Helicobacter pylori infection in Japan

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Abstract

The prevalence of Helicobacter pylori infection is gradually decreasing in Japan. On the main island of Japan, nearly all H. pylori isolates possess cagA and vacA with strong virulence. However, less virulent H. pylori strains are frequently found in Okinawa where cases of gastric cancer are the lowest in Japan. Eradication therapy for peptic ulcer, idiopathic thrombocytopenic purpura, gastric mucosa-associated lymphoid tissue lymphoma and early gastric cancer after endoscopic resection has been approved by the Japanese national health insurance system. However, the Japanese Society for Helicobacter Research recently stated that all ‘H. pylori infection’ was considered as the indication for eradication irrespective of the background diseases. To eliminate H. pylori in Japan, the Japanese health insurance system should approve the eradication of all H. pylori infections.

Keywords
guideline; Helicobacter pylori; Japan; management; resistance; treatment

Epidemiology

Helicobacter pylori infection is now regarded as a high risk factor for severe gastritis-associated diseases, including peptic ulcer and gastric cancer [1]. The infection persists for a long period of time in most infected patients, but only a small fraction of these patients develop associated diseases [2]. The transmission mechanism of H. pylori is not fully understood, but human-to-human spread through the oral–oral or fecal–oral routes is thought to be the most plausible [3]. Studies have demonstrated the presence of H. pylori in drinking water and indicated the influence of poor living conditions and sanitation on H. pylori infection, supporting the oral–fecal route of spread. In Japan, a rapid change occurred in the sanitary conditions and standard of living after World War II; clean public water systems were introduced in Japan in the 1950s. H. pylori infection rates gradually increased with age until 39 years of age, after which a high plateau was reached (i.e., more than 70%) at ages of

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40 years or above, according to a report published in 1992 (Figure 1) [4]. These rates are higher among individuals born before 1950 and lower for those born thereafter. Our report conducted from 2002 to 2006 also showed that the prevalence of H. pylori infection increased with age [5]. We examined the H. pylori infection rate for 5550 patients in our hospital from 2007 to 2011. Compared with previous reports, a decrease in the H. pylori infection rate was observed for each age group (Figure 1). Importantly, the H. pylori infection rate was decreased even after the rates shifted. Several antibiotics are used for other common infections in Japan, which may contribute to the decreased H. pylori infection rate. However, the H. pylori infection rate did not change among those below 40 years of age between 2002 and 2006, and 2007 and 2011 in our study, although the reason for this remains unclear. This suggests that H. pylori infection must be considered even in young patients. Moreover, reinfection of H. pylori should be considered even after successful eradication therapy. A recent study found the reinfection rate after successful eradication therapy in adults to be 0.22% per year [6]. Recrudescence or reinfection can often occur at during the first year of follow-up. Therefore, the status of H. pylori should be examined at least at the first-year follow-up. Overall, the H. pylori infection rate in Japan will likely continue to fall due to the improvement of sanitary conditions and the use of antibiotics. This suggests that the prevalence of H. pylori-related diseases will also decrease in the future. The prevalence of peptic ulcer and gastric cancer significantly decreased in 2005 compared with the prevalence observed in 1988 in Japan [7].

Virulence factors of H. pylori in Japan

In addition to host factors and diet, virulence factors of H. pylori, such as cagA, vacA, oipA, babA, hopQ and homA/B, have been demonstrated to be predictors of gastric atrophy, intestinal metaplasia and severe clinical outcomes [8]. Although gastric cancer and duodenal ulcer are at the opposite ends of the disease spectrum, H. pylori infection promotes the development of both diseases, and most putative H. pylori virulence factors have been associated with an increased risk of these diseases. However, these virulence factors cannot be used as disease-specific markers in east Asian countries such as Japan because nearly all H. pylori strains possess these virulence factors in these regions [8].

For example, cagA is the most studied virulence factor of H. pylori. Although cagA-positive strains are reported to be associated with severe clinical outcomes, particularly in Western countries, it is difficult to demonstrate the importance of cagA in clinical outcomes in Japan because nearly all H. pylori strains possess cagA [8]. However, subjects infected with H. pylori containing cagA do not always induce serum CagA antibody. Although most Japanese H. pylori strains possess cagA, incidence of CagA seropositivity in gastritis ranged from 53.7 to 83.3% in Japan [9,10]. We previously conducted a meta-analysis and reported that CagA seropositivity was higher in strains from patients with gastric cancer than those with gastritis, even in east Asian countries [11], although the odds ratio (OR) in east Asian countries was smaller than that in Western countries. This suggests that anti-CagA antibody can be used as a biomarker for gastric cancer in east Asian countries.

The cagA can be of two types: east Asian-type cagA and Western-type cagA according to the nucleotide sequences of the 3 region of cagA [8]. Individuals infected with east Asian-type cagA strains reportedly have an increased risk of peptic ulcer or gastric cancer compared with individuals with Western-type cagA strains [12]. Nearly all H. pylori strains in Japan possess east Asian cagA [13,14]; therefore, it is difficult to explain the outcomes based on the cagA genotype in Japan. However, interestingly, we found a relatively low rate (71.4%) of east Asian-type cagA strains in Okinawa compared with other parts of Japan [15]. Okinawa consists of small islands (2276 km²) in southwestern Japan, where the incidence of gastric cancer is the lowest in Japan. In Okinawa, Western-type cagA
cagA-negative strains were found to be 16 and 13.6%, respectively. Furthermore, we found that virulence factors such as east Asian-type cagA and vacA s1m1 were significantly associated with severe gastroduodenal diseases. Okinawa remained under the rule of the USA after World War II until 1972. Thus, Western-type cagA and cagA-negative strains may have spread horizontally from US populations living in Okinawa. However, the Western-type cagA sequence in Okinawa was different from that of the typical Western-type cagA present in Western countries [15,16]. This type has recently been named J-Western type cagA. We also reported that 12-base pair (bp) insertions in the cagA are specifically found in the J-Western cagA sequence compared with the typical Western cagA sequence [17]. Therefore, it is probable that these strains were not derived from the US populations after World War II. We also found specific EPIYA-like motifs (ESIYA and ESIYT) in the C-terminal region of CagA in strains isolated in Okinawa [15,18]. Interestingly, ESIYT sequences were also found in Amerindal strains [19]. Additionally, the CagA multimerization sequence was also similar to that in Amerindal and Okinawan strains [15,19]. These findings suggest that these strains share the same ancestry.

Duodenal ulcer-promoting (dupA) gene is the first genetic factor of H. pylori to be associated with a differential susceptibility to duodenal ulcer and gastric cancer, and thus, it can be considered as a disease-specific virulence marker even in Japan and Korea [20]. The prevalence of dupA was significantly higher in strains from patients with duodenal ulcer and lower in patients with gastric cancer, regardless of the patients’ nationality (Japan, Korea and Colombia; 42 vs 9% on average [20]). In a recent review, the prevalence of dupA in patients with gastritis worldwide was stated as 44.8% and differed significantly between nationalities and ethnicities [21]. An association between dupA status and disease development can be observed in mostly Asian countries. Our meta-analysis also showed that infection with the dupA-positive H. pylori increased the risk for duodenal ulcer (OR: 1.41; 95% CI: 1.12–1.76), particularly in Asian countries (OR: 1.57; 95% CI: 1.19–2.06), but not in Western countries (OR: 1.09; 95% CI: 0.73–1.62 [22]). Additionally, the presence of dupA was reported to be significantly associated with eradication failure [23]. A recent study revealed the importance of the length of dupA. Full sequence data revealed two types of dupA differing in length depending on the presence of approximately 600 bp in the putative 5’ region (long type and short type), which was not taken into account in previous studies. We found that intact long-type dupA (long type without frameshift mutation) is a virulence marker for severe gastroduodenal diseases in Okinawa [24].

Whole-genome analyses are also useful for investigating genetic factors related to differences in virulence among strains. Kawai et al. investigated the evolution of east Asian strains using 20 whole genomes of Japanese, Korean, Amerindian, European and west African strains [25]. Phylogenetic analysis revealed a greater divergence between east Asian and the European strain genomes in proteins related to host interaction, specifically virulence factors, outer membrane proteins and lipopolysaccharide synthesis enzymes. Next-generation sequencers, which can read DNA sequences in less time and at lower costs than Sanger sequencing, enabled efficient investigation of not only the evolution of H. pylori, but also novel virulence factors and genomic changes related to drug resistance.

**Management of H. pylori in Japan**

Peptic ulcer was the only ‘approved’ indication for H. pylori eradication therapy until 2009 in Japan. In June 2010, H. pylori eradication therapy for idiopathic thrombocytopenic purpura, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and early gastric cancer after endoscopic resection were approved by the Japanese health insurance system based on sufficient evidence.
Early, gastric cancer after endoscopic resection was approved by the Japanese health insurance system based on the results of a large-scale multicenter study (Japan Gast Study Group) in Japan published in 2008 [26]. This study clearly showed that successful treatment of *H. pylori* infection led to a decrease in gastric cancer development. This indicates that even in the background gastric mucosa of patients with gastric cancer, subsequent development of gastric cancer can be significantly suppressed by curing *H. pylori* infection, confirming the importance of carefully managing *H. pylori*-related gastritis. A recent systematic review showed that *H. pylori* eradication therapy statistically diminished the prevalence of clinical gastric cancer by approximately a third, in Japan [27]. Theoretically, eradicating all *H. pylori* infections will prevent approximately 150,000 deaths from gastric cancer over the next 5 years [28]. Because of the low prevalence of atrophic gastritis in persons below 40 years of age, *H. pylori* eradication therapy alone would result in nearly 100% prevention of development of gastric cancer in this age group [28]. However, a risk of gastric cancer exists even after curing the *H. pylori* infection. Take *et al.* followed 1674 patients who received *H. pylori* eradication therapy for up to 14.1 years (mean, 5.6 years [29]). The risk of developing gastric cancer in patients cured of *H. pylori* infection was 0.3% per year. The longest interval between *H. pylori* eradication and the occurrence of cancer was 13.7 years. Thus, follow-up endoscopic examination for more than 10 years is necessary even after curing *H. pylori* infection. The excellent long-term outcome of gastric MALT lymphoma after successful eradication therapy was also confirmed in a large-scale multicenter study [30].

Guidelines for *H. pylori* management published by the Japanese Society for Helicobacter Research (JSHR) were revised dramatically in January 2009 [31]. Although only a small fraction of individuals develop *H. pylori*-related diseases, the infection persists for a long period of time in most infected patients without spontaneous disappearance. Therefore, infected patients are at a high risk of developing *H. pylori*-related diseases, particularly gastric cancer. Additionally, successful eradication therapy induced a significant improvement of histological inflammation, activity and atrophy in 10-year prospective follow-up studies [32,33]. Thus, the JSHR concluded that all ‘*H. pylori* infection’ was considered to be an indication for eradication, irrespective of background diseases. However, eradication therapy for only four diseases, including peptic ulcer, idiopathic thrombocytopenic purpura, gastric MALT lymphoma and early gastric cancer after endoscopic resection is approved by the Japanese health insurance system as described above. It is necessary to eliminate *H. pylori* as soon as possible so that the Japanese national health insurance system can approve *H. pylori* eradication for all *H. pylori* infections.

The first-line therapy approved by the Japanese health insurance system is clarithromycin (CAM)-based triple therapy. Four proton pump inhibitors (PPIs) including lansoprazol, omeprazole, rabeprazole and esomeprazole. Triple therapy including LPZ, amoxicillin (AMPC) and CAM can be used as a one-sheet tablet prepared by the Takeda Pharmaceutical Company Ltd (Osaka, Japan). Although *H. pylori* eradication therapy was approved for only four diseases, the successful eradication rate is decreasing in Japan. CAM-resistant *H. pylori* is the main cause of unsuccessful eradication therapy in Japan [31]. The increase in CAM usage in pediatrics, respiratory and otorhinolaryngology practice is considered to be the cause. Annual surveillance conducted between 2002 and 2006 for 5 years showed that the mean nationwide CAM resistance rates had increased from 18.9 (2002) to 27.2% (2006 [34]). A large-scale, nationwide, multicenter prospective study conducted between 2007 and 2009 showed a successful eradication rate of 80.7% when AMPC + CAM + RPZ was used as a first-line eradication regimen [35].

When *H. pylori* eradication fails in patients undergoing CAM-based triple therapy, metronidazole (MNZ)-based triple therapy can be used as a second-line eradication regimen.
This second-line therapy was reported to be highly successful with an eradication rate of more than 90% [36–39]. Using the MNZ breakpoint of 8 µg/ml established by the European Study Group, resistance rates did not change from 2002 to 2003 and 2004 to 2005 (4.9 and 3.3%, respectively [34]). However, the resistance of anerobic bacteria and H. pylori to this therapy may also increase; thus, surveillance is important. It is necessary to investigate acceptable third-line eradication useful in the Japanese population as soon as possible. The guidelines state third-line eradication includes PPI + AMPC + fluoroquinolone or PPI + high-dose AMPC. However, sufficient evidence for the usefulness of these therapies has not been provided. We previously reported that the resistance rate for levofloxacin was 39%, whereas the minimum inhibitory concentration of sitafloxacin (STFX) was ≤1 µg/ml for all strains in Japan [40]. We observed superior antibacterial activity in vitro of STFX against H. pylori compared with that of levofloxacin and garenoxacin, even in the presence of mutations in gyrA [40]. Recent studies showed that STFX-based therapy was effective in approximately 80% of the patients, although the number of patients involved in the study was small [41,42]. Furthermore, the rate of successful eradication using STFX-based therapy was 74%, even for the strains containing a mutation in gyrA [42]. These findings show that STFX-based therapy should be used as third-line therapy. Additionally, there is recent interest in the use of a 10-day sequential therapy, which includes 5 days of treatment with a PPI and one antibiotic (typically, amoxicillin), followed by 5-day treatment with the PPI and two other antibiotics (typically, CAM and MNZ or tinidazole [43–46]). Although no clinical trials have examined sequential therapy in Japan, one case report has been published [47].

As mentioned above, most infections cannot be eradicated when the patients does not have one of the four diseases approved by the Japanese health insurance system. However, these patients hope to receive H. pylori eradication therapy. Therefore, some institutions have built a special clinic for the diagnosis and therapy for H. pylori, where the infection can be eradicated without the intervention of Japanese national health insurance system. In many cases, the physicians certified by JSHR treat these persons there. If all infected persons are cured, the development of many peptic ulcers and gastric cancers can be controlled in Japan. However, the risk of gastric cancer exists even after curing H. pylori infection. Additionally, informed consent should be provided to explain the side effects to these patients because eradication therapy has not been approved by Japanese health insurance system for this group of infected individuals. Follow-up endoscopic examination for more than 10 years is necessary even after curing the H. pylori infection.

**Expert commentary**

In Japan, the rate of prevalence of CAM-resistant strains is high, but bismuth-containing drugs are not available because bismuth, currently used for eradication therapy in other countries, has not been approved for use in Japan. Only CAM-based triple therapy has been approved as a first-line therapy by the Japanese national health insurance system. After failure of first-line therapy, MNZ-based triple therapy can be used as a second-line therapy. Sequential therapy is not common in Japan due to the long period of treatment, even if sequential therapy shows a high successful eradication rate. Many Japanese physicians currently prescribe CAM-based triple therapy according to the national health insurance system, even though they know that this regimen is not effective in areas with high prevalence of CAM-resistant strains. Recently, a second- generation PPI (esomeprazole) was approved for use in Japan [48]. Several studies have demonstrated the advantages of esomeprazole-based therapy compared with other PPIs in other countries [48]. It remains unclear whether CAM-based triple therapy containing esomeprazole is effective for CAM-resistant strains in Japan. Esomeprazole is a potent acid inhibitor; therefore, we hope CAM-based triple therapy containing esomeprazole is effective and can be used in the future in
Japan. The rate of prevalence of CAM-resistant strains is gradually increasing. It is necessary to eliminate *H. pylori* as soon as possible if the Japanese national health insurance system can approve *H. pylori* eradication for all ‘*H. pylori* infection’.

**Five-year view**

The issues considered important for the management of *H. pylori* infection in Japan over the next 5 years are discussed below.

- Continuous surveillance of *H. pylori* infection rate;
- Identification of factor(s) that can predict the effectiveness of eradication therapy against gastric MALT lymphoma, idiopathic thrombocytopenic purpura and early gastric cancer after endoscopic resection;
- Evaluation of the effectiveness of CAM-based triple therapy containing esomeprazole as first-line eradication therapy;
- Continuous investigation of the resistance rate to CAM and/or MNZ and collection of evidence of the effectiveness of the third-line eradication therapy;
- Extending drugs can be applied using the Japanese national health insurance system.

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**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


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Key issues

- The *Helicobacter pylori* infection rate in Japan is gradually decreasing.
- Although nearly all *H. pylori* strains possess most virulence factors in Japan, *cagA* was significantly associated with severe gastroduodenal diseases in Okinawa where the incidence of gastric cancer is the lowest in Japan.
- Eradication therapy for peptic ulcer, idiopathic thrombocytopenic purpura, gastric mucosa-associated lymphoid tissue lymphoma and early gastric cancer after endoscopic resection have been approved by the Japanese health insurance system.
- Guidelines for *H. pylori* management by the Japanese Society for Helicobacter Research in 2009 concluded that all ‘*H. pylori* infection’ was considered as an indication for eradication, irrespective of background diseases, although only a minority of infected persons have clinical outcomes accepted for *H. pylori* eradication therapy by the Japanese health insurance system.
- Gastric cancer can develop even after curing *H. pylori* infection.
- The increase in the clarithromycin-resistant *H. pylori* has caused a decline in the successful rate of the first-line eradication. The success of eradication therapy can be ensured by using metronidazole rather than clarithromycin for patients failing to respond to first-line eradication therapy.
Figure 1.
Prevalence of *Helicobacter pylori* infection in Japan.