

Helicobacter pylori Diagnosis

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Helicobacter pylori infection still remains one of the most prevalent infections worldwide, especially in low-resource countries, and the major risk factor for peptic ulcer and gastric cancer. The "test-and-treat" strategy is recommended by several guidelines and consensus. The choice of testing method is based on patient age, presence of alarm signs and/or symptoms, use of non-steroidal anti-inflammatory drugs, as well as local availability, test reliability and cost.

Culture is the gold standard to detect *H. pylori* and, possibly, to perform susceptibility testing, however, it requires upper endoscopy and dedicate labs. Recent advances in molecular biology provide new strategies in detecting the infection and antimicrobial resistance without invasive tests.

Helicobacter pylori

testing

antibiotic resistance

molecular techniques

artificial intelligence

1. Helicobacter pylori infection

The infection can be essentially detected by invasive and non-invasive tests. The choice of technique relies upon the patient needs. Presence of alarm symptoms, use of non-steroidal anti-inflammatory drugs (NSAIDs), advanced age (>45-50, years or >60 years) ^{[1][2][3][4]} history of premalignant conditions or follow up for a previous malignant disease dictates an upper endoscopy evaluation. The indication for esophago-gastric-duodenoscopy allows to directly observe the mucosa, to collect biopsy samples for histology examination, urease test, bacterial culture and molecular assay. In the absence of endoscopy recommendation, non-invasive tests such as urea breath testing or stool antigen assay are appropriate to confirm an active infection. Serology may be used in specific setting to assist the physician in the diagnosis of bacterial infection ^[5]. However, the diagnostic strategy cannot prescind from the local availability, costs of the test, labs reliability and patient preferences. As a rule of thumb, it is important for the physician to confirm the diagnosis, to evaluate the presence of gastric lesions induced by the infection according to the patient clinical history, to offer *H. pylori* eradication therapy and to check treatment success.

2. Invasive Tests

2.1. Endoscopy

For patients in whom an upper endoscopy is required, where available, advanced endoscopy techniques should be preferred to conventional endoscopy, especially for patients/subjects with a high pretest probability to harbor

premalignant lesions, such as those from countries or subpopulations with high prevalence of gastric cancer, or individuals with strong familiarity for gastric malignancy or those patients who need a strict endoscopy surveillance for previous diagnosed premalignant lesions.

By standard white light endoscopy (WLE) the infection may be identified on the base of specific gastric mucosa features such as the presence of antral nodularity with a sensitivity and a specificity ranging from 39.8% to 96.4% and from 83.6% to 100%, respectively [6]. Additional reports identified the erythema, erosions, thickened folds or absence of rugae, mosaic appearance with or without hyperemia and visible submucosal vessels in the gastric mucosa as the hallmarks of *H. pylori* infection [7][8][9][10] or gastric black spots associated with *H. pylori* eradication [11], and mucosal swelling (77%) associated with mild atrophy [12]. However, the low interobserver agreement may be a limitation to translate gastric mucosal features into a diagnosis of specific gastritis with or without *H. pylori* infection.

The results obtained with the narrow band imaging (NBI), which uses blue light from a laser source (415 nm) to highlight the vascular architecture of the gastric mucosa are more promising. Based on distinct patterns of the gastric mucosa the endoscopist may predict *H. pylori* infection by conventional NBI [13] and by the magnifying NBI technique the presence of intestinal metaplasia with a sensitivity and specificity greater than 95% [14]. Moreover, a high degree of concordance was observed between magnifying NBI and the operative link for gastritis and for gastric intestinal metaplasia assessment [15][16]. Interestingly, by this technique, specific morphological patterns, including reddish depressed lesions, are frequently observed in association with *H. pylori* eradication [14][17]. The magnifying endoscopy with NBI proved to be superior to WLE and chromoendoscopy in the diagnosis of early gastric cancer after *H. pylori* eradication [18]. The confocal laser endomicroscopy is more accurate than NBI for grading gastric premalignant lesions [19]. The blue laser imaging (BLI) and the linked color imaging (LCI) are also highly accurate in detecting *H. pylori* infection and premalignant lesions related to the infection [20][21][22][23][24][25]. Endocytoscopy (EC), an ultra-high magnification endoscopy, is able to provide histologic assessment *in vivo* [26]. Overall, high-definition endoscopy allows in real time the diagnosis of *H. pylori* infection, detection of premalignant and malignant gastric lesions and targeted mucosa biopsy sampling.

All recent developments of high-definition endoscopy for the diagnosis of *H. pylori* infection and detection of premalignant and malignant gastric lesions, allowing a real-time decision-making, prompted the revision of Kyoto endoscopic classification [27].

In the last years there was also an attempt to use more sophisticated tools to diagnose *H. pylori* by using artificial intelligence approach mimicking the brain neural network [28]. In a recent meta-analysis, the artificial intelligence algorithm demonstrated to be an accurate tool for the prediction of *H. pylori* infection during endoscopic procedures, although the real application needs to be evaluated in clinical studies [29].

2.2. Histology

The examination of gastric mucosal biopsy specimens remains the gold standard for detection of *H. pylori*, with a sensitivity of 95% and a specificity of 98%. In addition, it enables the visualization of gastric morphology at any time. In order to obtain an accurate diagnosis, two antral biopsies including one from the gastric angulus, and two biopsies from the corpus are necessary [30]. The widespread use of proton pump inhibitors (PPIs) may result in atypical presentation of gastritis or in density variation of bacteria at different sites [31], the accuracy of histologic diagnosis of *H. pylori* infection can be improved by using special staining techniques, specific immune stain or digital pathology [32][33]. Gastric biopsy specimens obtained by high-definition or conventional endoscopy can be used for molecular testing to assess the presence of *H. pylori* and its antibiotic susceptibility profile also in patients under PPI treatment. This is particularly useful for those patients who cannot stop the PPI treatment (for instance because of double antiplatelet treatments, or with a Zollinger Ellison syndrome or similar circumstances).

2.3. Rapid Urease Test

Upper endoscopy enables to collect also biopsy specimens for urease testing. The method is based on the presence of pre-formed urease by the bacteria and, in media containing urea, the enzyme releases ammonia increasing the pH and resulting in a color change of the medium.

The urease test is rapid (RUT), easy to perform, highly specific and inexpensive for *H. pylori* diagnosis, although it requires at least a 10^4 bacterial load in the gastric specimens [34]. False-negative results may occur with recent use of antibiotics, bismuth-containing compounds, PPIs, especially omeprazole and lansoprazole, and in children younger than five years [35]. To collect biopsies from the corpus rather than from the antrum, or combining antral and corpus biopsies has demonstrate to enhance RUT sensitivity [36][37]. In addition to false negative, also false-positive RUT may occur in presence of urease positive bacteria [34]. The gastric samples used for RUT can be re-used for molecular testing in order to identify bacterial resistance. However, compared with histology, RUT does not allow to plan a correct follow up for the patient.

2.4. Culture

In addition to histological examination and rapid urease testing, upper endoscopy offers the opportunity to collect gastric specimens for bacterial culture, susceptibility testing and even organism genotyping. Although culture is highly specific, it has a low sensitivity as *H. pylori* is difficult to grow and experienced laboratories are required. Sensitivity may be improved by sending the specimen to the laboratory within 30 minutes from collection, using a warm and non-selective culture medium, a longer incubation and the addition of hydrogen in the atmosphere, or by treating specimens with trypsin [38][39][40][41].

3. Non-invasive tests

Non-invasive tests can be divided into those able to detect an active infection, such as the urea breath test and stool antigen test, and those able to provide information on current or prior *H. pylori* infection without discrimination.

3.1. Urea breath test

The ^{13}C -urea breath test (UBT) is the non-invasive method of choice to determine *H. pylori* status when available. Similarly to RUT, the test takes advantage from the urease produced by the bacteria, which hydrolyzes urea generating CO_2 and ammonia. The urea substrate is enriched with a labeled carbon isotope that may be non-radioactive (^{13}C) or radioactive (^{14}C) and ingested, usually, with a test meal to prolong the permanence of urea in the stomach. Breath exhaled samples are collected in proper tubes before and after urea ingestion. Even though the dose of radiation is small in the ^{14}C -UBT, the non-radioactive ^{13}C test is routinely preferred. The test is also used to ascertain the eradication and it is recommended for the “test-and-treat” strategy in dyspeptic patients [1]. The test could also be successfully applied to patients with partial gastrectomy, especially when performed with the patient in the right position [42]. The ^{13}C -UBT shows high sensitivity (95%) and specificity (95% to 100%) [43].

The ^{13}C -urea is available in the market in different formulations such as a powder, capsules and tablets ranging between 50 and 100mg. The test meal containing citric acid or malic acid enhance ^{13}C -UBT performance increasing urease activity in the presence of bacteria [44]. However, quantitative results may be influenced by sex, age, body mass index, especially obesity, smoking, gastric atrophy and intestinal metaplasia and even by the socioeconomic status [45][46][47]. The most used cutoffs, expressed as delta over baseline (DOB), are 2‰, 2.4‰, 2.5‰ and 5‰ [48]. To analyze labeled $^{13}\text{CO}_2$ several detector devices are available in the market [49][50].

3.2. Stool antigen test

To culture *H. pylori* from feces is very difficult and time consuming [51], on the contrary non-invasive tests able to detect *H. pylori* antigen in stool specimens are simple to perform and large head-to-head comparisons with other tests demonstrated high diagnostic accuracy of this approach [52]. Nowadays several assays are available, the more recent ones are listed in table 1.

Table 1. Most recent stool antigen tests and their reported sensitivity and specificity.

Brand	Based on	Sensitivity	Specificity	Reference
LIAISON <i>H. pylori</i> SA assay (DiaSorin, Saluggia, Italy)	chemiluminescent immunoassay	90.1 95.5	92.4 97.6	Ramirez-Lazaro et al., 2016 [53]
Genx <i>H. pylori</i> card test (Genx Bioresearch, Kocaeli, Turkey)	monoclonal immunochromatographic assay	51.6	96.0	Korkmaz et al., 2015 [54]

Uni-Gold™ <i>H. pylori</i> Antigen (Trinity Biotech, Bray, Ireland)	monoclonal lateral flow immunochromatographic assays	83.2	87-89.3	Lario et al., 2016 [55]
RAPID Hp StAR (Oxoid Ltd., UK)	monoclonal lateral flow immunochromatographic assays	94-95	77.1 to 84.7	Lario et al., 2016 [55]
ImmunoCard STAT! HpSA (Meridian Diagnostics, USA)	monoclonal lateral flow immunochromatographic assays	79-81.5	90.8-91.6	Lario et al., 2016 [55]
IDEIA HpStAR®; ThermoFisher Sc., Waltham, USA	monoclonal antibodies and the ELISA technique	Before <i>Hp</i> treatment 93.6 After <i>Hp</i> treatment 100	Before <i>Hp</i> treatment 100 After <i>Hp</i> treatment 92.8	Moubri et al., 2018 [56]
Quick Chaser <i>H. pylori</i> ®, QCP, Misuho Medy, Tosu, Japan)	immunochromatography	92.3		Kakiuchi et al., 2019 [57]
Vstrip®HpSA, (Meridian),	immunochromatography	91%	97%	Fang et al., 2020 [58]
ImmunoCard STAT!® Campy (Meridian)	immunochromatography	76.9%	97%	Fang et al., 2020 [58]

Overall, stool monoclonal antibody tests are superior to polyclonal antibody tests and demonstrated a pooled sensitivity and specificity of 93% and 96%, respectively [\[59\]\[60\]](#). They also show an excellent diagnostic accuracy in pediatric setting, especially when tests are ELISA based rather than immunochromatography based [\[61\]](#). The use of

stool antigen test (or UBT) for the initial diagnosis of *H. pylori* infection and post-treatment (when endoscopy is not required), is recommended by the majority of guidelines and consensus [1][2][3][4].

The advantage of the UBT and of stool antigen test is that they assess the overall content of the stomach whereas histology and RUT test only the tiny biopsy specimen. Theoretically and practically, the UBT and stool antigen test are the best methods for detection of active *H. pylori* infection. However, any drug that will diminish *H. pylori* load below the detection threshold of can cause false negative tests, particularly recent use of PPIs, bismuth-containing compounds or antibiotics.

3.3. Molecular Testing

Molecular techniques should be preferred when available. The traditional or modified real-time (RT) PCR allows to detect the bacteria, and to screen for antibiotic sensitivity [62][63][64]. Moreover, real-time PCR is more accurate compared with other techniques for the detection of *H. pylori* in patients exposed to PPI [65], and is able to detect as low as 10 copies in adult [66] and children [67]. In addition to gastric biopsies, molecular testing can be applied to the gastric mucus present on biopsy forceps placed into water or into the RUT gel [68]. Alternatively, molecular tests to detect *H. pylori* and its susceptibility to antibiotics can be performed on gastric juice [69][70][71]. A droplet-digital PCR may also be applied to formalin-fixed, paraffin-embedded gastric tissue to determine the presence of clarithromycin resistance [72] or by next generation sequencing to determine levofloxacin and tetracycline resistance [73] (Figure 1).

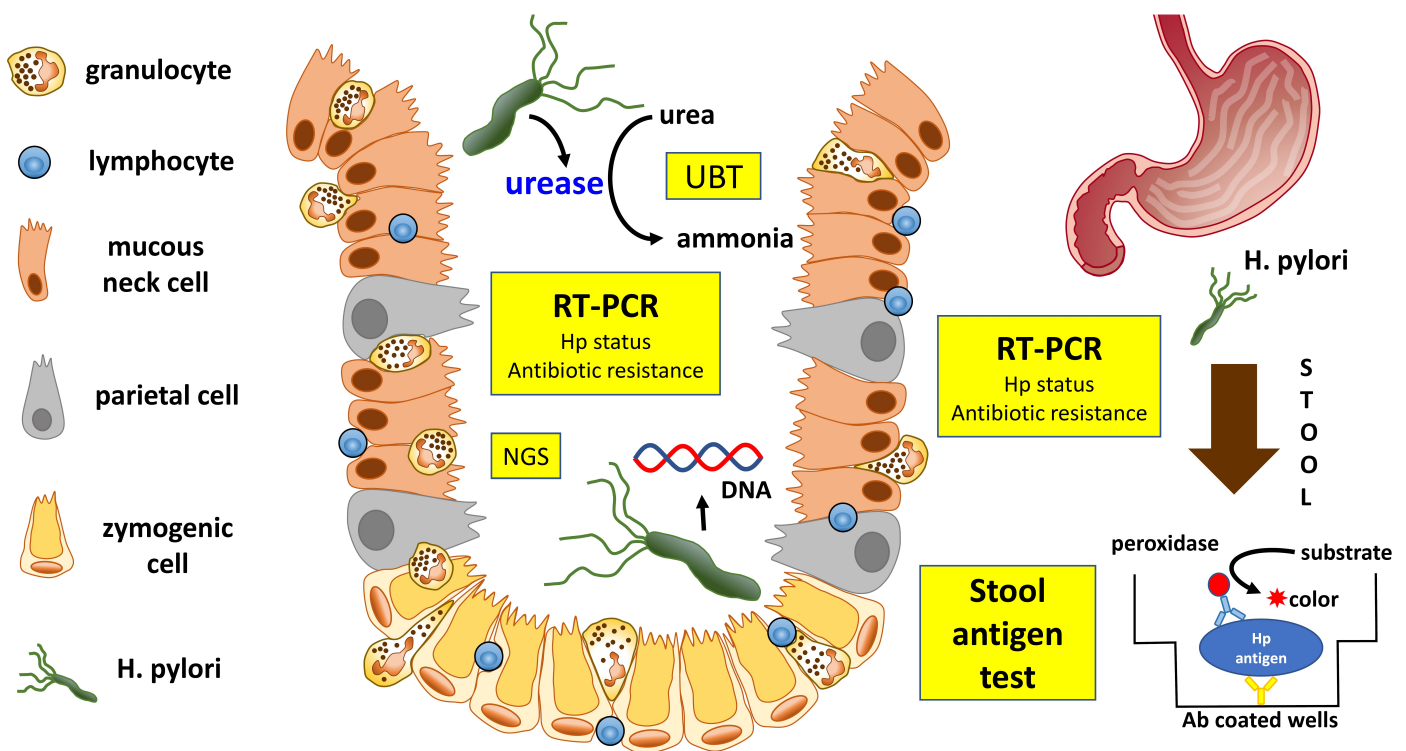


Figure 1. Invasive, non-invasive methods and molecular testing to detect *H. pylori* and its antibiotic resistance.

Several molecular tests have been developed in the last years to detect specific *H. pylori* antigens and/or resistance pattern in the stool (Table 2).

Table 2. Recent molecular assays available to detected *H. pylori* and its antibiotic resistance.

Molecular test	<i>H. pylori</i> DNA target	Reference
multiple genetic analysis system (MGAS)	16S rDNA and <i>ureC</i>	Zhou et al., 2015 [74]
allele-specific PCR	N87I mutation in the <i>gyrA</i>	Trespalcios et al., 2015 [75]
droplet-digital PCR (ddPCR)	<i>cagA</i> and its EPIYA phosphorylation motifs	Talarico et al., 2016 [64]
loop-mediated isothermal amplification (LAMP)	<i>ureC</i> gene	Yari et al., 2016 [76]
TaqMan RT-PCR	A2142C, A2142G and A2143G mutations	Beckman et al., 2017 [77]
droplet-digital PCR (ddPCR)	16S rDNA	Talarico et al., 2018 [72]
real-time PCR (THD fecal test [®])	23S ribosomal RNA	Iannone et al., 2018 [78]
MagNA Pure 96 (Roche)	DNA	Clines et al., 2019 [79]
Amplidiag [®] <i>H. pylori</i> + ClariR	<i>H. pylori</i> and CLA resistance mutations	Pichon et al., 2020 [80]

3.4. Serology

Unlike UBT and stool antigen testing, serology does not distinguish between an active or past infection, although in a recent study antibody response to *H. pylori* proteins such as VacA, GroEl, HcpC, CagA, Tip- α , HP1564 and HP0175 indicates an active *H. pylori* infection with a high diagnostic accuracy [81][82].

Detection of serum IgG against *H. pylori* is usually based on the enzyme-linked immunosorbent assays (ELISA). The latex immunoassay may be employed with the advantage to save time [83]. Several kits are available in the market and, overall, they are highly sensitive and specific; however, to maintain a high diagnostic accuracy, serologic tests need to be validated locally [84], especially when the kit uses strains' antigens from different geographic areas [85]. Because IgG titers decline slowly (over around six months) the test is not recommended to evaluate bacterial eradication after treatment. Serology testing does not have the ability to distinguish active infections from past infections. In addition, the positive predictive value of antibody testing is affected by the local prevalence of *H. pylori*, especially in those areas where the *H. pylori* prevalence is inferior to 20%.

3.5. Tests on plasma, blood, saliva and urine

The GastroPanel, especially the new-generation test, assesses simultaneously *H. pylori* antibodies and pepsinogen (PG) I plus PG II and gastrin-17 in the plasma, predicting *H. pylori* infection and the presence of atrophic gastritis with a likelihood of 94-95% [86]. The test is the most comprehensive non-invasive diagnostic test as it avoids false negative results respect to conventional tests [86][87][88][89][90]. A decreased PG1/2 ratio is associated with chronic atrophic gastritis and intestinal metaplasia ($p < 0.001$) and, inversely, an increased ratio correlates with gastritis [87]. The GastroPanel is useful under specific conditions. For example, in very old or fragile or with severe comorbidities patients, or healthy subjects from regions at low gastric cancer prevalence, but with gastric cancer familiarity who refuse to undergo upper endoscopy, evaluation with the GastroPanel may offer a comprehensive overview of the *H. pylori* and gastric mucosa status.

A plasma sample also offers the opportunity to detect circulating microRNAs (miRNAs) by molecular techniques. For example, the expression of four miR-28-3p, miR-143-3p, miR-151a-3p, and miR-148a-3p were found to be associated with *H. pylori* infection [91].

IgG antibodies against *H. pylori* may also be detected in dried blood spots, saliva and urine by ELISA with a reported good accuracy [92][93][94].

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