

Management of *Helicobacter pylori*

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Abstract

Meta-analysis has shown that successful *Helicobacter pylori* eradication therapy improved atrophic gastritis and intestinal metaplasia. Moreover, successful eradication therapy against atrophic gastritis has led to the suppression of the incidence of metachronous gastric cancer. Thus, the Japanese Society for Helicobacter Research concluded that all '*H. pylori*-infected persons' should be considered for eradication therapy, irrespective of any background diseases. Successful eradication can prevent transmission of this bacterium, and recent publications show that curing *H. pylori* infection seems to reduce the risk of gastric cancer.

Introduction and context

Helicobacter pylori is a common worldwide infection and is reported to cause various upper gastrointestinal tract diseases, such as atrophic gastritis, gastroduodenal ulcer, gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric hyperplastic polyp [1-3]. Although an infected person does not always develop these severe outcomes, he or she has a high risk of developing these diseases. Therefore, it is expected that successful eradication therapy will result in the improvement of histological gastritis and the prevention of subsequent diseases. In particular, this may contribute to the prevention of gastric cancer development, which is one of the biggest medical problems in the world.

Various guidelines for the management of *H. pylori* infection worldwide are available. For example, the European Helicobacter Study Group published guidelines in the Maastricht III Consensus Report in 2005 [4] and the American College of Gastroenterology (ACG) issued guidelines in 2007 [5]. The Asia-Pacific Gastric Cancer Consensus Conference was held in 2006, and the consensus guidelines were also reported [6]. The current consensus is that *H. pylori* screening and eradication

therapy are recommended for preventing the development of gastric cancer. The latest guidelines were reported from Japan in 2009 [7], and the most important point in the guidelines was that all '*H. pylori* infection' subjects were categorized as level A (i.e., there is strong scientific evidence and eradication therapy is strongly recommended).

Recent advances

The Japanese guidelines were revised dramatically in January 2009, 6 years after the second revision [7]. In particular, the results from the large-scale multicenter trial in Japan published in 2008 helped the revision greatly [8]. In that study, patients with early gastric cancer who received endoscopic mucosal resection were randomly divided into an eradication treatment group and a non-eradication control group and the development of metachronous gastric cancer was followed up for 3 years. As a result, the treatment group had significantly lower development of metachronous gastric cancer than the non-eradication group. This study clearly showed that the successful treatment of *H. pylori* infection led to a decrease in the development of gastric cancer. This shows that even in the background gastric mucosa of patients

with gastric cancer, the subsequent development of gastric cancer could be significantly suppressed by curing the *H. pylori* infection, confirming the importance of careful management of *H. pylori*-related gastritis.

It was recently reported from Taiwan that early eradication decreased the risk of gastric cancer in patients with peptic ulcer disease [9]. In that study, 80,255 patients hospitalized for peptic ulcer were evaluated for the incidence of gastric cancer by a retrospective cohort study. *H. pylori* infection was eradicated in a total of 54,576 patients within 1 year (median of 14 days) (early eradication group) and in 25,679 patients after 1 year (median of 1053 days) (late eradication group). On examination by Kaplan-Meier, the cumulative incidence of gastric cancer in the early eradication cohort was significantly lower than the cumulative incidence in the late eradication cohort. Using Cox multivariable proportional hazard analysis, early *H. pylori* eradication was found to be an independent protective factor for gastric cancer development. These data suggest that early eradication should be recommended for patients with peptic ulcer to prevent the development of gastric cancer.

The latest meta-analysis confirmed that successful eradication reduced the risk for gastric cancer [10]. The authors searched the relevant medical publications in all available sources, comparing *H. pylori*-positive patients who had undergone eradication treatment with those who had been untreated, and examined the number of gastric cancer cases detected during the follow-up period. Six randomized controlled trials met the criteria: four from China, one from Japan, and one from Colombia. The median follow-up period was 6 years. The pooled analysis yielded a relative risk for gastric cancer of 0.65 (95% confidence interval [CI] 0.43-0.89) by undergoing the successful eradication therapy (if data from two of the reported trials from China are excluded, the relative risk is 0.71, 95% CI 0.45-1.23). From a clinical point of view, even a small reduction in risk and incidence achieved with *H. pylori* eradication treatment would probably give a huge advantage in terms of social health, especially in high-risk areas.

Implications for clinical practice

These data confirmed that successful eradication was effective for the prevention of not only peptic ulcer but also gastric cancer. In the Maastricht III guidelines, peptic ulcer, gastric MALT lymphoma, and patient wishes (after full consultation with their physician) were all assigned a grade A recommendation for *H. pylori* eradication [4]. Established indications for treating *H. pylori* in the ACG guidelines include peptic ulcer, gastric MALT lymphoma, and uninvestigated dyspepsia. The Asia-Pacific Gastric

Cancer Consensus guidelines stated that *H. pylori* screening and treatment will reduce not only peptic ulcer and dyspepsia symptoms but also the risk of developing gastric cancer. As described above, the latest Japanese guidelines state that all '*H. pylori* infection' subjects should be categorized as level A. However, an insurance system (approval of health insurance coverage from the Japanese government) was not taken into consideration in the guidelines. Unfortunately, currently, peptic ulcer is the only 'approved' indication for *H. pylori* eradication therapy in Japan. Thus, the most *H. pylori*-infected persons, except those with peptic ulcers, could not have received the benefit of the eradication treatment. However, if all infected persons are to be treated, we should consider the increase in frequency of antibiotic resistance and unexpected consequences such as esophageal adenocarcinoma, asthma, and autoimmune disease [11].

It is clear that the countries with high incident rates of gastric cancer have a high prevalence of *H. pylori* infection. However, there are also populations, such as those of India and Thailand, with a high prevalence of *H. pylori* infection but purportedly low incidence rates of gastric cancer. Infection with cytotoxin-associated gene (*cagA*)-positive strains, especially East Asian *cagA*-positive strains, is believed to increase the risk for gastric cancer over the risk associated with the *cagA*-negative *H. pylori* infection [12]. Determining the *cagA* status in *H. pylori* infection may confer additional benefit in identifying populations at greater risk for gastric cancer. However, the prevalence of the *cagA* gene in Asia is extremely high, and currently identified *cagA* genotypes in the Asia-Pacific region are not associated with gastric cancer [6]. Interleukin-1 gene cluster polymorphisms are associated with a higher risk of hydrochlorhydria and gastric cancer in Western countries [13]; however, these polymorphisms are not involved in the development of gastric cancer in Asian countries [14]. These data suggest that bacterial virulence factors, host genetic factors, and environmental factors contribute to the risk for developing gastric cancer, and further studies investigating these factors in concert are necessary to assess the effect of *H. pylori* eradication on gastroduodenal pathogenesis.

Finally, it is important to recognize that the cure of *H. pylori* infection in patients who have already developed advanced precancerous gastric lesions does not completely prevent gastric cancer development [15]. The Asia-Pacific Gastric Cancer Consensus guidelines concluded that the optimal time to eradicate *H. pylori* is before preneoplastic lesions (atrophy or intestinal metaplasia) are present [4]. In high-risk populations such as those of Japan and Korea, endoscopic surveillance should continue to be performed.

Abbreviations

ACG, American College of Gastroenterology; *cagA*, cytotoxin-associated gene; CI, confidence interval; MALT, mucosa-associated lymphoid tissue.

Competing interests

The authors declare that they have no competing interests.

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