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ORIGINAL RESEARCH

Association Between Vitamin D Receptor Polymorphism and the Response to Helicobacter Pylori Treatment

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Background & Aims: This research aimed to determine how variations in the vitamin D receptor gene affected the response of *H. pylori* infections to eradication therapy.

Patients and Methods: On 105 adult *H. Pylori*-positive patients, a prospective cohort study was carried out. PCR was used to genotype all patients' VDR gene polymorphisms. The patients in the study received standard triple eradication medication (clarithromycin 500 mg, amoxicillin 1000 mg, and omeprazole 20 mg) twice daily for 14 days. A stool test for *H. pylori* Ag was conducted 4 weeks following the end of treatment.

Results: In our study, the usual triple therapy's *H. pylori* eradication rate was 75.2%. The successful eradication of H. pylori and VDR rs 2228570 gene polymorphisms was more prevalent in CT gene polymorphism (64.6%) compared to non-responders (19.2%), while treatment failure was more prevalent in CC gene polymorphism (73.1% in non-responders compared to responders 24.1%), which is statistically significant. In regards to the eradication of *H. pylori* and VDR rs7975232 gene polymorphisms, the success of eradication was more prevalent in AC gene polymorphism (54.4%) vs non-responders (30.4%), while all patients (14) with gene AA (17.7%) are responders to standard treatment, while the failure of treatment was more prevalent in CC gene polymorphism (69.2% in non-responder vs 27.8% in responders) which is statistically significant. Our findings demonstrated a strong correlation between patients' responses to *H. pylori* treatment and polymorphisms in the VDR gene (ApaI and TaqI) (P 0.05).

Conclusion: As far as we are aware, this is the first study to identify a potential link between the FokI and ApaI VDR polymorphism and treatment response in *H pylori*-positive patients. To evaluate the findings, more research with larger number of patients and different population is required.

Keywords: Helicobacter, infection, gene, polymorphism, response, eradication

Introduction

The spiral-shaped Gram-negative bacteria Helicobacter pylori (*H. Pylori*) exhibits a variety of processes and distinct virulence factors that impact the characteristics of the gastric mucosa and determine its adhesion and survival in this environment.[1] The main cause of persistent gastritis is infection with the *H. Pylori* bacteria. Nearly half of the world's population is impacted.[2]

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Additionally, a study conducted on Egyptian patients by Abo-Amer et al discovered that 538 patients (83.3%) of Egyptian patients had *H. pylori* infection.[3]

Other gastrointestinal conditions such peptic ulcer disease, gastric adenocarcinoma, and gastric lymphoma are influenced by *H. Pylori* in their aetiology. *H. pylori* infection is linked to most duodenal ulcers and stomach malignancies.[2] The strains that reside in the stomach mucosa and how they interact with the host's immune system determine the long-term colonisation of *H. pylori* and the production of chronic gastritis.[2] Additionally, the susceptibility and clinical development of the infection are also in part influenced by human genetic variations. They can create various levels of immune system mediators that are connected to infection rates, the eradication of *H. pylori* and colonisation by more virulent strains, the augmentation of stomach inflammation, and cell damage.[4]

The expression of the vitamin D receptor (VDR) in the stomach epithelia may improve as a result of *H. pylori* infection, according to a recent theory. Through the stimulation of cathelicidin antimicrobial peptides and the reduction of inflammatory cytokine and chemokine levels, it has been found in vitro that the active form of vitamin D, 1a,25-dihydroxy vitamin D3, exhibits immune modulators capabilities against this pathogen.[5] In metanalysis done by Yang et al[6] found that Vitamin D has a protective role in H pylori infection. Also, El Shahway et al,[7] found that low level of Vitamin D associated with failure of treatment while Shafrir et al[8] reported that increased vitamin D levels are associated with successful H. pylori eradication. The VDR gene, which spans a length of DNA larger than 60 kb, is found on the 12q13.11 chromosome.[9] The restriction fragment length polymorphism (RFLP) for the FokI, BsmI, ApaI, and TaqI restriction enzymes is being utilised in investigations of genetic vulnerability to infectious diseases as well as response to treatment.[10–12]

The FokI polymorphism (rs2228570; C>T), characterized by the change of thymine to cytosine (ATG to ACG)[13] and ApaI polymorphism (rs7975232, A>C) where cytosine is changed to adenine.[14] The FokI and Apal VDR polymorphism and *H. pylori* infection may go hand in hand.[15] This research aimed to determine how variations in the vitamin D receptor gene affected how *H. pylori* infections responded to eradication therapy.

Subject and Methods

Subject

From 176 adult H. Pylori-positive patients, only 105 H. Pylori-positive patients who meet the eligibility criteria, a prospective cohort study was carried out at Mahala Hepatology Teaching Hospital during the period from May 2021 to Jan 2022. Research was approved by Mahala Hepatology Teaching Hospital research ethical committee. No animals were used for studies that are the basis of this research. All human procedures followed were in accordance with the guidelines of Helsinki Declaration of 1975. Informed consent was obtained from all participants of this study.

Methods

All of the enrolled patients had their *H. pylori* status confirmed as positive using the Eliza procedure in accordance with the manufacturer's instructions.

The following is administered to all patients;

1) PCR was used to genotype all patients' VDR gene polymorphisms.
2) The widely used clarithromycin-based triple therapy, which includes omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg twice daily for 14 days.
3) Four weeks following the completion of treatment, a stool sample was tested for *H. pylori* Ag.

Laboratory Analysis

Genotyping and DNA extraction: The DNA was extracted using the QIAamp® DNA Blood Mini Kit. Using a Nano Drop® (ND-1000) Spectrophotometer (Nano Drop Technologies Inc., Washington, USA), the concentration of the isolated DNA was determined.

Genotyping of VDR SNPs: Applied Biosystems (Applied Biosystems-Life Technologies, Carlsbad, California, USA) genotyped the VDR FokI (rs2228570) and ApaI (rs7975232) SNPs.

All patients provided written, informed consent.

Exclusion Criteria

A proton pump inhibitor (PPI) was taken within the previous month by subjects or those who reported receiving *H. pylori* medication within the previous six months, being pregnant, abusing alcohol, or using illegal drugs were excluded from the study. Utilisation of corticosteroids, immunosuppressive therapy, anti-inflammatory medications, or antibiotics in the two months prior. Gastric surgery, renal failure, liver cirrhosis, autoimmune diseases with a history, liver cirrhosis, and cancers were disqualified.

Statistical Analysis

Statistical tests were performed using SPSS 21.0. Qualitative data were expressed as number and percentage and quantitative variables were expressed as the mean ± standard deviation (mean ±SD) for parametric data. Chi-square test was used to evaluate qualitative data. Regression analysis was done to determine the independent risk factors for the *H. pylori* eradication. A level for statistical significance was significant at $p < 0.05$.

Results

The study involved 105 patients, whose average age was 49.44 + 10.94. Male patients made up 56 (53.3%) and female patients were 49 (46.7%). Only 26 patients (24.8%) smoked, and their average BMI was 29.43 5.75. The average lab results for CBC, liver enzyme, and creatinine were displayed in (Table 1).

Table 1 Baseline Characteristic Features of the *H. Pylori* Infected Patients

Gender	49 (46.7%)
Male	49 (46.7%)
Female	56 (53.3%)
Age (year)	49.44 ± 10.94
Smoking	26 (24.8%)
BMI (kg/m^2)	29.43±5.75
Hemoglobin (g/dl)	11.74±1.13
WBCs ($10^3/\mu L$)	6.59±2.40
Platelets ($10^3/\mu L$)	206±44.81
ALT (U/L)	25.13±5.67
AST (U/L)	27.33±4.51
Total bilirubin (mg/dL)	0.83±0.21
Serum creatinine (mg/dL)	0.86±0.22
VDR rs 2228570	
TT	11 (10.5%)
CT	56 (53.3%)
CC	38 (36.2%)
VDR rs 2228570	
T	78 (37.14%)
Alleles	
C	132 (62.86)
VDR rs 7975232	
AA	14 (13.3%)
AC	51 (48.6%)
CC	40 (38.1%)
VDR rs 7975232	
A	79 (37.62%)
Alleles	
C	131 (62.38%)

Abbreviations: BMI, Body mass index; WBCs, White Blood Cells; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; VDR, vitamin D receptor.

Table 2 Gene Polymorphism of VDR in Relation to Gender

Gene Polymorphism of VDR		Gender		Total 105 (100%)	χ2	p- value
		Male 56 (53.3%)	Female 49 (46.7%)			
rs 2228570	TT	4 (7.1%)	7 (14.3%)	11 (10.5%)	2.99	0.224
	CT	28 (50.0%)	28 (57.1%)	56 (53.3%)		
	CC	24 (42.9%)	14 (28.6%)	38 (36.2%)		
rs 7975232	AA	7 (12.5%)	7 (14.3%)	14 (13.3%)	2.22	0.3296
	AC	24 (42.9%)	27 (55.1%)	51 (48.6%)		
	CC	25 (44.6%)	15 (30.6%)	40 (38.1%)		

Abbreviation: χ^2, chi-square.

Table 3 Gene Polymorphism of VDR in Relation to the Treatment Outcome of *H.pylori*

Gene Polymorphism of VDR		Outcome		Total 105 (100%)	χ^2	p- value
		Responder 79 (75.2%)	Non Responder 26 (24.8%)			
rs 2228570	TT	9 (11.4%)	2 (7.7%)	11 (10.5%)	20.78	< 0.0001*
	CT	51 (64.6%)	5 (19.2%)	56 (53.3%)		
	CC	19 (24.1%)	19 (73.1%)	38 (36.2%)		
rs 7975232	AA	14 (17.7%)	0 (0.0%)	14 (13.3%)	15.66	0.0004*
	AC	43 (54.4%)	8 (30.8%)	51 (48.6%)		
	CC	22 (27.8%)	18 (69.2%)	40 (38.1%)		

Note: *Significant difference.
Abbreviation: χ^2, chi-square.

As seen in Table 1, the distribution of TT, CT, and CC genotypes among the patients under study was 10.5%, 53.3%, and 36.2%, respectively. As shown in Table 2, the proportions of males and females with VDR rs 2228570 gene polymorphisms are 7.1%, 14.3%, 50.0%, and 57.1%, respectively, in TT, CT, and CC. The distribution of the genotypes AA, AC, and CC for the VDR rs 7975232 gene polymorphisms was 13.3%, 48.6%, and 38.1%, respectively, among the overall study population. According to Table 2, the percentages of males and females with VDR rs 7975232 gene polymorphisms are as follows: AA (12.5% and 14.3%), AC (42.9% and 55.1%), and CC (44.6% and 30.6%).

In 79 of the individuals under study, H pylori was completely eradicated (75.2% success rate). The successful eradication of *H. pylori* and VDR rs 2228570 gene polymorphisms was more prevalent in CT gene polymorphism (64.6%) compared to non-responders (19.2%), while treatment failure was more prevalent in CC gene polymorphism (73.1% in non-responders compared to responders 24.1%), which is statistically significant (Table 3). In regards to the eradication of *H. pylori* and VDR rs7975232 gene polymorphisms, the success of eradication was more prevalent in AC gene polymorphism (54.4%) vs non-responders (30.4%), while all patients (14) with gene AA (17.7%) are responders to standard treatment, while the failure of treatment was more prevalent in CC gene polymorphism (69.2% in non-responder vs 27.8% in responders) which is statistically significant.

The VDR rs 2228570 and VDR rs 7975232 gene polymorphisms were found to be independent risk factors for the elimination of *H. pylori* after regression analysis (Table 4). There were significant correlations between H.Pylori response to eradication therapy and VDR rs 2228570 and VDR rs 7975232 alleles (Table 5).

Discussion

The virulent strains of *H. pylori* are linked to gastric ulcers and cancer because they cause extensive immune cell infiltration in the gastric mucosa and cause noticeable inflammatory reactions.[16] Due to its ability to neutralise gastric acid through the potent action of its urease enzymes[4] and the activity of glutamyl transpeptidase enzyme, which supports

Table 4 Logistic Regression of *H.Pylori* Response to Eradication Therapy

Variable	Coefficient	Odds Ratio	95% CI	P
Age	0.037	1.037	0.970 to 1.108	0.276
Gender	0.093	0.734	0.193 to 2.789	0.895
Smoking	0.383	1.595	0.298 to 8.549	0.651
BMI	0.115	1.118	0.982 to 1.273	0.091
Hemoglobin	−0.569	0.558	0.287 to 1.085	0.088
WBCs	0.092	1.085	0.807 to 1.458	0.548
Platelets	0.099	0.712	0.184 to 2.489	0.840
ALT	−0.016	0.998	0.888 to 1.122	0.795
AST	0.142	1.147	0.970 to 1.356	0.096
Total Bilirubin	1.709	5.188	0.109 to 245.471	0.386
Creatinine	1.319	4.471	0.194 to 102.843	0.409
VDR rs 2228570	−1.982	0.150	0.046 to 0.491	0.002*
VDR rs 7975232	−1.308	0.276	0.093 to 0.816	0.030*
Constant	3.440			0.578

Note: *Significant difference.

Table 5 Logistic Regression Between *H.Pylori* Response to Eradication Therapy and VDR Rs 2228570 and VDR Rs 7975232 Alleles

Variable		Coefficient	Odds Ratio	95% CI	P
VDR rs 2228570	TT (11.4%) CT (64.6%) CC (24.1%)	−1.435	0.238	0.095 to 0.594	0.002*
VDR rs 7975232	AA (17.7%) AC (54.4%) CC (27.8%)	−1.534	0.216	0.086 to 0.540	0.001*
Constant		8.25978			<0.0001*

Note: *Significant difference.

its proliferation and survival in the gastric mucosa,[17] *H. pylori* can persist in the gastric mucosa for an extended period of time during infection. Treatment with vitamin D inhibits both mechanisms.[18] Because the vitamin D metabolites are implicated in the induction of antimicrobial activity and have anti-inflammatory and immune-system modulating properties.[19,20] Failure to eradicate *H. pylori* may be associated with vitamin D deficiency, necessitating vitamin D supplementation prior to *H. pylori* eradication.[21] VDR has a role in the immune-modulating abilities of active vitamin D.[22] Vitamin D receptor gene polymorphisms (ApaI and TaqI) lead to decreased vitamin D level which associated with the response to treatment. In patients with *H. pylori* infection, Guo et al[5] found a statistically significant positive connection between chronic inflammation and VDR mRNA expression.

105 patients who tested positive for *H. pylori* participated in the study. Our findings demonstrated a substantial correlation between patients' responses to *H. pylori* treatment and polymorphisms in the VDR gene (ApaI and TaqI). Also, the eradication of *H. pylori* is at risk due to polymorphisms in the VDR gene (ApaI and TaqI). According to Mohamed et al's findings, *H. pylori* infection and the FokI and Apal VDR polymorphism are related.[15] Additionally, Qadir et al discovered a substantial correlation between the VDR Bsml SNP and increased risk of gastric cancer, particularly in obese individuals.[23] In contrast to Martins et al,[24] who claimed that there were no appreciable changes between patients with *H. pylori* infection and control groups in terms of the allelic and genotypic distribution of the FokI and ApaI polymorphisms of the VDR gene. Additionally, Eom et al[25] discovered no conclusive associations between vitamin D intake and the prevalence of gastric cancer, and genetic variation related to vitamin D had no impact on these

associations. The rates of *H. pylori* eradication do, however, appear to be related to vitamin D levels, according to Huang et al.[26] The discrepancy in the findings could be attributed to the complex interactions between genetic, environmental, and societal factors that lead to *H. pylori* infections. Together with ethnic characteristics, these interactions—which are crucial for illness development and genetic makeup—were most likely responsible for the disparity in allelic frequencies observed in the research population. The results of Mohamed et al[15] were consistent with the lack of a statistically significant variation in the sex distributions across the various genotypes. This is consistent with our findings.

In our study, the usual triple therapy had a 75.2% *H. pylori* eradication rate, and other studies have reported rates between 61 and 77%.[27–30] In contrast to other studies, certain investigations[31,32] showed greater rates (85–94%). Therefore, it makes sense to assume that variations in eradication rates are correlated with the degree of adherence and/or the local susceptibility pattern of *H. pylori* in the investigated areas. A meta-analysis has recommended that antibiotic selection be localised in light of this regional diversity.[33] The present study found that there was a significant difference in the response to eradication therapy of *H.Pylori* regarding VDR (ApaI and TaqI) gene polymorphism. Also, the independent risk factors for *H. pylori* eradication were VDR rs 2228570 and VDR rs7975232 gene polymorphisms. There is also, a significant correlation between *H. Pylori* response to eradication therapy and VDR rs 2228570 and VDR rs 7975232 alleles.

Conclusion

According to our knowledge, this is the first study to have discovered a connection between H pylori positivity and the FokI and ApaI VDR polymorphism, which are separate risk factors for H pylori eradication. There is also, a significant correlations between *H. Pylori* response to eradication therapy and FokI and ApaI VDR polymorphism alleles. To evaluate the findings, more research with numerous populations is required.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Yang I, Nell S, Suerbaum S. Survival in hostile territory: the microbiota of the stomach. *FEMS Microbiol Rev*. 2013;37(5):736–761. doi:10.1111/1574-6976.12027
2. Rana R, Wang SL, Li J, Wang YX, Rao QW, Yang CQ. Helicobacter pylori infection: a recent approach to diagnosis and management. Review. *J Biomed Sci*. 2017;2:45–56. doi:10.7150/jbm.17612
3. Abo-Amer YE, Sabal A, Ahmed R, et al. Relationship between helicobacter pylori infection and nonalcoholic fatty liver disease (NAFLD) in a developing country: a cross-sectional study. *Diabetes Metab Syndr Obes*. 2020;13:619–625. doi:10.2147/dmso.S237866
4. Kusters JG, Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* Infection. *Clin Microbiol Rev*. 2006;19(3):449–490. doi:10.1128/cmr.00054-05
5. Guo L, Chen W, Zhu H, et al. Helicobacter pylori induces increased expression of the vitamin d receptor in immune responses. *Helicobacter*. 2014;19(1):37–47. doi:10.1111/hel.12102
6. Yang L, He X, Li L, Lu C. Effect of vitamin D on Helicobacter pylori infection and eradication: a meta-analysis. *Helicobacter*. 2019;24(5):e12655. doi:10.1111/hel.12655
7. El Shahawy MS, Hemida MH, El Metwaly I, Shady ZM. The effect of vitamin D deficiency on eradication rates of Helicobacter pylori infection. *JGH Open*. 2018;2(6):270–275. doi:10.1002/jgh3.12081
8. Shafrir A, Shauly-Aharonov M, Katz LH, Paltiel O, Pickman Y, Ackerman Z. The association between serum vitamin D levels and helicobacter pylori presence and eradication. *Nutrients*. 2021;13(1):278. doi:10.3390/nu13010278
9. Crofts LA, Hancock MS, Morrison NA, Eisman JA. Multiple promoters direct the tissue-specific expression of novel N-terminal variant human vitamin D receptor gene transcripts. *Proc Natl Acad Sci USA*. 1998;95(18):10529–10534. doi:10.1073/pnas.95.18.10529
10. Alagarasu K, Honap T, Mulay AP, Bachal RV, Shah PS, Cecilia D. Association of vitamin D receptor gene polymorphisms with clinical outcomes of dengue virus infection. *Hum Immunol*. 2012;73(11):1194–1199. doi:10.1016/j.humimm.2012.08.007
11. Sortica VA, Cunha MG, Ohnishi MD, et al. IL1B, IL4R, IL12RB1 and TNF gene polymorphisms are associated with Plasmodium vivax malaria in Brazil. *Malar J*. 2012;11:409. doi:10.1186/1475-2875-11-409
12. Salimi S, Farajian-Mashhadi F, Alavi-Naini R, Talebian G, Narooie-Nejad M. Association between vitamin D receptor polymorphisms and haplotypes with pulmonary tuberculosis. *Biomed Rep*. 2015;3(2):189–194. doi:10.3892/br.2014.402
13. Colin EM, Weel AE, Uitterlinden AG, et al. Consequences of vitamin D receptor gene polymorphisms for growth inhibition of cultured human peripheral blood mononuclear cells by 1, 25-dihydroxyvitamin D3. *Clin Endocrinol*. 2000;52(2):211–216. doi:10.1046/j.1365-2265.2000.00909.x
14. Sherry ST, Ward MH, Kholodov M, et al. dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res*. 2001;29(1):308–311. doi:10.1093/nar/29.1.308
15. Mohamed AA, Moussa S, Shaheen MM, et al. Association between vitamin d receptor gene polymorphisms and infection. *Open Biomark J*. 2020;10(1):8–14. doi:10.2174/1875318302010010008
16. Nogueira C, Figueiredo C, Carneiro F, et al. Helicobacter pylori genotypes may determine gastric histopathology. *Am J Pathol*. 2001;158(2):647–654. doi:10.1016/s0002-9440(10)64006-0

17. Gong M, Ling SS, Lui SY, Yeoh KG, Ho B. Helicobacter pylori gamma-glutamyl transpeptidase is a pathogenic factor in the development of peptic ulcer disease. *Gastroenterology*. 2010;139(2):564–573. doi:10.1053/j.gastro.2010.03.050
18. Kawaura A, Takeda E, Tanida N, et al. Inhibitory effect of long term 1α-hydroxyvitamin administration on helicobacter pylori infection. *J Clin Biochem Nutr*. 2006;38(2):103–106. doi:10.3164/jcbn.38.103
19. Youssef DA, Miller CW, El-Abbassi AM, et al. Antimicrobial implications of vitamin D. *Dermatoendocrinol*. 2011;3(4):220–229. doi:10.4161/derm.3.4.15027
20. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. *Inflamm Res*. 2014;63(10):803–819. doi:10.1007/s00011-014-0755-z
21. Yildirim O, Yildirim T, Seckin Y, Osanmaz P, Bilgic Y, Mete R. The influence of vitamin D deficiency on eradication rates of Helicobacter pylori. *Adv Clin Exp Med*. 2017;26(9):1377–1381. doi:10.17219/acem/65430
22. White JH. Vitamin D metabolism and signaling in the immune system. *Rev Endocr Metab Disord*. 2012;13(1):21–29. doi:10.1007/s11154-011-9195-z
23. Qadir J, Majid S, Khan MS, Wani MD. Association of Vitamin D receptor gene variations with Gastric cancer risk in Kashmiri population. *Mol Biol Rep*. 2021;48(4):3313–3325. doi:10.1007/s11033-021-06376-z
24. Martins DJ, Matos GC, Loiola RS, D'Annibale V, Corvelo T. Relationship of vitamin D receptor gene polymorphisms in Helicobacter pylori gastric patients. *Clin Exp Gastroenterol*. 2018;11:19–27. doi:10.2147/ceg.S143332
25. Eom SY, Yim DH, Kim DH, et al. Dietary vitamin D intake and vitamin D related genetic polymorphisms are not associated with gastric cancer in a hospital-based case-control study in Korea. *J Biomed Res*. 2018;32(4):257–263. doi:10.7555/jbr.32.20170089
26. Huang B, Yan S, Chen C, Ye S. Effect of 25-hydroxyvitamin D on Helicobacter pylori eradication in patients with type 2 diabetes. *Wien Klin Wochenschr*. 2019;131(3–4):75–80. doi:10.1007/s00508-018-1416-y
27. Ramas M, Donday MG, McNicholl AG, Gisbert JP. Efficacy and safety of rifaximin associated with standard triple therapy (omeprazole, clarithromycin and amoxicillin) for H. pylori eradication: a Phase IV pilot clinical trial. *Gastroenterol Hepatol*. 2017;40(10):658–662. doi:10.1016/j.gastrohep.2017.05.017
28. Ahmed HM, Abd-Elsalam S, Mahrous MA. Moxifloxacin based triple therapy as alternative to standard therapy in Helicobacter Pylori Eradication. *Anti-Infective Agents*. 2021;19(3):299–302. doi:10.2174/2211352518999200925154501
29. Abd-Elsalam S, Kobtan A, El-Kalla F, et al. A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for Helicobacter pylori eradication: a single center experience. *Medicine*. 2016;95(24):e3879. doi:10.1097/md.0000000000003879
30. Shehata MA, Talaat R, Soliman S, Elmesseri H, Soliman S, Abd-Elsalam S. Randomized controlled study of a novel triple nitazoxanide (NTZ)-containing therapeutic regimen versus the traditional regimen for eradication of Helicobacter pylori infection. *Helicobacter*. 2017;22:5.
31. Fock KM, Chelvam P, Lim SG. Triple therapy in the eradication of Helicobacter pylori in patients with duodenal ulcer disease: results of a multicentre study in South-East Asia. South-East Asia Multicenter Study Group. *Aliment Pharmacol Ther*. 2000;14(2):225–231. doi:10.1046/j.1365-2036.2000.00691.x
32. Gebeyehu E, Nigatu D, Engidawork E. Helicobacter pylori eradication rate of standard triple therapy and factors affecting eradication rate at Bahir Dar city administration, Northwest Ethiopia: a prospective follow up study. *PLoS One*. 2019;14(6):e0217645. doi:10.1371/journal.pone.0217645
33. Xin Y, Manson J, Govan L, et al. Pharmacological regimens for eradication of Helicobacter pylori: an overview of systematic reviews and network meta-analysis. *BMC Gastroenterol*. 2016;16(1):80. doi:10.1186/s12876-016-0491-7