REVIEW

Thailand Consensus on *Helicobacter pylori* Treatment 2015

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Abstract

Management of *Helicobacter pylori* infection is an important aspect of many upper gastrointestinal tract diseases, such as chronic gastritis, peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. The Thailand Consensus on *H. pylori* treatment 2015 consisted of 22 national experts who took active roles, discussed all important clinical information and investigated clinical aspects in four workshops, focuising on: (1) Diagnosis (2) Treatment (3) Follow-up after eradication and (4) *H. pylori* infection and special conditions. Experts were invited to participate on the basis of their expertise and contribution to *H. pylori* works and/or consensus methodology. The results of each workshop were taken to a final consensus vote by all experts. Recommendations were developed from the best evidence and availability to guide clinicians in management of this specific infection associated with variety of clinical outcomes.

Keywords: *Helicobacter pylori* - infection - treatment - guidelines - Thailand 2015

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Introduction

Helicobacter pylori (*H. pylori*) infection remains an important consideration in the management of (upper gastro-intestinal) UGI tract diseases. Understanding the role of these bacteria in variety of clinical conditions is one of the keys to treatment success. The Thailand Consensus on *H. pylori* Treatment was initiated in 2010 and gathered key opinion leaders in this field to review and discuss all clinical information and set recommendations for the management of *H. pylori* infection in clinical practice in Thailand. The present Thailand Consensus on *H. pylori* Treatment 2015 consisted of 22 national experts and the meeting mainly focused on (1) Diagnosis (2) Treatment (3) Follow up after eradication and (4) *H. pylori* infection and special conditions including gastroesophageal reflux disease (GERD), proton pump inhibitor (PPI) and precancerous lesion.

Methodology of the Consensus Process

All available clinical information and key important clinical studies were reviewed at the introduction part. Each working group reviewed and discussed the following subjects according to *H pylori* infection: (1) Diagnosis (2) Treatment (3) Follow up after eradication and (4) *H. pylori* infection and special conditions. Each question led by members of the working group was submitted to each participant, discussed and adapted to fit a standard template. The strength of recommendations and the level of evidence were graded as summarized in Table 1. The statements and recommendations were modified

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Table 1. Level of Evidence and Grade of Recommendation

Level of evidence
Ia. Systematic review of randomised controlled trial (RCT) of good methodological quality and with homogeneity.
Ib. Individual RCT with narrow CI
Ic Individual RCT with risk of bias
IIa. Systematic review of cohort studies (with homogeneity)
IIb. Individual cohort study (including low quality RCT, eg. <80% follow up)
IIc. Non-controlled cohort studies/ecological studies.
IIIa. Systematic review of case-control studies (with homogeneity)
IIIb. Individual case-control study
IV. Case series/poor quality cohort or case-control studies
V Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'

Classification of recommendations: A. Strong for using; B. Weak for using; C. Weak against using; D. Strong against using

and accepted upon at the final face-to-face meeting. Consensus was defined as support by 80% or more of the participants. Commentaries on statements were written by the secretary and proofed by the chairmen of each working group. After acceptance was achieved, each statement of recommendation based on supporting evidence was formally established. The recommendations reports of this important process are summarized in this manuscript.

Diagnosis Statements

Statement 1: A *Helicobacter pylori* test was recommended in patients who had: *i)*. Peptic ulcer diseases and gastric erosions; *ii)*. Chronic NSAIDs/ASA use with a history of peptic ulcer diseases or multiple risk factors of upper GI bleeding; *iii)*. Marginal zone B-cell lymphoma (MALT type); *iv)*. Dyspepsia that did not respond to anti-secretory drugs; *v)*. Family history of gastric cancer in a 1st degree relative; *vi)*. Gastric cancer

Level of evidence 1b Grade of recommendation A Agreement 87%

H. pylori eradication therapy is effective in the treatment and prevention of recurrence of *H. pylori*-positive peptic ulcer disease (Leodolter et al., 2001; Ford et al., 2006). In addition, *H. pylori* eradication therapy plus ulcer-healing drugs (UHD) are more effective than UHD alone in the healing of duodenal ulcer, but not in the healing of gastric ulcer. After ulcer healing, *H. pylori* eradication can reduce duodenal ulcer recurrence from 64% to 14% and reduce gastric ulcer recurrence from 52% to 15%. Furthermore, *H. pylori* eradication is as effective as maintenance UHD in preventing the recurrence of duodenal ulcer, (Ford et al., 2006) and is cost effective in the prevention of peptic ulcer recurrence (Ford et al., 2004). Concerning gastric erosions, a recent consensus report on *H. pylori* gastritis stated that gastric erosions can be observed in *H. pylori* gastritis, but the clinical

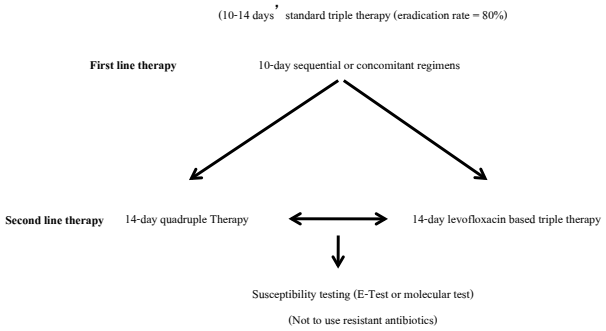

Figure 1. Algorithm for the Management of *H. pylori* Infection in Thailand

significant is not clear and they are more frequently caused by ASA and NSAIDs (Sugano et al., 2015). Therefore, *H. pylori* eradication is not recommended in this context. However, most of the voters are more comfortable with the eradication of *H. pylori* in this setting.

H. pylori infection independently increased the risk of NSAID/ASA-induced ulcers and ulcer complications (Huang et al., 2002). As a result, *H. pylori* eradication can significantly reduce NSAID/ASA-induced ulcers and ulcer complications, especially when *H. pylori* was eradicated prior to starting NSAID therapy (Chan et al., 2013; Chan et al., 1997; Chan., 2002). After *H. pylori* eradication, the incidence of recurrent ulcer bleeding with ASA use did not differ significantly from that of new ASA users without a history of ulcers (Chan et al., 2013). Therefore, *H. pylori* eradication is essential for the prevention of peptic ulcer in chronic NSAID/ASA users with a history of peptic ulcer disease. However, *H. pylori* eradication seems to be less effective than a maintenance proton pump inhibitor (PPI) treatment for preventing NSAID-associated ulcers (Vergara et al., 2005). In addition, the combination of NSAIDs and ASA, concomitant anticoagulant therapy, clopidogrel or corticosteroids further increased the risk of NSAID/ASA-induced ulcer bleeding (Abraham et al., 2010). As a result, *H. pylori* eradication may be considered in this group of patients (Abraham et al., 2010).

Most marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) in the stomach is associated with *H. pylori* infection and successful eradication of *H. pylori* can cure early stage, low grade MALT lymphoma in approximately 80% of cases (Wotherspoon et al., 1993; Chen et al., 2005; Hong et al., 2006; Stathis et al., 2009; Zullo et al., 2009). However, patients should be closely followed up to confirm *H. pylori* eradication and to evaluate the response to treatment (Zullo et al., 2009; Ruskone et al., 2011).

A meta-analysis of randomized trials comparing *H. pylori* eradication therapy with placebo for *H. pylori*-positive functional dyspepsia demonstrated an advantage of eradication therapy, with a NNT of 13 compared with placebo (level of evidence Ia) (Moayyedi et al., 2011). Although the effect of *H. pylori* eradication on functional dyspepsia is likely to be cost effective when compared with acid suppression therapy, (Moayyedi et al., 2000) the voters still preferred testing and eradication in patients who do not respond to acid suppression therapy.

Two meta-analyses, of which most of the studies were

performed in Asia, reported that *H. pylori* eradication seems to reduce gastric cancer risk, although the NNT were rather high (Ford et al., 2014; Fuccio et al., 2009). Accordingly, it is justified to consider testing and eradication of *H. pylori* in high-risk patients. One meta-analysis indicated that the risk of gastric cancer, gastric atrophy and gastric intestinal metaplasia increased approximately 2-fold in first-degree relatives of patients with gastric cancer; (Rokkas et al., 2010); consequently, many international consensuses recommended the testing and eradication of *H. pylori* in this group of patients (Malfertheiner et al., 2012; Kim et al., 2014; Zagari et al., 2015). Many studies reported that *H. pylori* eradication can prevent metachronous gastric cancer after endoscopic mucosal resection (EMR) for early gastric cancer (Kato et al., 2007; Fukase et al., 2008; Asaka et al., 2010; Maehata et al., 2012). As a result, *H. pylori* eradication is indicated in this group of patients. Some international consensuses also included early gastric cancer patients after surgical resection in the recommendations (Malfertheiner et al., 2012; Zagari et al., 2015). However, the voters would like to expand the indications to all stages of gastric cancer.

Statement 2: Pretreatment diagnosis of active *H. pylori* can be made by an endoscopy-based diagnosis, urea breath test or stool Ag test. PPIs should be discontinued at least two weeks before the test. Urease test is the most practical test in Thailand

Level of evidence 2b Grade of recommendation BAgreement 100%

The urea breath test (UBT) is a noninvasive test that provides the best accuracy for the diagnosis of *H. pylori* infection and confirmation of eradication (Leodoltor et al., 1999; Graham and Klein., 2000; Gisbert and Pajares, 2005). PPIs and antibiotics produce false negative results in all tests except serology (Gatta et al., 2004). PPIs have anti-*H. pylori* activity by suppressing the density of *H. pylori* and result in false-negative result in a urease test, UBT and stool Ag test (Gatta et al., 2004). High intragastric pH reduces the viability of the organism and directly inhibits urease activity (Graham et al., 2003). Antibiotics and bismuth compounds should be discontinued at least four weeks before the tests (Bravo et al., 1999).

Statement 3: A serology test is not recommended for the detection of an active *H. pylori* infection.

Evidence level 1C Grade of recommendation: A Agreement 100%

The detection of antibodies indicates past or present exposure. The favoured method is ELISA technology to detect immunoglobulin G (IgG) antibodies. Twenty-nine different serological test kits exist, with sensitivities ranging from 55.6% to 100%, specificities ranging from 59.6% to 97.9 %, positive predictive values ranging from 69.8% and 100% and negative predictive values ranging from 68.3% and 100% (Burucoa et al., 2013). In a study from Thailand, a serology test for IgG detected by ELISA had a sensitivity of 96.8% and a relatively low specificity of 73.1% (Kullavanijaya et al., 2004).

Other noninvasive tests have high sensitivity and specificity. UBT has both high sensitivity and specificity: 88-95% and 95%-100%, respectively (Howden and Hunt, 1998). Similar to UBT, the stool antigen test (SAT) has a sensitivity of 94% and a specificity of 92% (Vaira et al., 1999).

Serology is not recommended to detect active *H. pylori* infection. The advantages of the serology test are its availability and low cost. Although serology is not affected by PPIs, it is recommended only if the UBT and stool antigen test are not available because it has lower specificity than the UBT and stool antigen test (Loy et al., 1996; Wilcox et al., 1996; Patel et al., 2014).

Treatment Statements

Statement 1: 10-14 days of triple therapy results in an 80% eradication rate. Either 10 days of sequential therapy or 10 days of concomitant therapy is the alternative treatment for first-line *H. pylori* eradication in Thailand.

Evidence level 2b, Grade of recommendation B Agreement 100%

The Guidelines for the Management of Dyspepsia and *Helicobacter pylori* issued by the Gastroenterology Association of Thailand in 2010 suggested that standard PPI-based triple therapy should be the first-line therapy. However, the Masstricht IV (2014) consensus guidelines suggested that the standard PPI-based triple therapy should not be used as the first-line eradication therapy for *H. pylori* when the clarithromycin resistance rate is greater than 15%-20% (Malfertheiner et al., 2012). Although a survey of five teaching hospitals revealed that the clarithromycin resistance rate in Thailand varies from 5%-29.20% (median=13.8%), the *H. pylori* eradication rate with the 7-day PPI-based triple therapy in Thailand is less than 80% (Jeajaroonwong, 2003; Mahachai and Vilaichone, 2011; Pittayanon et al., 2015). Therefore, 7-day PPI-based triple therapy should not be used as first-line therapy for *H. pylori* eradication. However, a recent study in Thailand demonstrated that 14-day PPI-based triple therapy provided an eradication rate of 85% (Pittayanon et al., 2015).

The 10-day sequential therapy, consisting of a PPI plus amoxicillin (1 g) twice a day for five days, then a PPI plus metronidazole (500 mg) twice a day and clarithromycin (1 g) for five consecutive days, achieved an eradication rate of more than 90% (Sirimontaporn et al., 2010; Varocha et al., 2011). The concomitant *H. pylori* eradication therapy consisted of rabeprazole (20 mg) twice daily, amoxicillin 1 g twice daily, metronidazole 400 mg three times a day, and clarithromycin MR 1 g once daily for 10 days, achieved an eradication rate as high as 96.4% (95% CI 87.4-99.5%) (Kongchayanun et al., 2012).

Statement 2: After failure of first-line therapy, either 14 days of levofloxacin-amoxicillin triple therapy or bismuth-containing quadruple therapy should be used as second-line treatment

Evidence level: 1a Grade of recommendation: A Agreement 100%

After failure of first-line treatment of *H. pylori*,

either bismuth-containing quadruple therapy or 10-day levofloxacin-containing triple therapy as second-line treatment should be considered. A recent meta-analysis of RCTs confirmed 10-day levofloxacin-containing triple therapy as a second-line therapy for *H. pylori* eradication (Di Caro et al., 2012). The efficacy of triple therapy with a PPI + levofloxacin + amoxicillin was not inferior to bismuth-containing quadruple therapy. On the other hand, the incidence of side effects was lower with levofloxacin-containing triple therapy than with bismuth-containing quadruple therapy. A low-dose regimen was preferred because there was no significant difference in effectiveness between 500 mg (either once daily or 250 mg twice a day) and 1000 mg (500 mg twice a day) regimens. Two different levofloxacin-containing regimens, a 10-day sequential and a 5-day concomitant, have both shown high eradication rates (Romano et al., 2010; Federico et al., 2012). However, the rapid resistance may jeopardize the efficacy. It is also advised that levofloxacin may not be used in patient with a chronic pulmonary infection who have previously received fluoroquinolones.

Bismuth-containing quadruple therapy, a PPI combined with bismuth subsalicylate (524 mg four times daily) and two antibiotics (eg. metronidazole 250 mg four times daily and tetracycline 500 mg four times daily) given for 10 to 14 days, represents an alternative second-line treatment for *H. pylori* infection (Chung et al., 2011). Bismuth-containing quadruple therapy has the advantage of using compounds for which resistance has rarely been reported, with the exception of metronidazole; however, metronidazole resistance can be at least partially overcome by increasing the dose and duration of therapy (Fischbach and Evans, 2007).

Statement 3: After failure of second-line therapy, if possible, antimicrobial susceptibility testing should be done for appropriate regimen.

Evidence level: 2c Grade of recommendation: B Agreement 87%

Antibiotic resistance is one of the important factors related to treatment failures. After two treatment failures, it has been suggested that an antibiotic susceptibility test be performed (eg. The epsilometer test [E-test]) whenever possible. This method may indicate the best choice for the next treatment regimen (Lamouliatte et al., 2003; Cammarota et al., 2004; Vilaichone et al., 2006; Malfertheiner et al., 2012; Kanizaj and Kunac, 2014; Alahdab and Kalayci, 2014). Molecular genetic testing may be an alternative to antibiotic testing when a culture laboratory is not available (Smith et al., 2014).

Statement 4: Probiotics may be used as adjuvant therapy to decrease the side effects of eradication regimens

Evidence level 1c Grade of recommendation: D Agreement 100%

Many strains of probiotics are used in combination with *H. pylori* eradication regimens, such as *Bifidobacterium longum, Saccharomyces boulardii, lactoferrin, Lactobacillus rhamnosus* CG, *Bacillus clausii* AB, yoghurt with unspecified lactobacilli and Bifidobacteria, Lactobacillus casei DN-114 001 in fermented milk with Lactobacillus bulgarium and Streptococcus thermophilus. Although there are meta-analyses on the effect of probiotics on *H. pylori* eradication, most of the studies are of poor quality (small number of subjects, high heterogeneous different in species and strains of probiotics). Further well designed studies need to be performed in order to determine the best strain and optimum dose and duration of probiotic administration as well as to explore the side effects and contraindications of probiotics (Franceschi et al., 2007; Malfertheiner et al., 2012; Chitapanarux et al., 2015; Zhang et al., 2015). Cost effectiveness also needs to be analysed before general recommendations are made.

Statement 5: 10 days of quadruple therapy or a 10-day PPI-CLR-MNZ regimen should be used as first-line treatment regimens for *H. pylori* eradication in penicillin allergic patients

Evidence level: 2b Grade of recommendation: B Agreement 100%

PPI-clarithromycin-metronidazole can be used as first-line treatment in penicillin allergic patients only in low clarithromycin-resistant areas. However, data on the clarithromycin resistance rate are not available in this specific group of patients in Thailand (Gisbert et al., 2005; Thailand Consensus for the Management of Dyspepsia and *Helicobacter pylori*, 2010). First-line treatment with 10 days of bismuth-containing quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be a good option (Gisbert et al., 2015). An alternative first-line therapy could be a 10-day triple PPI-clarithromycin-metronidazole regimen. The algorithm for the management of *H. pylori* infection is summarized in Figure 1.

Follow-up Statements

Statement 1: The confirmation test to determine the success of eradication is recommended for all patients who receive anti-*H. pylori* therapy.

Level: 1d Grade of recommendation: A Agreement: 100%

Because of the availability of accurate, relatively inexpensive, noninvasive tests (stool and breath tests) and increasing antibiotic resistance, confirmation of eradication is recommended for all patients receiving treatment for *H. pylori* (Howden and Hunt, 1998; Chey and Wong, 2007). The test is especially essential in patients who receive treatment for *H. pylori* of peptic ulcer disease, individuals with persistent dyspeptic symptoms despite the test-and-treat strategy, those with *H. pylori*-associated MALT lymphoma and individuals who have undergone resection of early gastric cancer (Sheila, 2015).

Statement 2: The UBT and stool antigen test are the recommended noninvasive tests to determine the success of eradication. There is no role for the serological test.

Level: 1b Grade of recommendation: A Agreement: 100%

The UBT and stool antigen tests have high sensitivity and specificity (Howden and Hunt, 1998; Vaira et al., 1999), are relatively inexpensive and require no special set-up. These tests are the recommended tests to determine

the success of eradication. In GU, gastric MALT lymphoma and other clinical conditions for which follow up with upper GI endoscopy is necessary, endoscopy-based testing may be considered appropriate. Endoscopy-based testing could also be used for confirmation of eradication where the recommended non-invasive test is not available. It should be recognized that the endoscopy-based test has a higher false-negative rate. The serology test should not be used for confirmation of eradication because it is unable to discriminate active disease from complete eradication (Cutler et al., 1998).

Statement 3: The optimal time of testing for confirmation of *H. pylori* eradication should be at least four weeks after the end of treatment and at least two weeks after discontinuation of PPIs.

Level: 2b Grade of recommendation: B Agreement: 100%

The urea breath test performed at least four weeks after treatment has been promoted as the test of choice to confirm eradication of infection. Stool antigen testing is a widely available alternative. The stool antigen test at four weeks may be less accurate than the UBT (Perri et al., 2002); however, performing it more than four weeks later to improve accuracy is still inconclusive. Recent antibiotics taken for reasons other than *H. pylori* eradication or recent treatment with bismuth or PPIs can affect test results. Antibiotics and bismuth should be discontinued before testing for at least four weeks and PPIs for at least two weeks to reduce the false-negative rate (Gatta et al., 2004). The confirmation of eradication while receiving PPIs has a higher false-negative rate (Laine et al., 1998; Gatta et al., 2004). The test should be delayed, if possible, until complete ulcer healing is achieved four to six weeks after eradication and at least two weeks after PPI discontinuation. An alternative therapy by switching from PPIs to H2RA or antacids for two weeks prior to the test could possibly reduce the false-negative rate, but supporting evidence is inconclusive (Cutler et al., 1998; Savarino et al., 2001).

Statement 4: Prolonged acid inhibition with PPIs is not necessary in patients with uncomplicated duodenal ulcer after *H. pylori* eradication therapy.

Level: 1a Grade of recommendation: A Agreement: 100%

Statement 5: In patients with gastric ulcer and complicated duodenal ulcer, prolonged acid inhibition therapy with PPIs is recommended.

Level: 1bGrade of recommendation: B Agreement: 100%

H. pylori is one of the important factors in peptic ulcer pathogenesis. *H. pylori* eradication is strongly recommended for DU and GU with *H. pylori* infection because the previous studies have been demonstrated that *H. pylori* eradication could be achieved peptic ulcer healing rates of >90% (Ford et al., 2006; Leodolter et al., 2001; Lam et al., 1997). Continued acid inhibition with PPI is not necessary after achieving *H. pylori* eradication in uncomplicated DU (Ford et al., 2006; van Zanten et al., 2008).

Furthermore, the reason to continue PPI for GU healing after *H. pylori* cure is still uncertain (Higuchi et al., 2003; Marzio et al., 2003; Gisbert and Pajares, 2005). GU might be required longer acid blocker for healing than DU and repeat gastrocsopy is required to confirm GU healing. *H. pylori* eradication should be confirmed in all GU patients. However, continuing the PPI might be benefit for ulcer healing when eradication has fail to success. Prior studies on complicated DU and GU have been recommending prolonged PPI therapy after *H. pylori* eradication. To the best knowledge, continue PPI treatment should be performed after *H. pylori* eradication treatment in GU until complete ulcer healing is confirmed and in complicated DU until curing of *H. pylori* eradication is achieved. Long-term maintenance therapy is not necessary in DU and GU, including bleeding ulcer, after successful *H. pylori* eradication and proven ulcer healing (Gisbert et al., 2004; Arkkila et al., 2005). Other etiologic causes of peptic ulcer should be reviewed in every patient with unalleviated symptoms after therapy (Laine et al., 1998; Jyotheeswaran et al., 1998). NSAID consumption, in association with *H. pylori* infection, is the major cause of ulcer recurrence (Laine et al., 1998).

Special interests

GERD and *H. pylori* infection

Statement 1: Epidemiologic studies demonstrate a negative association between prevalence of *H. pylori* and severity of GERD and the incidence of esophageal adenocarcinoma.

Evidence level: 2b Grade of recommendation: B Agreement 100%

Several reports have suggested that *H. pylori*-positive patients were less likely to have GERD and, when present, the severity of esophagitis was decreased compared to those who were *H. pylori* negative (O'Connor, 1999; Hackelsberger et al., 1997; Shirota et al., 1999; Chung et al., 2011). A lower prevalence of Barrett's metaplasia and aesophageal adenocarcinoma has also been described in individuals who were *H. pylori* positive (Wang et al., 2009).

Statement 2: Testing for H. pylori infection in GERD patients is not recommended except when other indications exist.

Evidence level: 1a Grade of recommendation: A Agreement 100%

Many previous studies show convincingly that eradication of *H. pylori* has no effect on the development of heartburn and in fact does not exacerbate GERD symptoms when they are present at baseline (Tan et al., 2015). *H. pylori* infection itself clearly does not cause GERD nor, in fact, does it have any dramatic effect on symptoms. Eradication of *H. pylori* does not appear to affect the natural history of or the treatment of GERD at all (Vakil et al., 2000). Therefore, if the clinical presentation mandates investigation for Helicobacter (suspicion of gastric ulcer, duodenal ulcer or, in certain situations, functional dyspepsia), testing for *H. pylori* is warranted.

H. pylori and proton pump inhibitors

Statement: *H. pylori*-positive patients receiving long-term PPI therapy are subject to increased risk of corpus atrophy. However, no gastric cancer has been found.

Evidence level: 1a Grade of recommendation: A Agreement 100%

PPIs reduce acid secretion by blocking the hydrogen-potassium ATPase pump on the luminal border of gastric parietal cells, and are more effective antisecretory agents than are H2-receptor antagonists. PPIs also have in vitro antimicrobial activity against *H. pylori* (Vilaichone et al., 2006). However, the major activity of PPIs is believed to be increasing intraluminal gastric pH and allowing antibiotics to work properly (Figura et al., 1997; Graham et al., 2003; Vilaichone et al., 2006). Long-term use of PPIs affects pattern, distribution of gastritis and might be developed corpus-predominant gastritis which lead to atrophic gastritis. In *H. pylori*-positive cases, active inflammation increases in corpus and decreases in antrum during PPI therapy, finally increasing corpus atrophy (Schenk et al., 2000; Shirin et al., 2005; Lundell et al., 2006). Long-term PPI treatment could be induced moderate hypergastrinemia in nearly all patients and increased prevalence of enterochromaffin-like (ECL) cell hyperplasia. *H. pylori*-positive patients receiving long-term PPI treatment were exposed to higher risk of corpus atrophy than *H. pylori*-negative patients. Neither neuroendocrine tumours nor gastric cancers were found (Lundell et al., 2015). The CYP2C19 genotype especially rapid metabolizer (RM) may affect the pharmacokinetics and pharmacodynamics of PPIs and be related to a higher probability of treatment failure. The RM genotype was found in approximately 40% of Thai people (Prapitpaiboon et al., 2015). Recent studies in Thailand demonstrated that a high dose of PPI in treatment regimens provided a better eradication rate, regardless of the CYP2C19 genotype (Srinarong et al, 2014; Prapitpaiboon et al, 2015).

H. pylori infection and precancerous lesions

Statement 1: *H. pylori* causes gastric precancerous lesions, including chronic atrophic gastritis, gastric intestinal metaplasia (GIM) and dysplasia

Evidence level: 2a Grade of recommendation: A Agreement 100%

According to the Correa pathway (Correa 1992), *H. pylori* infection is one of the contributing factors in the aetiology of gastric cancer. *H. pylori* infection aggravates chronic atrophic gastritis, GIM, dysplasia and eventually, gastric cancer. Half of chronic atrophic gastritis patients have *H. pylori* infection (Sipponen et al., 1994). From 10-year follow up, 49% of patients with *H. pylori* infection had progressed to GIM, whereas GIM were not found in patients without *H. pylori* infection (Asaka et al., 2001; de Vries et al., 2008). Moreover, RCT in China confirmed that gastric atrophy, GIM and dysplasia were associated with an HR of 2.97 for the development of gastric cancer (Wong et al., 2004). In addition, hyperplastic polyps larger than 2 cm associated with *H. pylori* infection have a possibility of becoming gastric cancer (Goddard et al., 2010). Recently, a nation-wide study in a low-risk western population showed that 1 in 50 patients with atrophic gastritis, 1 in 39 with intestinal metaplasia and 1 in 19 with dysplasia will develop gastric cancer within 20 years compared with 1 in 256 with normal mucosa and 1 in 85 with gastritis (Song et al., 2015).

Statement 2: *H. pylori* eradication can degrade chronic atrophic gastritis but not dysplasia. However, the effect of eradication on gastric intestinal metaplasia (GIM) has been inconclusive.

Evidence level: 1c Grade of recommendation: A Agreement 100%

From a meta-analysis conducted in 2011, the authors concluded that *H. pylori* infection is strongly associated with atrophic gastritis of the corpus, but not the antrum (Wang et al., 2011). In addition, this study revealed a correlation between *H. pylori* infection and GIM. However, one 5-year follow-up RCT study in 2004, which had not been included in the previous meta-analysis study, revealed that *H. pylori* eradication can retract the progression of GIM (Leung et al., 2004). Recently, another meta-analysis in 2015 emphasized that *H. pylori* eradication cannot reduce GIM and dysplasia (Chen et al., 2016). Unfortunately, they combined GIM and dysplasia in the same category and did not provide information for each (Chen et al., 2015).

Statement 3: All patients with gastric precancerous lesions should be tested for *H. pylori* and treated accordingly.

Evidence level: 1a Grade of recommendation: A Agreement 100%

According to the fact that *H. pylori* infection is the aggravating factor in gastric cancer development (Wong et al., 2004), the presence of *H. pylori* infection should be terminated. If patients with *H. pylori* infection have severe gastric atrophy or GIM, they will be at risk of gastric cancer (Uemura et al., 2001). In contrast, the incidence of gastric cancer was not increased in patients with no precancerous lesions at 7.5-year follow up, regardless of *H. pylori* infection status (Wong et al., 2004).

Statement 4: After successful H. pylori eradication, precancerous lesions should be followed up as per the following: *i)*. Chronic atrophic gastritis and GIM at both corpus and antrum or immature-type GIM should be followed up at next year and then every three years if those findings remained; *ii)*. Low-grade dysplasia should be followed up within one year; *iii)*. High-grade dysplasia should be followed up as soon as possible.

Evidence level: 2c Grade of recommendation: C Agreement 100%

According to the European guidelines for the management precancerous lesions in the stomach, the diagram suggests scheduling endoscopic follow up every three years in GIM with eradicated *H. pylori* infection (Dinis et al., 2012). However, GIM management under a different set of guidelines recommended that the follow-up period of extensive-type (more than two locations or immature-type) GIM should be less than one year (Dinis

et al., 2004; Correa et al., 2010). From the unpublished data in King Chulalongkorn Memorial Hospital, only immature-type GIM can turn to gastric cancer. In addition, the guidelines for gastric polyp management recommended performing polypectomy on gastric polyps larger than 1 cm and a biopsy on the surrounding gastric mucosa, which can be a guide for the follow-up interval (Goddard et al., 2010).

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