Is Validation of *Helicobacter pylori* Eradication Necessary?

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Most gastroenterologists believe that a positive test for *Helicobacter pylori* should prompt an eradication trial to prevent the future possibility of ulcer, cancer or lymphoma [1]. But opinions are divided when the issue is validation of successful eradication. Many physicians contend that validation by the ^{13}C-urea breath test should be performed only in patients with continuous dyspepsia. A proper evaluation of this subject demands that certain questions be addressed:

- What is the primary success rate in clinical trials versus daily practice and in specific populations? If the success rate is high, the chance of failure is low and validation of successful eradication may be a waste of time and money.
- Is the success rate in second-line therapy high? If the second-line therapy is condemned to fail, validation is not needed.
- What is the prognosis of persistent infection? If the natural history of *H. pylori* infection is not altered after failure of the eradication trial, patients may be exposed to the same malicious bacterium and inflammation mediators in the future as they were in the past.
- Is there a correlation between bacteria resistance and aggressiveness?
- For the many patients who need aspirin or non-steroidal anti-inflammatory drugs, will they be plagued by persistent *H. pylori* infection and a higher rate of gastritis, ulcer and ulcer complications?
- Are patients who fail eradication therapy sources of contamination?
- Is the policy to validate successful *H. pylori* eradication in every patient cost-effective?

What is the primary success rate in clinical trials versus daily practice and in specific populations?

In a clinical trial, triple therapy with a proton pump inhibitor and two antibiotics will be successful in 75.5–90.6% of cases, in intention-to-treat analysis, according to the regimen used [2]. Recently, a lower rate was reported due to primary resistance of 11% of the isolated *H. pylori* strains for clarithromycin and 41% for metronidazole [3]. In a meta-analysis of 15 studies, PPI-based triple therapy was successful in 74% of the cases [4]. In a study conducted in Israel, metronidazole resistance was demonstrated in 38.2% of 110 *H. pylori* strains isolated from untreated patients and in 60.7% of strains isolated from patients in whom eradication therapy failed [5]. The correspondence rates for clarithromycin were 8.2% and 46.4%, respectively. Meyer et al. [6], in a meta-analysis of 20 clinical trials of *H. pylori* eradication, found 10% resistance to clarithromycin and 37% to metronidazole. Older age, female gender, and history of peptic ulcer were found to be risk factors for clarithromycin resistance, and female gender and Asian origin for metronidazole resistance [6]. Genetic polymorphism for P450-CYP2C19, the enzyme responsible for PPI metabolism, may cause diversity in this regard [7]. The eradication success rate increased from 72.7% in homozygous extensive metabolizers to 97.8% in poor metabolizers [7]. Thus the success rate of the first-line therapy may not be so high and should not be taken for granted.

PPI = proton pump inhibitor

Is the success rate of second-line therapy high?

Second-line therapy should be highly successful to justify validation of the first-line trial; otherwise this step has no therapeutic logic. Clarithromycin-based second-line therapy after failed metronidazole-based regimens was 74–100% according to 12 studies [8]. A similar success rate (70–95%) was found for metronidazole-based second-line therapy after failed clarithromycin-based regimens [8].

What is the prognosis of persistent infection?

Peptic ulcer and ulcer complications such as bleeding, distal gastric cancer (especially in relatives of gastric cancer patients), mucosa-associated lymphatic tissue lymphoma, are all associated with persistent infection [9]. According to the classic trials with histamine 2 receptor antagonists, we know that duodenal ulcer will recur in 70% of cases after discontinuation of medication and no eradication therapy [10]. When duodenal scar is present, a 30% recurrence rate versus no recurrence after eradication was reported [11]. Rebleeding from peptic ulcer was found to be up to 2% per year after eradication, but 33% per year without eradication [12]. Correa [13] described the "Correa cascade" that occurs after *H. pylori* infection – several years of infection and chronic gastritis followed by the development of hypochlorhydria, atrophy, intestinal metaplasia, and finally dysplasia. These premalignant states can be

observed before cancer develops. After a 10 year endoscopic follow-up, Gutta et al. [14] found intestinal metaplasia in 34% of cases when eradication failed, as compared to 12% when it succeeded. One in 100 *H. pylori*-positive cases will develop gastric adenocarcinoma [15]. This is particularly evident in developing countries with a high prevalence of the infection [16]. The correlation between *H. pylori* infection and gastric cancer was established in six prospective studies [16] as well as in a meta-analysis [17], but the main contribution in this field was two prospective controlled studies by a Japanese group that demonstrated a significantly higher rate of gastric cancer in infected patients [18,19]. Relatives of a gastric cancer patient are at higher risk than the general population to develop gastric cancer [20–24]. The recent experience of treating *H. pylori*-related gastric MALT lymphoma [25] summarized that a response rate higher than 75% is mandatory, that in these cases validation is essential, and that chemotherapy can therefore be planned for the persistent infection. Furthermore, case reports have described hypochlorhydria, vitamin B12 deficiency and homocysteine elevation [26], gastric polyposis [27], Menetrie disease [28], halitosis [29], and hyperammonemia in liver cirrhosis [30].

Is there a correlation between bacterial resistance and aggressiveness?

No correlation has yet been reported between bacterial resistance and aggressiveness, and similar eradication rates were found in peptic ulcer disease patients and in non-ulcer dyspepsia [31]. Also, eradication rates were similar in Cag A-positive and negative strains [32].

Does persistent *H. pylori* infection put patients on regular NSAID therapy at risk for higher rates of gastritis, ulcer and ulcer complications?

This complicated issue was recently resolved in a prospective, randomized, controlled study [33]. Chan et al. [33] demonstrated a significantly higher rate of gastric ulceration in 51 arthritic patients who were randomized to continue diclofenac without *H. pylori* eradication, as compared to 51 such patients in whom the bacterium was successfully eradicated. This was confirmed in a large meta-analysis demonstrating that NSAID-taking *H. pylori*-positive patients are 61 times more likely to have ulcer than non-takers who are *H. pylori*-negative [34].

Are patients who fail eradication therapy sources of contamination?

While the rate of re-infection in developed countries is very low, around 1% per year [35], it is high in developing countries and may be a significant health problem. Recently, re-infection in Poland was found to be 10% a year [36]. Thus, patients with a persistent infection may become a contamination source, especially in developing countries.

Is the policy to validate successful *H. pylori* eradication in every patient cost-effective?

In three cost-effectiveness studies, according to the Markov mathematical model, *H. pylori* population screening and eradication (test and treat policy) was found to be cost-effective for prevention of gastric cancer [37–39]. The cost per year of life saved in the general United States population was $25,000, but less in high risk groups. Thus, validation is cost-effective, at least for cancer prevention.

Conclusion

Validation is necessary in peptic ulcer disease, complicated ulcer, after surgery for gastric cancer, and after treatment of gastric MALT lymphoma. Validation should be recommended in gastric polyposis, Menetrie disease, halitosis, liver diseases, and in elderly Asian women. Validation may be advised for non-ulcer dyspepsia. An alternative may be the Maastricht II recommendation: namely, always validate successful eradication [23]. Successful eradication should be confirmed by the urea breath test or by an endoscopy-based test if endoscopy is clinically indicated. Patient reassurance and risk removal should direct further management on an individual basis – i.e., re-treatment or symptomatic therapy.

MALT = mucosa-associated lymphatic tissue
NSAID = non-steroidal anti-inflammatory drug

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Capsule

Prions – do they get up your nose?

News that pathologic prion protein is deposited in the neuroepithelium of the olfactory mucosa in patients with sporadic Creutzfeldt-Jakob disease (sCJD) is both useful and alarming. Monaco and colleagues obtained the brain, the cribriform plate with attached olfactory mucosa, and the surrounding respiratory epithelium at autopsy from nine patients with neuropathologically confirmed sCJD. Control samples were obtained postmortem and by biopsy from age-matched controls and from controls with other neurodegenerative diseases. Tissues were analyzed by light microscopy, immunohistochemistry, and western blotting for pathologic changes and for deposition of PrPSc. Prion deposition was found in the olfactory cilia and central olfactory pathway of all nine patients with sCJD, but not in the respiratory mucosa. None was detected in the samples from controls.

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