

Chromoendoscopy for *H. pylori* infection - Time for a reaction?

Chromoendoscopy provides both a better characterization of mucous lesions in the gut and an increased diagnostic yield in endoscopic procedures (1). This was originally achieved by applying dyes directly on the mucosa via a spray catheter or through the working channel (2). Virtual chromoendoscopy techniques were later developed –NBI (3,4), FICE (5) and i-Scan (6)– to obviate the need for said dyes or pigments.

Dyes used for endoscopic diagnosis are classified according to their capacity of interaction with the digestive mucosa (7): 1. *Contrast agents*: indigo carmine is the greatest exponent. It is a bluish pigment that deposits itself within mucosal irregularities to enhance morphology. It allows an easier detection and characterization of early gastrointestinal neoplasms. 2. *Absorption or vital dyes*: methylene blue is deposited in the cytoplasm of absorptive cells, and is therefore used to enhance intestinal metaplasia areas in the esophagogastrroduodenal tract, as well as in the screening of dysplasia in inflammatory bowel disease. Lugol's solution selectively stains glycogen within the esophageal squamous epithelium's cells, hence it has been used for epidermoid neoplasm screening. Acetic acid reversibly denatures cytoplasmic proteins and is mainly used to characterize the mucosal pattern seen in Barrett's esophagus. Finally, crystal violet deposits itself in cell nuclei, and has proven useful, associated with magnification, for the characterization of the crypt pattern seen in early colorectal cancer, primarily when invasive patterns are suspected. 3. *Reactive dyes*: Congo red is a pH-dependent dye that turns from red to bluish black at $\text{pH} < 3$. Its usefulness has been suggested in the guiding of biopsies towards paler areas in the screening of individuals at risk in families affected by hereditary diffuse gastric cancer (8). These hyporeactive areas suggest the presence of early cancer foci with no parietal cells, and therefore no acid secretion. It was previously used to assess effectiveness following vagotomy (9). Finally, phenol red is also a pH-dependent reagent that turns from yellow to red in areas with a higher pH, and hence was suggested for the guidance of biopsies towards gastric mucosa areas with *Helicobacter pylori* infection, which become reddish in color. Both phenol red and Congo red staining represent functional tests, that is, they to establish whether or not gastric acid secretion exists should staining yield a negative result, whether this was due to the absence of parietal cells or merely some kind of inhibition of acid secretion cannot be determined.

The use of phenol red for the diagnosis of *H. pylori* infection was initially described, in 1991, by Kohli et al. who used it to assess infection distribution in the gastric mucosa (10). Subsequently, Iseki et al. (11) used this dye to identify the presence of *H. pylori* in patients with early gastric cancer. In this last study the dye's sensitivity and specificity to detect infection were 95 and 92%, respectively. In both cases, the technique included the administration of antisecretory agents before the procedure, as well as a mucolytic to prevent false negative results, and an anticholinergic drug to reduce gastric motility.

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Furthermore, the dye solution administered 5% urea in addition to phenol red. With this technique the color change occurred within 1 to 3 minutes after dosing and persisted for at least 15 minutes. In another report, Mitsuhashi et al. described a sensitivity and specificity for chromoendoscopy using phenol red in the detection of *H. pylori* infection of 74.3 and 100%, respectively, on gastrectomy specimens from patients with early gastric cancer. Positive and negative predictive values were 100 and 72.7%, respectively. Immunohistochemistry was the gold-standard technique for the diagnosis of infection in this study (12). More recently, the Korean team formed by Cho et al. reported a sensitivity and specificity of 81.3 and 81.5%, respectively, using histology as their gold standard. This sensitivity reached 97.1% where areas reactive to the staining were more extensive, and decreased to 65.8% for patchy areas (13). On the other hand, Sekine et al. used Congo red to characterize the pattern of secretory gastric mucosa return following eradication of *H. pylori* infection (14).

In this issue of the *Spanish Journal of Gastroenterology*, Hernández-Garcés et al. (15), from Cuba, report on a study for the validation of a diagnostic test: phenol red chromoendoscopy for the detection of *H. pylori* infection *versus* histology as gold standard. Phenol red staining sensitivity was 72.6% and specificity was 75.5%. The likelihood ratio obtained with these data is 2.96. Therefore, a positive result occurs less than 3 times more commonly in infected *versus* noninfected individuals. This is far from ideal in a diagnostic test. The test's positive predictive value was 89.8% and its negative predictive value was 48.1%. Consistency between the study test and the gold standard was poor, with a kappa index of 0.4.

Among invasive studies the rapid urease test is a first-choice option for the diagnosis of *H. pylori* infection given its simplicity (only one biopsy sample from the gastric antrum is required), availability, reliability, low cost, and rapidity (results are available within a few hours) (16). Its sensitivity and specificity are above 85%, and similar to the values obtained from histology (17). From all the above, it is the primary alternative to phenol red.

On the other hand, chromoendoscopy with phenol red has the primary advantage of potentially guiding biopsy for diagnosis, and the added value of histological assessment, which is lost with rapid urease testing. It also has the drawback of requiring longer examinations (if an exploration of the gastric mucosa in greater depth can be thus considered), and the potential presence of errors during image reading and interpretation by observers.

Summing up, reactive chromoendoscopy represents a nexus between histology and mucosal function. Its moderate diagnostic accuracy might be counter balanced by this added value. However, as long as its diagnostic yield remains below that of rapid urease testing, its potential to replace the latter as the predominant modality in the invasive diagnosis of *H. pylori* infection remains far removed, to say the least.

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