Microb Health Dis 2024; 6: e1046

HELICOBACTER PYLORI: PATHOGENESIS

P. Sabanas, L. Jonaitis

Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania

Corresponding Author: Povilas Sabanas, MD; email: povilas.sabanas@kaunoklinikos.lt; povilas.sabanas@lsmu.lt

Abstract – In this review, we analyze the research articles and findings related to the pathogenesis of *Helicobacter pylori* infection, which were published between April 2023 and March 2024. *H. pylori* is the most common infectious disease worldwide. The clinical consequences of *H. pylori* infection are closely linked with the expression of virulence factors produced by the bacterium. To improve diagnostic tools and optimize the treatment outcomes of *H. pylori* infection it is essential to understand its pathogenesis. The latest mechanisms of how *H. pylori* interact with host tissue and microbiome, induces and modulates its pathogenicity, and influences the development of malignant disease as well as extragastric pathologies are represented in our review article. Treatment success rates by the current guidelines-based regimens remain suboptimal due to the increasing antimicrobial resistance of *H. pylori*. The mechanisms of resistance are still in the scope of research. We also describe the studies related to the possible mechanisms of resistance of *H. pylori* to antibacterial drugs.

Keywords: *Helicobacter pylori*, *H. pylori*, Pathogenesis, Gastric cancer, Carcinogenesis, Microbiota.

BACKGROUND AND METHODS

In this review, we will focus on the research articles and findings related to the pathogenesis of *Helicobacter pylori* infection, which were published between April 2023 and March 2024. By using the keywords listed further, we have conducted a comprehensive literature search in the PubMed database and a thorough revision of filtered abstracts. In this review article, we used published manuscripts deemed to be most relevant for this special issue in accordance with the selected date. *H. pylori* is the most common infectious disease worldwide. The clinical consequences of *H. pylori* infection are closely linked with the expression of virulence factors produced by the bacterium. To improve diagnostic tools and optimize the treatment outcomes of *H. pylori* infection, it is essential to understand its pathogenesis. The latest mechanisms of how *H. pylori* interacts with host tissue and microbiome, induces and modulates its pathogenicity, and influences the development of malignant disease as well as extra gastric pathologies are represented in our review article. Treatment success rates by the current guidelines-based regimens remain suboptimal due to the increasing antimicrobial resistance of *H. pylori*. The mechanisms of resistance are still in the scope of research. We also describe the studies related to the possible mechanisms of resistance of *H. pylori* to antibacterial drugs.

INTERACTION OF *HELICOBACTER PYLORI* AND GASTRIC CELLS OF THE HOST

Helicobacter pylori (*H. pylori*) colonizes gastric mucosa by many mechanisms, including spiral shape, multiple unipolar flagella, and the secretion of urease that protects bacteria from the acidity of the stomach. Mostly studied and relevant virulence factors are cytotoxin-associated

gene A (CagA), its pathogenicity island (cagPAI), vacuolating cytotoxin (VacA), bacterial flagellum and *H. pylori* Type-4 secretion system (T4SS) that secretes 18 different proteins into host tissue[1-3].

The translocation of *H. pylori* oncogenic factors to the host cells is a relevant mechanism initiating inflammation and interaction of immune cells with pathogen and gastric cells. CagA is an oncoprotein injected by T4SS into the gastric cells. Blanc et al[4] analyzed CagI protein, which is a compound of T4SS. Authors revealed that CagI has a unique dimeric structure in which the C terminal of the domain interacts with gastric cells. The study found that designed ankyrin repeat proteins (DARPins) interacted with CagI by inhibiting T4SS and translocation of CagA into gastric cells. This study has been the first to describe DARPin inhibition of cagT4SS and pave the way for strategies targeting *H. pylori*-specific extracellular determinants of the CagA translocation[4]. López-Luis et al[5] focused on CagY, the largest and most essential component of the T4SS of *H. pylori*. By studying its sequence and structure, the authors built the structural model of CagY. It has been revealed that this protein takes a central role by forming a tunnel from the inner membrane of *H. pylori* to the gastric cells of the host through which CagA is transported. A better understanding of the structure and functions of CagY may suggest possible ways to prevent or modulate the pro-inflammatory activity of the T4SS, for example, by designing the molecules that may block the binding of CagY[5]. The findings of these studies are beneficial in identifying novel and effective treatment targets by inhibiting the translocation of oncogenic factors to the host cells[4,5].

Natural killer and cytotoxic T cells play an essential role in mucosal immunity and tumor immunosurveillance. Interesting findings were made by Anthofer et al[6], who have investigated the effect of *H. pylori* on the natural killer group, member 2 (NKG2D) system, to the immune response, which is important for the elimination of infected and transformed cells. It was identified that *H. pylori* toxin vacA induces *NKG2D-L* gene expression, which could activate an immune response against infected gastric epithelial cells. CagA in this case appeared to trigger the shedding of NKG2D, resulting in reduced immunogenic visibility of the cells. These findings contribute to the knowledge of the carcinogenesis mechanism in the development of gastric cancer and may fuel the development of immunotherapy approaches[6].

Liu et al[7] investigated flagella and type IV pili (TFP) appendages that form the flagellar motor of *H. pylori*. The authors are the first to discover that these two appendages shared proteins PilM, PilN, and PilO, and these coopted proteins, despite the motility of flagella, give the ability to adhere to microcolony and biofilm formation[7]. *H. pylori* adhesin A (HpaA) is an outer membrane protein that is an essential virulence factor for the colonization of gastric cells of the host and leading to the damage of gastric mucosa. Based on this knowledge, Gao et al[8] performed an experimental study and isolated the variable domain of immunoglobulin new antigen receptor (VNAR). VNARs showed high binding capability to *H. pylori* and were characterized by stability in the acidic environment of the stomach, ease of modification, and production. These recombinant antibodies could recognize and bind to HpaA and interrupt attachment to HpA receptors and, in such a way, may serve as potential therapeutic agents[8].

H. pylori Infection in Relation to Microbiota and Extraintestinal Diseases

Studies have demonstrated that *H. pylori* affects the diversity of gastric microbiota and thus may contribute to the development of gastric diseases such as gastric cancer or even contribute to the pathogenesis of extraintestinal diseases[9-12]. Last year, Yu et al[9] investigated the composition of gastric microbiota in *H. pylori*-infected symptomatic, asymptomatic, and uninfected groups. They found that bacterial diversity among *H. pylori*-positive symptomatic and asymptomatic groups did not differ significantly, with *Epsilonbacteraeota* being the dominant phylum for both groups. In the *H. pylori*-negative group, the abundance of *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* was higher compared to *H. pylori*-positive groups consistent with previous studies[10]. These findings indicated that *H. pylori* infection causes gastric dysbacteriosis regardless of whether digestive symptoms developed[9].

To evaluate the relationship between Parkinson's disease and gut microbiota and pathogens, Zhou et al[11] conducted a meta-analysis of 11 studies examining the association between *H. pylori* and Parkinsonism. They found that the prevalence of *H. pylori* infection was significantly higher

in the Parkinson's group compared with controls. It has been suggested that *H. pylori* contributes to Parkinson's disease by secreting endotoxins, which cause microglia to produce inflammatory markers that lead to microglia-mediated neuroinflammation[11].

Candelli et al[12] reviewed the topic of gastric microbiota and *H. pylori* in relation to extra gastric diseases focusing on atherosclerosis. The authors highlighted the importance of CagA-positive *H. pylori* strains, which induce reactive oxygen species (ROS) that affect the endothelium and are more likely to lead to atherosclerosis. An important finding is that epithelial cells injected with CagA *via* the T4SS release exosomes containing this protein in systemic circulation and deposit it into endothelial cells. Additionally, CagA induces IL-6 production and macrophage cell formation, which contributes to the development of atherosclerotic plaque formation[12].

New Insights in Gastric Cancer Pathogenesis in *Helicobacter pylori* Infection

The World Health Organization has classified *H. pylori* infection as a class I carcinogen, thereby establishing it as the foremost risk factor in the development of gastric cancer. A comprehensive understanding of the molecular mechanisms by which *H. pylori* affects tumorigenesis is required to improve current diagnostic, prognostic, and therapeutic approaches[1,13].

Liang et al[14] discovered that *H. pylori* triggers the cGAS/STING/IRF-3 mediated kynurenine pathway of tryptophan metabolism stimulating xanthurenic acid (XA) production, which contributes to intestinal metaplasia (IM)[14]. Li et al[15] found that in 20% of cases with *H. pylori* infection patients, precancerous conditions develop, among which metaplasia is the most critical. Authors highlighted the interest in spasmolytic polypeptide-expressing metaplasia (SPEM), which is derived from *H. pylori* infection and may be more linked to gastric adenocarcinoma than intestinal metaplasia[15].

H. pylori infection causes aberrant DNA methylation and contributes significantly to gastric cancer pathogenesis[13,16]. Liu et al[13] investigated the nucleotide-binding protein subunit beta-4 (GNB4) involved in tumorigenic processes. Authors found that *H. pylori* induces *GNB4* mRNA and protein expression, reduces the methylation level of *GNB4* promoter region, and upregulates ten-eleven translocation 1 (TET1) methylcytosine dioxygenases expression through NF-κB activation. The study demonstrated that increased *GNB4* expression is associated with aggressive clinical characteristics and poor survival outcomes[13].

Li et al[17] conducted a study on *H. pylori* and gastric fibroblast (GFs), confirming enhanced α-smooth muscle actin (α-SMA+) and fibroblast activation protein (FAP) in GFs cocultured with *H. pylori* indicating GFs activation and transformation into cancer-associated fibroblasts (CAFs)[17]. Chen et al[18] elucidated that *H. pylori* NF-κB subsequently triggered the PIEZO1-YAP1-CTGF axis, leading to the accumulation of α-SMA+ CAFs. Enhanced microenvironment stiffness perpetuates PIEZO1 activation in a positive feedback loop associated with poor clinical outcomes in *H. pylori*-positive gastric cancer tissue[18].

Chen et al[19] investigated how *H. pylori* virulence factor CagA triggers the development of cancer stem cells (CSCs). Study findings demonstrate that infection with CagA-positive *H. pylori* activates the PI3K/AKT pathway, leading to the transcriptional inactivation of intracellular FOXO3a phosphorylation and induction of features resembling gastric cancer stem cells (GCSCs)[19].

PD-L1 is an immune checkpoint associated with malignancies, including gastroesophageal junction carcinoma, cervical carcinoma, and non-small cell lung cancer[20]. Wang et al[21] investigated the impact of CagA on PD-L1 antibodies and found that the PD-L1 protein levels in exosomes derived from plasma of CagA-positive gastric cancer were generally higher than those in CagA-negative cases. CagA may promote PD-L1 expression through regulating signaling pathways mediated by p53 and miR-34a. It seems that CagA might upregulate the protein level of exosomal PD-L1 in *H. pylori* infected GC. According to recent findings[21], the positive rate of PD-L1 expressions ranges from 25% to 65% and is associated with the poor prognosis of GC.

Changes of miRNAs in *H. Pylori* Infection

MicroRNAs (miRNAs) and circular RNAs (circRNAs) are non-coding types of RNA that contribute to various carcinogenic pathways by downregulating or upregulating their target gene[22-25].

For instance, Malespín-Bendaña et al[23] observed a significant downregulation of miR-203a in human gastric carcinoma cell line AGS in response to *H. pylori* infection. This downregulation promotes angiogenesis in the gastric mucosa by enhancing pro-angiogenic gene *(ANGTPT2)* expression and favoring the process of chronic inflammation that contributes to the etiology of gastric cancer independently of virulence factors CagA or T4SS[23]. In another study, Zhao et al[22] found increased circPGD expression in *H. pylori*-infected human cells. The increased circPGD expression contributed to gastric cancer development by facilitating cell migration, proliferation, and epithelial-mesenchymal transition (EMT) while attenuating apoptosis[22]. Huang et al[25] identified miR-21 as the most upregulated miRNA in gastric cancer cells. The upregulation of miR-21 is mediated by NF-κB activation. Their study showed that miR-21 targets the apoptosis-stimulating of the P53 Protein 2 *(ASPP2)* gene, whose expression was lower in *H. pylori* gastric cancer tissues. Silencing of *ASPP2* reduced CHOP-mediated apoptotic signaling in gastric cancer cells following *H. pylori* infection[25].

Qi et al[24] analyzed the relationship between Forkhead box protein O1 (FOXO1), which inhibits the growth of gastric cancer, and miR-183 expression in gastric cancer patients with *H. pylori* infection. They found that FOXO1 and mRNA from gastric tissues and serum were markedly reduced compared with the control group. *In vitro* experiments confirmed that inhibition of miR-183 expression in gastric cancer AGS cells led to upregulation of FOXO1 expression. These findings highlight the biological pathway of the miR-183/FOXO1 in gastric cancer cells[24]. Significant findings were made by Karimi et al[26]. They evaluated the relationship between miR-146a and miR-155 in patients with gastric cancer infected with *H. pylori*, compared to *H. pylori*-infected patients without malignancies and healthy individuals. These miRs have been identified recently, and they seem to target multiple genes associated with carcinogenesis. The study showed that in both the *H. pylori* and gastric cancer-positive group and the *H. pylori*-positive group without cancer, the expression of miR-146a and miR-155 increased significantly[26]. The findings of these studies provide a theoretical basis for the prevention, diagnosis, and treatment of gastric cancer[24,26].

Impact of New Pathogenetic Findings for New Treatment Options in the Eradication of *Helicobacter pylori*

Antibiotics such as amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, and rifampicin are being used in the treatment of *H. pylori* infection[27]. However, existing combination therapies fail to eradicate the infection in 10-30% of cases, primarily due to antimicrobial resistance. Biofilm formation *in vivo* contributes to the development of multidrug resistance in *H. pylori*[27]. Despite a decreasing number of studies in the field of *H. pylori* pathogenesis, genetic analysis and the search for new mutations remain crucial for understanding the mechanisms of antimicrobial resistance and developing new therapeutic approaches[29].

Lyu et al[30] conducted a study based on whole-genome sequencing of *H. pylori*. They found that missense mutations in the *fliJ* and *cheA* genes, which are mainly involved in chemotaxis and flagellar motility, help the bacteria evade antibiotics[30]. a Šamanić et al[29] investigated clarithromycin (CAM) and levofloxacin (LVX) resistance genes in *H. pylori* in Croatia. Three genes from nine *H. pylori* isolates were selected for the study: *23S rRNA*, *gyrA*, and *gyrB*. The mutations they found coincide with global findings, indicating that these mutations are not restricted to a specific population or strain of *H. pylori* [27,29]. Additionally, they identified *H. pylori* strains that were dual resistant to CAM and LVX, highlighting the bacteria's successful evolution and its increased risk to human health due to resistance to antibiotics[29].

CONCLUSIONS

H. pylori plays a pivotal role in the development of precancerous and cancerous conditions in the stomach. The mentioned studies highlight the importance of studying the molecular mechanism of how *H. pylori* interacts with host cells and where new diagnostic approaches and therapeutic options could be implied. A good understanding of the pathogenic pathways and

mechanisms associated with virulence factors is essential to identify new potential drug targets and develop new therapeutic strategies by inhibiting the biological axis of virulence factors and, in such a way, preventing the development of *H. pylori*-associated conditions.

Conflict of Interest

There are no conflicts of interest for any of the authors regarding the content of this manuscript.

Ethics Approval and Informed Consent

Not applicable.

Authors' Contribution

PS performed the literature search and prepared the primary and final versions of the manuscript. LJ performed the additional literature search and was responsible for the primary and final revision and corrections of the manuscript.

AI Disclosure

We acknowledge the use of the AI tool, ChatGPT, developed by OpenAI, only for grammar correction and language refinement in the preparation of this manuscript.

Fundings

None.

ORCID ID

P. Sabanas: 0009-0009-6468-7837
L. Jonaitis: 0000-0001-9086-3675

REFERENCES

1) Xi Y, Zhang XL, Luo QX, Gan HN, Liu YS, Shao SH, Mao XH. *Helicobacter pylori* regulates stomach diseases by activating cell pathways and DNA methylation of host cells. Front Cell Dev Biol 2023; 11: 1187638.
2) Kesharwani A, Dighe OR, Lamture Y. Role of *Helicobacter pylori* in Gastric Carcinoma: A Review. Cureus 2023; 15: e37205.
3) Zhou X, Rahman MM, Bonny SQ, Xin Y, Liddelow N, Khan MF, Tikhomirova A, Homman-Ludiye J, Roujeinikova A. Pal power: Demonstration of the functional association of the *Helicobacter pylori* flagellar motor with peptidoglycan-associated lipoprotein (Pal) and its preliminary crystallographic analysis. Biosci Trends 2023; 17: 491-498.
4) Blanc M, Lettl C, Guérin J, Vieille A, Furler S, Briand-Schumacher S, Dreier B, Bergé C, Plückthun A, Vadon-Le Goff S, Fronzes R, Rousselle P, Fischer W, Terradot L. Designed Ankyrin Repeat Proteins provide insights into the structure and function of CagI and are potent inhibitors of CagA translocation by the *Helicobacter pylori* type IV secretion system. PLOS Pathog 2023; 19: e1011368.
5) López-Luis MA, Soriano-Pérez EE, Parada-Fabián JC, Torres J, Maldonado-Rodríguez R, Méndez-Tenorio A. A Proposal for a Consolidated Structural Model of the CagY Protein of *Helicobacter pylori*. Int J Mol Sci 2023; 24: 16781.
6) Anthofer M, Windisch M, Haller R, Ehmann S, Wrighton S, Miller M, Schernthanner L, Kufferath I, Schauer S, Jelušić B, Kienesberger S, Zechner EL, Posselt G, Vales-Gomez M, Reyburn HT, Gorkiewicz G. Immune evasion by proteolytic shedding of natural killer group 2, member D ligands in *Helicobacter pylori* infection. Front Immunol 2024; 15: 1282680.
7) Liu X, Tachiyama S, Zhou X, Mathias RA, Bonny SQ, Khan MF, Xin Y, Roujeinikova A, Liu J, Ottemann KM. Bacterial flagella hijack type IV pili proteins to control motility. Proc Natl Acad Sci 2024; 121: e2317452121.
8) Gao Y, Wang R, Liu L, Feng S, Xi X, Yu W, Gu Y, Wang Y. Identification and characterization of shark VNARs targeting the *Helicobacter pylori* adhesin HpaA. Artif Cells Nanomedicine Biotechnol 2023; 51: 509-519.
9) Yu T, Lu T, Deng W, Yao D, He C, Luo P, Song J. Microbiome and function alterations in the gastric mucosa of asymptomatic patients with *Helicobacter pylori* infection. Helicobacter 2023; 28: e12965.
10) Spiegelhauer MR, Kupcinskas J, Johannesen TB, Urba M, Skieceviciene J, Jonaitis L, Frandsen TH, Kupcinskas L, Fuursted K, Andersen LP. Transient and Persistent Gastric Microbiome: Adherence of Bacteria in Gastric Cancer and Dyspeptic Patient Biopsies after Washing. J Clin Med 2020; 9: 1882.
11) Zhou S, Li B, Deng Y, Yi J, Mao G, Wang R, Zeng W, Liu B, Wu D, Liu F. Meta-analysis of the relations between gut microbiota and pathogens and Parkinson's disease. Adv Clin Exp Med 2023; 32: 613-621.

12) Candelli M, Franza L, Cianci R, Pignataro G, Merra G, Piccioni A, Ojetti V, Gasbarrini A, Franceschi F. The Interplay between *Helicobacter pylori* and Gut Microbiota in Non-Gastrointestinal Disorders: A Special Focus on Atherosclerosis. Int J Mol Sci 2023; 24: 17520.
13) Liu D, Liu Y, Zhu W, Lu Y, Zhu J, Ma X, Xing Y, Yuan M, Ning B, Wang Y, Jia Y. *Helicobacter pylori*-induced aberrant demethylation and expression of GNB4 promotes gastric carcinogenesis via the Hippo–YAP1 pathway. BMC Med 2023; 21: 134.
14) Liang X, Du W, Huang L, Xiang L, Pan W, Yang F, Zheng F, Xie Y, Geng L, Gong S, Xu W. *Helicobacter pylori* promotes gastric intestinal metaplasia through activation of IRF3-mediated kynurenine pathway. Cell Commun Signal 2023; 21: 141.
15) Li ML, Hong XX, Zhang WJ, Liang YZ, Cai TT, Xu YF, Pan HF, Kang JY, Guo SJ, Li HW. *Helicobacter pylori* plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia. World J Clin Cases 2023; 11: 3714-3724.
16) Tahara S, Tahara T, Yamazaki J, Shijimaya T, Horiguchi N, Funasaka K, Fukui T, Nakagawa Y, Shibata T, Naganuma M, Tsukamoto T, Ohmiya N. *Helicobacter pylori* infection associated DNA methylation in primary gastric cancer significantly correlates with specific molecular and clinicopathological features. Mol Carcinog 2024; 63: 266-274.
17) Li J, Li X, Zhang Z, Wang S, Huang X, Min L, Li P. *Helicobacter pylori* promotes gastric fibroblast proliferation and migration by expulsing exosomal miR-124-3p. Microbes Infect 2024; 26: 105236.
18) Chen B, Liu X, Yu P, Xie F, Kwan JSH, Chan WN, Fang C, Zhang J, Cheung AHK, Chow C, Leung GWM, Leung KT, Shi S, Zhang B, Wang S, Xu D, Fu K, Wong CC, Wu WKK, Chan MWY, Tang PMK, Tsang CM, Lo KW, Tse GMK, Yu J, To KF, Kang W. *H. pylori* -induced NF-κB-PIEZO1-YAP1-CTGF axis drives gastric cancer progression and cancer-associated fibroblast-mediated tumour microenvironment remodelling. Clin Transl Med 2023; 13: e1481.
19) Chen Z, Dong Z, Xiang H, Chen S, Yu W, Liang C. *Helicobacter pylori* CagA protein induces gastric cancer stem cell-like properties through the Akt/FOXO3a axis. J Cell Biochem 2024; 125: e30527.
20) Layfield LJ, Zhang T, Esebua M. PD-L1 immunohistochemical testing: A review with reference to cytology specimens. Diagn Cytopathol 2023; 51: 51-58.
21) Wang J, Deng R, Chen S, Deng S, Hu Q, Xu B, Li J, He Z, Peng M, Lei S, Ma T, Chen Z, Zhu H, Zuo C. *Helicobacter pylori* CagA promotes immune evasion of gastric cancer by upregulating PD-L1 level in exosomes. iScience 2023; 26: 108414.
22) Zhao W, Yao Z, Cao J, Liu Y, Zhu L, Mao B, Cui F, Shao S. *Helicobacter pylori* upregulates circPGD and promotes development of gastric cancer. J Cancer Res Clin Oncol 2024; 150: 104.
23) Malespín-Bendaña W, Ferreira RM, Pinto MT, Figueiredo C, Alpízar-Alpízar W, Une C, Figueroa-Protti L, Ramírez V. *Helicobacter pylori* infection induces abnormal expression of pro-angiogenic gene ANGPT2 and miR-203a in AGS gastric cell line. Braz J Microbiol 2023; 54: 791-801.
24) Qi C, Liu L, Wang J, Jin Y. Up-regulation of microRNA-183 reduces FOXO1 expression in gastric cancer patients with *Helicobacter pylori* infection. Histol Histopathol 2023; 38: 1349-1357.
25) Huang BS, Chen CT, Yeh CC, Fan TY, Chen FY, Liou JM, Shun CT, Wu MS, Chow LP. miR-21 Targets ASPP2 to Inhibit Apoptosis via CHOP-Mediated Signaling in *Helicobacter pylori*-Infected Gastric Cancer Cells. J Oncol 2023; 2023: 1-20.
26) Karimi M, Mohammadnia A, Amini MA, Shamekh AG, Derakhshanfar E, Hosseini F. Overexpression of miR-146a and miR-155 are Potentially Biomarkers and Predict Unfavorable Relationship between Gastric Cancer and *Helicobacter pylori* Infection. Chonnam Med J 2023; 59: 167.
27) Fernández-Caso B, Miqueleiz A, Alarcón T. Whole Genome Sequencing for Studying *Helicobacter pylori* Antimicrobial Resistance. Antibiotics 2023; 12: 1135.
28) Zhao Y, Cai Y, Chen Z, Li H, Xu Z, Li W, Jia J, Sun Y. SpoT-Mediated NapA Upregulation Promotes Oxidative Stress-Induced *Helicobacter pylori* Biofilm Formation and Confers Multidrug Resistance. Antimicrob Agents Chemother 2023; 65: e00152-21.
29) Šamanić I, Dadić B, Sanader Maršić Ž, Dželalija M, Maravić A, Kalinić H, Vrebalov Cindro P, Šundov Ž, Tonkić M, Tonkić A, Vuković J. Molecular Characterization and Mutational Analysis of Clarithromycin- and Levofloxacin-Resistance Genes in *Helicobacter pylori* from Gastric Biopsies in Southern Croatia. Int J Mol Sci 2023; 24: 14560.
30) Lyu T, Cheung KS, Deng Z, Ni L, Chen C, Wu J, Leung WK, Seto WK. Whole genome sequencing reveals novel genetic mutations of *Helicobacter pylori* associating with resistance to clarithromycin and levofloxacin. Helicobacter 2023; 28: e12972.