

Current Helicobacter Pylori Diagnostics

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Helicobacter pylori (*H. pylori*) is one of the most common human pathogens and a leading etiological factor for various gastroduodenal diseases, including chronic gastritis, peptic ulcers, gastric adenocarcinoma, and MALT lymphoma. According to the latest systematic review with meta-analysis, 44.3% (95% CI: 40.9–47.7) of the global population are infected with this microorganism. Timely diagnosis and subsequent eradication of *H. pylori* in adults allows one to resolve inflammatory changes in the gastric mucosa and prevent the development of precancerous conditions (atrophic gastritis and intestinal metaplasia).

Keywords: *Helicobacter pylori* (*H. pylori*) ; diagnosis ; endoscopy ; artificial intelligence ; histology ; molecular methods ; serology ; stool antigen test ; urea breath test

1. Overview

The high prevalence of *Helicobacter pylori* and the variety of gastroduodenal diseases caused by this pathogen necessitate the use of only accurate methods both for the primary diagnosis and for monitoring the eradication effectiveness. There is a broad spectrum of diagnostic methods available for detecting *H. pylori*. All methods can be classified as invasive or non-invasive. The need for upper endoscopy, different clinical circumstances, sensitivity and specificity, and accessibility defines the method chosen. This article reviews the advantages and disadvantages of the current options and novel developments in diagnostic tests for *H. pylori* detection. The progress in endoscopic modalities has made it possible not only to diagnose precancerous lesions and early gastric cancer but also to predict *H. pylori* infection in real time. The contribution of novel endoscopic evaluation technologies in the diagnosis of *H. pylori* such as visual endoscopy using blue laser imaging (BLI), linked color imaging (LCI), and magnifying endoscopy is discussed. Recent studies have demonstrated the capability of artificial intelligence to predict *H. pylori* status based on endoscopic images. Non-invasive diagnostic tests such as the urea breathing test and stool antigen test are recommended for primary diagnosis of *H. pylori* infection. Serology can be used for initial screening and epidemiological studies. The histology showed its value in detecting *H. pylori* and provided more information about the degree of gastric mucosa inflammation and precancerous lesions. Molecular methods are mainly used in detecting antibiotic resistance of *H. pylori*. Cultures from gastric biopsies are the gold standard and recommended for antibiotic susceptibility tests.

2. Helicobacter Pylori

Helicobacter pylori (*H. pylori*) is one of the most common human pathogens and a leading etiological factor for various gastroduodenal diseases, including chronic gastritis, peptic ulcers, gastric adenocarcinoma, and MALT lymphoma [1][2]. According to the latest systematic review with meta-analysis, 44.3% (95% CI: 40.9–47.7) of the global population are infected with this microorganism [3]. Timely diagnosis and subsequent eradication of *H. pylori* in adults allows one to resolve inflammatory changes in the gastric mucosa and prevent the development of precancerous conditions (atrophic gastritis and intestinal metaplasia) [4][5][6].

There are several diagnostic methods for detecting *H. pylori* infections. All methods can be broadly classified as invasive or non-invasive (Table 1). Invasive methods require upper endoscopy and analysis of the gastric biopsy. Preference should be given to non-invasive diagnostic methods. If the patient requires upper endoscopy, a histological analysis, rapid urease testing, molecular methods, or culture can be performed to diagnose the *H. pylori* infection [7][8]. The main limitation of these methods is their invasiveness and the ability to analyze only a small part of the gastric mucosa. Table 1 shows the general characteristics of the diagnostic methods for *H. pylori*, their applications in clinical practices, as well as the choice of diagnostic tests in different clinical conditions. Non-invasive tests include immunological methods (serology, stool antigen test), the 13 C-urea breath test (UBT), and molecular methods, i.e., a PCR study with determination of *H. pylori* DNA in feces (PCR from stool) [7].

Table 1. Overview of the diagnostic methods for *H. pylori*.

	Initial Diagnosis	Follow-up after Eradication	Requires Excluding PPI, Antibiotics, Bismuth Before Testing	Gastroduodenal Bleeding	Detection of Antibiotic Resistance	Sensitivity	Specificity
Invasive (require upper endoscopy)							
Histology	+	+	+	–	–	91–93%	100%
RUT	+	–	+	–	–	85–95%	95–100%
Culture	+	–	+	–	+	76–90%	100%
Molecular method (PCR)	+	+	+	+	+	95%	95%
Non-Invasive							
UBT	+	+	+	+	–	96–100%	93–100%
SAT	+	+	+	–	–	95.5%	97.6%
Serology	+	–	–	+	–	76–84%	79–90%
Stool PCR test	+	–	+	+	+	71%	96%

Any of the tests can be used for the primary diagnosis of *H. pylori*. The urease breath test is a “gold standard” in the diagnosis of *H. pylori* infection [7][8][9][10].

Modern non-invasive tests provide high reliability in *H. pylori* detection due to their high sensitivity and specificity. However, all of these methods have limitations. The choice of a particular test will depend on its sensitivity, specificity, and the clinical circumstances [11].

3. Molecular Invasive and Non-Invasive Methods for *H. pylori*

Molecular diagnostic methods are based on the amplification of nucleic acid using a conventional polymerase chain reaction (PCR) or PCR in real time (RT-PCR). Genetic material (DNA) of *H. pylori* can be detected in gastric biopsy, saliva, feces, or dental samples. PCR can be considered as either an invasive or non-invasive method for detecting *H. pylori* depending on the applied material. It demonstrates up to 95% sensitivity and 95% specificity [12]. Molecular methods are more expensive than other methods, and the laboratory must have appropriate equipment and experience. PCR allows for the detection of specific mutations leading to antibiotic resistance and bacterial virulence factors such as CagA and VacA.

There are a number of molecular assays commercially available for *H. pylori* and clarithromycin-resistance detection. Several studies have found different sensitivities and specificities of the method depending on the DNA extraction method and the PCR assay used. The *H. pylori* Taqman® real-time PCR assay in stool specimens shows a high sensitivity of 93.8%. The ClariRes assay shows a low sensitivity (ranging from 63% to 84%) for *H. pylori* detection in stool specimens when compared to those of the stool antigen test and *H. pylori* culture from gastric biopsy specimens [13].

One of the new approaches to diagnosing *H. pylori* is next-generation sequencing (NGS) by sequencing *H. pylori* DNA directly from formalin-fixed paraffin-embedded (FFPE) gastric biopsy specimens. NGS reveals mutations in genes that lead to resistance to antibiotics (clarithromycin, levofloxacin, and tetracycline) and their correlation with phenotypic drug resistance. Using NGS, mutations in the *gyrA*, 23S rRNA, and 16S rRNA genes were identified and analyzed [14]. The sensitivity of the method is 95%. The study showed the possibility of using NGS to detect multidrug resistance in culture-negative biopsies and on clinical specimens collected during the standard of care [15].

Studies show that clarithromycin resistance is based on point mutations at nucleotide positions A2146 and A2147 in the 23S rRNA gene [14][15]. The rRNA 16S gene is a much more sensitive method for detecting *H. pylori* in gastric biopsies compared to other methods [14].

Sequencing *H. pylori* DNA from gastric biopsy specimens is a laborious method. *H. pylori* must be cultured from multiple gastric biopsy specimens, then, multiple colonies must be picked from agar plates for DNA extraction in order not to miss

the drug-resistant subpopulations; the strains should be sequenced with sufficient coverage to detect heteroresistance; usually, multiple susceptible and resistant strains of *H. pylori* are sequenced [13].

The detection of *H. pylori* DNA in stool samples is a very convenient, fast, sensitive, and accurate method. Stool RT-PCR analysis can detect *H. pylori* DNA sequences and antibiotic resistance point mutations. The conducted meta-analysis showed that most diagnostic candidate genes identified in stool samples were 23S rRNA, 16S rRNA, and glmM. Stool DNA PCR had a performance of 71% (95% CI: 68–73) sensitivity and 96% (95% CI: 94–97) specificity in the diagnosis of *H. pylori*. Analysis showed that the 23S rRNA gene has high sensitivity for the detection of *H. pylori* in clinical samples [16]. Three mutations (A2142G, A2143G, and A2142C) in a gene in 23S rRNA were associated with *H. pylori* resistance to clarithromycin, and these mutations have been associated with treatment failure [14].

Undoubtedly, stool DNA PCR has its advantages: it gives faster results, fewer bacteria are required in the sample for analysis, it does not need special processing supplies or transportation of the material, and the result can be obtained in a fairly short time (<4 h).

Despite the high specificity of the test, a number of studies have revealed a high percentage of false-positive results, especially when the test is carried out 4–6 weeks after successful eradication therapy. False-positive results in treated patients can be explained by persistence in the feces of coccoidal forms of *H. pylori*, which, over time, begin to decrease and completely disappear at 8–12 weeks [17].

In geographic regions with high clarithromycin resistance, stool RT-PCR testing with determination of clarithromycin resistance is a useful diagnostic option for young dyspeptic patients who do not require endoscopy and should preferably be treated with clarithromycin-containing regimens [18].

4. Conclusions

The high prevalence and etiopathogenetic relationship of *H. pylori* with the most significant diseases of the stomach highlights the need to optimize the diagnosis of this infection, taking into account the sensitivity and specificity of the tests, as well as the conditions for their use. The infection must be detected before therapy is prescribed, and its success must be confirmed after treatment.

The developments of current diagnostic methods allow for a more accurate and reliable diagnosis of *H. pylori* infection. The choice of method will depend on the accessibility, their advantages and disadvantages, sensitivity and specificity, and different clinical circumstances of each patient.

Leading international experts dictate the rules for the diagnosis of *H. pylori* infection; however, the majority of mistakes are still made when assessing the effectiveness of eradication, namely, the use of inadequate methods or lack of control. According to the European Registry on *H. pylori* management (Hp-EuReg), confirmation of the eradication was performed in 94% of the cases [19].

References

1. Feldman, M.; Friedman, L.S.; Brandt, L.J. Sleisenger and Fordtran's Gastrointestinal and Liver Disease E-Book: Pathophysiology, Diagnosis, Management, 11th ed.; Elsevier: Amsterdam, The Netherlands, 2020.
2. Suzuki, H.; Warren, R.; Marshall, B. *Helicobacter Pylori*; Springer: Tokyo, Japan, 2016.
3. Zamani, M.; Ebrahimitabar, F.; Zamani, V.; Miller, W.H.; Alizadeh-Navaei, R.; Shokri-Shirvani, J.; Derakhshan, M.H. Systematic review with meta-analysis: The worldwide prevalence of *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther.* 2018, 47, 868–876.
4. Zhou, L.; Sung, J.J.; Lin, S.; Jin, Z.; Ding, S.; Huang, X.; Xia, Z.; Guo, H.; Liu, J.; Chao, W. A five-year follow-up study on the pathological changes of gastric mucosa after *H. pylori* eradication. *Chin. Med. J.* 2003, 116, 11–14.
5. Lee, Y.C.; Chen, T.H.; Chiu, H.M.; Shun, C.T.; Chiang, H.; Liu, T.Y.; Wu, M.S.; Lin, J.T. The benefit of mass eradication of *Helicobacter pylori* infection: A community-based study of gastric cancer prevention. *Gut* 2013, 62, 676–682.
6. Okubo, M.; Tahara, T.; Shibata, T.; Nakamura, M.; Yoshioka, D.; Maeda, Y.; Yonemura, J.; Ishizuka, T.; Arisawa, T.; Hirata, I. Changes in gastric mucosal patterns seen by magnifying NBI during *H. pylori* eradication. *J. Gastroenterol.* 2011, 46, 175–182.

7. Pichon, M.; Pichard, B.; Barrioz, T.; Plouzeau, C.; Croquet, V.; Fotsing, G.; Chéron, A.; Vuillemin, É.; Wangermez, M.; Haineaux, P.A.; et al. Diagnostic Accuracy of a Noninvasive Test for Detection of *Helicobacter pylori* and Resistance to Clarithromycin in Stool by the Amplidiag H. pylori+ClariR Real-Time PCR Assay. *J. Clin. Microbiol.* 2020, 58, e01787-19.
8. Ricci, C.; Holton, J.; Vaira, D. Diagnosis of *Helicobacter pylori*: Invasive and non-invasive tests. *Best Pract. Res. Clin. Gastroenterol.* 2007, 21, 299–313.
9. Gisbert, J.P.; De la Morena, F.; Abaira, V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: A systematic review and meta-analysis. *Am. J. Gastroenterol.* 2006, 101, 1921–1930.
10. Malfertheiner, P.; Megraud, F.; O'Morain, C.A.; Gisbert, J.P.; Kuipers, E.J.; Axon, A.T.; Bazzoli, F.; Gasbarrini, A.; Atherton, J.; Graham, D.Y.; et al. European *Helicobacter* and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection—The Maastricht V/Florence Consensus Report. *Gut* 2017, 66, 6–30.
11. Patel, S.K.; Pratap, C.B.; Jain, A.K.; Gulati, A.K.; Nath, G. Diagnosis of *Helicobacter pylori*: What should be the gold standard? *World J. Gastroenterol.* 2014, 20, 12847–12859.
12. Szymczak, A.; Ferenc, S.; Majewska, J.; Miernikiewicz, P.; Gnus, J.; Witkiewicz, W.; Dąbrowska, K. Application of 16S rRNA Gene Sequencing in *Helicobacter pylori* detection. *PeerJ* 2020, 8, e9099.
13. Pohl, D.; Keller, P.M.; Bordier, V.; Wagner, K. Review of current diagnostic methods and advances in *Helicobacter pylori* diagnostics in the era of next generation sequencing. *World J. Gastroenterol.* 2019, 25, 4629–4660.
14. Godbole, G.; Mégraud, F.; Bessède, E. Review: Diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2020, 25 (Suppl. 1), e12735.
15. Nezami, B.G.; Jani, M.; Alouani, D.; Rhoads, D.D.; Sadri, N. *Helicobacter pylori* mutations detected by Next-Generation Sequencing in Formalin-fixed, paraffin-embedded gastric biopsy specimens are associated with treatment failure. *J. Clin. Microbiol.* 2019, 57, e01834-18.
16. Khadangi, F.; Yassi, M.; Kerachian, M.A. Review: Diagnostic accuracy of PCR-based detection tests for *Helicobacter Pylori* in stool samples. *Helicobacter* 2017, 22, e12444.
17. Trevisani, L.; Sartori, S.; Galvani, F.; Rossi, M.R.; Ruina, M.; Chiamenti, C.; Caselli, M. Evaluation of a new enzyme immunoassay for detecting *Helicobacter pylori* in feces: A prospective pilot study. *Am. J. Gastroenterol.* 1999, 94, 1830–1833.
18. Giorgio, F.; Ierardi, E.; Sorrentino, C. *Helicobacter pylori* DNA isolation in the stool: An essential pre-requisite for bacterial noninvasive molecular analysis. *Scand. J. Gastroenterol.* 2016, 51, 1429–1432.
19. Nyssen, O.P.; Vaira, D.; Tepes, B.; Kupcinskis, L.; Bordin, D.; Pérez-Aisa, Á.; Gasbarrini, A.; Castro-Fernández, M.; Bujanda, L.; Garre, A.; et al. Room for Improvement in the Treatment of *Helicobacter pylori* Infection: Lessons from the European Registry on *H. pylori* Management (Hp-EuReg). *J. Clin. Gastroenterol.* 2021.

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