validation in the United States (Ford AC et *al.*,2006) Non–Bismuth-Based Quadruple Therapy (Concomitant Therapy) This approach involves the addition of metronidazole 500 mg or tinidazole 500 mg twice daily to the standard triple regimen. It is less complex than sequential therapy with similar eradication rates (Molina-Infante et *al.*,2012). Additionally, non–bismuth-based quadruple therapy may be more effective than sequential therapy in patients with dual antibiotic resistance to clarithromycin and metronidazole (Berning M et *al.*,2011). It has the highest eradication rate, about 90%, even in areas with high clarithromycin and metronidazole resistance (Lanza FL et *al.*, 2009, Rostom A et *al.*,2002) but would presumably cost more than sequential therapy because clarithromycin is taken for 10 days.

C. Bismuth-Based Quadruple Therapy

This is the traditional quadruple regimen and includes a bismuth salt (subsalicylate 525 mg or subcitrate potassium 420 mg), metronidazole 250 mg, and tetracycline 375 to 500 mg, all taken four times daily, in addition to a PPI taken twice per day **(** Chey WD et *al.*,2011). Bismuth-based quadruple therapy is often employed as salvage therapy if first-line treatment fails, but it may be used as first-line therapy in areas of high resistance or when cost is an important consideration. A three-in-one combination capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline has been developed to help reduce the pill burden, but patients still have to take three capsules four times per day in addition to a PPI. The regimen is usually given for 10 to 14 days.

D. Levofloxacin-Based Triple Therapy

This is a 10-day regimen of a PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg (Levaquin) once daily. The ACG states that this regimen requires validation in the United States (Ford AC et *al.*, 2006). It should be reserved for second-line therapy and is better tolerated than bismuth-based quadruple therapy(Houben MH et *al.*,1999).

E. Tailored Therapy

Since antibiotic resistance is the main cause of eradication failure, a tailored therapy that selects the most appropriate regimen to overcome antibiotic resistance would be the optimal treatment. However, tailored therapies are complex and costly. Therefore, a new method to detect antibiotic resistance is needed. One such solution is the polymerase chain reaction (PCR) kit, which uses the dual-priming oligonucleotide-based multiplex PCR test. This kit identifies the presence of point mutations of clarithromycin 23S rRNA that are known to be associated with resistance, namely, A2142G and A2143G, using a PCR(M. Gerrits et al., 2006). The test can be performed with a sample of gastric mucosa and takes only a few hours, making it relatively simple to use; its sensitivity and specificity are approximately 80–85% (T. J. Hwang et *al.*,2010).

F. Potassium-Competitive Acid Blocker

The potassium-competitive acid blocker (P-CAB), vonoprazan, could improve eradication rates by increasing the intragastric pH and thus increasing bacterial antibiotic susceptibility. Vonoprazan 20 mg demonstrated a more rapid and sustained acid-inhibitory effect than esomeprazole 20 mg or rabeprazole 10 mg (Y. Sakurai et *al.*,2015). Recent studies revealed that P-CAB based triple therapy was more effective than PPI-based triple therapy as a first-lineH. pylori eradication method (S. Shichijo et al.,2016, K. Murakami et *al.*,2016,S. Suzukiet *al.*,2016). Furthermore, even in the presence of clarithromycin-resistant strains, P-CAB-based triple therapy showed good eradication rates that were superior to those for PPI-based triple therapy (76.1% versus 40.2%) (A. Federico et *al.*, 2014).

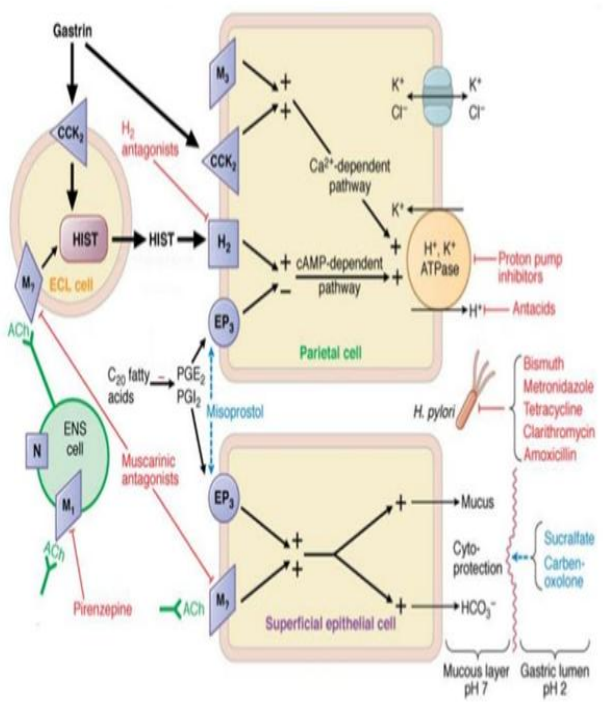

Figure 5: Drug Mechanism

IV. CONCLUSION

Many studies have determined that novel agents and treatment regimens can improve eradication of *H. pylori*. With Standard Triple Therapy, high doses of PPI are used which prolongs, therapy duration and increase eradication rates: indeed, in Europe and some regions of Asia these results are improved further with sequential Therapy. Sequential therapy is less affected by antibiotic resistance, which adds value as an alternative treatment. Newer agents, nontraditional therapy, and microtechnology are also expected to play a major role in *H. pylori* eradication.

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REFERENCES

1. Ananthakrishnan N, Kate V. Helicobacter pylori: The rapidly changing scenario G.I. Surgery annual. Vol. 5. New Delhi: Byword; 1998. p. 1- 20.
2. Berning M, Krasz S, Miehlke S. Should quinolones come first in Helicobacter pylori therapy? Therapy Adv Gastroenterol. 2011;4(2):103–114.
3. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007;102 (8):1808–1825.
4. Federico, A. G. Gravina ,A. Miranda, C. Loguercio, and M. Romano, "Eradication of Helicobacter pylori infection: which regimen first?" World Journal of Gastroenterology, vol. 20, no. 3, pp. 665–672, 2014.
5. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database Syst Rev. 2006;19(2):CD003840.
6. Gisbert JP, Calvet X, O'Connor A, et al. Sequential therapy for Helicobacter pylori eradication. Journal Clin Gastroenterol. 2010;44 (5):313–325.
7. Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobater pylori. Aliment Pharmacol Ther. 2011;34(6):604–617.
8. H. Matsumoto, A. Shiotani, R. Katsumata et al., "Helicobacter pylori eradication with proton pump inhibitors or potassium-competitive acid blockers: the effect of clarithromycin resistance," Digestive Diseases and Sciences, vol. 61, no. 11, pp. 3215–3220, 2016.
9. H. Noda., S. Noguchi, T. Yoshimine et al., "A novel potassium-competitive acid blocker improves the efficacy of Clarithromycin-containing 7-day triple therapy against Helicobacter pylori," Journal of Gastrointestinal and Liver Diseases, vol. 25, no. 3, pp. 283–288, 2016.
10. Houben MH, van de Beek D, Hensen EF, de Craen AJ, Rauws EA, Tytgat GN. A systematic review of Helicobacter pylori eradication therapy—the impact of antimicrobial resistance on eradication rates. Aliment Pharmacol Ther. 1999;13(8):1047–1055.
11. K. Murakami, Y. Sakurai, M. Shiino, N. Funao, A. Nishimura, and M. Asaka, "Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study," Gut, vol. 65, no. 9, pp. 1439–1446, 2016.
12. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104(3):728–738.
13. M. M. Gerrits, A. H. van Vliet, E. J. Kuipers, and J. G. Kusters, "Helicobacter pylori and antimicrobial resistance: molecular mechanisms and clinical implications," Lancet Infectious Diseases, vol. 6, no. 11, pp. 699–709, 2006.
14. Malfertheiner P, Megraud F, O'Morain CA, et al.; European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report. Gut. 2012;61(5):646–664
15. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA. 2006;295(13):1566–1576.
16. Molina-Infante J, Pazos-Pacheco C, Vinagre-Rodriguez G, et al. Nonbismuth quadruple (concomitant) therapy: empirical and tailored efficacy versus standard triple therapy for clarithromycin-susceptible Helicobacter pylori and versus sequential therapy for clarithromycin-resistant strains. Helicobacter. 2012;17(4):269–276.
17. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastro-duodenal ulcers. Cochrane Database Syst Rev. 2002;(4):CD002296.
18. S. Shichijo, Y. Hirata, R. Niikura et al., "Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori: a multicenter retrospective study in clinical practice," Journal of Digestive Diseases, 2016.
19. S. Suzuki, T. Gotoda, C. Kusano, K. Iwatsuka, and M. Moriyama, "The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day, PPI-based low-dose clarithromycin triple therapy," The American Journal of Gastroenterology, vol. 111, no. 7, pp. 949–956, 2016.
20. Shimoyama T. Stool antigen tests for the management of Helicobacter pylori infection. World J Gastroenterol. 2013;19(45):8188–8191.
21. Szajewska H, HorvathA, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. [published correction appears in Aliment Pharmacol Ther. 2010;32(11–12):1408]. Aliment Pharmacol Ther. 2010;32(9):1069–1079.
22. T. J. Hwang, N. Kim, H. B. Kim et al., "Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of H. pylori in a single center of Korea," Journal of Clinical Gastroenterology, vol. 44, no. 8, pp. 536–543, 2010.
23. Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324–2337.
24. Tandon R. Second national workshop on Helicobacter pylori: Consensus Statements Treatment of Helicobacter pylori in peptic ulcer disease. Indian Journal Gastroenterol 2000; 19:S37
25. Wu DC, Hsu PI, Wu JY, et al. Sequential and concomitant therapy with four drugs is equally effective for eradication of H pylori infection. Clin Gastroenterol Hepatol. 2010;8(1):36–41.e1.
26. Y. Sakurai, Y. Mori, H. Okamoto et al., "Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—A Randomised Open-Label Cross-Over Study," Alimentary Pharmacology and Therapeutics, vol. 42, no. 6, pp. 719–730, 2015.
27. Zou J, Dong J, Yu X. Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for Helicobacter pylori eradication. Helicobacter. 2009;14(5):97–107.

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