Helicobacter

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Guidelines for the Management of *Helicobacter pylori* Infection in Japan: 2009 Revised Edition

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Abstract

Background: Over the past few years, the profile of *Helicobacter pylori* infection has changed in Japan. In particular, the relationship between *H. pylori* and gastric cancer has been demonstrated more clearly. Accordingly, the committee of the Japanese Society for Helicobacter Research has revised the guidelines for diagnosis and treatment of *H. pylori* infection in Japan.

Materials and Methods: Four meetings of guidelines preparation committee were held from July 2007 to December 2008. In the new guidelines, recommendations for treatment have been classified into five grades according to the Minds Recommendation Grades, while the level of evidence has been classified into six grades. The Japanese national health insurance system was not taken into consideration when preparing these guidelines.

Results: *Helicobacter pylori* eradication therapy achieved a Grade A recommendation, being useful for the treatment of gastric or duodenal ulcer, for the treatment and prevention of *H. pylori*-associated diseases such as gastric cancer, and for inhibiting the spread of *H. pylori* infection. Levels of evidence were determined for each disease associated with *H. pylori* infection. For the diagnosis of *H. pylori* infection, measurement of *H. pylori* antigen in the feces was added to the tests not requiring biopsy. One week of proton-pump inhibitor-based triple therapy (including amoxicillin and metronidazole) was recommended as second-line therapy after failure of first-line eradication therapy.

Conclusion: The revised Japanese guidelines for *H. pylori* are based on scientific evidence and avoid the administrative restraints that applied to earlier versions.

The Japanese Society for *Helicobacter* Research first published ''Guidelines for the Management of *Helicobacter pylori* (*H. pylori*) Infection in Japan'' in 2000 [1]. At that time, the guidelines included the information needed for routine medical management because approval for diagnosis and treatment of *H. pylori* infection under the Japanese national health insurance system was expected to be granted soon. As it was necessary to maintain consistency with the Japanese national health insurance system as well as with a high level of evidence, a final consensus was only established after lively discussion at a number of meetings. For this reason, these guidelines were rather conservative with respect to the indications, diagnosis, and treatment of *H. pylori* compared with guidelines published in Europe and the USA. However, the Japanese Ministry of Health and Welfare attached greater importance to these guidelines than we had expected, and made great endeavors to obtain approval for *H. pylori* treatment to be covered by the national health insurance system. The dose of clarithromycin was set at 400 or 800 mg according to the results of Japanese clinical studies, and

not at the international standard dose of 800 or 1000 mg. It is unusual for the results of a Japanese clinical study to influence the authorities, as local studies have not been rated highly.

In April 2002, another proton-pump inhibitor (PPI) was approved for coverage by the national health insurance system, making it necessary to revise the *H. pylori* eradication therapy protocol. In the addition, a test for *H. pylori* antigen in feces that was commonly used in Western countries became available in Japan. Therefore, the guideline preparation committee held another meeting after an interval of 2 years. In addition to making some changes to the recommendations for diagnosis and treatment, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric/duodenal ulcer were added as new indications for eradication therapy. In addition to early gastric cancer after endoscopic mucosal resection, atrophic gastritis, and hyperplastic gastric polyps were included in the list of diseases for which *H. pylori* eradication was recommended. Thus, the 2003 revised guidelines described indications for the diagnosis and treatment of *H. pylori* infection that were superior to the initial guidelines designed in conformity with the Japanese national health insurance scheme.

Five years have passed since the revised guidelines were published, and further revision is needed because metronidazole has become available as a second-line agent for eradication therapy, the relation between *H. pylori* and gastric cancer has been demonstrated more clearly, and the relation of *H. pylori* with various extragastric diseases has been demonstrated. The guideline preparation committee was convened in June 2007 at a meeting of the Japanese Society for *Helicobacter* Research. A consensus was established at that meeting to prepare fresh guidelines based on scientific evidence that were free from administrative restraints. Additional indications were the chief issue when preparing the revised guidelines, and the committee decided to investigate additional indications according to data on evidence-based medicine obtained in Japan.

In a large-scale multicenter Japanese study, patients who had received endoscopic treatment for early gastric cancer were randomized to *H. pylori* eradication and non-eradication groups for investigation of metachronous recurrence after 3 years, and it was demonstrated that metachronous recurrence was markedly inhibited in the eradication group [2]. These findings provided a definite answer about whether *H. pylori* eradication can inhibit the development of gastric cancer. In the newly revised guidelines, addition of *H. pylori* infection as an indication for eradication was unanimously accepted.

It is problematic that the treatment recommended by the guidelines cannot always be provided under the Japanese national health insurance system. However, the Society decided to include the latest standard therapy in the guidelines, even if it is more difficult to utilize in routine medical practice. We feel confident that these improved guidelines are suitable for Japanese patients and are useful for the conscientious management of *H. pylori* infection.

Grading of Recommendations and Levels of Evidence

In these guidelines, the recommendations for treatment are classified into five grades from Level A (highest) to Level D (lowest) according to the Minds Recommendation Grades (Table 1). These grades are based on the level of evidence, the amount of evidence, the results of treatment, clinical efficacy, feasibility (physician's skills, regional availability, medical resources, and health insurance system), evidence of harm, and cost. The presence or absence of coverage by the Japanese national health insurance system was not taken into consideration when setting the recommendations for these guidelines. The level of evidence for each recommendation was classified from Level I to Level VI (Table 2). If there were multiple items of evidence with different levels, the evidence of higher quality was accepted.

Table 1 Minds recommendation grades

Level	Type of recommendation
A	Strongly recommended based on strong evidence
B	Recommended based on evidence
C1	May be under evaluation although there is no evidence
C2	Not recommended because there is no evidence
D	Not recommended because there is evidence showing ineffectiveness or harm

Table 2 Classification of the levels of evidence

Level	Type of evidence
I	Systematic review/meta-analysis
II	At least one randomized controlled clinical trial
III	Non-randomized controlled clinical studies
IVa	Analytical epidemiologic study (cohort study)
IVb	Analytical epidemiologic study (case–control study, cross-sectional study)
V	Descriptive study (Case report or case series)
VI	Opinion of an expert committee or individual specialist, not based on patient data

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Indications

Indications for *H. pylori* Eradication Therapy

***Helicobacter pylori* infection (Recommendation grade A)**

Helicobacter pylori eradication is not only useful for the treatment of gastric/duodenal ulcer, but also for the treatment and prevention of *H. pylori*-associated diseases such as gastric cancer, as well as for inhibiting the spread of this infection.

When the gastric mucosa is infected with *H. pylori*, gastritis occurs [3–5]. *Helicobacter pylori* infection often persists throughout life, and can lead to various upper gastrointestinal tract diseases, such as atrophic gastritis, gastric/duodenal ulcer, gastric cancer, gastric MALT lymphoma, and hyperplastic gastric polyps [6–16]. In addition, *H. pylori* infection influences gastric function, including gastric acid secretion, and alters the intragastric environment [17,18]. An association between *H. pylori* infection and some diseases occurring outside the gastrointestinal tract, such as idiopathic thrombocytopenic purpura (ITP) and iron-deficiency anemia, has also been indicated [19,20]. It is known that approximately half the population of Japan is infected with *H. pylori* [21,22]. Although not all infected people have the above-mentioned diseases, they form a high-risk population for such complications. Successful eradication of *H. pylori* improves histologic gastritis and may prevent various diseases associated with *H. pylori* infection, such as gastric/duodenal ulcer and gastric cancer [2,23,24]. Accordingly, persons without any of these diseases may undergo eradication therapy on a preventive basis. In the 2003 edition of ICD-10 (International Statistical Classification of Diseases and Related Health Problems), *H. pylori* infection was approved as a disease name. When *H. pylori* infection is accepted as a disease unit by the Japanese national health scheme and diagnosis/treatment of *H. pylori*-related diseases can be performed in routine medical practice, it is possible that such therapy will contribute to the treatment and prevention of various diseases, including the prevention of gastric cancer (which is still a major problem in Japan). Moreover, *H. pylori* eradication therapy is necessary to prevent the spread of this infection, and may lead to reduction of medical costs in the future. As failure of eradication due to drug resistance may occur or treatment may have to be discontinued due to adverse reactions, providing a careful explanation about this therapy to patients and obtain their informed consent are required before starting *H. pylori* eradication therapy.

Evidence for Each Indicated Disease

Gastric/duodenal ulcer (Evidence level 1)

Helicobacter pylori eradication prevents the recurrence of gastric/duodenal ulcers unrelated to nonsteroidal anti-inflammatory agents (NSAIDs), and can improve ulceration.

High-level evidence obtained in Japan and overseas, including several meta-analyses, indicates that *H. pylori* eradication therapy inhibits the recurrence of *H. pylori*-positive gastric/duodenal ulcer and decreases complications such as bleeding [25–30]. In statistical studies, *H. pylori* eradication therapy inhibits recurrence and improves medical economy compared with conventional therapy [31–33]. Therefore, it is a consensus among international guidelines (including the Japanese guidelines) that unless a patient is allergic to any of the drugs for eradication therapy or has complications that could interfere with eradication, such therapy should be the first-line treatment for *H. pylori*-positive peptic ulcer [1,34–40]. Because gastric and duodenal ulcers tend to recur after treatment, eradication therapy should be performed even in *H. pylori*-positive patients with healed ulcers to achieve withdrawal from anti-ulcer medications. Care should be taken with eradication therapy in the elderly and children from the standpoint of safety, although it has been suggested that there are no major safety problems for the elderly [41]. The guidelines for children require dose reduction based on body weight and care with respect to the timing of eradication [42–44]. Care should also be taken when eradication therapy is performed in patients with systemic complications such as severe hepatic disease or renal dysfunction, and the indications and dosage should be considered for each case. In patients with renal failure, a high eradication rate was reported after triple therapy at the usual dose [45], but another study showed that PPI + clarithromycin + metronidazole therapy achieved a higher eradication rate compared with PPI + amoxicillin (1.5 g/day) + clarithromycin therapy and was also safer with a low risk of acute renal failure [46]. In patients on dialysis, it has been reported that sufficient efficacy was obtained by triple therapy with half the usual dose of amoxicillin (750 mg/day) [47]. Therefore, when triple therapy is given to patients with renal failure, a lower dose of amoxicillin may be effective or amoxicillin may be omitted depending on the circumstances. In patients with cirrhosis, it was reported that *H. pylori* infection increases the risk of peptic ulcer [48]. Accordingly, eradication therapy is performed in patients with cirrhosis, but the need for dose adjustment remains unclear. It was also reported that in patients with cirrhosis, the rate of ulcer

recurrence was not decreased after successful *H. pylori* eradication [49]. Thus, it should be remembered before performing eradication therapy that ulcer recurrence cannot be prevented by *H. pylori* eradication alone.

In patients who are scheduled to start long-term treatment with NSAIDs pretreatment *H. pylori* eradication was reported to decrease the risk of ulcer [50–54]. However, there have also reports that there is no decrease of ulcer risk after *H. pylori* eradication in patients taking NSAIDs [54,55], and that ulcer healing is actually delayed [56], so eradication therapy is not always recommended for patients taking NSAIDs. In *H. pylori*-positive patients who are scheduled to start low-dose aspirin therapy, pretreatment *H. pylori* eradication decreases the risk of peptic ulcer bleeding [53], but the effect is weaker than that of PPIs and eradication therapy alone is insufficient for high-risk patients [57].

As described above, *H. pylori* eradication therapy can decrease the risk of peptic ulcer or bleeding associated with NSAIDs or low-dose aspirin, but the effect is limited [54,55,57]. To minimize the risk of ulcers or bleeding associated with these drugs, it is necessary to take preventive measures such as inhibition of acid secretion by PPI therapy after *H. pylori* eradication, at least in high-risk patients [58].

Gastric MALT lymphoma (Evidence level III)

Helicobacter pylori eradication produces histologic and endoscopic improvement, as well as regression of lymphoma.

Helicobacter pylori eradication leads to histologic and endoscopic improvement, as well as regression of MALT lymphoma, in 60–80% of *H. pylori*-positive patients with gastric MALT lymphoma [15,16,59]. Therefore, *H. pylori* eradication therapy should be the treatment of first choice. In Japan, a large-scale multicenter clinical study of *H. pylori* eradication therapy for gastric MALT lymphoma has been completed [60], while a large-scale clinical study of *H. pylori* eradication therapy combined with radiation therapy for ineffective cases is still underway [61]. Due to the low frequency and the nature of this disease, it is difficult to perform placebo-controlled randomized trials, so a clinical study that could provide high-level evidence has not been conducted. However, *H. pylori* eradication is also a first-line treatment for gastric MALT lymphoma according to overseas guidelines. As predictors of the efficacy of eradication therapy, the endoscopic findings, depth of invasion, chimeric transcript analysis [62–64], and genetic aberrations have been investigated. In the Japanese multicenter clinical study, predictors of the efficacy of eradication therapy were the presence/absence of *H. pylori* infection, the clinical stage, the depth of invasion, and the AP12MALT1 chimeric transcript [60]. However, involvement of other genetic aberrations has been reported [65–69], so their evaluation is still needed. Accordingly, it is recommended that histopathologic diagnosis (including immunohistochemistry), endoscopic diagnosis (including endoscopic ultrasound), and genetic analysis should all be conducted whenever possible. For patients in whom *H. pylori* eradication therapy is ineffective, radiation therapy [61–70], chemotherapy, or rituximab [71] is indicated. In the ongoing large-scale clinical study of *H. pylori* eradication combined with radiotherapy for ineffective cases, almost all patients have responded to combination therapy. There is some concern about the late toxicity of chemotherapy, so evaluation of the long-term prognosis is needed. The outcome of *H. pylori* eradication has already been reported after 6 years or longer [72–75], but further follow-up and evaluation is required.

Idiopathic thrombocytopenic purpura (Evidence level I)

In Japan, the platelet count is increased by eradication therapy in approximately 50% of *H. pylori*-positive patients with ITP.

Idiopathic thrombocytopenic purpura is an acquired blood disease that features a low platelet count, and approximately 30,000 patients are known to have chronic ITP in Japan. Patients with chronic ITP have autoantibodies (particularly directed against platelet glycoprotein IIb/IIIa or Ib/IV) [76], and excessive destruction of platelets by the reticuloendothelial system due to B- and T-cell activation by the immune response to these autoantibodies is considered to be the mechanism of thrombocytopenia [77,78].

To inhibit autoantibody production, corticosteroids, immunoglobulin therapy, splenectomy, and immunosuppressants are the standard treatments [79]. As the first report by Gasbarrini et al. [80], a number of authors have indicated that *H. pylori* eradication therapy is effective for *H. pylori*-positive patients with chronic ITP, but most of these reports have been from a few countries (Japan, Italy, and Spain) [80–92]. According to the six reports on 50 or more patients [81,85,86,89–92], an increase of the platelet count was observed in 40–60% of *H. pylori*-positive ITP patients after eradication therapy. Positivity for *H. pylori* is necessary before *H. pylori* eradication will promote hematologic remission [86,87], because an increase of the platelet count is not found after *H. pylori* eradication therapy in *H. pylori*-negative patients and platelets do not increase after failed eradication [93]. A meta-analysis of 17 studies revealed

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a significant increase of the platelet count after *H. pylori* eradication therapy [19]. Concerning the long-term prognosis after *H. pylori* eradication, there have been reports that improvement of the platelet count is maintained in patients with an increase due to eradication therapy [83,84,88,90,94]. In contrast, some reports from the USA, Spain, and France have suggested a low efficacy of eradication therapy, so further analysis of the contribution of cellular factors and host factors is needed [87,95–109]. Because *H. pylori* eradication therapy is not always effective, identification of factors predicting the response to eradication is needed to improve the results of treatment.

Considering the adverse reactions associated with long-term corticosteroid therapy, the cost and short-term effect of high-dose immunoglobulin treatment, and the risk of bleeding/postoperative infection associated with splenectomy, *H. pylori* eradication therapy should be the treatment of first choice for *H. pylori*-positive patients with chronic ITP (at least in Japan).

Patients after endoscopic treatment of early gastric cancer (Evidence level II)

Evidence for the prevention of metachronous gastric cancer has been established in Japan, and this is an indication for eradication therapy. Periodical follow-up after eradication is required.

It has been reported that *H. pylori* eradication from the residual gastric mucosa after endoscopic treatment of early gastric cancer has an inhibitory effect on the occurrence of metachronous gastric cancer [110,111], and eradication is recommended by various guidelines, including some from Western countries. As this report was not based on a randomized controlled study, a multicenter randomized clinical trial was subsequently conducted in Japan that demonstrated an inhibitory effect of eradication therapy on metachronous gastric cancer [2]. Because this evidence was obtained in Japan, *H. pylori* eradication is strongly recommended for patients with gastric cancer.

However, the residual gastric mucosa after endoscopic treatment of early gastric cancer has a high risk of undergoing transformation, so metachronous gastric cancer should be followed up carefully during and/or after eradication therapy.

Atrophic gastritis (Evidence level I)

Improvement of gastric mucosal atrophy, inhibition of the progression of intestinal metaplasia, and a preventive effect on gastric cancer are expected, so eradication therapy is strongly recommended.

In Japan, the majority of cases of atrophic gastritis are related to *H. pylori* [112]. *Helicobacter pylori* eradication therapy obviously improves histologic gastritis, but there are conflicting opinions about the reversibility of gastric mucosal atrophy (a characteristic feature of atrophic gastritis) and intestinal metaplasia after eradication therapy. Based on the latest results, however, this conflict has largely been resolved

Improvement of gastric mucosal atrophy by H. pylori *eradication*

In various small-scale observational studies, definite improvement of atrophy by eradication was not observed by some authors [113–115], whereas significant improvement was observed by others [116–118]. In a Japanese cohort study and an overseas randomized controlled study, consensus was reached that ''progression of gastric mucosal atrophy is inhibited by eradication'' or ''gastric mucosal atrophy is improved by eradication'' [119–124]. In addition, the interim findings of a large-scale clinical study in Japan have revealed improvement of the histologic atrophy score [125]. According to the meta-analysis of Rokkas et al. based on the literature up to 2006 [126], gastric mucosal atrophy is improved in the antrum and body by *H. pylori* eradication therapy. As indicated above, eradication of *H. pylori* improves histologic gastric mucosal atrophy.

Improvement of intestinal metaplasia by eradication therapy

An observational study and a cohort study did not reveal definite improvement of intestinal metaplasia after *H. pylori* eradication therapy [113,114], whereas progression was inhibited according to other authors [118,121] and improvement was observed in some studies [116–119]. Thus, the findings have differed so far. An overseas randomized controlled study [121,127] showed that progression of intestinal metaplasia is inhibited by eradication of *H. pylori*, while the interim report on a large-scale Japanese clinical study [125] revealed significant improvement of the intestinal metaplasia score. According to the meta-analysis of Rokkas et al. based on the literature up to 2006 [126], improvement of intestinal metaplasia is observed after eradication therapy, but this improvement is not significant. Thus, inhibition of the progression of intestinal metaplasia is observed after eradication of *H. pylori*, but improvement was not observed in some studies although significant improvement was observed in others. Accordingly, further investigation of the influence of *H. pylori* subtypes is required.

Prevention of gastric cancer by H. pylori *eradication in patients with atrophic gastritis*

Prospective Japanese cohort studies [12,128,129] have demonstrated that patients with atrophic gastritis secondary to *H. pylori* infection are a high-risk group for gastric cancer, and have suggested that development of gastric cancer could be inhibited by eradicating *H. pylori* to improve gastritis [130–132]. In addition, a randomized controlled study of patients with chronic atrophic gastritis who underwent endoscopic resection of early gastric cancer confirmed the inhibitory effect of *H. pylori* eradication on the development of new gastric cancer [2].

The usefulness of *H. pylori* eradication therapy for patients with atrophic gastritis is based on improvement of gastric mucosal atrophy, inhibition of the progression of intestinal metaplasia, and prevention of the development of gastric cancer, so eradication therapy is strongly recommended for atrophic gastritis.

Gastric hyperplastic polyps (Evidence level II)

Disappearance or regression of hyperplastic gastric polyps is expected to occur after eradication of *H. pylori*.

Disappearance and/or regression of hyperplastic gastric polyps have been reported after eradication of *H. pylori* [13,133–137]; regression occurred in 70% of patients from a randomized intervention study [13,133]. Eradication therapy is recommended for patients with multiple hyperplastic polyps, but endoscopic polypectomy should be considered for large polyps.

In contrast, the rate of *H. pylori* infection is low in patients with fundic gland polyps [138], and eradication therapy is not useful. In fact, the development of fundic gland polyps has been reported after eradication [139].

Functional dyspepsia (Evidence level I)

Eradication of *H. pylori* is effective for the improvement of symptoms in some patients with functional dyspepsia.

The diagnostic standard for functional dyspepsia is the Rome III classification [140]. Functional dyspepsia is defined as the persistence for at least 3 months during follow up of one or more symptoms centered around the epigastric region that started at least 6 months before presentation, with the absence of any organic disease that can explain the symptoms.

Histamine receptor antagonists, PPIs, gastric prokinetic agents, and antidepressants are all used for the treatment of this condition [140,141]. Concerning the value of *H. pylori* eradication therapy for functional dyspepsia, both clinical efficacy and economic benefit have been reported [14,142–144], but opposing results have also been obtained [145–151], and differing outcomes have even been found in the Japanese studies [148–151]. However, significant efficacy has been shown by a number of meta-analyses [39,152–154] and eradication was recommended in the Mastricht III Consensus report [38], so eradication therapy is strongly recommended for patients with *H. pylori* positive functional dyspepsia. However, further investigation will be required to determine the actual value of eradication therapy for Japanese patients.

Reflux esophagitis (Evidence level II)

As an increase in the incidence and symptoms of reflux esophagitis rarely occurs after eradication of *H. pylori*, the presence of reflux esophagitis is not an impediment to performing eradication therapy.

The *H. pylori* infection rate is generally low in patients with reflux esophagitis, treatment of which is based on inhibition of acid secretion. For this purpose, long-term continuous PPI therapy is frequently prescribed. However, as reported by Kuipers et al. [155], it has become a concern that long-term PPI therapy may aggravate gastritis and induce the progression of gastric mucosal atrophy in *H. pylori*-positive patients. For this reason, whether or not *H. pylori* should be eradicated in patients with reflux esophagitis who are on long-term PPI therapy has been discussed. However, the validity of the results reported by Kuipers et al. has been questioned because surgical patients were included in the control group, and objections to the conclusions have been published [156]. A study comparing patients with or without *H. pylori* eradication on long-term PPI therapy showed that progression of atrophy did not occur after 1 year of observation [157]. Also, another study conducted by Kuipers et al. to investigate the progression of gastric mucosal atrophy in patients on long-term PPI therapy under stricter conditions found no difference in the progression of atrophy or intestinal metaplasia between patients with or without eradication after at least 2 years [158]. This study showed that inflammation was alleviated and atrophy of gastric body mucosa was improved in the eradicated group, while inflammatory cell invasion of the gastric mucosa persisted in the non-eradicated group, suggesting the possibility that progression of atrophy and development of gastric cancer could occur over a longer period. Therefore, the Maastricht III consensus report recommends testing for *H. pylori* infection before starting long-term

maintenance PPI therapy for reflux esophagitis, and suggests that eradication therapy should be considered for *H. pylori*-positive patients. However, it has been reported that routine testing for *H. pylori* infection is not necessary in patients other than those described above [38]. According to this guideline, as described in the opening section on *H. pylori* infection, eradication therapy is recommended, even in patients with reflux esophagitis. These recommendations were made after concern about a possible increase in the incidence of reflux esophagitis following eradication of *H. pylori* [159] was alleviated by several reports from Western countries [160–162], and because an increase of the PPI dose after eradication was also excluded [158]. Nevertheless, in the Maastricht III consensus report, the above recommendation is restricted to Western countries. This may have been decided in consideration of Japanese and Chinese reports about increased acid secretion after *H. pylori* eradication, leading to a higher incidence of reflux esophagitis and a higher failure rate of low-dose PPI maintenance therapy [163–166].

In Japan, it has been reported that acid secretion increases after *H. pylori* eradication, with temporary appearance or aggravation of reflux esophagitis, or an increase in its incidence [162,164,166]. In contrast, there have been reports that reflux esophagitis does not increase after *H. pylori* eradication in patients with peptic ulcer [167], or that esophagitis is improved in patients with reflux esophagitis and duodenal ulcer [168], suggesting that reflux esophagitis may actually be inhibited by *H. pylori* eradication therapy depending on the underlying pathology. In either event, although the incidence of reflux esophagitis increases somewhat after successful eradication *H. pylori* in Japan [166], it remains similar to that in persons without *H. pylori* infection [169]. When long-term observation of patients with reflux esophagitis is performed following *H. pylori* eradication, most of them remain in grade A or B of the Los Angeles Classification and their symptoms may not become more severe [169]. In patients with peptic ulcer, *H. pylori* eradication is still cost-effective, even allowing for the cost of treating reflux esophagitis [32], so an increased incidence of reflux esophagitis may not be an impediment to performing eradication therapy. In Japan, there have been reports about a high incidence of reflux esophagitis in patients with corpus gastritis or hiatus hernia [167,169], so it is necessary to explain these issues to patients before eradication therapy is performed.

The guidelines released by the American College of Gastroenterology do not discuss the progression of atrophy, but it is mentioned that reflux esophagitis is not an indication for diagnosis and treatment of *H. pylori* because the effect of *H. pylori* eradication therapy on reflux esophagitis (aggravation or improvement) is unclear [39].

Diseases outside the gastrointestinal tract (excluding ITP)

The efficacy of *H. pylori* eradication for iron-deficiency anemia and chronic urticaria has not been reported.

The relationship of *H. pylori* infection to various diseases has been reported, and the effect of *H. pylori* eradication therapy has been reported for the following diseases. Data on idiopathic Parkinson's disease have only been reported from one institution, so further investigation is required.

Iron-deficiency anemia (Evidence level III)

Improvement of iron-deficiency anemia has been reported in children (≤18 years old) after eradication of *H. pylori* [20,170–172]. Although the evidence is not sufficient, eradication therapy may be considered for the treatment of iron-deficiency anemia, but further investigation is required because of the small number of reports.

Chronic urticaria (Evidence level III)

Improvement and remission of skin symptoms has been reported in patients with chronic urticaria after eradication of *H. pylori* [173–176], but further investigation is required because of the small number of Japanese reports. Accordingly, further investigation is needed to determine the role of *H. pylori* eradication therapy in the treatment of chronic urticaria.

Diagnosis

Diagnosis of *H. pylori* Infection and Assessment of *H. pylori* Eradication

1 When attempting to detect *H. pylori* infection before and after eradication therapy, at least one of the following tests should be used. Employing multiple tests should increase the accuracy of diagnosis. As each test has its own advantages and disadvantages, selection should be performed after gaining an understanding of the characteristics of each test (see the supplementary information below).

2 Assessment of the efficacy of *H. pylori* eradication therapy should be performed at least 4 weeks after the completion of treatment.

3 Test methods

1 Tests requiring endoscopic biopsy: (i) rapid urease test (ii) histology (iii) culture

2 Tests not requiring endoscopic biopsy: (i) urea breath test (ii) measurement of *H. pylori* antibody (iii) measurement of *H. pylori* antigen in feces

Supplementary Information

1 Biopsy should preferably be performed on the greater curvature of the gastric antrum and also at the upper to middle part of the gastric body because *H. pylori* may be distributed unevenly in the stomach and antral specimens are more likely to give a false-negative result due to intestinal metaplasia [177,178].

2 As the number of micro-organisms is also decreased after unsuccessful eradication therapy, false-negative results of culture may be obtained. When in doubt, the patient should be followed up and retested.

3 For assessment of *H. pylori* eradication in patients with MALT lymphoma, multiple tests should preferably be employed to increase the accuracy of diagnosis.

4 If drugs with a bacteriostatic effect on *H. pylori*, such as PPIs or some mucosal defense potentiators, are being used to treat a patient, administration of such drugs should preferably be discontinued for at least 2 weeks before and after *H. pylori* eradication therapy to allow diagnostic testing [179–181].

5 For the detection of persistent *H. pylori* infection after eradication therapy, the urea breath test [182,183] and the monoclonal stool antigen test are useful [184].

6 Characteristics of the diagnostic tests:

1 Rapid urease test

The rapid urease test is a rapid, simple, and accurate method for identifying *H. pylori.* The test itself cannot be preserved as evidence [185–189] and there is great variability in the sensitivity of this test after eradication therapy [190]. When the rapid urease test is performed, it is preferable to simultaneously collect biopsy specimens for histology. If the rapid urease test is positive, it is safe to conclude that *H. pylori* infection is present because of its high specificity [185–189]. If the test is negative, histologic examination of the biopsy specimens should be performed for confirmation [191].

Accuracy of diagnosis: Before *H. pylori* eradication therapy, the sensitivity is 85–95% and the specificity is 95–100% [189]. After eradication therapy, the sensitivity is 61–100% and the specificity is 91–100% [190].

2 Histology

Histology provides a permanent record as evidence. In addition to the detection of *H. pylori*, this test allows histologic examination to be performed for assessment of the extent of inflammation, intestinal metaplasia, and mucosal atrophy, as well as for diagnosis of other diseases [7,192]. It is preferable to use special stains such as Giemsa stain concurrently with hematoxylin and eosin (H&E) stain [193–199]. Immunostaining is useful for distinguishing *H. pylori* from other micro-organisms and also for detecting coccoid forms of *H. pylori* [195,198].

Accuracy of diagnosis: With H&E stain, histology has a sensitivity of 47–99% and a specificity of 72–100% [200–206]. With Giemsa stain, it has a sensitivity of 87–96% and a specificity of 79–99% [202,205,207–209].

3 Culture

Culture is the only direct method of identifying *H. pylori*. It is highly specific and the strain identified can be preserved for future studies. Typing of strains and testing of sensitivity to antimicrobial drugs are also possible. It is preferable to perform sensitivity testing whenever possible.

Accuracy of diagnosis: The sensitivity is 68–98% and the specificity is 100% [210].

4 Urea breath test

The urea breath test is simple, noninvasive, and highly sensitive and specific [183,211–216]. In the patient has a negative urea breath test, it is very likely that *H. pylori* eradication therapy has been successful [182]. Using film-coated tablets of ^{13}C-urea should increase the accuracy of the test [216]. A false-negative urea breath test is common during administration of anti-ulcer drugs and immediately after their discontinuation [179–181,217–220]. When the urea breath test is positive, but is near the cut-off value, it is preferable to perform another test for assessment of *H. pylori* eradication or repeat the urea breath test after follow-up because incorrect results can be obtained [212].

Accuracy of diagnosis: The overall sensitivity is 98% and the specificity is 97% [183].

Before eradication: The urea breath test has a sensitivity of 95% and a specificity of 95% [182].

After eradication: Its sensitivity and specificity are still both 95% [182].

5 Tests for *H. pylori* antibody (serum, whole blood, urine, and saliva)

Tests are available for detection of *H. pylori* antibody in serum [221–225], whole blood [226–228], urine [229,230], and saliva [231]. Since it may take a year or more after successful eradication therapy for the antibody to disappear or the titer to decrease significantly, antibody testing is not suitable for patients who wish to know the outcome of eradication therapy at an early date [232]. When antibody testing is used for the assessment of *H. pylori* eradication, the antibody titers before and ≥6 months after eradication therapy must be compared quantitatively. If the antibody titer decreases

to half or less of the pretreatment value, eradication of *H. pylori* is judged to be successful [233,234]. Detection of *H. pylori* antibody in serum is useful during treatment or immediately after discontinuation of anti-ulcer drugs, as well as in diseases associated with a low bacterial count (atrophic gastritis [235] and MALT lymphoma [236]). As the accuracy and usefulness of *H. pylori* antibody testing depends on the strain of *H. pylori* employed as the source of antigen [237] and the prevalence rate of that strain [238], local validation of these tests is required. *Helicobacter pylori* antibody kits with antigens extracted from domestic strains have been reported to be suitable for use in Japan [229,230,239].

It has been reported that the accuracy of testing for *H. pylori* antibody in urine samples is equal to or higher than that of serum testing [229,230], but the usefulness of measuring urine *H. pylori* antibody testing after eradication therapy has not been investigated sufficiently.

Accuracy: Serum *H. pylori* antibody tests have a sensitivity of 91–100% and a specificity of 50–91% [239].

6 Fecal *H. pylori* antigen test:

The test for *H. pylori* antigens in the feces is noninvasive, simple, and highly sensitive and specific [184,240–247]. This monoclonal antibody method is reliable for making a diagnosis of *H. pylori* infection before eradication therapy and for assessing the efficacy of eradication therapy [184].

Accuracy (monoclonal antibody method): Before treatment, the sensitivity is 96% and the specificity is 97% [184]. After treatment, the sensitivity is 95% and the specificity is 97% [184].

Treatment

First-Line Therapy for Eradication of *H. pylori*

One week of triple therapy using a PPI combined with amoxicillin and clarithromycin is recommended as the treatment of first choice for eradicating *H. pylori*. The success rate of triple therapy in combination with a PPI plus amoxicillin and clarithromycin has recently fallen to 80% or below because of increasing incidence of clarithromycin resistance. Therefore, PPI based triple therapy using clarithromycin is considered not to be good first choice according to the Maastricht III consensus report [38]. We are considering to alter the first-line therapy in the next version of guideline after more data will accumulate in Japan.

Supplementary information 1

The first-line drugs covered by the Japanese national health insurance system are currently as follows:

1 Lansoprazole (30 mg) one capsule (tablet) twice daily, oromeprazole (20 mg) one tablet twice daily, orrabeprazole (10 mg) one tablet twice daily
2 Amoxicillin (250 mg) three capsules (tablets) twice daily
3 Clarithromycin (200 mg) 1–2 tablets twice daily

Three drugs from the above nos 1–3 should be administered after breakfast and dinner for 1 week.

Supplementary information 2

Proton-pump inhibitor-based triple therapy is currently the first choice for *H. pylori* eradication worldwide, and eradication rates of 80–90% have been reported [35,248]. Mainstream Japanese therapy does not include metronidazole among the first-line drugs because it is an antiprotozoal agent. In addition, eradication therapy with a PPI + amoxicillin + clarithromycin is reported to be associated with less clarithromycin resistance after unsuccessful eradication than treatment with a PPI + clarithromycin + metronidazole [249,250]. A comparison of eradication regimens based on the three PPIs available in Japan (omeprazole, lansoprazole, and rabeprazole) showed no differences of the eradication rate between them [251–253]. Thus, PPI-based triple therapy (PPI + amoxicillin + clarithromycin) was selected as the first-line regimen for eradication of *H. pylori*.

In March 2000, a phase III double-blind study of lansoprazole + clarithromycin + amoxicillin was completed in patients with *H. pylori*-positive peptic ulcer disease [254]. Patients were treated for 1 week with either lansoprazole (30 mg) twice a day (group A), lansoprazole (30 mg) + amoxicillin (750 mg) + clarithromycin (200 mg) twice a day (group B), or clarithromycin (400 mg) twice a day (group C). The *H. pylori* eradication rates obtained in the full analysis set were respectively 0%, 87.5%, and 89.2% for patients with gastric ulcer versus 4.4%, 91.1%, and 83.7% for patients with duodenal ulcer. The results were considered to be reliable because this was a large-scale multicenter double-blind trial. A difference of the eradication rate between 400 and 800 mg doses of clarithromycin was not seen in this study [255,256]. It has been reported that administration for 7 days is necessary with the PPI + amoxicillin + clarithromycin therapy. A comparison of efficacy between treatment for 5 or 7 days with rabeprazole (10 mg b.i.d.) + amoxicillin (750 mg b.i.d.) + clarithromycin (400 mg b.i.d.) showed that the eradication rate was significantly lower with the former regimen, i.e., 66% (46/70) versus 84% (58/69), respectively [257]. Comparison of efficacy between 5 and 7 days of clarithromycin-based triple therapy (lansoprazole (30 mg

b.i.d.) + amoxicillin (500 mg q.i.d.) + clarithromycin (200 mg b.i.d.)) for non-resistant *H. pylori* infection showed a significantly lower eradication rate with the 5-day regimen, i.e., 75% (36/84) versus 93% (39/42), respectively [258].

The results of a phase III double-blind study of triple therapy were reported in 2001. The eradication rate achieved with 1 week of omeprazole (20 mg b.i.d.) + amoxicillin (750 mg b.i.d.) + clarithromycin (400 mg b.i.d.) (low-dose group) versus omeprazole (20 mg b.i.d.) + amoxicillin (1000 mg b.i.d.) + clarithromycin (500 mg b.i.d.) (high-dose group) was 77.8% (89/113) and 83.0% (93/112), respectively [259]. In a subsequent randomized double-blind study of omeprazole (20 mg b.i.d.) + amoxicillin (750 mg b.i.d.) + clarithromycin (200 or 400 mg b.i.d.), the eradication rates were 81.1% (116/143) and 80.0% (116/145), respectively, showing no significant difference [260].

A randomized double-blind study of rabeprazole-based therapy (rabeprazole (10 or 20 mg b.i.d.) + amoxicillin (750 mg b.i.d.) + clarithromycin (200 or 400 mg b.i.d.) for 1 week) showed eradication rates of 86% (102/119), 89% (97/109), 91% (106/116), and 90% (104/115), respectively, with no significant differences among the groups [261].

National health insurance coverage for *H. pylori* eradication therapy was approved in November 2000 for lansoprazole, in April 2002 for omeprazole-based clarithromycin therapy (800 mg), in January 2007 for omeprazole-based clarithromycin therapy (400 mg), and in January 2007 for rabeprazole.

Adverse effects

Adverse effects associated with *H. pylori* eradication therapy are reported in 14.8–66.4% of patients [251,254,259,262–264]. Diarrhea and soft stools occur most frequently (10–30%), followed by dysgeusia, glossitis, and stomatitis (5–15%), as well as skin rash (2–5%). Other symptoms, such as abdominal pain, flatulence, borborygmi, constipation, headache, liver dysfunction, dizziness, and itching, are less frequently reported. It has been reported that concomitant administration of an antiflatulence agent is effective for the prevention of diarrhea [265]. In 2–5% of patients, severe adverse effects occur that require the cessation of treatment (including diarrhea, fever, rash, pharyngeal edema [251], and hemorrhagic enterocolitis [266]). In a post-marketing surveillance study of 325 patients aged 65 years or older, the incidence of adverse effects was 10.15%, so these events are not frequent in elderly patients [267]. Thus, it is not necessary to avoid eradication therapy due to fear of adverse effects in the elderly.

Bacterial resistance

In patients with clarithromycin-resistant *H. pylori*, it has been reported that the eradication rate achieved with clarithromycin-based regimens shows a marked decrease [268,269]. Clarithromycin resistance has also been reported to develop after unsuccessful eradication therapy [249,268,269], suggesting that inadequate therapy increases the risk of bacterial resistance. When patients are treated with clarithromycin in the pediatric, respiratory, and otorhinolaryngology fields, clarithromycin resistance is possibly being created.

A 5-year nationwide survey of bacterial resistance was conducted by the Japanese Society for Helicobacter Research from 2002 to September 2007 to determine the status of bacterial resistance in Japan and investigate guidelines for future eradication therapy [270]. At the 2008 meeting of the Japanese Society for Helicobacter Research [271], it was reported that the mean national clarithromycin resistance rates from 2002 to 2006 were 18.9%, 21.2%, 27.7%, 29.0%, and 27.2%. The mean nationwide clarithromycin resistance rate determined by the Japanese Society of Chemotherapy was 7.0% (21/302) in 2000 [272], so there has been an increase of resistance by approximately 20% over several years. Despite differences among institutions and the number of bacterial strains isolated, it is considered that the current primary resistance rate remains around 30%.

From the above results, it appears that the incidence of clarithromycin-resistant *H. pylori* is increasing rapidly, so a decrease of the eradication rate achieved by the therapy currently available under the national health insurance scheme is a concern. According to some reports, the eradication rate has fallen to approximately 70%.

Sequential therapy

As a first-line regimen for *H. pylori* eradication, 10 days of sequential therapy, i.e., 5 days of PPI + one antimicrobial drug (generally amoxicillin) followed by 5 days of PPI + two antimicrobial drugs (generally clarithromycin and 5-nitromidazole), is currently attracting attention. A meta-analysis of studies comparing sequential therapy with standard PPI-based triple therapy showed that the eradication rate was higher with sequential therapy [273]. However, the results are controversial because only one double-blind study was included, almost all of the subjects were Italian, the number of patients was small, and there was publication bias in the studies selected as well as no description of the randomization method. Thus, the

results of studies conducted in other countries are still needed.

Concomitant therapy

Sequential therapy is relatively complex, requiring the patient to switch from a dual to a triple therapy as midpoint. In concomitant therapy, a PPI plus amoxicillin, clarithromycin and nitroimidazole were given concomitantly [274,275]. Meta-analysis showed superiority of concomitant therapy over triple therapy [276]. The success rate of concomitant therapy was 95% in clarithromycin resistant infections [277]. Concomitant therapy appears to be an effective alternative to triple therapy. However, we have not had enough data to evaluate the superiority of concomitant therapy over triple therapy in Japan.

Second-Line Treatment

The chief reason for failure to achieve eradication is clarithromycin resistance [278,279], so only low eradication rates can be expected if a clarithromycin-based regimen is used as second-line therapy [280,281]. Thus, a different regimen is needed for second-line treatment. As eradication cannot be expected even if the dose of clarithromycin is increased to 800 mg.

When first-line therapy with a PPI + amoxicillin + clarithromycin failed and a PPI + amoxicillin + metronidazole was given for 5–10 days as second-line treatment, the eradication rate (intent-to-treat) was a high 81–96% [282]. Therefore, PPI + amoxicillin + metronidazole is strongly recommended as second-line treatment.

Supplementary information

The following second-line regimens were approved for use under the national health insurance scheme on the basis of published information in August 2007 without any clinical trials:

1 lansoprazole (30 mg) one capsule (tablet) twice daily, oromeprazole (20 mg) one tablet twice daily, orrabeprazole (10 mg) one tablet twice daily
2 amoxicillin (250 mg) three capsules twice daily
3 metronidazole (250 mg) one tablet twice daily

Three drugs from the above nos 1–3 should be administered after breakfast and dinner for 1 week.

The above therapy (PPI/AM therapy) is only indicated when first-line eradication therapy based on clarithromycin is unsuccessful. It has been reported that evaluation of eradication therapy employing three different PPIs showed no differences in the eradication rate [283]. Currently, PPI/AM cannot be used as first-line eradication therapy for the following reasons: market research is required for 5 years after authorization because the therapy was approved based on published information without any clinical trial, an increase of bacterial resistance with increased use of metronidazole is a concern, occurrence of cancer after exposure to metronidazole has been reported (although the risk is extremely low) [284], and there are not enough data about first-line PPI/AM eradication therapy.

It was reported that adverse reactions occurred in 8–26% of patients, with the major adverse reaction being diarrhea. However, symptoms were mild in most cases, and discontinuation of treatment or an influence on compliance was only found in 1–5% of patients [280,285–288]. Drinking alcohol should be avoided during metronidazole therapy because a disulfiram-like reaction can occur, leading to abdominal pain, vomiting, and a burning sensation among other symptoms.

Third-line treatment (not covered by the national health insurance scheme)

If second-line eradication therapy fails, a PPI + amoxicillin + levofloxacin is recommended [289]. This therapy is expected to be effective with a relatively low incidence of adverse reactions, although new quinolones are currently used at a high rate and emergence of resistance is increasing, which may influence the eradication rate. Further investigation is needed with regard to the respiratory new quinolones that will be marketed in the future. High-dose dual therapy is done with a PPI + high-dose amoxicillin. After treatment with amoxicillin at a dose of four times higher than that of the PPI for 2 weeks, it is expected that gastric acid secretion will be inhibited sufficiently and the effect of amoxicillin will be exerted [290]. This therapy is effective for clarithromycin- and metronidazole-resistant *H. pylori*.

Problems arising after successful eradication

As described above, it has been reported that onset or aggravation of reflux esophagitis may occur after eradication of *H. pylori* in 3–19% of patients, although the observation period differed between studies [163, 291–296]. It is rare for severe reflux esophagitis to occur, but informed consent must be obtained from patients before treatment. The current consensus is that the transient onset or aggravation of reflux esophagitis or gastresophageal reflux disease symptoms after *H. pylori* eradication therapy should not interfere with treatment. Attention should also be paid to reports

about the appearance of lifestyle-related diseases, such as obesity or hypercholesterolemia, after successful eradication of *H. pylori* [297], and instructions about lifestyle modification should be given to patients after successful eradication. Recurrence of *H. pylori* infection after successful eradication has also been reported [298,299], and the reinfection rate is considered to be approximately 0–2%/year..

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