Key Issues Associated with *Helicobacter pylori* Eradication

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**Eradication and Gastric Mucosa**

Eradication of *Helicobacter pylori* causes improvement of gastric atrophy and intestinal metaplasia. Gastric acid secretion levels in corpus predominant gastritis increase after eradication. These changes can increase the risk of reflux esophagitis and low-dosage aspirin ulcers. Although eradication may reduce the overall risk of gastric cancer, a certain degree of risk remains, related to the extent of atrophy and intestinal metaplasia. Many post-eradication gastric cancers are the early depressed type, with low levels of epithelial atypia, and therefore can be difficult to distinguish endoscopically from benign erosion. Further research is required in this area.

The rate of *Helicobacter pylori* (HP) infection has dropped sharply in Japan in recent years, by approximately 30% [1], while the number of HP-negative patients is rising. There are 2 types of HP-negative patients: those who have not been infected and those who have undergone successful eradication treatment. It has been reported that the number of HP eradication procedures in Japan has jumped 165% since February 2013 [2], when eradication was added to the list of treatments for endoscopic gastritis covered by health insurance. The number of HP-eradicated patients is expected to increase rapidly in the near future.

**Abstract**

Eradication of *Helicobacter pylori* causes improvement of gastric atrophy and intestinal metaplasia. Gastric acid secretion levels in corpus predominant gastritis increase after eradication. These changes can increase the risk of reflux esophagitis and low-dosage aspirin ulcers. Although eradication may reduce the overall risk of gastric cancer, a certain degree of risk remains, related to the extent of atrophy and intestinal metaplasia. Many post-eradication gastric cancers are the early depressed type, with low levels of epithelial atypia, and therefore can be difficult to distinguish endoscopically from benign erosion. Further research is required in this area.

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**Eradication and Gastroesophageal Reflux Disease**

The potential link between eradication and gastroesophageal reflux disease (GERD) is a controversial subject. A 1994 report by Labenz et al. [6] suggested that HP eradication exacerbates GERD; however, more recent meta-analyses have found no evidence of a link between the two [7], either qualitative or quantitative. Similarly, a Japanese study [8] compared an eradication group with a control group and found that HP eradication was statistically more likely to result in a higher incidence of reflux esophagitis, but only as a transient effect and only in relatively mild cases. Older HP-positive patients with complications such as hiatus hernia or reduced functioning of the lower esophageal sphincter had severe atrophic gastritis, including extremely low gastric acid secretion. For this reason, eradication to improve gastric acid secretion can be expected to lead to an increase in non-erosive reflux disease and other forms of GERD [9].

**Eradication and Peptic Ulcers**

The 2 main causes of peptic ulcers (PUs) are HP and non-steroidal anti-inflammatory drugs (NSAIDs) [10]. With HP infection rates declining and eradication treatment becoming popular, the incidence of PU is also decreasing. The increase in the elderly population (≥65 years), combined with high rates of gonarthrosis and lumbago in older people, has led to a sharp increase in prescriptions of NSAIDs in recent years [11]. Because antiplatelet therapies, such as low-dosage aspirin (LDA), to reduce clotting have been shown to have secondary prevention benefits for myocardial and cerebral infarction patients, there has been a pronounced increase in patients on LDA regimens [12], which has led to a higher incidence of PU associated with NSAIDs and LDA, often accompanied by hemorrhaging [13].

Reports from the United States, Europe and South Asia cite HP eradication as an effective therapy for the treatment of PU associated with NSAIDs and LDA [14]. This reflects the higher rates in these countries of APG, where eradication successfully reduces and normalizes gastric acid secretion levels. However, in Japan, as noted earlier, elderly patients with HP are more likely to present with CPG at an advanced stage of atrophy, which means that eradication may result in higher secretion levels, thereby increasing the risk of LDA-associated ulcers [15]. A recent study by Iijima et al. [16] named gastric acid as a key exacerbating factor in gastric mucosal damage associated with LDA. Thus, we may conclude that HP infection and NSAIDs and LDA are the main cause of gastric mucosal damage before HP eradication; on the other hand, gastric acid and NSAIDs and LDA are the main cause after HP eradication (fig. 2).

**Eradication and Gastric Cancer**

There is some confusion surrounding the effect of HP eradication following excision of a gastric epithelial neoplasia. Fukase et al. [17] found eradication to be beneficial, but others have claimed the opposite [18]. In a meta-analysis of 13 studies in Japan and South Korea, Yoon et al. [19] found a statistically significant suppression ben-

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**Fig. 1.** Histological change before and after *H. pylori* eradication. Gastric mucosa was taken from the lesser curvature of mid-corpus. Neutrophilic and monocytic infiltration improved, but no remarkable improvement of atrophy and intestinal metaplasia was recognized histologically at 2 and 24 months after HP eradication.
Fig. 2. Relation between HP, NSAID and gastric acid with reference to gastric mucosal damage before and after HP eradication. The 2 main causes of PU are HP and NSAIDs and LDA before HP eradication; on the other hand, gastric acid and NSAIDs and LDA are the main cause after HP eradication.

Fig. 3. Endoscopic findings of benign and malignant depressive lesions using GIF-HQ290 after H. pylori eradication. Case 1: mottled patchy erythema (non-cancerous lesion: Vienna classification: C1) in lesser curvature of upper body. Left side: (white light image) clear and irregular margin, spiny depression. Middle: (indigo carmine dye-staining) clear and irregular margin, red irregular depression. Right side: (NBI, near focus) demarcation line (+), abnormality of mucosal pattern (-). Case 2: gastric cancer (0-IIc) (cancerous lesion: Vienna classification: C4) in posterior wall of middle body. Left side: (white light image) irregularity of mucosa, unclear and irregular margin, spiny depression. Middle: (indigo carmine dye-staining) unclear and irregular margin, irregular depression. Right side: (NBI, near focus) demarcation line (+), abnormality of mucosal pattern (+).
efit in the eradication groups relative to the control groups (RR 0.42 with 95% CI 0.32–0.56).

Red and depressed early gastric cancers are common endoscopic findings of post-eradication gastric cancer, and several histological studies have reported the discovery of epithelium with low-grade atypia on the surface of gastric cancers [20–22].

In general, endoscopic findings indicate rapid improvement in redness and edema, with improvements in atrophic changes also occurring over time. But there have been reports of worsening and/or increasing mottled patchy erythema as an endoscopic finding after eradication [23, 24]. Mottled patchy erythema is characterized by flat, reddish depression that can be difficult to distinguish from early gastric cancer with white light and dye-staining. The authors reported that close observation with narrow-band imaging (NBI, near focus) is useful to discriminate between benign and malignant in depressive lesions (with reference to demarcation line and abnormality of mucosal pattern; fig. 3) [25].

It is clear that HP infection can be considered a cause of gastric cancer. Eradication may reduce the risk of gastric cancer but would not eliminate it altogether. For this reason, regular endoscopic examination is still required following eradication. Atrophic changes are considered to be the single most important determining factor for post-eradication gastric cancer [26]. A better understanding of the pathology of post-eradication gastric cancer is vital for its prevention. In the absence of clear guidelines on the frequency of post-eradication endoscopic examinations, annual examination is thought to be sufficient.

Disclosure Statement

The authors declare no conflict of interest for this article.

References


