Diagnosis of Helicobacter pylori Infection

Subjects: Gastroenterology & Hepatology

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Helicobacter pylori (H. pylori) infects approximately 50% of the world population. Its infection is associated with gastropathies, extra-gastric digestive diseases, and diseases of other systems. There is a canonical process from acute-on-chronic inflammation, chronic atrophic gastritis (CAG), intestinal metaplasia (IM), dysplasia, and intraepithelial neoplasia, eventually to gastric cancer (GC). H. pylori eradication abolishes the inflammatory response and early treatment prevents the progression to preneoplastic lesions.

Keywords: diagnosis of Helicobacter pylori ; endoscopy ; artificial intelligence ; polymerase chain reaction

1. Introduction

Helicobacter pylori (*H. pylori*) infection is chronic and usually acquired in childhood. Globally, *H. pylori* infects an estimated 50% of the global population which is influenced by socioeconomic status, sanitation, regions, and age. For continents, it was reported that Africa had the highest prevalence of *H. pylori* infection (70.1%), whereas Oceania had the lowest prevalence (24.4%). For countries, the prevalence of *H. pylori* infection varied from as low as 18.9% in Switzerland to 87.7% in Nigeria [1]. One meta-analysis reported an overall prevalence of 44.3% involving 410,879 participants from 73 countries in six continents, with a rate of 50.8% in developing countries compared with 34.7% in developed countries, 42.7% in females compared to 46.3% in males, and 48.6% in adults (≥18 years) compared to 32.6% in children [2]. *H. pylori* gastritis was defined as an infectious disease and should be offered eradication therapy. If there is *H. pylori*-associated dyspepsia or functional dyspepsia, eradication of *H. pylori* is the first-line treatment. Symptoms can be attributed to *H. pylori* gastritis if sustained symptoms get remission after 6–12 months [3][4]. Regarding gastric cancer (GC), some potential changes caused by *H. pylori* infection may contribute to the progress of GC, which includes gastric dysbacteriosis [5], changing gastric mucosal, and cellular immunity as one component of inflammatory microenvironment [6][7], aberrant deoxyribonucleic acid (DNA) methylation [8], abnormal expression of ribonucleic acids (RNAs) (micro RNAs, long noncoding RNA, and messenger RNAs) [9][10], and single-nucleotide polymorphisms [11], et al. Chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) are precancerous conditions in which dysplasia (neoplastic precancerous lesion) and adenocarcinoma may occur. GC incidence of mild, moderate, and severe atrophy is 0.04–0.10%/year, 0.12–0.34%/year, and 0.31–1.60%/year, respectively [12][13]. GC incidence in patient with IM is 0.038–1.708%/year, and the progressing rate to dysplasia in IM patient was estimated to be 1.251%/year [14][15]. Endoscopic assessment, *H. pylori* infection diagnosis, and surveillance are recommended in patients with precancerous conditions. Endoscopically visible lesion harboring low- or high-grade dysplasia or GC should undergo staging and treatment [16][17]. *H. pylori* eradication heals acute inflammation and nonatrophic chronic gastritis and may lead to regression of atrophic gastritis and reduce the risk of GC in patients with nonatrophic and atrophic gastritis. *H. pylori* eradication is recommended in patients who have family history of GC, CAG, IM, dysplasia, or cancer and in patients with gastric neoplasia or early GC after endoscopic therapy or by subtotal gastrectomy to prevent metachronous recurrence [16][17].

2. Endoscopic Diagnosis

2.1. Conventional White Light Imaging (WLI)

Globally, the prevalence of gastritis is near 50%, which was shown from 40.7% to 56.0% and included 20–30% chronic atrophic gastritis. *H. pylori*-negative gastritis was from 17.7% to 20.5%, in which chronic gastritis accounted for 10–15% [18][19][20]. It indicates that *H. pylori* infection is generally consistent with the prevalence of gastritis and *H. pylori*-positive gastritis generally accounts for more than 80%. Therefore, it is the basis of clinical application of gastritis in Kyoto classification, as only a small proportion of gastritis may not be infected by *H. pylori*. Endoscopic findings of conventional white light imaging (WLI) can initially predict the status of *H. pylori* and the suspicious infection according to gastritis in Kyoto classification, and then biopsies are taken according to Sydney system [3][21]. Kyoto classification of gastritis including diffuse redness, regular arrangement of collecting venules (RAC), fundic gland polyp (FGP), atrophy, xanthoma, hyperplastic polyp, map-like redness, intestinal metaplasia, nodularity, mucosal swelling, white and flat elevated lesion,

sticky mucus, depressive erosion, raised erosion, red streak, and enlarged folds. Regarding validation research, RAC, FGP, and red streak were demonstrated with satisfactory diagnostic odds ratios (DOR) for predicting uninfected status. Nodularity, diffuse redness, mucosal swelling, enlarged fold and sticky mucus were significantly associated with current infection. Map-like redness was responsible for past infection, and the overall diagnostic accuracy rate of Kyoto classification of gastritis was more than 80% [22][23][24][25]. Furthermore, with regard of uninfected status, one study showed RAC had excellent negative predictive value (NPV) of about 90% and sensitivity value of up to 85% [26]. A meta-analysis including 4070 patients also showed RAC was a valuable endoscopic feature of uninfected status with 0.80 sensitivity, 0.97 specificity, and 0.97 area under the curve (AUC) [27]. With regard of current infection, Kyoto classification score (including atrophy, IM, enlarged folds, nodularity, and diffuse redness) ≥2 could predict *H. pylori* infection with 89.7% accuracy, 78.3% sensitivity, and 92.0% specificity in patients with a high-negative titer of anti-*H. pylori* antibody [28]. One study showed an AUC for *H. pylori* infection of WLI was 0.81 in the corpus and 0.71 in the antrum and indigo carmine contrast (IC) method was useful in gastric swelling areas [29]. Other research reported 0.82–0.92 AUC used self-assembled score systems to predict *H. pylori* infection [30][31]. However, there are two problems that cannot be ignored in real time clinical practice. The first one is the professional level and experience, as well as interobserver agreement. A brief mini-lecture on the Kyoto Classification of Gastritis could improve the accuracy from 90.3% to 96.5% [32]. The second one is the clinical routine that biopsy rather than other detecting methods (UBT, Hp SAT, or serological test) will be taken after primary prediction via Kyoto Classification of Gastritis. From the data mentioned above, Kyoto Classification of Gastritis is more characterized with higher specificity and slightly inferior sensitivity. One clinical research reported no endoscopic features (alone or in combination) showed a sensitivity of more than 57% for *H. pylori* infection [33], which may further result in increasing missed diagnosis rate. The uneven distribution of *H. pylori* inevitably leads to sampling errors in biopsy-based examinations including rapid urease test (RUT), histology, or culture. Biopsies from multipoints can improve the accuracy of detection. Two samples (one from the antrum avoiding areas of ulceration and obvious IM and one from normal appearing corpus) can provide the highest yield for RUT, as well as time saving [34]. The sensitivity of RUT was reported to vary between 80% and 100%, and its specificity is between 97% and 99% [35]. If less than 10^4 bacterial cells are present in the gastric biopsy, false-negative results are obtained most probably [36]. It is essential to improve the sensitivity. Therefore, many efforts were done on newer imaging techniques such as image-enhanced endoscopy (IEE) and aiding systems such as AI.

2.2. Image-Enhanced Endoscopy (IEE)

IEE including magnifying endoscopy and digital chromoendoscopy such as narrow-band imaging (NBI), autofluorescence imaging (AFI), blue laser imaging (BLI), and linked color imaging (LCI) offered advantages in diagnosing *H. pylori*.

Magnifying endoscopy (ME) can provide more precise information concerning the collecting venules, the network of capillaries surrounding the gastric pits, the swelling of the surface epithelium between pits, and the enlargement and destruction of the pits, which was considered useful for the diagnosis of histopathologic gastritis [37][38]. Type Z-0: subepithelial capillary network (SECN) with regular arrangement of collecting venules and gastric pits resembling pinholes. The sensitivity, specificity, positive predictive value (PPV), and NPV of the type Z-0 pattern for predicting normal gastric mucosa were 90.3–92.7%, 93.9–100%, 100%, and 83.8% [39][40][41]. Types Z-1 and 2 patterns (enlarged gastric pits, irregular or loss of SECN, and an absence of collecting venules) were reported with sensitivity, specificity, PPV, and NPV for predicting *H. pylori* infection were 100%, 92.7%, 83.8%, and 100% [39][40]. A meta-analysis involving 1897 patients reported the pooled sensitivity and specificity of ME to predict *H. pylori* infection were 0.89 and 0.82, respectively, with an AUC of 0.95 [42]. Compared with that of conventional WLI, ME can be superior for the diagnosis of *H. pylori* gastritis. The “pit plus vascular pattern” classification in the gastric corpus observed by ME was able to accurately predict the status of *H. pylori* infection with a pooled sensitivity and specificity of 0.96 and 0.91, respectively, with an AUC of 0.99 [42]. The sensitivity and specificity of irregularly arranged antral ridge pattern for the prediction of antral gastritis were 89.3–96.3% and 65.2–73.7%, respectively [41][43]. Indigo carmine staining increased sensitivity and specificity up to 97.6% and 100% for corporal gastritis, and up to 88.4% and 75.0% for antral gastritis, respectively [41].

2.3. Electronic Chromoendoscopy

Non-M-NBI endoscopy is an optical image enhancement technique to enhance the visualization of mucosal microscopic structure and capillaries of the superficial mucosal layer. One study firstly and retrospectively found NBI could be a promising method for *H. pylori* infection identification [44]. According to five gastric mucosal morphologic patterns of non-M-NBI, type 3 (rod-shaped gastric pits with prominent sulci), 4 (ground glass-like morphology), or 5 (dark brown patches with bluish margin and irregular border) morphologies were statistically significant in predicting *H. pylori* positive status and achieved 94.28% sensitivity, 96.66% specificity, 98.50% PPV, and 87.87% NPV [45]. A further retrospective study on the site-specific biopsy guided by NBI of abnormal mucosa rather than the random biopsy for the diagnosis of *H. pylori* showed higher 95.4% sensitivity and 97.3% specificity [46]. However, a multicenter prospective study demonstrated no

difference in the accuracy of diagnosing *H. pylori* gastritis between NBI and WLI (74% NBI vs. 73% WLI), although NBI demonstrated slightly higher sensitivity (69% vs. 57) but reduced specificity (67% vs. 79%) [47].

2.4. Linked-Color Imaging and Blue Laser Imaging

Linked color imaging (LCI) can show mucosal color similar to WLI but produce more color patterns of the mucosa due to emission intensity at wavelengths different from WLI [48]. These colors allow endoscopists to diagnose a variety of lesions such as inflammation areas because of the high color contrast with surrounding mucosa. Blue laser imaging (BLI) is another IEE that combines narrow-spectrum blue laser with white light to make up the deficiency of NBI [49]. The push of a single button during endoscopy allows one to switch between LCI and BLI. LCI is brighter than WLI, and BLI is brighter than NBI. LCI produces particularly bright images in the stomach and is useful when screening gastric lesions, whereas BLI-bright and BLI are also useful in displaying mucosal structure and vessels in close-up views inside the stomach, as well as relatively close views, especially the antrum [50]. Some research has indicated *H. pylori* infection could be identified by LCI and BLI. With regard of BLI, one study included patients' mucosal patterns observed by BLI and divided into Spotty, Cracked, and Mottled pattern groups with results of 12/77, 105/17, and 138/90 negative/positive for *H. pylori* infection, respectively. The specificity and PPV for endoscopic diagnosis with positive *H. pylori* infection based on the Spotty pattern were 95.3% and 86.5% [51]. On the aspect of LCI which is more suitable in wide-lumen organ than BLI, studies based on Kyoto Classification of Gastritis to assess the visibility of LCI, WLI, and BLI found that LCI could improve visibility especially for diffuse redness, spotty redness, map-like redness, patchy redness and red streaks [52][53][54]. When compared with that of WLI, LCI could identify *H. pylori* infection by enhancing endoscopic images of the diffuse redness of the fundic gland and achieve more optimal diagnostic power (accuracy 85.8% vs. 74.2%, sensitivity 93.3% vs. 81.7%, and specificity 78.3% vs. 66.7%) [55]. Another study reported that the application of LCI at the corpus to identify *H. pylori* infection could be reliable and superior to WLI with the highest accuracy among groups (81.2% vs. 64.3–76.5%), as well as higher sensitivity (85.41%) and specificity (79.71%) [56]. A prospective study also indicted the accuracy of LCI was higher than that of WLI (accuracy 86.6% vs. 79.5%, sensitivity 84.4% vs. 84.4%, and specificity 88.9% vs. 74.6%) [57]. When compared with ME, one study recruiting 122 patients (36 had *H. pylori* infection) showed that LCI could play a similar role with ME and demonstrated diagnostic abilities of *H. pylori* infections by LCI (78.38% accuracy, 70.97% sensitivity, 82.5% specificity, 59.46% PPV and 87.84% NPV), ME (81.98% accuracy, 81.25% sensitivity, 83.87% specificity, 64.10% PPV and 91.67% NPV), and both LCI and ME (78.38% accuracy, 80.65% sensitivity, 76.25% specificity, 57.78% PPV, and 92.42% NPV) [58].

2.5. AI: One of Present Advances in Endoscopic Diagnosis of H. Pylori Infection

In the field of endoscopy, the application of AI has received wide attention including gastrointestinal cancers and benign diseases based on endoscopic images, videos and histopathologic slides [59]. *H. pylori* infection, as a dominant cause of CAG and GC, was also detected via AI methods based on endoscopic images. One meta-analysis including 8 studies and 1719 patients (385 patients with *H. pylori* infection vs. 1334 controls) diagnosed by WLI, BLI, or LCI reported that the sensitivity, specificity, DOR, and AUC of AI for the prediction of *H. pylori* infection were 0.87, 0.86, 40, and 0.92, respectively. The accuracy of the AI algorithm reached 82% for discrimination between noninfected images and posteradication images [60]. Regarding WLI, a DCNN model trained and verified by WLI of gastric antrum showed a power in diagnosing atrophic gastritis with 94% accuracy, 0.95 sensitivity, and 0.94 specificity, which were higher than those of experts [61], and AI diagnosis could be done in a considerably shorter time less than 200 s [62][63]. On the aspect of ME, a CNN system was pretrained using 1492 early gastric cancer (EGC) and 1078 *H. pylori* associated gastritis images from M-NBI to differentiate between EGC and gastritis and evaluated by a separate test data set (151 EGC and 107 gastritis images based on ME-NBI). Finally, it achieved a diagnostic ability with 85.3% accuracy, 95.4% sensitivity, 71.0% specificity, 82.3% PPV and 91.7% NPV, respectively, and 51.83 images/second overall test speed (0.02 s/image) [64]. In terms of LCI, a study developed a machine learning method to diagnose *H. pylori* infection with 87.6% accuracy, 90.4% sensitivity, 85.7% specificity, 80.9% PPV and 93.1% NPV [65]. One study developed two different CAD systems, one for LCI (LCI-CAD) and one for WLI (WLI-CAD) and achieved a comparable diagnostic accuracy to that of experienced endoscopists and a higher diagnostic accuracy of the LCI-CAD system (84.2% for uninfected, 82.5% for currently infected, and 79.2% for posteradication status) than that of WLI-CAD [66]. Another study used GoogLeNet, a 22-layer DCNN pretrained by BLI-bright and LCI and tested by 222 patients (105 *H. pylori*-positive) to achieve a significantly higher diagnostic ability of *H. pylori* infection from BLI-bright (0.96 AUC, 96.7% sensitivity, and 86.7% specificity) and LCI (0.95 AUC, 96.7% sensitivity and 83.3% specificity) than that of WLI (0.66 AUC, 66.7% sensitivity and 60.0% specificity) [67]. The research indicates that AI aiding different endoscopies to diagnose *H. pylori* infection can achieve acceptable accuracies in preclinical stage and more efforts in need to promote the real time endoscopic diagnosis directly in the future.

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