Journal of Gastroenterology and Hepatology
JGHF
doi:10.1111/j.1440-1746.2009.05982.x

SPECIAL ARTICLE

Second Asia–Pacific Consensus Guidelines for *Helicobacter pylori* infection

K Ming Fock,* Peter Katelaris,† Kentaro Sugano,‡ Tiing Leong Ang,* Richard Hunt,§ Nicholas J Talley,¶ Shiu Kum Lam,** Shu-Dong Xiao,†† Huck Joo Tan,‡‡ Chun-Ying Wu,§§ Hyun Chae Jung,¶¶ Bui Huu Hoang,*** Udom Kachintorn,††† Khean-Lee Goh,‡‡‡ Tsutomu Chiba§§§ and Abdul Aziz Rani¶¶¶

*Division of Gastroenterology, Department of Medicine, Changi General Hospital, Singapore; †Concord Hospital, University of Sydney, Sydney, Australia; ‡Jichi Medical University, Tochigi-ken, Japan; §McMaster University Medical Center, Ontario, Canada; ¶Mayo Clinic, College of Medicine, Rochester, New York, USA **University of Hong Kong, Hong Kong, China; ††Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; ‡‡Sunway Medical Center, Selangor, Malaysia; §§Taichung Veterans General Hospital, Taichung, Taiwan; ¶¶Seoul National University College of Medicine, Seoul, Korea; ***University Medical Center of Ho Chi Minh City, Ho Chi Minh City, Vietnam; †††Siriraj Hospital, Mahidol University, Bangkok, Thailand; ‡‡‡University of Malaya Medical Center, Kuala Lumpur, Malaysia; §§§Kyoto University, Kyoto, Japan; ¶¶¶University of Indonesia Cipto Mangunkusumo Hospital, Indonesia

Key words
helicobacter pylori:diagnosis, *helicobacter pylori*:treatment and antimicrobial resistance, *H. pylori* and gastric cancer.

Accepted for publication 26 May 2009.

Correspondence
Professor Kwong Ming Fock, Changi General Hospital, Division of Gastroenterology, Department of Medicine, Changi General Hospital, 2 Simei Street 3, Singapore 529 889. Email: kwong_ming_fock@cgh.com.sg

Abstract

The Asia–Pacific Consensus Conference was convened to review and synthesize the most current information on *Helicobacter pylori* management so as to update the previously published regional guidelines. The group recognized that in addition to long-established indications, such as peptic ulcer disease, early mucosa-associated lymphoid tissue (MALT) type lymphoma and family history of gastric cancer, *H. pylori* eradication was also indicated for *H. pylori* infected patients with functional dyspepsia, in those receiving long-term maintenance proton pump inhibitor (PPI) for gastroesophageal reflux disease, and in cases of unexplained iron deficiency anemia or idiopathic thrombocytopenic purpura. In addition, a population 'test and treat' strategy for *H. pylori* infection in communities with high incidence of gastric cancer was considered to be an effective strategy for gastric cancer prevention. It was recommended that *H. pylori* infection should be tested for and eradicated prior to long-term aspirin or non-steroidal anti-inflammatory drug therapy in patients at high risk for ulcers and ulcer-related complications. In Asia, the currently recommended first-line therapy for *H. pylori* infection is PPI-based triple therapy with amoxicillin/metronidazole and clarithromycin for 7 days, while bismuth-based quadruple therapy is an effective alternative. There appears to be an increasing rate of resistance to clarithromycin and metronidazole in parts of Asia, leading to reduced efficacy of PPI-based triple therapy. There are insufficient data to recommend sequential therapy as an alternative first-line therapy in Asia. Salvage therapies that can be used include: (i) standard triple therapy that has not been previously used; (ii) bismuth-based quadruple therapy; (iii) levofloxacin-based triple therapy; and (iv) rifabutin-based triple therapy. Both CYP2C19 genetic polymorphisms and cigarette smoking can influence future *H. pylori* eradication rates.

Introduction

Helicobacter pylori is one of the most common human infections worldwide. It is clinically important because of the etiological association with gastroduodenal disease, particularly peptic ulcer disease and gastric malignancies. The first Asia–Pacific *H. pylori* Consensus Conference was held in Singapore in August 1997, and published in 1998.[1] Since then, new scientific information concerning the management of *H. pylori* infection has become available, and updates of the management guidelines and consensus statements from North America[2,3] and Europe[4,5] have been published in recent years. A review of the initial Asia–Pacific Consensus Statements was felt to be timely, and a Consensus Conference was convened to review and synthesize the most current information on *H. pylori* management in the region.

Methods

Nature and extent of background preparation

The Asia–Pacific *H. pylori* Consensus Conference was convened specifically to address two main areas: (i) changing epidemiology and indications for treatment of *H. pylori* infection since the last consensus; and (ii) treatment of *H. pylori* infection.

The consensus conference was held on 14–15 June 2008 in Bangkok, Thailand and was sponsored by the Asia–Pacific Association of Gastroenterology (APAGE). The Journal of Gastroenterology and Hepatology Foundation (JGHF) provided financial support through an unrestricted educational grant. Eighteen gastroenterologists from the Asia–Pacific region and two external experts were invited to participate on the basis of their expertise

Table 1 Level of evidence, classification of recommendations and voting scheme

Quality of evidence
Ia. Evidence obtained from meta-analysis of randomized trials.
Ib. Evidence obtained from at least one randomized controlled trial.
IIa. Evidence obtained from at least well-designed controlled study, without randomization.
IIb. Evidence obtained from at least one other type of well designed quasi-experimental study.
III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies.
IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.
Classification of recommendations
A. Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.
B. Requires the availability of well conducted clinical studies, but no randomized clinical trials on the topic of the recommendation.
C. Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.
Voting on the recommendations†
a. Agree
b. Disagree

†Accept statement when more than two-thirds of participants voted a.

(Appendix). Participants were not remunerated for their involvement in the meeting.

Prior to the conference, relevant areas were identified and selected relevant papers were circulated. At the conference, an overview of each area, based on comprehensive published work searches, was presented by selected participants with specific expertise. This was followed by a period of discussion, in which the existing data were evaluated and critiqued. Thereafter, a statement of recommendation was formulated. For all data related to treatment and some data related to epidemiology and indications, the level of evidence and the classification of evidence relative to the recommendation were assessed. Formal voting for each statement was undertaken and the acceptance of a statement was based on agreement of at least two-thirds of the votes (Table 1).

Preparation process and format of the report

The manuscript was drafted by a working group, and this was then circulated to and reviewed by all conference participants, all of whom approved the final draft.

Consensus statements

Each statement is followed by a brief summary, in which the quality of supporting evidence, a classification of the recommendation and the results of voting are presented and discussed.

Table 2 Indications for treatment

Indications (grade of recommendation)
Peptic ulcer disease (A)
MALToma (A)
Atrophic gastritis (B)
After gastric cancer resection (B)
Patients who have first degree relatives of patients with gastric cancer (B)
Patients' wishes (after full consultation with their physician) (A)
Non-ulcer dyspepsia (A)
To reduce the risk of peptic ulcer and upper gastrointestinal bleeding in non-steroidal anti-inflammatory drug-naive users (A)
Before starting long-term aspirin therapy for patients at high risk for ulcers and ulcer-related complications (B)
Patients receiving long-term low-dose aspirin therapy and who have a past history of upper gastrointestinal bleeding and perforation (B)
Gastroesophageal reflux disease patients requiring long-term proton pump inhibitor (B)
As a strategy for gastric cancer prevention in communities with high incidence of gastric cancer (A)
Unexplained iron-deficiency anemia, or idiopathic thrombocytopenic purpura (C)

Consensus statements

I: Epidemiology and indications for treatment of *H. pylori* infection (Table 2)

Statement 1: The prevalence of *H. pylori* infection has been declining in the Asia–Pacific Region.

Level of agreement: 100%; Level of evidence: III

This was agreed upon with significant qualification. The Asia–Pacific is a vast and heterogeneous region and within it the prevalence of *H. pylori* infection varies both between and within countries.[1] This relates to the known determinants of infection, particularly socioeconomic standards of living. Within the region there are countries with a high prevalence of infection and others where the prevalence is considered intermediate.[6,7] In countries where there has been rapid economic development with associated improvements in standards of living, there is some evidence that the prevalence of infection is declining.[8,9] However, there are few longitudinal community prevalence surveys and many reports derive from single center audits of secondary and tertiary centers.[8] As referral patterns for *H. pylori* treatment have changed in the last decade, with more treatment being conducted in primary care, these data are subject to significant potential bias. Moreover, there is likely to be publication bias in the published work as prevalence reports are more common from more developed countries. Nonetheless, in parts of the Asia–Pacific region (and elsewhere) a declining prevalence of infection is considered a real phenomenon. However, there is heterogeneity of infection rates even within more developed countries, with well-defined high-risk groups. These groups include the elderly, those who live in poorer conditions, migrants from high prevalence areas, the institutionalized and possibly rural dwellers in some areas.

Most acquisition of infection occurs in childhood.[3] In countries where improved socioeconomic conditions over recent genera-

tions have resulted in reduced transmission, infection rates in future generations of adults will continue to decline. However, large proportions of many adult populations remain infected so the burden of infection manifesting as peptic ulcer disease and gastric cancer will continue to be an important problem across the region for years to come. Worldwide, gastric cancer remains the second most common cause of cancer death, and much of this burden is borne by the Asia–Pacific region.[10]

The need for higher quality prospective epidemiological data was emphasized as a guide for planning *H. pylori* management strategies across the region.

Statement 2: *H. pylori* eradication is indicated for *H. pylori* positive patients with investigated dyspepsia (non-ulcer dyspepsia).

Level of agreement: 78%; Level of evidence: 1A; Grade of recommendation: A

There was a high level of agreement with this statement. Evidence over the last decade has strengthened support for treating infected patients in the absence of ulcer disease after investigation.[11,12] The evidence includes: (i) a small but clinically relevant likelihood of an improvement in symptoms in the short and long term;[11] (ii) a long-term benefit in terms of reducing risks for subsequent peptic ulcer disease and gastric cancer;[13] (iii) a lack of a clinical cost-effective superior alternative treatment; (iv) cost effectiveness data from a number of different populations (although there are few regional data);[11] and (v) recognition of the rights of the patient and the obligation of the clinician to offer the option of treatment in this setting.[5] Given all these issues, it was considered that the decision not to treat *H. pylori* infection must be an active one rather than the default position.

It was recognized that within the region there are countries with regulatory positions that act as barriers to treating patients in this context and delegates who disagreed with this statement were from these countries. On the other hand, in some countries the governments fund expensive endoscopic radiological and/or endoscopic surveillance programs to detect early gastric cancer but do not fund *H. pylori* eradication programs.

Statement 3: In *H. pylori*-positive patients with uninvestigated dyspepsia and with no alarm features, H. pylori "Test and Treat" is an appropriate strategy.

Level of agreement: 78%; Level of evidence: 1A; Grade of recommendation: A

There was a high level of agreement with this statement. It was considered that more recent data affirm this long-standing recommendation.[14,15] The benefits of treating *H. pylori* infection in this context are broadly similar to treating infected dyspeptic patients after investigation in which *H. pylori* chronic gastritis is the only finding. That is, the same benefits with respect to symptom relief, long-term risk reduction and choice also pertain to those with uninvestigated dyspepsia. Importantly, in this group there will be a subset of patients who have undiagnosed ulcer disease and eradication of *H. pylori* infection will confer a particular benefit, while obviating the need for endoscopy in many cases.

The ongoing dilemma related to the fear of missing gastric cancer remains an issue. While it was recognized that symptomatic gastric cancer is rarely found at an early and curable stage the issue is emotive as there is understandable patient and doctor fear related to this issue. Although delaying referral for endoscopy for a brief time is unlikely to affect prognosis in gastric cancer, anxiety remains a major driver of referral for endoscopy in patients with dyspepsia, despite the lack of alarm symptoms. It was agreed that previous recommendations for a cascade approach remain relevant with thresholds for referral for endoscopy being related to the age of the patient, the prevalence of gastric cancer in the community and the availability of endoscopy.[1] It was further noted that there is no consistent relationship between early gastric cancer and the presence of symptoms and recognition of this underpinned screening (rather than case finding) programs in some countries, such as Japan and Korea, where the prevalence of gastric cancer is high.

As some of the benefit of treating uninvestigated patients with dyspepsia relates to long-term risk reduction and health economic benefits, the issue of screening and treating patients for *H. pylori*, irrespective of symptoms, needs further study. There are certainly some data, although little from the region, that suggest a benefit in terms of reducing health-care costs for dyspepsia; this has been demonstrated in populations with a relatively low prevalence of infection and gastric cancer, and over a relatively short timespan.[16] It is likely that any benefits will be magnified over time, given the lifetime risks of infection.[16]

Statement 4: Routine "Test and Treat" for *H. pylori* infection is not recommended for patients with gastroesophageal reflux disease (GERD).

Level of agreement: 89%; Level of evidence: IV; Grade of recommendation: C

This statement was contentious and was considered in two contexts, depending on whether or not endoscopy had been done. In European studies of patients undergoing endoscopy for reflux symptoms, more than two-thirds will not have esophageal erosions present. In many countries of the Asia–Pacific region, an even higher proportion will be 'endoscopy negative'.[17] In these patients, it is often not clear whether symptoms are due to reflux or non-ulcer dyspepsia or another cause, as there is a marked overlap of symptoms. A substantial proportion of such patients will have *H. pylori* infection. In these patients the management strategy involves the choice between a trial of PPI therapy or *H. pylori* eradication therapy or both given sequentially. The reasons to consider eradication therapy are the same as for investigation of dyspepsia (see Statement 2): symptom improvement in some, long-term risk reduction, cost benefit and choice. When symptoms do not improve, the other benefits still pertain and this is not the case if only the PPI strategy is tried and fails. Many patients with predominant heartburn will need PPI therapy to control symptoms, so a sequential approach of *H. pylori* eradication followed by PPI therapy may be offered.

In patients who are endoscoped and found to have erosive esophagitis and *H. pylori* infection, PPI therapy is usually the mainstay of treatment for symptom control; treatment of *H. pylori* infection in this context relates to long-term risk reduction rather than symptom control.

The second group of patients are those with a clinical diagnosis of reflux disease in whom endoscopy is not warranted or not

available. The reasons to test for and treat *H. pylori* infection in such patients are similar to those for endoscopy-negative patients. Community data suggest that a proportion of patients with uninvestigated heartburn will respond symptomatically following eradication therapy; issues of risk reduction, cost and choice are again relevant.[18] As for patients with uninvestigated dyspepsia (overlapping symptoms may occur in up to 40%), those with unrecognized ulcer disease will be cured.

International consensus statements diverge with European[4,5] and Canadian[19] guidelines recommending treatment, while US guidelines[2] do not recommend treatment. In the Asia–Pacific region, where reflux disease is less common while ulcer disease and gastric cancer are more common, it was recognized that the likelihood and benefit of treating *H. pylori* infection will be commensurately greater.

Given the absence of definitive long-term data, it was agreed that the decision to test for and treat *H. pylori* infection in those with reflux predominant symptoms or endoscopically proven esophagitis should be considered on a case-by-case basis.

Lastly, there was consensus that eradication of *H. pylori* neither conferred an increased risk of causing GERD, nor of making pre-existing GERD harder to control with PPI therapy.[20] In Asia, some studies have shown an increase in GERD prevalence after *H. pylori* eradication,[21–24] whereas others have shown no effect on GERD incidence, or even improvement of pre-existent GERD symptoms.[25,26] Another long-term observational study indicated that even any increase in GERD incidence would not pose any serious problems for case management.[27]

Statement 5: *H. pylori* testing should be considered in patients receiving long-term maintenance treatment with PPI for gastroesophageal reflux disease.

Level of agreement: 100%; Level of evidence: IIA; Grade of recommendation: B

It was agreed that GERD is increasing in prevalence in some countries within the Asia–Pacific region.[8] It is likely therefore that there will be greater numbers of patients taking PPI therapy, including those who will need long-term maintenance therapy. It is accepted that long-term use of PPI causes a worsening of the histological grade of gastritis in *H. pylori*-infected patients. There is an accelerated risk of gastric mucosal atrophy that is not seen when PPI are used in uninfected patients or in those in whom eradication therapy has been given prior to long-term PPI use.[28,29] Gastric mucosal atrophy is known to be a risk factor for the development of gastric adenocarcinoma, so there is reason to consider eradicating *H. pylori* infection prior to long-term PPI use, particularly in younger patients. However, proof of any long-term benefits of such a strategy is not yet available, as existing data relate to intermediate histological end-points rather than the end-point of gastric cancer. For this reason, opinion is divided as to whether testing for and treating *H. pylori* infection should always precede long-term PPI therapy in GERD patients.[30] Decision making on a case-by-case basis was recommended. The cost-effectiveness of treating *H. pylori* in long-term PPI users in primary care has recently been shown with the benefit related to reduced symptom severity and a reduction in PPI use and other health-care costs.[31]

Statement 6: Screen and treat for *H. pylori* infection in communities with high incidence of gastric cancer is an effective strategy for gastric cancer prevention.

Level of agreement: 100%; Level of evidence: Ib; Grade of recommendation: A

Data from the region have emerged recently to allow estimation of the magnitude of gastric cancer risk associated with *H. pylori* infection. In a cohort in Taiwan, 1.3% of infected subjects developed gastric malignancy after a mean of just 6 years compared with no cases in non-infected subjects.[32] Given the lifelong risks of gastric cancer related to *H. pylori*, it is likely that the magnitude of the risk would increase significantly over time.

The Consensus Group endorsed a recent Asia–Pacific consensus guideline that concluded that screening and treating *H. pylori* was an evidenced-based and reasonable strategy in selected communities where the burden of gastric cancer is high.[13] Prospective evidence of a reduction in occurrence of gastric cancer is available from an 8-year prospective study in China.[33] In that cohort, eradication of *H. pylori* infection in those who had not already developed intestinal metaplasia and gastric mucosal atrophy resulted in a lower rate of gastric cancer over the study period compared to those who did not have eradication therapy. No such difference was seen in those patients who were given eradication but had pre-existing *H. pylori*-associated intestinal metaplasia and atrophy. However, it is plausible even in this group that rates of cancer may be lowered over a lifetime, and a longer duration of follow up is needed.

Other supportive data come from prospective studies of histological changes after eradication therapy. In one study, a histological score related to adverse changes including intestinal metaplasia, atrophy and dysplasia were all lower in those who had been given eradication therapy compared to those who had not.[34] As intestinal metaplasia and atrophy are known to be the dominant precursor and major risk factors for gastric cancer, this is important and persuasive information. Given the strength of the data from high prevalence regions, the need to screen and treat infected subjects to prevent cancer, rather than rely on radiological and/or endoscopy screening programs to find early cancers, has been emphasized.[35]

As tests to determine the individual host susceptibility to gastric cancer or the carcinogenic potential of the strain of *H. pylori* infecting an individual are not readily available in clinical practice, there is little opportunity at present to be selective about offering treatment to reduce individual and community risks for gastric cancer. There was agreement that the new data over the last decade confirm the value of a 'screen and treat' strategy in populations of high prevalence, although significant logistical issues need to be addressed for such a strategy to be widely adopted. Modeling data in high prevalence countries, such as China, suggest screening will be cost-effective.[36] Even in countries with relatively low prevalence of gastric cancer, modeling suggests that a 'screen and treat' strategy may be cost-effective at a level that may even exceed that of breast cancer and cervical cancer screening.[37] Further, recent intervention data that demonstrated a reduced risk of metachronous gastric cancer after eradication therapy have also confirmed the value of *H. pylori* eradication in secondary prevention.[38]

Statement 7: In areas with a high prevalence of both *H. pylori* infection and gastric cancer, eliminating *H. pylori* infection through improvements in public health and education will have the greatest impact in reducing the burden of gastric cancer.

Level of agreement: 100%; Level of evidence: III; Grade of recommendation: B

The prevalence of gastric cancer is in decline in developed and rapidly developing countries and this relates to a decline in *H. pylori* prevalence.[39] Nonetheless, gastric cancer still causes approximately 700 000 deaths globally each year.[39] There was consensus that notwithstanding the benefits of a 'screen and treat' strategy in regions of high prevalence of infection and gastric cancer, by far the greatest reduction in the burden of cancer will occur with improvements in public health and education. As with other great epidemic and endemic infections of populations over the ages, including tuberculosis, viral hepatitis and cholera, improvements in overall living standards will have the greatest impact by reducing the transmission and therefore the prevalence of *H. pylori* infection. Indeed, the decline in prevalence of *H. pylori* infection and of gastric cancer already witnessed in many places around the world is more likely to be attributable to changes in living standards and public health measures than medical treatment. Epidemiological data suggest that the prevalence of *H. pylori* infection in developed countries was already in decline prior to the recognition of the organism in the 1980s. The well-documented cohort effect is evidence of this change.[40] Unfortunately at present, only a tiny minority of those infected with *H. pylori* will ever get access to appropriate therapy. While treatment of an individual may reduce their risk of gastric cancer only a small minority of the population will be treated and such a strategy will have little impact on the overall population burden of gastric cancer. It is therefore incumbent on physicians to advocate at every level of government and health administration for public health measures to reduce the burden of *H. pylori* (as well as other common and important pathogens).

Statement 8: In non-steroidal anti-inflammatory drug (NSAID)-naive users, *H. pylori* eradication will reduce the risk of peptic ulcer and upper gastrointestinal bleeding.

Level of agreement: 100%; Level of evidence: Ia; Grade of recommendation: A

Much of the recent data relating to *H. pylori* and NSAID-associated risk for peptic ulcer and ulcer bleeding has been derived within the Asia–Pacific region, most notably from Hong Kong.[41–44] It constitutes a body of randomized controlled intervention trials that provides a high level of evidence for practice within the region.

It was recognized that the risk for NSAID-associated ulcer disease varies according to host risk factors. These include advanced age (with those aged > 75 years at particularly increased risk of complications), comorbidity, co-prescription of other drugs associated with ulceration and bleeding (aspirin, antiplatelet drugs, anticoagulants, corticosteroids and selective serotonin reuptake inhibitors), smoking and a past history of peptic ulcer disease or bleeding.[45,46] The relative risk of NSAID-associated peptic ulceration and bleeding also varies according to the relative toxicity of the NSAID used (related to the half life of the drug), the duration of therapy and the dose.[47]

Helicobacter pylori and NSAIDs are synergistic risk factors for the occurrence of peptic ulceration, and additive for bleeding. In endoscopic studies, the odds ratio (OR) for the presence of an ulcer when both risk factors are present is 60 (i.e. 6000% relative risk compared to when neither risk factor is present); for bleeding the OR is 6.[48]

For primary prevention of peptic ulcer in NSAID users, randomized, placebo-controlled Asian data demonstrate that eradication therapy prior to NSAID use reduces peptic ulcer and ulcer bleeding significantly, irrespective of whether PPI are also given.[43] These data are supported by a recent global meta-analysis that confirms that eradication of *H. pylori* infection prior to NSAID use significantly reduces the risk of peptic ulceration.[49]

It is not clear whether such data should be applied to all patients prior to commencing long-term NSAID therapy rather than selectively applying this information to those at greatest risk. There is agreement that risk assessment should be stratified according to the known host and drug-related risk factors but less agreement exists about those at apparently low risk.[50]

Statement 9: In patients receiving long-term NSAIDs who have a past history of peptic ulcer disease or complications of peptic ulcer disease, *H. pylori* eradication alone is not sufficient to prevent ulcer recurrence and/or bleeding.

Level of agreement: 100%; Level of evidence: 1b; Grade of recommendation: A

This group of patients comprises those who are susceptible to NSAID-related peptic ulceration and in whom *H. pylori* infection may be coincidental or additive rather than causal. Eradication alone in this group is therefore often insufficient to abolish the risk of recurrent ulceration or bleeding although it may lower that risk somewhat. A randomized controlled trial showed a greater benefit of PPI therapy over *H. pylori* eradication in this context.[42] It was agreed that treatment of both risk factors, namely, eradication therapy and PPI therapy, was likely to afford the greatest protection,[43] and that, in those who needed on-going NSAID therapy, co-administration of PPI was appropriate.

In contrast, for patients with an *H. pylori*-associated ulcer, or a past history of ulcer disease, *prior* to NSAID use, eradication is mandatory before NSAIDs are administered, as this is a core indication for treatment (i.e. *H. pylori*-associated peptic ulcer disease).

Statement 10: Before starting long-term aspirin therapy for patients at high risk for ulcer and ulcer-related complications, testing for and eradication of *H. pylori* infection are indicated.

Level of agreement: 100%; Level of evidence: 1b; Grade of recommendation: B

The risk of aspirin-related upper gut bleeding is dose-related[51] and independent of the formulation (enteric coated, buffered or plain).[52] The risk of peptic ulcers seen at endoscopy in elderly, *H. pylori*-infected aspirin users is more than twice that seen in

uninfected subjects.[53] The risk of upper gut bleeding in aspirin users is also increased by concomitant *H. pylori* infection (OR = 4.7) or a past history of ulcer disease (OR = 15.2).[54] The value of prophylactic eradication prior to aspirin use in all patients is uncertain, but it is reasonable to consider treatment in those with other significant risk factors for ulcer or bleeding.[55] Other factors suggesting high risk are an older age (> 60 years, but especially when > 75 years), concomitant use of anticoagulants and systemic corticosteroids, and severe comorbid diseases.[56]

Statement 11: Treating *H. pylori* infection in patients receiving long-term low-dose aspirin therapy and who have a past history of upper gastrointestinal bleeding and perforation will reduce risk of recurrent hemorrhage.

Level of agreement: 100%; Level of evidence: 1b; Grade of recommendation: B

A randomized controlled trial of *H. pylori* eradication or PPI therapy showed no difference between these two treatments in the secondary prevention of ulcer bleeding in patients continued on low-dose aspirin. In 250 high-risk patients continuing low-dose aspirin, the 6-month recurrent ulcer bleeding rates after eradication therapy or with omeprazole 20 mg daily were 1.9% and 0.9%, respectively.[42] Another randomized controlled trial showed a marked reduction in recurrent ulcer complications in low-dose aspirin-users following sequential *H. pylori* eradication therapy and then PPI prophylaxis. In 123 high-risk patients who had prior ulcer complications, the risk of recurrent complications with continued low-dose aspirin was reduced from 15% in those who had *H. pylori* eradication therapy alone (on an intention-to-treat basis) to 1.6% in those given eradication therapy followed by lansoprazole 30 mg daily.[57] Based on these data, the recommended strategy is for *H. pylori* eradication therapy, followed by PPI prophylaxis in high-risk patients. The value of prophylactic eradication is less certain for aspirin users with no prior history of ulcer or ulcer complication and with no other risk factors.

Statement 12: *H. pylori* infection should be sought for and treated in patients with unexplained iron deficiency anemia and idiopathic thrombocytopenic purpura (ITP).

Level of agreement: 83%; Level of evidence: III; Grade of recommendation: C

It was agreed that there is sufficient evidence from a number of studies to conclude that *H. pylori* may play a small role in iron deficiency.[58] Infection has been shown to be a stressor of iron stores in some children and in women.[58,59] It was emphasized, however, that *H. pylori* infection should never be considered the sole cause of iron deficiency in uninvestigated patients, and that investigation of iron deficiency always should proceed along usual clinical lines irrespective of *H. pylori* status. The effect of *H. pylori* on iron stores may be greatest in those with marginal dietary iron intake or other stressors of iron stores. In the absence of any other definable cause for iron deficiency, following investigation, it was considered reasonable to treat *H. pylori* infection, while recognizing that this may benefit only a minority of such patients.

Data relating to ITP were agreed to be suboptimal and inconclusive. A recent meta-analysis and a systematic review were not convincing as they were based on less than ideal data.[60,61] Nonetheless, there is some evidence for an association, and it is reasonable to treat *H. pylori* infection when found in this context. It is accepted that only a minority of such patients may respond.

Statement 13: Urea breath tests and monoclonal stool antigen tests are accurate and appropriate tests for confirmation of *H. pylori* eradication.

Level of agreement: 100%; Level of evidence: IIb; Grade of recommendation: B

When endoscopy is not indicated, C^{13} or C^{14} urea breath tests are accepted as accurate non-invasive tests for initial diagnosis and for the determination of the outcome of *H. pylori* eradication therapy. However, local validation is required. This is because some providers have modified a number of the test parameters, including the dose of isotope, duration of breath collection, requirement to fast, use of a test drink to slow gastric emptying and analytical equipment. There is a greater weight of evidence validating the ^{13}C urea test in the context of outcome assessment; it is non-radioactive in nature, and European guidelines recommend this test, although either test is acceptable in the Asia–Pacific region after appropriate validation. Breath tests consistently show the highest diagnostic accuracy among non-invasive tests, and results are comparable to biopsy-based tests.[5,62,63]

Newer stool antigen tests have been validated for use in outcome assessment, and have an accuracy rate comparable to breath tests.[64] As with breath tests, their accuracy rate may be affected by concomitant or recent PPI or antibiotic use. Test accuracy is also affected by not storing stool samples appropriately; sensitivity declines when samples are left at room temperature.[64] The accuracy of stool tests in routine use has been less studied outside of specialized units in the Asia–Pacific context.

In general, outcome assessment after eradication therapy is recommended, as a significant proportion of patients fail to achieve eradication after initial therapy. Unrecognized ongoing *H. pylori* infection leaves the patient vulnerable to the medical complications of infection, and the physician vulnerable to any medico-legal consequences. The importance of determining outcome will vary according to the indication for therapy. In those with ulcer disease, especially complicated ulcer disease, or a family history of gastric cancer there is more to gain from successful eradication and more to risk if treatment fails than among patients treated only for dyspepsia. While it was agreed that outcome assessment in these patients is recommended, there was discordant opinion about the necessity or feasibility of providing outcome assessment in all treated patients. It was agreed that practice varies between countries and health systems. Moreover, access and regulatory approval of tests varies between countries in the region. The availability of appropriate salvage or maintenance therapies will also influence practice. Outcome assessment should be done not less than 4 weeks after the completion of eradication therapy, and PPI should be withheld for 1 and preferably 2 weeks prior to testing.[65]

Statement 14: Serological tests have a limited role in the management of *H. pylori* infection.

Level of agreement: 100%; Level of evidence: IIa; Grade of recommendation: B

It was affirmed that serological tests are the least accurate diagnostic test for *H. pylori* infection, and are not useful to determine the outcome of therapy. In some countries they are not accepted as accurate enough for individual diagnostic decision-making, whereas in others they are the mainstay of diagnosis because of their availability and low cost. It was agreed that where better alternative tests are accessible, these are preferred. There are a few instances where a supplementary serological test may aid decision-making, such as in cases with discordant biopsy-based tests, or in whom biopsies reveal active chronic gastritis in the absence of organisms. Such histology is highly suggestive of infection, and a high titer serological test is helpful in this context. Similarly in bleeding patients, biopsy-based tests for *H. pylori* have a higher false-negative rate, and a high titer serological test is also useful in this context. As PPI and antibiotic use increase the false-negative rate of biopsy, breath and stool antigen tests, a serological test may be helpful when use of these agents cannot be avoided. Serological tests must be validated locally. There is variable cross-reactivity with other bacterial antigens and the antigenicity of a locally prevalent strain may be different from strains used for immunoassays by manufacturers, thus lowering the sensitivity.

Serological tests provide a high negative predictive value in low prevalence areas, and may be useful in high prevalence areas when there are no better alternatives; in this context, they have higher positive predictive value. However, published comparisons of serological tests show very variable accuracy.[66] This lack of precision is considered too great for use in individual clinical decisions when better alternatives are available. Use of such tests for seroepidemiological studies remains practical and reasonable. In general, laboratory-based serological tests are more accurate than office-based tests.

II: Treatment of *H. pylori* infection (Table 3)

Statement 15: In Asia, the currently recommended first-line therapy for *H. pylori* infection is PPI, amoxicillin and clarithromycin for 7 days.

Level of agreement: (a) 94%; (b) 6%; Level of evidence: I; Grade of recommendation: A

Table 3 Treatment regimens for *Helicobacter pylori*

Standard proton pump inhibitor (PPI)-based triple therapy: 7–14 days
PPI, amoxicillin 1 g, clarithromycin 500 mg twice daily
PPI, metronidazole 400 mg, clarithromycin 500 mg twice daily
PPI, amoxicillin 1 g, metronidazole 400 mg twice daily
Quadruple therapy: 7–14 days
PPI twice daily, bismuth 240 mg twice daily, metronidazole 400 mg twice daily or three times daily, tetracycline 500 mg four times daily
Levofloxacin-based triple therapy: 10 days
PPI, levofloxacin 250 mg (or 500 mg), amoxicillin 1 g twice daily
Rifabutin-based triple therapy: 7–10 days
PPI, rifabutin 150 mg, amoxicillin 1 g twice daily

This was similar to the 1997 Asia–Pacific Consensus. In several multicenter studies, the use of a regimen containing PPI, amoxicillin and clarithromycin each given twice daily for a week, has been shown to achieve high eradication rates; these reach 90% or greater by per-protocol analysis (PPA), and 80% or greater by ITT analysis.[1,67–69] Although some other studies have shown a lower eradication rate, they were still 80% or higher on an ITT analysis.[70–74] Metronidazole is an acceptable alternative to amoxicillin or clarithromycin in triple-therapy regimens, with similar eradication rates[5,69,71] However, it has not been as widely used in the Asia–Pacific region, where the amoxicillin-containing combinations are preferred over those containing metronidazole, especially in countries where rates of metronidazole resistance exceed 30%. In Japan, the use of metronidazole is limited because of a lack of regulatory approval for its use in *H. pylori* eradication therapies.[75]

When a patient has penicillin allergy, the most common first-line choice of therapy is to substitute metronidazole for amoxicillin in triple therapy. This fails in 20–25% of cases, and secondary dual resistance is common. Another choice is to use bismuth-based quadruple therapy as first-line treatment. An alternative approach, when the history of allergy is not certain, is to formally test for penicillin allergy using the radioallergosorbent test and skin prick tests; if both are negative, a medically supervised oral challenge with amoxicillin is reasonable. In a small study using such an approach, 80% of patients previously excluded on history from using amoxicillin were able to be safely treated with amoxicillin-based first and/or salvage therapies, and eradication was achieved in every case.[76]

Statement 16: There is an increasing rate of resistance to clarithromycin and metronidazole in parts of Asia. This has led to reduced efficacy of PPI-based triple therapy.

Level of agreement: (a) 100%; Level of evidence: III

In parts of Asia, increasing rates of primary resistance to clarithromycin and high or increasing rates of metronidazole resistance have been reported. In Japan, a working group of the Japanese Society for Helicobacter Research undertook a surveillance study to determine the current antimicrobial susceptibility profiles of *H. pylori* isolates during the period 2002–2005.[77] A total of 37 institutions were involved and 3707 isolates analyzed. Resistance to clarithromycin increased from 19% to 28% over the 3-year period. Unlike other parts of Asia, this study showed that resistance to metronidazole in Japan remained low at 3.3–4.9% during the study period, reflecting the restricted use of metronidazole in Japan.

In Korea, a study of 652 isolates from 1994–1999 revealed that resistance to metronidazole and clarithromycin increased from 33% to 48%, and 4.8% to 7.7%, respectively.[78] In another smaller Korean study of 135 isolates, primary resistance to clarithromycin was reported to have increased from 2.8% in 1994 to 14% in 2003, while that for metronidazole rose from 53% in 1987 to 66% in 2003.[79] In Beijing, China, resistance rates of *H. pylori* to metronidazole and clarithromycin in 1999–2000 were 36% and 10%, respectively, and increased to 43% and 18%, respectively, in 2001–2002.[80] In Hong Kong, a single center study showed that the prevalence of metronidazole resistance increased from 22% in

1991 to 73% in 1995.[81] In a more recent single center study, the point prevalence of *H. pylori* strains resistant to metronidazole and clarithromycin were 49% and 11%, respectively.[82] In Taiwan, the point prevalence of metronidazole resistance published in 2000 and 2007 from two different centers was 32%[83] and 52%,[84] respectively. A 2003 multicenter Indian study showed that the *H. pylori* resistance rate was 78% for metronidazole and 45% for clarithromycin.[85] Although time-trend data are not available, this shows the magnitude of the current problem of antibiotic resistance in India. When considering the increase in primary antibiotic resistance, there is a possibility of sampling bias because most studies are from referral centers and may not reflect true community prevalence. In Japan, there is a national reference laboratory making data more robust. There is a need for systematic prospective surveillance of antibiotic resistance rates in the region.

In a longitudinal observational study from Korea, the yearly *H. pylori* eradication rates by PPA for the years 1998–2005 were 84%, 80%, 81%, 79%, 75%, 78%, 79% and 78% consecutively.[86] The differences are not statistically significant, so the impact of any possible rise in resistance is not yet evident. An analysis of outcome data from recently published trials noted that eradication rates for PPI, amoxicillin, clarithromycin triple therapy had fallen below 80% on an ITT basis, and that this most likely reflected the increasing rate of clarithromycin resistance.[87] The impact of antibiotic resistance on treatment efficacy was clearly shown in a meta-analysis of 93 studies embracing 10 178 patients.[88] In patients receiving triple therapy consisting of a PPI, amoxicillin and clarithromycin, clarithromycin resistance decreased treatment efficacy by 66% (95% confidence interval [CI]: 58–74%). When the triple therapy consisted of PPI, metronidazole and clarithromycin, clarithromycin resistance reduced treatment efficacy by 35% (25–45%). In the presence of metronidazole resistance, the efficacies of triple therapy with PPI, amoxicillin and metronidazole, and PPI, clarithromycin and metronidazole, were reduced by 30% (95% CI: 22–38%) and 18% (95% CI: 13–23%), respectively. Primary resistance to clarithromycin and metronidazole reflects the wider community use of these antibiotics as monotherapy for other indications. To address the problem of decreased efficacy of *H. pylori* eradication therapies, the amount of monotherapy use should be reviewed. In addition, national epidemiological surveillance of resistance rates should be monitored, as this will affect local choices of first-line treatment based on resistance thresholds. The Maastricht Consensus recommended that the threshold of clarithromycin resistance at which it should not be used, or when susceptibility testing needs to be performed, was 15–20%. The corresponding threshold for metronidazole was 40%, notwithstanding the possibility of discordance between *in vitro* and *in vivo* resistance.[5]

Statement 17: Fourteen-day triple therapy confers limited advantage over 7-day triple therapy in *H. pylori* eradication rates.

Level of agreement: (a) 94%; (b) 6%; Level of evidence: I; Grade of recommendation: A

A meta-analysis of randomized controlled trials examined the effect of treatment duration on success rate.[89] Of 21 studies, 14 were from Europe, three from USA, two from Asia and one from South Africa. Thirteen of the studies (1982 patients), compared 7 versus 10 days of treatment, while 13 studies (2849 patients) compared 7 with 14 days of treatment. Meta-analysis yielded relative risks (RR) for eradication of 1.05 (95% CI: 1.01–1.10) for 7-day compared with 10-day triple therapy; the eradication rates were 77% for 7-day therapy, and 81% for 10-day therapy. When 7- and 14-day treatments were compared, the RR was 1.07 (95% CI: 1.03–1.12); the eradication rates were 73% and 78%, respectively. For the single Asian study in the meta-analysis that compared 14- with 7-day treatment, there was no difference in *H. pylori* eradication rates.[90] Despite the minor statistical difference between 7- and 14-day treatments in the meta-analysis, it was concluded that extending triple therapy beyond 7 days was unlikely to be a clinically useful strategy, because the difference in magnitude was small. In addition, it may not be cost-effective, and adverse effects, cost and compliance to treatment need to be addressed.

Statement 18: Bismuth-based quadruple therapy is an effective alternative first-line therapy for *H. pylori* eradication.

Level of agreement: (a) 88%; (b) 12%; Level of evidence: I; Grade of recommendation: A

A meta-analysis compared quadruple therapy with triple therapy for *H. pylori* eradication. There was no difference between either strategy by both PPA and ITT. In PPA, eradication was achieved in 88% with quadruple therapy (95% CI: 84–90%) and in 85% with triple therapy (95% CI: 81–88%), and the OR was 0.81 (95% CI: 0.55–1.20; $P = 0.3$). By ITT, the eradication rate was 81% with quadruple therapy (95% CI: 77–84%) and 78% with triple therapy (95% CI: 74–81%). The OR was 0.83 (95% CI: 0.61–1.14; $P = 0.3$).[91] This meta-analysis included the results of a multicenter North American randomized study that was initially only available in abstract form, but was subsequently published in full the same year.[92] In that study, the *H. pylori* eradication rate was similar between bismuth-based quadruple therapy and PPI-based triple therapy, with ITT eradication rates of 88% and 83%, respectively ($P = 0.29$). The consensus group agreed unanimously on the efficacy of bismuth-based quadruple therapy; disagreement on its indication as first time therapy reflected the view of some that it should be reserved for use as a second-line therapy, and the fact that this regimen is not available in some countries such as Japan and Australia.

Statement 19: There are currently insufficient data to recommend sequential therapy as an alternative first line for *H. pylori* therapy in Asia.

Level of agreement: 100%; Level of evidence: IV; Grade of recommendation: C

There is recent interest in the use of a 10-day sequential therapy which consists of 5 days of treatment with a PPI and one antibiotic (usually amoxicillin), followed by 5-day treatment with the PPI and two other antibiotics (usually clarithromycin and a 5-nitroimidazole). The rationale for this approach is that amoxicillin may weaken the bacterial cell wall in the initial phase of treatment, and prevent the development of drug efflux channels that inhibit clarithromycin from binding to ribosomes and thus help to improve the efficacy of clarithromycin in the second phase of treatment. A meta-analysis involving 10 randomized controlled

trials with 2747 patients calculated an eradication rate of 93% (95% CI: 91–96%) for sequential therapy and 77% (95% CI: 71–83%) for standard triple therapy (RR reduction, 71% [95% CI: 64–77%]; absolute RR, 16% [95% CI: 14–19%]).[93] Commentators have pointed out the likelihood of publication bias and other deficiencies in the current data. There is therefore a clear need for multicenter, multi-region randomized trials to determine whether this therapy offers any real advantage. In the single published Asian study, no difference was found between a 10-day sequential therapy and a PPI-based triple therapy. By PPA, eradication rates were 86% and 77% respectively ($P = 0.15$); by ITT analysis, eradication rates were 78% and 72%, respectively ($P = 0.361$).[94] The Consensus Group agreed that it was premature to recommend the use of sequential therapy in Asia.

Statement 20: Salvage therapy for *H. pylori* eradication includes: (i) a standard triple therapy that has not been previously used; (ii) bismuth-based quadruple therapy; (iii) levofloxacin-based triple therapy; and (iv) rifabutin-based triple therapy.

Level of agreement: (a) 94%; (b) 6%; Level of evidence: I; Grade of recommendation: A

It was agreed that there was a lack of well-powered multicenter randomized trials of salvage therapies and a paucity of direct comparison between salvage options. Nonetheless, there was enough evidence of efficacy to allow recommendations for the choices of salvage treatments.

1: Standard triple therapy that has not been previously used. An option after first-line eradication failure is to use a standard triple therapy that contains an antibiotic that has not been used previously. In Japan, for instance, where the prevalence of metronidazole resistance is low, in the event of failure of PPI, amoxicillin, clarithromycin triple therapy, the use of PPI, amoxicillin and metronidazole triple therapy is a viable alternative. Such a second-line strategy in Japan has been reported to achieve eradication rates of 88% by ITT (without susceptibility testing) or 94% with susceptibility testing.[95] Very similar results have been reported in another Japanese multicenter study using this strategy.[96] In patients who had failed metronidazole-based triple therapy treatment with amoxicillin, amoxicillin-based triple therapy or quadruple therapy revealed PPA and ITT efficacies of 82% (95% CI: 64–100%) and 75% (95% CI: 56–94%) for triple therapy and 80% (96% CI: 64–96%) and 71% (95% CI: 54–88%) for quadruple therapy, respectively. These differences were not statistically significant.[97]

2: Bismuth-based quadruple therapy. Bismuth-based quadruple therapy is useful as a second-line therapy after failure of PPI-based triple therapy. In a study that evaluated PPI, bismuth, tetracycline and metronidazole as salvage therapy after failed PPI, amoxicillin and clarithromycin in 53 patients, on an ITT basis, the eradication rate was 70% by PPA and 82% by ITT.[98] In another study of 118 patients that evaluated PPI, bismuth, tetracycline, metronidazole quadruple therapy as either first-line or salvage therapy, the PPA eradication rate was 98% and 95% (95% CI: 90–98%) per ITT.[99] In another study with 78 patients that evaluated salvage PPI, bismuth, amoxicillin and clarithromycin quadruple therapy after unsuccessful bismuth-based triple therapy (bismuth, metronidazole, tetracycline), successful eradication was achieved in 83% (95% CI: 75–91%).[100] A recent study with 133 patients compared the efficacy of *H. pylori* eradication with pantoprazole-based 7-day triple therapy (pantoprazole 40 mg b.i.d., amoxicillin 1.0 g b.i.d., clarithromycin 500 mg b.i.d.) (PAC) versus 7- or 10-day quadruple therapy (pantoprazole 40 mg b.i.d., bismuth potassium citrate 220 mg b.i.d., metronidazole 400 mg t.i.d., tetracycline 750 mg b.i.d.) (PBMT). The *H. pylori* eradication rates by PPA were 75%, 83% and 91%, respectively; while by ITT analysis in the 7-day PAC group, 7- and 10-day PBMT groups, the rates were 73%, 79% and 89%, respectively. The eradication rate in the 7-day PAC group was significantly lower than that in the 10-day PBMT group.[101] It was concluded that the 10-day quadruple regimen could be considered as the first-choice therapy for *H. pylori* infection when the efficacy of 7-day standard triple therapy was decreased.

3: Levofloxacin-based triple therapy. The efficacy of salvage therapy with levofloxacin-based triple therapy compared with quadruple therapy was addressed in a recent meta-analysis of 14 studies with 977 patients. All but four studies prescribed levofloxacin at doses of 250 mg twice daily or 500 mg once daily. In two studies, higher doses of levofloxacin (500 mg b.i.d.) were given. Most of the studies combined a PPI and amoxicillin with levofloxacin, and only three studies used azithromycin, rifabutin or furazolidone instead of amoxicillin. The overall *H. pylori* eradication rate with levofloxacin-based regimens was 80% (95% CI: 77–82%). When administered for 7 days, the rate was 73% (95% CI: 68–79%) and 81% (95% CI: 78–84%) when 10-day regimens were used ($P < 0.01$). When levofloxacin-based triple regimens were compared with quadruple regimens, the eradication rate (pooled data) with levofloxacin was 81% (95% CI: 78–85%) and 70% (95% CI: 66–74%) with the quadruple regimen. When only more rigorous studies were considered, the advantage of the levofloxacin regimen over the quadruple regimen increased (88% [95% CI: 84–92%] vs 64% [95% CI: 58–70%]), with an OR of 4.11 (95% CI: 1.89–8.95). There were also less adverse effects with the levofloxacin regimen (19% vs 44%; OR = 0.27; 95% CI: 0.16–0.46).[102]

4: Rifabutin-based triple therapy. Rifabutin is derived from rifampicin and is used in rescue treatment of tuberculosis. It has activity against *H. pylori in vitro*, achieving lower levels of minimum inhibitory concentration than obtained by clarithromycin and amoxicillin and its effectiveness does not depend on the pH of the medium.[103] Rifabutin-based triple therapy has been found to be a useful salvage therapy. A 10-day rifabutin triple therapy of pantoprazole, amoxicillin and rifabutin (either 150 or 300 mg) against quadruple therapy (pantoprazole, bismuth, metronidazole, tetracycline) revealed higher eradication rates in the rifabutin 300-mg group (87% ITT), compared with the other groups (67%).[104] On an ITT basis, the eradication rate was highest. Results of case series giving triple therapy with twice daily PPI, rifabutin 150 mg, amoxicillin 1 g for 7 and 10 days have shown PPA, ITT eradication rates of 86%, 72% and 76%, 72%, respectively.[105,106] In the latter study, when rifabutin was used as a second-line therapy, the eradication rate was 95%, compared to

68% when two or more previous treatments had been given. In another study of 10-day PPI, rifabutin 150 mg and amoxicillin therapy as a third-line treatment, the PPA and ITT eradication rates were 62% and 61%, respectively.[107] Conversely, a comparison of omeprazole, amoxicillin, rifabutin 1-week triple therapy with omeprazole, bismuth, tetracycline, metronidazole 1-week quadruple therapy, as second-line treatment, favored the quadruple therapy in both PPA (77% vs 44%) and ITT (70% vs 45%).[108] A comparison of a 10-day levofloxacin-based triple therapy (PPI, amoxicillin, levofloxacin) with rifabutin-based triple therapy (PPI, amoxicillin, rifabutin) in patients who had previously failed standard triple therapy and second-line quadruple therapy, favored levofloxacin-based triple therapy. The PPA and ITT eradication rates were 45% versus 85% and 45% versus 81%, respectively.[109] PPI and rifabutin have been combined with moxifloxacin[110] or levofloxacin.[111] Results of past studies are promising with PPA/ITT eradication rates of 83%/73%[110] and 91%/91%,[111] respectively. Rifabutin carries a small risk of neutropenia, and this has sometimes led to it being used after failure of other second-line therapies. However, its efficacy is greater as second rather than subsequent treatment.

Quadruple therapy has been used as a salvage therapy for the longest time and experience with it is therefore more extensive than for other salvage therapies. However, recent data do provide clinicians more options. The choice of salvage therapy depends on factors such as the local pattern of antibiotic resistance, drug availability, previous treatment, and perhaps the local prevalence of tuberculosis in the context of rifabutin use. For instance, levofloxacin-based triple therapy may be an effective second-line therapy in areas with low levofloxacin resistance rates, and rifabutin, if available, may be considered in regions with low prevalence of tuberculosis.

Statement 21: CYP2C19 polymorphisms may affect *H. pylori* eradication rates in PPI-based triple therapy. Choice of PPI or increasing the dose is a more practical approach than CYP2C19 genotyping in the clinical setting to overcome CYP2C19 polymorphisms in the context of salvage therapy.

Level of agreement: (a) 94%; (b) 6%; Level of evidence: IV; Grade of recommendation: C

PPI are crucial to *H. pylori* eradication regimens. PPI make the acid-labile antibiotics more stable and by increasing the concentration of antibiotics in the gastric juice they increase the sensitivity of *H. pylori* to antibiotics.[112] PPI also possess modest intrinsic antimicrobial properties. Metabolism of PPI depends on hepatic cytochrome P450 enzymes, especially the CYP2C19 genotype. The CYP2C19 genotype exists as three polymorphisms which effect rates of drug metabolism and thereby effect the pharmacodynamics of PPI. The most common, wild-type, homozygous extensive metabolizer (HomEM) genotype consists of two normal alleles, with resulting normal enzyme levels. Thus, people who are CYP2C19 EM metabolize the PPI at a higher rate, limiting bioavailability, and consequently lowering antisecretory efficacy. The heterozygous EM (HetEM) contains one wild-type allele and one mutant allele, resulting in compromised production of the enzyme and thus, slower metabolism of the PPI. In the poor metabolizer (PM) genotype, both alleles are mutated. This results in a much slower rate of PPI metabolism, ensuring greater bioavailability and subsequently increased antisecretory efficacy. The antisecretory efficacy of various PPI is affected by CYP2C19 polymorphisms to different degrees; omeprazole is most affected, followed by lansoprazole and rabeprazole, which is least affected.[112]

A meta-analysis analyzed the effect of the CYP2C19 genotype on *H. pylori* eradication rates when omeprazole, lansoprazole and rabeprazole were used.[112] When all eradication rates, regardless of PPI used, were combined there was no significant difference between PM and HetEM, but there was a significant difference between HetEM and HomEM (OR = 1.90; 95% CI: 1.38–2.60; $P < 0.0001$). Subanalysis of individual PPI revealed that dual and triple omeprazole therapies significantly favored higher *H. pylori* eradication rates in PM over HomEM (OR = 4.03; 95% CI: 1.97–8.28; $P = 0.0001$) and over HetEM (OR = 2.24; 95% CI, 1.09–4.61; $P = 0.03$). Dual and triple rabeprazole and triple lansoprazole therapies did not show significantly different *H. pylori* eradication rates between PM and HomEM.

The effect of CYP2C19 polymorphism on esomeprazole-based triple therapy was also assessed. An increased dose of esomeprazole 40 mg twice daily in triple therapy may improve the *H. pylori* eradication rate compared to omeprazole-based therapy for HomEM of CYP2C19.[113] Two hundred *H. pylori*-infected dyspeptic patients were randomized to receive clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily plus either omeprazole 20 mg or esomeprazole 40 mg twice daily for 1 week. For patients classified as HomEM, the PPA *H. pylori* eradication rate was significantly higher in the esomeprazole group than in the omeprazole group (93% vs 76%, $P < 0.05$). A study of the role of the CYP2C19 genotype in the success of eradication of *H. pylori* infection in patients receiving pantoprazole- or esomeprazole-based triple therapy reported an overall eradication rate in PM that was significantly higher than in the EM groups (97% vs 83%; $P = 0.016$). This difference was present whether pantoprazole (95.7% vs 80.8%) or esomeprazole (100% vs 87%) were used.[114]

A recent editorial commented that the impact of CYP2C19 gene polymorphisms on the success of *H. pylori* eradication therapies may be significant in Asia because PM account for 15–23% or more of the population.[115,116] This raises the question of whether determination of CYP2C19 genotype is required before starting *H. pylori* therapy in Asia. The Consensus Group considered that this was not yet practical because of the cost and limited availability of genotyping tests. PPI choice and/or dose, rather than CYP2C19 genotyping, could be a more practical approach to assure the highest *H. pylori* eradication rates in a clinical setting.[115]

Statement 22: Smoking adversely affects the outcome of *H. pylori* eradication therapy.

Level of agreement: (a) 94%; (b) 6%; Level of evidence: I; Grade of recommendation: A

Smoking increases the number of treatment failures of *H. pylori* eradication therapy. A meta-analysis of 22 studies and 5538 patients found that the summary OR for eradication failure among smokers relative to non-smokers was 1.95 (95% CI: 1.55–2.45; $P < 0.01$). This corresponded to a difference in eradication rate of 8.4% (95% CI: 3.3–13.5%; $P < 0.01$) between smokers and non-smokers, in favor of non-smokers.[117] Conversely, stopping smoking during *H. pylori* therapy may improve eradication rates

among smokers. Smokers who stopped smoking during eradication therapy showed the same efficacy as non-smokers, whereas those who continued smoking experienced a worse result on average.[118]

Mechanisms postulated to explain the negative effect of smoking on *H. pylori* eradication include the following: (i) possible reduction of delivery of antibiotics to the gastric mucosa on account of the reduction in gastric mucosal blood flow and mucus secretion by smoking; and (ii) association of smoking with other confounders, such as reduced compliance to treatment.[117]

Conclusions

There is an increasing rate of resistance to clarithromycin and metronidazole in Asia, leading to reduced efficacy of PPI-based triple therapy. Knowledge of the local resistance pattern is important to guide the choice of appropriate therapy. Salvage therapies include standard triple therapy that has not been previously used, bismuth-based quadruple therapy, levofloxacin-based or rifabutin-based triple therapy. Smoking cessation and changing the dose or choice of PPI, may improve eradication rates. The role of antibiotic sensitivity testing was not addressed specifically, but it should be considered for surveillance of trends in antibiotic resistance, as well as in selected cases as a guide to salvage therapies. In most cases, however, it will not influence the choice of second- or third-line therapies.

References

1 Lam SK, Talley NJ. Report of the 1997 Asia–Pacific Consensus Conference on the management of *Helicobacter pylori* infection. *J. Gastroenterol. Hepatol.* 1998; **13**: 1–12.

2 Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 2007; **102**: 1808–25.

3 Bourke B, Ceponis P, Chiba N *et al.* Canadian Helicobacter Study Group Consensus Conference: Update on the approach to *Helicobacter pylori* infection in children and adolescents–an evidence-based evaluation. *Can. J. Gastroenterol.* 2005; **19**: 399–408.

4 Caselli M, Zullo A, Maconi G *et al.* "Cervia II Working Group Report 2006": guidelines on diagnosis and treatment of *Helicobacter pylori* infection in Italy. *Dig. Liver Dis.* 2007; **39**: 782–9.

5 Malfertheiner P, Megraud F, O'Morain C *et al.* Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772–81.

6 Shi R, Xu S, Zhang H. Prevalence and risk factors for *Helicobacter pylori* infection in Chinese populations. *Helicobacter* 2008; **13**: 157–65.

7 Hoang TTH, Bengtsson C, Phung DC, Sorberg M, Granstro M. Seroprevalence of *Helicobacter pylori* infection in urban and rural Vietnam. *Clin. Diagn. Lab. Immunol.* 2005; **12**: 81–5.

8 Tan HJ, Goh KL. Changing epidemiology of *Helicobacter pylori* in Asia. *J. Dig. Dis.* 2008; **9**: 186–9.

9 Yim JY, Kim N, Choi SH *et al.* Seroprevalence of *Helicobacter pylori* in South Korea. *Helicobacter* 2007; **12**: 333–40.

10 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J. Clin. Oncol.* 2006; **24**: 2137–50.

11 Moayyedi P, Deeks J, Talley NJ, Delaney B, Forman D. An update of the cochrane systematic review of *helicobacter pylori* eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *Am. J. Gastroenterol.* 2003; **98**: 2621–6.

12 Hsu PI, Lai KH, Lo GH *et al.* Risk factors for ulcer development in patients with non-ulcer dyspepsia: a prospective two year follow up study of 209 patients. *Gut* 2002; **51**: 15–20.

13 Fock KM, Talley N, Moayyedi P *et al.* Asia-Pacific Gastric Cancer Consensus Conference. Asia-Pacific consensus guidelines on gastric cancer prevention. *J. Gastroenterol. Hepatol.* 2008; **23**: 351–65.

14 Chiba N, van Zanten S, Sinclair P, Ferguson R, Escobedo S, Grace E. Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment – *Helicobacter pylori* positive (CADET-Hp) randomised controlled trial. *BMJ* 2002; **324**: 1012–16.

15 Mahadeva S, Chia YC, Vinothini A, Mohazmi M, Goh KL. Cost-effectiveness of and satisfaction with a *Helicobacter pylori* "test and treat" strategy compared with prompt endoscopy in young Asians with dyspepsia. *Gut* 2008; **57**: 1214–20.

16 Lane JA, Murray LJ, Noble S *et al.* Impact of *Helicobacter pylori* eradication on dyspepsia, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial. *BMJ* 2006; **332**: 199–204.

17 Sharma P, Wani S, Romero Y, Johnson D, Hamilton F. Racial and geographic issues in gastroesophageal reflux disease. *Am. J. Gastroenterol.* 2008; **103**: 2669–80.

18 Schwizer W, Thumshirn M, Dent J *et al. Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001; **357**: 1738–42.

19 Veldhuyzen van Zanten SJ, Bradette M, Chiba N *et al.* Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. *Can. J. Gastroenterol.* 2005; **19**: 285–303.

20 Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon AT. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001; **121**: 1120–6.

21 Hamada H, Haruma K, Mihara M *et al.* High incidence of reflux oesophagitis after eradication therapy for *Helicobacter pylori*: impacts of hiatal hernia and corpus gastritis. *Aliment. Pharmacol. Ther.* 2000; **14**: 729–35.

22 Koike T, Ohara S, Sekine H *et al.* Increased gastric acid secrection after *Helicobacter pylori* eradication may be a factor for developing reflux oesophagitis. *Aliment. Pharmacol. Ther.* 2001; **15**: 813–20.

23 Wu JCY, Chan FKL, Ching JYL *et al.* Effect of *Helicobacter pylori* eradication on treatment of gastrooesophageal reflux disease: a double blind, placebo controlled, randomized trial. *Gut* 2004; **53**: 174–9.

24 Kawanishi M. Development of reflux esophagitis following *Helicobacter pylori* eradication. *J. Gastroenterol.* 2005; **40**: 1024–8.

25 Tsukada K, Miyazaki T, Katoh H *et al.* The incidence of reflux oesophagitis after eradication therapy for *Helicobacter pylori*. *Eur. J. Gastroenterol. Hepatol.* 2005; **17**: 1025–8.

26 Ishiki K, Mizuno M, Take S *et al. Helicobacter pylori* eradication improves pre-existing reflux esophagitis in patients with duodenal ulcer disease. *Clin. Gastroenterol. Hepatol.* 2004; **2**: 474–9.

27 Sasaki A, Haruma K, Manabe N, Tanaka S, Yoshihara M, Chayama K. Long-term observation of reflux oesophagitis developing after *Helicobacter pylori* eradication therapy. *Aliment. Pharmcol. Ther.* 2003; **17**: 1529–34.

28 Klinkenberg-Knol EC, Nelis F, Dent J *et al.* Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy,

safety, and influence on gastric mucosa. *Gastroenterology* 2000; **118**: 661–9.
29 Moayyedi P, Wason C, Peacock R *et al.* Changing patterns of *Helicobacter pylori* gastritis in long-standing acid suppression. *Helicobacter* 2000; **5**: 206–14.
30 Katelaris PH. Gastro-oesophageal reflux disease and *Helicobacter pylori*. *Minerva Gastroenterol. Dietol.* 2003; **49**: 235–41.
31 Mason JM, Raghunath AS, Hungin AP, Jackson W. *Helicobacter pylori* eradication in long-term proton pump inhibitor users is highly cost-effective: economic analysis of the HELPUP trial. *Aliment. Pharmacol. Ther.* 2008; **28**: 1297–303.
32 Hsu PI, Lai KH, Hsu PN *et al. Helicobacter pylori* infection and the risk of gastric malignancy. *Am. J. Gastroenterol.* 2007; **102**: 725–30.
33 Wong BC, Lam SK, Wong WM *et al. Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187–94.
34 Mera R, Fontham ET, Bravo LE *et al.* Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut* 2005; **54**: 1536–40.
35 Sugano K. Prevention of gastric cancer: urgent need to implement *Helicobacter pylori* eradication therapy as a primary preventive measure in Japan. *J. Gastroenterol.* 2007; **42** (Suppl. 17):1–2.
36 Yeh JM, Kuntz KM, Ezzati M, Goldie SJ. Exploring the cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer in China in anticipation of clinical trial results. *Int. J. Cancer* 2008; **124**: 157–66.
37 Hunt R, Fallone C, Veldhuyzan van Zanten S *et al.* Update on the management of *Helicobacter pylori* - an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H. pylori infection. *Can. J. Gastroenterol.* 2004; **18**: 547–54.
38 Fukase K, Kato M, Kikuchi S *et al.* Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 350–2.
39 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J. Clin.* 2005; **55**: 74–108.
40 Roosendaal R, Kuipers EJ, Buitenwerf J *et al. Helicobacter pylori* and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am. J. Gastroenterol.* 1997; **92**: 1480–2.
41 Leung WK, To KF, Chan FK, Lee TL, Chung SC, Sung JJ. Interaction of *Helicobacter pylori* eradication and non-steroidal anti-inflammatory drugs on gastric epithelial apoptosis and proliferation: implications on ulcerogenesis. *Aliment. Pharmacol. Ther.* 2000; **14**: 879–85.
42 Chan FK, Chung SC, Suen BY *et al.* Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N. Engl. J. Med.* 2001; **344**: 967–73.
43 Chan FK, To KF, Wu JC *et al.* Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomized trial. *Lancet* 2002; **359**: 9–13.
44 Bhatt DL, Scheiman J, Abraham NS *et al.* ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J. Am. Coll. Cardiol.* 2008; **52**: 1502–17.
45 Weil J, Langman MJ, Wainwright P *et al.* Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000; **46**: 27–31.
46 Loke YK, Trivedi AN, Singh S. Meta-analysis gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment. Pharmacol. Ther.* 2008; **27**: 31–40.
47 Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract:. Indigestion and non-steroidal anti-inflammatory drugs. *BMJ* 2001; **323**: 12369.
48 Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; **359**: 14–22.
49 Vergara M, Catalán M, Gisbert JP, Calvet X. Meta-analysis: role of *Helicobacter pylori* eradication in the prevention of peptic ulcer in NSAID users. *Aliment. Pharmacol. Ther.* 2005; **21**: 1411–18.
50 Pounder RE. *Helicobacter pylori* and NSAIDs - the end of the debate? *Lancet* 2002; **359**: 3–4.
51 Weil J, Colin-Jones D, Langman M *et al.* Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995; **310**: 827–30.
52 Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996; **348**: 1413–16.
53 Pilotto A, Franceschi M, Longoa MG *et al. Helicobacter pylori* infection and the prevention of peptic ulcer with proton pump inhibitors in elderly subjects taking low-dose aspirin. *Dig. Liver Dis.* 2004; **36**: 666–70.
54 Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sáinz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment. Pharmacol. Ther.* 2002; **16**: 779–86.
55 Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. *Curr. Med. Res. Opin.* 2007; **23**: 163–73.
56 Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001; **120**: 594–606.
57 Lai KC, Lam SK, Chu KM *et al.* Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N. Engl. J. Med.* 2002; **346**: 2033–8.
58 DuBois S, Kearney DJ. Iron-deficiency anemia and *Helicobacter pylori* infection: a review of the evidence. *Am. J. Gastroenterol.* 2005; **100**: 453–9.
59 Seo JK, Ko JS, Choi KD. Serum ferritin and *Helicobacter pylori* infection in children: a sero-epidemiologic study in Korea. *J. Gastroenterol. Hepatol.* 2002; **17**: 754–7.
60 Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* 2007; **60**: 237–46.
61 Stasi R, Sarpatwari A, Segal JB *et al.* Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura. A systematic review. *Blood* 2009; **113**: 1231–40.
62 Perri F, Manes G, Neri M, Vaira D, Nardone G. *Helicobacter pylori* antigen stool test and 13C-urea breath test in patients after eradication treatments. *Am. J. Gastroenterol.* 2002; **97**: 2756–62.
63 Gisbert JP, Pajares JM. Review article: C-urea breath test in the diagnosis of *Helicobacter pylori* infection – a critical review. *Aliment. Pharmacol. Ther.* 2004; **20**: 1001–17.
64 Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic review. *Helicobacter* 2004; **9**: 347–68.
65 Connor SJ, Seow F, Ngu MC, Katelaris PH. The effect of dosing with omeprazole on the accuracy of the 13C-urea breath test in *Helicobacter pylori*-infected subjects. *Aliment. Pharmacol. Ther.* 1999; **13**: 1287–93.
66 Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial

serological kits for *Helicobacter pylori* infection differ in accuracy? A meta-analysis. *Am. J. Gastroenterol.* 1996; **91**: 1138–44.
67 Lind T, Veldhuyzen van Zanten S, Unge P *et al.* Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study. *Helicobacter* 1996; **1**: 138–44.
68 Huang JQ, Chiba N, Wilkinson J, Hunt RH. Which combination therapy can eradicate > 90% Helicobacter pylon' infection? A meta-analysis of amoxicillin, metronidazole, tetracycline and clarithromycin containing regimes. *Gastroenterology* 1997; **112**: A19.
69 Fock KM, Chelvam P, Lim SG. Triple therapy in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease: results of a multicentre study in South-East Asia. South-East Asia Multicenter Study Group. *Aliment. Pharmacol. Ther.* 2000; **14**: 225–31.
70 Katelaris PH, Forbes GM, Talley NJ, Crotty B. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The QUADRATE Study. *Gastroenterology* 2002; **123**: 1763–9.
71 Malfertheiner P, Bayerdörffer E, Diete U *et al.* The GU-MACH study: the effect of 1-week omeprazole triple therapy on *Helicobacter pylori* infection in patients with gastric ulcer. *Aliment. Pharmacol. Ther.* 1999; **13**: 703–12.
72 Zanten SJ, Bradette M, Farley A *et al.* The DU-MACH study: eradication of *Helicobacter pylori* and ulcer healing in patients with acute duodenal ulcer using omeprazole based triple therapy. *Aliment. Pharmacol. Ther.* 1999; **13**: 289–95.
73 Wong BC, Chang FY, Abid S *et al.* Triple therapy with clarithromycin, omeprazole, and amoxicillin for eradication of *Helicobacter pylori* in duodenal ulcer patients in Asia and Africa. *Aliment. Pharmacol. Ther.* 2000; **14**: 1529–35.
74 Zagari RM, Bianchi-Porro G, Fiocca R *et al.* Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for *Helicobacter pylori* eradication: the HYPER Study. *Gut* 2007; **56**: 475–9.
75 Shimoyama T, Fukuda S, Mikami T *et al.* Efficacy of metronidazole for the treatment of clarithromycin-resistant *Helicobacter pylori* infection in a Japanese population. *J. Gastroenterol.* 2004; **39**: 927–30.
76 Kwok A, Walls R, Katelaris PH. Treating *Helicobacter pylori* infected patients who have a history of penicillin allergy: a role for immunological testing. *Aliment. Pharmacol. Ther.* 2009; (in press).
77 Kobayashi I, Murakami K, Kato M *et al.* Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005. *J. Clin. Microbiol.* 2007; **45**: 4006–10.
78 Kim JJ, Reddy R, Lee M *et al.* Analysis of metronidazole, clarithromycin and tetracycline resistance of *Helicobacter pylori* isolates from Korea. *J. Antimicrob. Chemother.* 2001; **47**: 459–61.
79 Kim JM, Kim JS, Jung HC *et al.* Distribution of antibiotic MICs for *Helicobacter pylori* strains over a 16-year period in patients from Seoul, South Korea. *Antimicrob. Agents Chemother.* 2004; **48**: 4843–7.
80 Cheng H, Hu FL The epidemiology of *Helicobacter pylori* resistance to antibiotics in Beijing. *Zhonghua Yi Xue Za Zhi* 2005; **85**: 2754–7.
81 Ling TK, Cheng AF, Sung JJ *et al.* An increase in *Helicobacter pylori* strains resistant to metronidazole: a five-year study. *Helicobacter* 1996; **1**: 57–61.
82 Wang WH, Wong BC, Mukhopadhyay AK *et al.* High prevalence of *Helicobacter pylori* infection with dual resistance to metronidazole and clarithromycin in Hong Kong. *Aliment. Pharmacol. Ther.* 2000; **14**: 901–10.
83 Huang AH, Sheu BS, Yang HB *et al.* Impact of *Helicobacter pylori* antimicrobial resistance on the outcome of 1-week lansoprazole based triple therapy. *J. Formos. Med. Assoc.* 2000; **99**: 704–9.
84 Hu CT, Wu CC, Lin CY *et al.* Resistance rate to antibiotics of *Helicobacter pylori* isolates in eastern Taiwan. *J. Gastroenterol. Hepatol.* 2007; **22**: 720–3.
85 Thyagarajan SP, Ray P, Das BK *et al.* Geographical difference in antimicrobial resistance pattern of *Helicobacter pylori* clinical isolates from Indian patients: Multicentric study. *J. Gastroenterol. Hepatol.* 2003; **18**: 1373–8.
86 Choi YS, Cheon JH, Lee JY *et al.* The trend of eradication rates of first-line triple therapy for *Helicobacter pylori* infection: single center experience for recent eight years. *Korean J. Gastroenterol.* 2006; **48**: 156–61.
87 Graham DY, Lu H, Yamaoka Y A report card to grade *Helicobacter pylori* therapy. *Helicobacter* 2007; **12**: 275–8.
88 Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment. Pharmacol. Ther.* 2007; **26**: 343–57.
89 Fuccio L, Minardi ME, Zagari RM *et al.* Meta-analysis: Duration of first-line proton-pump inhibitor-based triple therapy for *Helicobacter pylori* eradication. *Ann. Intern. Med.* 2007; **147**: 553–62.
90 Kim BG, Lee DH, Ye BD *et al.* Comparison of 7-day and 14-day proton pump inhibitor-containing triple therapy for *Helicobacter pylori* eradication: neither treatment duration provides acceptable eradication rate in Korea. *Helicobacter* 2007; **12**: 31–5.
91 Gené E, Calvet X, Azagra R, Gisbert JP. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis. *Aliment. Pharmacol. Ther.* 2003; **17**: 1137–43.
92 Laine L, Hunt R, El-Zimaity H *et al.* Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. *Am. J. Gastroenterol.* 2003; **98**: 562–7.
93 Jafri N, Hornung CA, Howden CW. Meta-analysis: Sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann. Intern. Med.* 2008; **148**: 1–10.
94 Choi WH, Park DI, Oh SJ *et al.* Effectiveness of 10 day-sequential therapy for *Helicobacter pylori* eradication in Korea. *Korean J. Gastroenterol.* 2008; **51**: 280–4.
95 Nagahara A, Miwa H, Kawabe M *et al.* Second-line treatment for *Helicobacter pylori* infection in Japan: proton pump inhibitor-based amoxicillin and metronidazole regimen. *J. Gastroenterol.* 2004; **39**: 1051–5.
96 Matsuhisa T, Kawai T, Masaoka T *et al.* Efficacy of metronidazole as second-line drug for the treatment of *Helicobacter pylori* Infection in the Japanese population: a multicenter study in the Tokyo Metropolitan Area. *Helicobacter* 2006; **11**: 152–8.
97 Magaret N, Burm M, Faigel D *et al.* A randomized trial of lansoprazole, amoxycillin, and clarithromycin versus lansoprazole, bismuth, metronidazole and tetracycline in the retreatment of patients failing initial *Helicobacter pylori* therapy. *Dig. Dis.* 2001; **19**: 174–8.
98 Ang TL, Fock KM, Ng TM *et al.* Efficacy of quadruple therapy for *Helicobacter pylori* eradication after failure of proton pump inhibitor-based triple therapy in Singapore. *Chin. J. Dig. Dis.* 2003; **4**: 35–9.
99 Dore MP, Graham DY, Melee R *et al.* Colloidal bismuth subcitrate–based twice-a-day quadruple therapy as primary or

salvage therapy for *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 2002; **97**: 857–60.
100 Lin CK, Hsu PI, Lai KH *et al.* One-week quadruple therapy is an effective salvage regimen for helicobacter pylori infection in patients after failure of standard triple therapy. *J. Clin. Gastroenterol.* 2002; **34**: 547–51.
101 Zheng Q, Dai J, Li XB, Lu H, Xiao SD. Comparison of the efficacy of pantoprazole-based triple therapy versus quadruple therapy in the treatment of *Helicobacter pylori* infection: a single-center, randomized, open and parallel-controlled study. *Chin. J. Gastroenterol.* 2009; **14**: 8–11.
102 Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment. Pharmacol. Ther.* 2006; **23**: 35–44.
103 Rossi R, Jabes D, Della Bruna C. *In vitro* activity of rifabutin, a potential antibiotic in the therapy of *Helicobacter pylori*. Abstract Book of the 6th International Congress for Infectious Diseases, Prague (Czech Republic) 1994: 69.
104 Perri F, Festa V, Clemente R *et al.* Randomized study of two "rescue" therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am. J. Gastroenterol.* 2001; **96**: 58–62.
105 Bock H, Koop H, Lehn N, Heep M. Rifabutin-based triple therapy after failure of *Helicobacter pylori* eradication treatment: preliminary experience. *J. Clin. Gastroenterol.* 2000; **31**: 222–5.
106 Van der Poorten D, Katelaris PH. The effectiveness of rifabutin triple therapy for patients with difficult-to-eradicate *Helicobacter pylori* in clinical practice. *Aliment. Pharmacol. Ther.* 2007; **26**: 1537–42.
107 Gonzalez Carro P, Perez Roldan F, De Pedro Esteban A *et al.* Efficacy of rifabutin-based triple therapy in *Helicobacter pylori* infected patients after two standard treatments. *J. Gastroenterol. Hepatol.* 2007; **22**: 60–3.
108 Navarro-Jarabo JM, Fernandez N, Sousa FL *et al.* Efficacy of rifabutin-based triple therapy in *Helicobacter pylori* infected patients after two standard treatments. *BMC Gastroenterol.* 2007; **7**: 31.
109 Gisbert JP, Gisbert JL, Marcos S *et al.* Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two *Helicobacter pylori* treatment failures. *Aliment. Pharmacol. Ther.* 2006; **15**: 1469–74.
110 Miehlke S, Schneider-Brachert W, Kirsch C *et al.* One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter* 2008; **13**: 69–74.
111 Wong WM, Gu Q, Lam SK *et al.* Randomized controlled study of rabeprazole, levofloxacin and rifabutin triple therapy vs. Quadruple therapy as second-line treatment for *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther.* 2003; **17**: 553–60.
112 Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *Am. J. Gastroenterol.* 2006; **101**: 1467–75.
113 Sheu BS, Kao AW, Cheng HC *et al.* Esomeprazole 40 mg twice daily in triple therapy and the efficacy of *Helicobacter pylori* eradication related to CYP2C19 metabolism. *Aliment. Pharmacol. Ther.* 2005; **21**: 283–8.
114 Kang JM, Kim N, Lee DH *et al.* Effect of the CYP2C19 polymorphism on the eradication rate of *Helicobacter pylori* infection by 7-day triple therapy with regular proton pump inhibitor dosage. *J. Gastroenterol. Hepatol.* 2008; **23**: 1287–91.
115 Sheu BS, Fock KM. CYP2C19 genotypes and *Helicobacter pylori* eradication. *J. Gastroenterol. Hepatol.* 2008; **23**: 1163.
116 Goldstein JA, Ishizaki T, Chiba K *et al.* Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizer phenotype in various oriental, Caucasian, Saudi Arabian and American black populations. *Pharmacogenetics* 1997; **7**: 59–4.
117 Suzuki T, Matsuo K, Ito H *et al.* Smoking increases the treatment failure for *Helicobacter pylori* eradication. *Am. J. Med.* 2006; **119**: 217–24.
118 Matsuo K, Hamajima N, Ikehara Y *et al.* Smoking and polymorphisms of fucosyltransferase gene Le affect success of *H. pylori* eradication with lansoprazole, amoxicillin, and clarithromycin. *Epidemiol. Infect.* 2003; **130**: 227–33.