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Diagnosis of *Helicobacter pylori* infection

A short review

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Summary *Helicobacter pylori* infections represent an important factor in the pathogenesis of chronic gastritis, peptic ulcer, MALT lymphoma and gastric adenocarcinoma. The recently published Maastricht V/Florence consensus report indicated that the urea breath test using 13 C urea still remains the best non-invasive test to diagnose *H. pylori* infections with high sensitivity and specificity. Among the stool antigen tests, the ELISA monoclonal antibody test is a rational option. Effective therapy should be based only on susceptibility testing in regions with documented high clarithromycin resistance (>15%). Advanced high-resolution endoscopic technologies enable increased diagnostic accuracy for detection of *H. pylori* infections.

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Introduction

This short review aims to establish current diagnostic non-invasive and invasive tests for *Helicobacter pylori* infections. Given the recent guidelines, the first-line therapy selected must be effective (>90% per protocol efficacy) [1]. Generally, treatment of *H. pylori* infection is efficient if antimicrobial therapy is prescribed to which *H. pylori* is susceptible and the patients are adherent [1–3]. Therefore, an appropriate diagnostic procedure is a key step for efficient eradication therapy. There are numerous methods for detection of *H. pylori* infections. Invasive methods include upper endoscopy with biopsy for histological analysis, rapid urease testing, molecular methods or culture [1, 3]. Testing should be performed 2 weeks after the end of proton pump inhibitors (PPI) treatment or 4 weeks after the end of antibiotic therapy. Urea breath test or monoclonal fecal antigen testing are the first line non-invasive methods for establishing an active *H. pylori* infection [1].

Non-invasive tests

Urea breath test

Urea breath test (UBT) is a non-invasive test suitable for diagnosis of *H. pylori* infection and also for confirming eradication after the treatment. This test is the gold standard among non-invasive tests with high sensitivity and specificity [4, 5]. The UBT can also be used for epidemiological studies. This test is based on the fact that after ingestion of ^{13}C or ^{14}C-labeled urea by patient, labelled CO_2, as a result of degradation of urea by the enzyme urease produced by *H. pylori*

present in the stomach of the patient, can be measured in the exhaled air. Although ^{14}C-UBT has lower costs it exposes patients to some radiation and it is contraindicated in children and pregnant women [6]. The labeled urea can be administered in encapsulated or non-encapsulated form. It was shown that sensitivity of encapsulated ^{14}C-UBT is lower compared to non-encapsulated ^{14}C-UBT because of possible incomplete resolution of the capsule in the stomach, as presented by dynamic scintigraphy images [7]. The most widely used protocol includes citric acid and 75 mg of urea [1]. Breath samples are collected 10–15 min after urea ingestion. False negative results can occur in patients taking PPI as they interfere with the sensitivity of UBT [8]. To avoid a false negative result, antibiotics should also be stopped for at least 4 weeks prior to UBT. In order to prove eradication of *H. pylori*, UBT should be done at least 4–8 weeks after completing *H. pylori* eradication [9].

Stool antigen test (SAT)

Stool antigen test (SAT) is a non-invasive test used to detect *H. pylori* antigen in the stool sample of the patient. The SAT is used as an enzyme immunoassay (EIA) or immunochromatographic assay (ICA). In SAT tests, monoclonal or polyclonal antibodies are used. In the study of Gisbert et al. monoclonal antibody-based tests showed sensitivity and specificity of 94% and 97%, respectively [10]. Monoclonal antibody-based tests are more accurate than polyclonal antibody tests [10, 11]. In the study of Calvet et al. the diagnostic accuracy of 3 monoclonal stool tests (2 rapid immunochromatographic monoclonal tests, RAPID Hp Star and ImmunoCard STAT HpSA and an enzyme immunoassay monoclonal test, Amplified IDEIA Hp STAR) for diagnosing *H. pylori* infections was compared [12]. Amplified IDEIA Hp STAR tests were the most accurate test for diagnosing *H. pylori* infections while ICA tests are fast and easy to use. [12]. The SAT can be used for the initial diagnosis of *H. pylori* infection, and for confirming eradication after the treatment [13]. The time for performing SAT after treatment should be at least 4 weeks [13]. The SAT is also very suitable for the diagnosis of *H. pylori* infection in children [14]. The study of Shimoyama showed that the accuracy of SAT is lower when the stool samples are unformed or watery, because *H. pylori*-specific antigens are diluted. Temperature and the interval between stool sample collection and measurement also affect the results of SATs [15]. False negative result may occur in the case of low bacterial load, and in case PPI or antibiotics were recently used [16].

Serological testing

Serological testing is used to determine the titer of IgG anti-*H. pylori* antibodies in the patient's serum. Many tests for this purpose are commercially available, enzyme linked immunosorbent assays (ELISA) or immunochromatographic assays (ICA). According to the study of Burucoa et al. the ELISA test is more accurate than ICA [17]. Because IgG antibodies are present for a very long time during a patient's life, this kind of testing is not acceptable for proving current infection. It cannot distinguish between past and acute infections. For the same reason, serology cannot be used to monitor eradication. After eradication, antibodies can persist lifelong [18]. Most frequently, serological tests are used in epidemiological studies [19, 20]. The accuracy of serological testing depends on antigens present in the commercial kit and the antigenic composition of specific *H. pylori* strain present in a specific population, in a specific geographical area [21]. Because of that, these tests should be locally validated [22]. An advantage of serology is that results of these tests are not affected by PPI therapy, or previous antibiotic use [1].

Invasive tests

Endoscopy

Endomicroscopy is a novel technique which allows ultra-high magnification in real time. A meta-analysis performed by Qi et al. pointed out that magnifying endoscopy was able to accurately predict the status of H. pylori infections, either in magnifying white light endoscopy or magnifying chromoendoscopy mode [23]. They further determined that "pit plus vascular pattern" classification in the gastric corpus is an optimal diagnostic criterion [23].

Despite significant technological advances in the field of endoscopy, these methods are not yet clearly positioned for routine clinical practice in the diagnosis of *H. pylori* infection. Furthermore, these methods require specially trained experts and are also time-consuming [23–25].

Rapid urease test

H. pylori is a strong producer of the enzyme urease, which is the basis for the rapid urease test (RUT). Urease enzyme produced by *H. pylori* present in the biopsy specimen degrades urea reagent in the test, causing ammonia to be formed which can be detected by change in the color of the test reagent because of the change in pH. The RUT is invasive but cheap, rapid and with specificity above 95% [26]. It is available as gel, paper or liquid-based test. Some of the tests provide results after 24 h, like CLO (Campylobacter-like organism) test (Halyard, Alpharetta, Georgia, USA), and some others after 5 min [27, 28]. It is necessary to strictly follow the recommendations of the manufacturer regarding the time of reading RUT [27]. On the result of the RUT can affect low density of the bacteria in the biopsy specimen, and also PPI, bismuth, antibi-

otics, achlorchydria and bleeding [29, 30]. Sensitivity of RUT can be below 70% in patients with bleeding peptic ulcers [29]. It is recommended to avoid the use of PPI for 2 weeks and antibiotics for 4 weeks before RUT [30]. Also, sensitivity of RUT is higher when dual biopsy is used, from gastric corpus and antrum [31–33]. Sensitivity is even better when these two specimens are combined and tested together, not separately [32, 33].

Histology

Histology is still considered to be the gold standard for direct diagnosis of *H. pylori* infection [34]. In addition to the routine hematoxylin and eosin (*H. pylori*) stain, there are several other techniques; however, Giemsa staining has become the most used method worldwide for detection of *H. pylori* because it is sensitive, cheap, easy to perform and reproducible [35, 36]. Use of immunohistochemistry (IHC) should be restricted to cases with low levels of organisms, some chronic gastritis, atrophic gastritis (with extensive intestinal metaplasia), or in follow-up biopsies after eradication treatment. This method is more specific but more expensive, and not available in all laboratories [37, 38]. Mapping studies in which multiple biopsy specimens have been taken from *H. pylori*-positive subjects confirm that careful examination of four specimens (lesser and greater curvature and antrum and corpus) has a high probability of establishing the correct *H. pylori* status [39]. Other authors showed that two antral or even one biopsy from the greater curvature were sufficient to detect *H. pylori*. In patients with duodenal ulcer *H. pylori* colonization is more dense in the antrum, and antral biopsies are recommended to assess the density of *H. pylori* [40]. Corpus biopsies are particularly valuable for yielding positive results after treatment, especially where proton pump inhibitors have been used. Then organisms may become rare or disappear from the antrum, but remain in the oxyntic mucosa, which may also develop cystic dilatations with hypertrophy of the parietal cells. Furthermore, biopsy specimens from the corpus are essential to establish the pattern of gastritis, which has important implications for the risk of associated diseases; however, maximum degrees of gastric mucosal atrophy and intestinal metaplasia are consistently found in the region of incisura angularis, which is also the site most likely to reveal premalignant dysplasia [41]. The Sydney grading system for chronic gastritis and its updated Houston version are the most commonly used nomenclature for gastritis. This system categorized gastritis according to intensity of mononuclear inflammatory cellular infiltrates, polymorphic activity, atrophy, intestinal metaplasia, and *H. pylori* density into mild, moderate and severe categories [41]. Nonstandard histology reporting formats are still widely used for gastritis, and even specialists are often frustrated by the histological definitions that make it difficult to identify candidates for clinical endoscopic surveillance [42].

Culture

Isolation of *H. pylori* is performed by cultivation of gastric biopsy specimens using selective media such as Pylori agar, Columbia agar with horse blood and antibiotic supplement and other similar media [43]. Because *H. pylori* is a fastidious, microaerophylic bacteria, sensitive to atmospheric conditions, biopsy specimens must be kept and transported in liquid transport medium which can be obtained from a microbiological laboratory. It is recommended to send one biopsy specimen from the corpus and one from the antrum for cultivation [44]. Storing of biopsy specimens is possible for up to 24 h at 4 °C. Transportation to the laboratory must also be done at 4 °C [45]. Prolonged time of transportation and increase of transport temperature decrease the cultivation rate [46]. Biopsy specimens should be gently homogenized and plated on a selective medium which is then cultivated under microaerophilic conditions for at least 7 days at 37 °C. Identification of *H. pylori* is made by typical colony morphology and positive oxidase, urease and catalase test. After primary growth of *H. pylori*, further subcultivation, e.g. on Columbia agar with horse blood, under the same conditions, is necessary to get enough colonies to perform antibiotic susceptibility testing. Each of these two steps requires incubation for at least 3 days. In conclusion, the time to result can be as soon as 6 days. This method is time-consuming, it is not cheap, and requires microbiology laboratory staff experienced in isolating this bacterium. Isolation of *H. pylori* allows first of all for comprehensive susceptibility testing and futhermore for studying genotypic characteristics of the bacterium in specific populations. According to the Maastricht V Consensus Report, culture and antibiotic susceptibility testing should be performed if primary resistance to clarithromycin in a specific geographic area is more than 15% or after failure of second-line treatment [1]. Factors such as bleeding peptic ulcer, highly active gastritis, consummation of alcohol, use of H_2 receptor antagonists, PPI and low bacterial load can reduce the success of cultivation [44, 47]. These drugs should be avoided 2 weeks before endoscopy. Antibiotics also have a negative impact on cultivation of *H. pylori* and should be avoided 4 weeks before endoscopy [48].

Molecular methods

Molecular methods, most often amplification of nucleic acid by conventional polymerase chain reaction (PCR) or real-time PCR are being increasingly more used to detect *H. pylori* DNA in biopsy samples or other types of specimens, like saliva or feces [49]. So, PCR can be categorized as invasive or non-invasive method regarding the type of specimen tested. Real-

time PCR has sensitivity and specificity greater than 95% compared to other, classical tests (RUT, culture, histology, SAT, UBT), and is also convenient in patients with bleeding [48]. The PCR-based techniques allow detection of specific mutations leading to antibiotic resistance, bacterial virulence factors, and bacterial quantification [49]. Advantages of molecular methods are that they are faster, more sensitive and accurate than others, but more costly and the laboratory must have appropriate equipment and experienced staff [48]. In regions of high clarithromycin resistance rates stool real-time PCR, also allowing for clarithromycin susceptibility testing, may represent a useful diagnostic option for younger, dyspeptic patients, who do not need to undergo endoscopy and should preferably be treated by a clarithromycin containing regimen [50]. Combination of PCR and hybridization test is the Genotype HelicoDR assay (Hain-Lifescience, Nehren, Germany) assay which allows detection of *H. pylori* in gastric biopsy specimens and clarithromycin and fluoroquinolones resistance. Despite good results in some previous studies, Genotype HelicoDR in the study of Lee et al. from 2014 in Korea showed relatively low sensitivity and specificity and was not accurate for clarithromycin and fluoroquinolones resistance, compared to culture-based methods [51, 52]. Recently, a peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) method, has been described [53], which appears to be a simple, quick, and accurate method for detecting *H. pylori* and the three most prevalent point mutations associated with clarithromycin resistance in paraffin-embedded biopsy specimens [53].

Conclusion

Currently, a broad spectrum of diagnostic tests are available, most of them with high sensitivity and specificity. The ^{13}C urea test still remains the best non-invasive test for diagnosing *H. pylori* infection. The ELISA monoclonal fecal antigen test is also acceptable because of high sensitivity and specificity when ^{13}C urea is not available. *H. pylori* causes an infectious disease and should be diagnosed and treated as infectious disease. Therefore, in regions with documented high clarithromycin resistance (>15%), efficient therapies should be based primarily on susceptibility testing (culture or molecular methods). Novel developments in high-resolution endoscopic technologies can contribute to increased diagnostic accuracy of the detection of *H. pylori* infection. The choice of diagnostic tests should always take into account clinical conditions, availability of certain diagnostic methods, as well as cost-effectiveness.

Conflict of interest A. Tonkic, J. Vukovic, P. Vrebalov Cindro, V. Pesutic Pisac, and M. Tonkic declare that they have no competing interests.

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