Gastroenterology 2016;151:51–69

CONSENSUS STATEMENT

The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults

Carlo A. Fallone,[1] Naoki Chiba,[2,3] Sander Veldhuyzen van Zanten,[4] Lori Fischbach,[5] Javier P. Gisbert,[6] Richard H. Hunt,[3,7] Nicola L. Jones,[8] Craig Render,[9] Grigorios I. Leontiadis,[3,7] Paul Moayyedi,[3,7] and John K. Marshall[3,7]

[1]*Division of Gastroenterology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada;* [2]*Guelph GI and Surgery Clinic, Guelph, Ontario, Canada;* [3]*Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada;* [4]*Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada;* [5]*Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas;* [6]*Gastroenterology Service, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain;* [7]*Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada;* [8]*Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, Departments of Paediatrics and Physiology, University of Toronto, Toronto, Ontario, Canada; and* [9]*Kelowna General Hospital, Kelowna, British Columbia, Canada*

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e25. Learning Objective: Upon completion of this examination, successful learners will be able to establish a treatment plan for patients with *H pylori* infection.

BACKGROUND & AIMS: *Helicobacter pylori* infection is increasingly difficult to treat. The purpose of these consensus statements is to provide a review of the literature and specific, updated recommendations for eradication therapy in adults. **METHODS:** A systematic literature search identified studies on *H pylori* treatment. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an online platform, finalized, and voted on by an international working group of specialists chosen by the Canadian Association of Gastroenterology. **RESULTS:** Because of increasing failure of therapy, the consensus group strongly recommends that all *H pylori* eradication regimens now be given for 14 days. Recommended first-line strategies include concomitant nonbismuth quadruple therapy (proton pump inhibitor [PPI] + amoxicillin + metronidazole + clarithromycin [PAMC]) and traditional bismuth quadruple therapy (PPI + bismuth + metronidazole + tetracycline [PBMT]). PPI triple therapy (PPI + clarithromycin + either amoxicillin or metronidazole) is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. Recommended rescue therapies include PBMT and levofloxacin-containing therapy (PPI + amoxicillin + levofloxacin). Rifabutin regimens should be restricted to patients who have failed to respond to at least 3 prior options. **CONCLUSIONS:** Optimal treatment of *H pylori* infection requires careful attention to local antibiotic resistance and eradication patterns. The quadruple therapies PAMC or PBMT should play a more prominent role in eradication of *H pylori* infection, and all treatments should be given for 14 days.

Keywords: Helicobacter pylori; Eradication; Resistance; Proton Pump Inhibitor; Amoxicillin; Bismuth; Clarithromycin; Metronidazole; Tetracycline; Levofloxacin; Rifabutin.

Although the prevalence of *H pylori* is decreasing in some parts of the world, the infection remains present in 28% to 84% of subjects depending on the population tested.[1] Even studies in Western nations, which tend to have the lowest general prevalence,[1–4] report high proportions of infected individuals in certain communities (eg, 38%–75% of Alaskan or Canadian aboriginal populations).[2,3,5–8]

H pylori is implicated in the development of and its eradication is recommended in the treatment of duodenal or gastric ulcers, early gastric cancer, and gastric mucosa-associated lymphoid tissue lymphomas (in <0.01%).[4,9–14] Treatment has been suggested for prevention of gastric cancer in high-risk individuals,[11–13,15] as well as in patients with uninvestigated[16] and functional dyspepsia,[17] given evidence that eradication of the infection leads to sustained improvements in symptoms in a proportion of patients.[10,16,17]

The increasing prevalence of antibiotic-resistant strains of *H pylori* has led to reduced success with traditional *H*

Abbreviations used in this paper: **BPAL, bismuth compounds + proton pump inhibitor + amoxicillin + levofloxacin; CAG, Canadian Association of Gastroenterology; CI, confidence interval; GRADE, Grading of Recommendation Assessment, Development and Evaluation; ITT, intention-to-treat; NNT, number needed to treat; PA, proton pump inhibitor + amoxicillin; PAC, proton pump inhibitor + amoxicillin + clarithromycin; PAL, proton pump inhibitor + amoxicillin + levofloxacin; PAM, proton pump inhibitor + amoxicillin + metronidazole; PAMC, proton pump inhibitor + amoxicillin + metronidazole + clarithromycin; PAR, PPI + amoxicillin + rifabutin; PBMT, proton pump inhibitor + bismuth compounds + metronidazole + tetracycline; PICO, Population, Intervention, Comparator, Outcomes; PMC, proton pump inhibitor + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; RD, risk difference.**

Most current article

© 2016 by the AGA Institute
0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.04.006

pylori treatments.[18–24] Proton pump inhibitor (PPI) triple therapies (a PPI plus two of the following antibiotics: clarithromycin, amoxicillin, or metronidazole) for 7 to 10 days were once standard and recommended as first-line therapy[11–13,25] but have become increasingly ineffective, with some studies reporting eradication in less than 50% of cases.[21,22,26–28] Suboptimal patient compliance may be another cause of treatment failure.[4,29–31]

It has been suggested that the goal of *H pylori* therapy should now be eradication in ≥90% of treated patients.[32] This arbitrary threshold is not easily achieved, especially in real-world settings. However, the most efficacious therapies available should be used first to avoid the cost, inconvenience, and risks associated with treatment failure.

Some of the more common regimens for *H pylori* eradication include bismuth quadruple therapy (PPI + bismuth compounds + metronidazole + tetracycline [PBMT]), nonbismuth quadruple therapy (concomitant [PPI + amoxicillin + metronidazole + clarithromycin {PAMC}] or sequential [PPI + amoxicillin {PA} followed by PPI + metronidazole + clarithromycin {PMC}]), PPI triple therapy (PPI + amoxicillin + clarithromycin [PAC], PMC, or PPI + amoxicillin + metronidazole [PAM]), and quinolone-containing regimens (PPI + amoxicillin + levofloxacin [PAL]). Definitions of these and other regimens discussed in this consensus paper are shown in Table 1, with suggested doses listed in Table 2.

The increasing prevalence of antibiotic-resistant strains and evidence of more frequent failures of triple therapies suggest the need for more effective therapies given for a longer duration (14 days instead of 10 or 7 days) than were recommended in prior consensus statements.[11,12] For this reason, as well as the existence of new therapies, the Canadian Association of Gastroenterology (CAG) and the Canadian *Helicobacter* Study Group determined that an update was needed. The purpose of this consensus process was to systematically review the literature relating to the management of *H pylori* infection and to provide specific, updated recommendations for eradication therapy in adults. This consensus was limited to adults, because updated pediatric recommendations are currently in progress from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Methods

Scope and Purpose

The consensus development process was initiated in the summer of 2013 with the first meeting of the steering committee and lasted approximately 2 years, with the meeting of the full consensus group taking place in June 2015.

Sources and Searches

The Editorial Office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University

Table 1. Recommendations for Regimens Used for the Eradication of *H pylori*

Recommendation	Regimen	Definition (see dose table)
First line		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Concomitant nonbismuth quadruple (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin
Restricted option[b]	PPI triple (PAC, PMC, or PAM)	PPI + amoxicillin + clarithromycin PPI + metronidazole[a] + clarithromycin PPI + amoxicillin + metronidazole[a]
Not recommended	Levofloxacin triple (PAL)	PPI + amoxicillin + levofloxacin
Not recommended	Sequential nonbismuth quadruple (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Prior treatment failure		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Levofloxacin-containing therapy (usually PAL)	PPI + amoxicillin + levofloxacin[c]
Restricted option[d]	Rifabutin-containing therapy (usually PAR)	PPI + amoxicillin + rifabutin
Not recommended	Sequential nonbismuth quadruple therapy (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Undetermined	Concomitant nonbismuth quadruple therapy (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin

[a]Tinidazole may be substituted for metronidazole.
[b]Restricted to areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%) (see statement 5).
[c]There is some evidence that adding bismuth to this combination may improve outcomes.
[d]Restricted to cases in which at least 3 recommended options have failed (see statement 13).

Table 2. Recommendations for Dose of Agents Used in *H pylori* Eradication Therapies

Doses for agents in bismuth quadruple therapy		
Bismuth	X mg[a]	QID[b]
Metronidazole	500 mg	TID to QID[c]
PPI	Y mg[d]	BID
Tetracycline	500 mg	QID
Doses for agents in all regimens other than bismuth quadruple therapy (includes PPI triple, concomitant and sequential nonbismuth quadruple, levofloxacin, and rifabutin therapies)		
Amoxicillin	1000 mg	BID
Clarithromycin	500 mg	BID
Levofloxacin	500 mg	QD[e]
Metronidazole	500 mg	BID
PPI	Y mg[d]	BID
Rifabutin	150 mg	BID

NOTE. These are the doses in North America; they may vary in different parts of the world (eg, 400 mg of metronidazole or 200 mg of clarithromycin may be the preferred doses in parts of Europe and Asia, respectively).
QID, 4 times a day; TID, 3 times daily; BID, twice daily; QD, once daily.
[a]The dose depends on the formulation used. In clinical trials, the most common doses were as follows: bismuth subsalicylate (262 mg), 2 tablets QID; colloidal bismuth subcitrate (120 mg), 2 tablets BID or 1 tablet QID; bismuth biskalcitrate (140 mg), 3 tablets QID; Pylera (Aptalis Pharma US, Inc) (the combination pill; bismuth subcitrate potassium; 140 mg), 3 tablets QID.
[b]Studies (from China) have suggested that giving double the dose of bismuth twice daily is also effective.[62]
[c]Good evidence for QID dosing of metronidazole is lacking; however, some members of the consensus group suggested that a QID regimen may help simplify dosing for patients (400 mg QID dosing for metronidazole would also be acceptable in countries where a 400-mg dose is available).
[d]The dose depends on the PPI used. Standard doses are esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg (see statement 8 for discussion of high-dose PPI use). In fact, in many countries, double doses (eg, esomeprazole 40 mg BID) are more commonly used (vs standard doses). Although evidence is lacking, the presumed dose for dexlansoprazole is either 30 mg or 60 mg.
[e]In clinical trials, eradication appears to be similar in studies that use levofloxacin 250 mg BID or 500 mg QD dosing.[138]

performed a systematic literature search of the Cochrane Register, MEDLINE, EMBASE, and CENTRAL for trials published from January 2008 to December 2013. The main focus of all literature searches was to identify data on cure rates of *H pylori* infection. We did not systematically search the literature before 2008 because we did not want older data, where higher eradication success rates were likely a result of lower antibiotic resistance, to confound newer data. Key search terms were *Helicobacter pylori*, eradication, bismuth, clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and rifabutin, among others, to address each of the statements. Search strategies were limited to the English language and human studies, and further details are provided in Supplementary Appendix 1.

A formal systematic review was performed for every statement. This included a literature search and, as described in more detail in the following text, a review of the citations to identify potentially relevant articles, review of selected full-text articles to identify articles that satisfied the predefined PICO components (Population, Intervention, Comparator, Outcomes), a risk-of-bias assessment, and at least a qualitative synthesis of evidence presented formally to the panel members verbally and/or with slide presentations at the face-to-face meeting. The panel also had access to the entire text of all the selected articles should they choose to refer to it.

The literature search produced 2943 citations; after removal of duplicates, 2373 citations remained. These citations were sorted into three separate lists: (1) results enriched with randomized controlled trials (RCTs), systematic reviews/meta-analyses, and practice guidelines (1509 citations); (2) results enriched with Canadian studies (an additional 13 citations); and (3) the remaining 851 citations. Additional focused, updated searches up to June 2015 were conducted for presentation at the consensus meeting. In the absence of updated systematic reviews or meta-analyses on a specific treatment, a meta-analysis was performed for this consensus when sufficient data were available. When a recent well-done meta-analysis was found, a literature review was also performed to see if more current data altered the results and conclusions.

Review and Assessment of Evidence

Two nonvoting methodologists (GIL and PM) assessed the quality (certainty) of evidence using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) method.[33] The methodologists assessed the risk of bias (of individual studies and overall across studies), indirectness, inconsistency, imprecision, and other considerations (including publication bias) to determine the overall quality of evidence for each statement. GRADE assessments were then reviewed and agreed on by voting members of the consensus group at the meeting.

The quality of evidence for each statement was graded as high, moderate, low, or very low, as described in GRADE[33,34] and prior CAG consensus documents.[35,36]

Approved product labeling from government regulatory agencies varies from country to country; although not ignored, recommendations are based on evidence from the literature and consensus discussion and may not fully reflect the product labeling for a given country.

Consensus Process

The consensus group was composed of 8 voting members (5 participants and 3 steering committee members), including gastroenterologists, clinical epidemiologists (one of whom was not a gastroenterologist), and microbiologists from Canada, the United States, and Europe with expertise in managing *H pylori* infection. There was representation from a pediatric and community, nonacademic gastroenterologist (not an *H pylori* expert), and there was a nonvoting moderator for the meeting (Dr John K. Marshall). Although there was no primary care representative, the impact of the recommendations on primary care physicians, as well as community resources and local availability, was discussed before voting for each statement.

Before the 2-day consensus meeting was held in Toronto, Ontario, Canada, in June 2015, CAG facilitated the majority of the consensus process through the use of a web-based consensus

platform (ECD Solutions, Atlanta, GA). The steering committee (CAF, NC, SVvZ) developed the initial statements using PICO components of the underlying research question for each statement (eg, for statement 3, the PICO components were as follows: population, patients with *H pylori* infection who have not undergone previous eradication attempts; intervention, traditional bismuth quadruple therapy for 14 days; comparator, any other individual eradication therapy [standard triple, sequential, concomitant, levofloxacin-based triple, and so on] or compared with a standard threshold for efficacy [eg, >80% intention-to-treat {ITT} eradication rate] and safety; outcomes, ITT eradication rate and safety). They then reviewed the literature search results for every statement (each article reviewed by at least 2 people) through the web-based platform and "tagged" (selected and linked) all relevant references to a specific statement. Only one member was required to tag a reference for it to remain linked to the statement. Subsequently, the tagged references were again assessed by the steering committee; when a meta-analysis (of sufficient quality) was tagged to a statement, any tagged study that was already included in the meta-analysis was removed from that particular statement. Any studies performed after the meta-analysis remained tagged and were used to determine if the more current data altered the results or conclusions of the meta-analysis. At the end of this process, 116 papers were selected and uploaded onto the online platform. All members of the consensus group had access to complete copies of the "tagged" references. The entire consensus group then voted anonymously on their level of agreement with the specific statements using a modified Delphi process.[37,38] Two subsequent iterations of the statements that incorporated suggested changes from the group followed, after which the statements were finalized at the live meeting.

At the 2-day face-to-face meeting, the methodologists, epidemiologists, and other members of the panel who had conducted systematic reviews or meta-analyses for the conference presented, for each statement, a summary of data from existing meta-analyses from the literature as well as the systematic reviews or meta-analyses conducted for that statement. The evaluations regarding the GRADE approach for the statements were also reviewed, and all panelists discussed the findings and other issues before finalization of the phrasing for individual statements. Any PICO components that are unequivocally implied were removed from the final statements to make the message clearer to the readers. Finally, participants were asked to vote on their level of agreement for each specific statement. A statement was accepted if >75% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1 to 5 (with 1, 2, and 3 representing disagree strongly, disagree, and uncertain, respectively).

Once a statement was accepted, the participants then voted on the "strength" of the recommendation, which was accepted with a 51% vote. Per the GRADE system, the strength of each recommendation was assigned as strong ("we recommend…") or conditional ("we suggest…"). The strength of the recommendation considers risk-benefit balance, patients' values and preferences, cost and resource allocation, and quality of the evidence. Therefore, it is possible for a recommendation to be classified as strong despite having low-quality evidence to support it or conditional despite the existence of high-quality evidence to support it.[39] Based on the GRADE approach, a strong recommendation indicates the statement should be applied in most cases, while a conditional recommendation signifies that clinicians "…should recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences."[39]

The steering committee drafted the initial manuscript, which was revised by all members of the consensus group and all authors, after which it was made available to all members of CAG for comments before submission for publication. Per CAG policy, all participants provided written disclosure of relevant potential conflicts of interest for the 24 months before the meeting, which were made available to the other group members.

Role of the Funding Sources

CAG administered all aspects of the meeting, which was cofunded by CAG and the Canadian *Helicobacter* Study Group with no external funding sources.

Recommendation Statements

The individual recommendation statements are provided and include the quality of supporting evidence as assessed by the GRADE method and the voting results; a discussion of the evidence considered for the specific statement is also presented. The quality of evidence was determined to be low for some statements, largely because of high risk of bias (most often due to lack of adequate blinding). Acknowledging the importance of quality of evidence, the consensus group also considered other factors in issuing strong rather than conditional recommendations for certain statements despite lower quality of evidence. The strength of these recommendations was driven by consequences of therapeutic failure, including the negative consequences of peptic ulcer disease, such as gastrointestinal bleeding, an increased risk of the development of gastric cancers, and an increased risk of the development of resistant strains.[20,40,41] In addition, eradication success is highest with initial therapy and decreases with subsequent rescue therapy attempts.[42,43] Hence, a treatment option may have been strongly recommended even if the evidence was not high quality to avoid the negative consequences of failure.

A summary of the recommendation statements is provided in Table 3. The most important evidence for each of the statements is summarized in Supplementary Tables 1 to 14.

All Patients

Statement 1. In patients with *H pylori* infection, we recommend a treatment duration of 14 days. *GRADE: Strong recommendation; quality of evidence moderate for PAC and very low for PBMT, PAMC, and PAL. Vote: strongly agree, 87.5%; agree, 12.5%.*

Key evidence (Supplementary Table 1). A Cochrane meta-analysis of RCTs found that a 14-day duration of PPI triple therapy was associated with a significantly greater proportion of eradication compared with shorter durations (ITT: 45 studies, 14 vs 7 days, 82% vs 73%; 12 studies, 14 vs 10 days, 84% vs 79%).[28] A significant effect was seen in

Table 3. Summary of Consensus Recommendations for the Treatment of *H pylori* Infection

All patients
1. In patients with *H pylori* infection, we recommend a treatment duration of 14 days. *GRADE: Strong recommendation; quality of evidence moderate for PAC and very low for PBMT, PAMC, and PAL*.
First-line therapy
2. In patients with *H pylori* infection, we recommend that the choice of first-line therapy consider regional antibiotic resistance patterns and eradication rates. *GRADE: Strong recommendation; quality of evidence low.*
3. In patients with *H pylori* infection, we recommend traditional bismuth quadruple therapy (PBMT) for 14 days as one of the options for first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate for efficacy and very low for duration.*
4. In patients with *H pylori* infection, we recommend concomitant nonbismuth quadruple therapy (PAMC) for 14 days as one of the options for first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate for efficacy and very low for duration.*
5. In patients with *H pylori* infection, we recommend restricting the use of PPI triple therapy (PAC or PMC for 14 days) to areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%). *GRADE: Strong recommendation; quality of evidence moderate for efficacy of PPI triple therapy for 14 days and low for restrictions.*
6. In patients with *H pylori* infection, we recommend against the use of levofloxacin triple therapy (PAL) as a first-line therapy. *GRADE: Strong recommendation; quality of evidence very low.*
7. In patients with *H pylori* infection, we recommend against the use of sequential nonbismuth quadruple therapy (PA followed by PMC) as a first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate.*
Prior failure
8. In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend traditional bismuth quadruple therapy (PBMT) for 14 days as an option for subsequent therapy. *GRADE: Strong recommendation; quality of evidence low.*
9. In patients who have previously failed to respond to *H pylori* eradication therapy, we suggest levofloxacin-containing therapy for 14 days as an option for subsequent therapy. *GRADE: Conditional recommendation; quality of evidence low.*
10. In patients who have previously failed to respond a clarithromycin-containing *H pylori* eradication therapy, we recommend against the use of clarithromycin-containing regimens as subsequent therapy. *GRADE: Strong recommendation; quality of evidence low.*
11. In patients who have previously failed to respond to a levofloxacin-containing *H pylori* eradication therapy, we recommend against the use of levofloxacin-containing regimens as subsequent therapy. *GRADE: Strong recommendation; quality of evidence low.*
12. In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend against the use of sequential nonbismuth quadruple therapy (PA followed by PMC) as an option for subsequent therapy. *GRADE: Strong recommendation; quality of evidence very low.*
13. We recommend restricting the use of rifabutin-containing regimens to cases in which at least 3 recommended options have failed. *GRADE: Strong recommendation; quality of evidence very low*.
Supplemental therapy
14. In patients with *H pylori* infection, we recommend against routinely adding probiotics to eradication therapy for the purpose of reducing adverse events. *GRADE: Strong recommendation; quality of evidence very low.*
15. In patients with *H pylori* infection, we recommend against adding probiotics to eradication therapy for the purpose of increasing eradication rates. *GRADE: Strong recommendation; quality of evidence very low*.

NOTE. The consensus group concluded that there was insufficient evidence to support or refute the efficacy of PAMC as a second-line option and thus was unable to recommend for or against this regimen as a rescue therapy. Similarly, the group concluded that there was insufficient evidence to make a recommendation on high-dose dual therapy with a PPI and amoxicillin. See Tables 1 and 2 for more details on regimens and dosing.

the PAC subgroup (34 studies of 14 vs 7 days; relative risk of *H pylori* persistence, 0.65 [95% confidence interval {CI}, 0.57–0.75]; number needed to treat [NNT], 12 [95% CI, 9–16]) as well as in the PPI, amoxicillin, and quinolone subgroup (2 studies of 14 vs 7 days; relative risk, 0.37 [95% CI, 0.16–0.83]; NNT, 3 [95% CI, 2–10]) (Table 4). There was

Table 4. Relative risks for *H pylori* Persistence According to Duration of Regimen

Studies (n = 75)	14 vs 7 days	10 vs 7 days	14 vs 10 days
PPI triple therapy (n = 59)	0.66 (0.60–0.74); NNT, 11 (9–14); (n = 45)	0.80 (0.72–0.89); NNT, 21 (15–38); (n = 24)	0.72 (0.58–0.90); NNT, 17 (11–46); (n = 12)
PAC (n = 34)	0.65 (0.57–0.75); NNT, 12 (9–16); (n = 34)	0.80 (0.70–0.91); NNT, 21 (14–48); (n = 17)	0.69 (0.52–0.91); NNT, 16 (10–54); (n = 10)
PMC (n = 4)	0.87 (0.71–1.07); (n = 4)	0.99 (0.55–1.79); (n = 2)	—
PAQ (n = 2)	0.37 (0.16–0.83); NNT, 3 (2–10); (n = 2)	0.58 (0.36–0.95); NNT, 7 (5–59); (n = 2)	—
PPI bismuth quadruple therapy (n = 6)	0.71 (0.44–1.15); (n = 3)	0.70 (0.43–1.14); (n = 2)	1.13 (0.59–2.18); (n = 1)

NOTE. Based on data from a meta-analysis by Yuan et al.[28] Values are relative risk for *H pylori* persistence (95% CI); NNT (95% CI); studies (n).
PAQ, PPI + amoxicillin + quinolone.

no increase in discontinuations due to adverse events with increasing duration of therapy.

With regard to quadruple therapies, a systematic review of cohort studies found a trend toward greater treatment success with longer durations (from 3 to 10 days) of non-bismuth quadruple therapy (PAMC) (see statement 4).[44] A 14-day optimized PAMC combination also achieved higher eradication rates compared with standard 10-day PAMC (ITT, 93% vs. 87%; $P < .01$); however, the optimized regimen was not only of longer duration but also included an increased PPI dose.[45]

Finally, for bismuth quadruple therapy, the Cochrane meta-analysis of RCTs did not find that duration has a significant effect on therapeutic success for first-line therapy (Table 4),[28] but there are very few studies with this comparison and a trend was suggested (see statement 3). A meta-analysis performed for the consensus meeting assessed the duration of this regimen for the treatment of those who previously failed to achieve eradication. Overall, 51 RCT and cohort studies were included (see statement 8), and meta-analysis showed that the ITT eradication rate was numerically but not statistically higher with the 14-day regimen versus the 10-day regimen (78.7% vs 75.6%; $P = .33$).

Other issues and discussion. The increasing prevalence of resistant strains of *H pylori* has led to increasing proportions of failure of traditional *H pylori* treatments.[18–22] In a RCT of clarithromycin-containing triple therapies, the eradication success rate of resistant strains was 35% lower than that of sensitive strains.[46] The impact was greatest among regimens of the shortest duration; the eradication success rate of sensitive versus resistant strains was 42% higher in the 7-day group, 33% higher in the 10-day group, and 22% higher in the 14-day group. Therefore, indirect evidence supports increased efficacy with longer durations of therapy in resistant strains. The differences in efficacy between therapies in the studies presented are likely underestimated, because many of the studies are older and the proportion of resistant strains has increased since they were conducted.

Decisions. In light of the higher eradication rates with longer durations of therapy compared with regimens of shorter durations, the consensus group strongly recommended that all *H pylori* regimens (both first-line and rescue therapies) be administered for 14 days. This prolonged use of antibiotics for all patients is warranted because the increased failures with shorter regimens would result in resistant strains and less successful future treatments. It is best to achieve the maximum cure rates from the start.

First-Line Therapy

Statement 2. In patients with *H pylori* infection, we recommend that the choice of first-line therapy consider regional antibiotic resistance patterns and eradication rates. *GRADE: Strong recommendation; quality of evidence low. Vote: strongly agree, 100%.*

Key evidence (Supplementary Table 2). Although no study directly examined the impact of tailoring first-line therapy to local antibiotic resistance patterns and eradication rates, a meta-analysis of 5 RCTs (n = 701) found that culture-guided triple therapy resulted in a significantly lower risk of treatment failure compared with empirical standard triple therapy (ITT relative risk, 0.84; 95% CI, 0.77–0.90; $P < .00001$; eradication rate, 85.4% vs 71.5%).[47]

Other issues and discussion. H pylori–resistant strains have become more prevalent over time.[19] Studies from the 1990s showed a low prevalence of clarithromycin resistance ranging from 1% to 8%,[18,19] which has risen to 16% to 24% in more recent studies from around the world.[48–50] Primary resistance to metronidazole appears to have remained relatively stable over time at 20% to 40%.[4,18–20,51] *H pylori* resistance to amoxicillin generally remains low at approximately 1% to 3%.[4,18,19,50,51]

In addition, the prevalence of secondary resistance to clarithromycin and metronidazole is very high: up to 67% to 82% for clarithromycin and 52% to 77% for metronidazole.[20,40,50]

RCTs confirm that the proportion of successful eradication is significantly lower in resistant compared with sensitive strains, especially with triple therapy[46,52–55] and therapy of shorter duration.[46] The increasing prevalence of clarithromycin resistance is likely the main factor contributing to the increasing failure of non–culture-guided *H pylori* therapies over time, especially clarithromycin-based triple therapies.[21,22] A meta-analysis of 12 studies found that success of eradication with bismuth quadruple therapy remained stable at approximately 80% in studies from 2006 to 2011 compared with those from 2000 to 2005, but the efficacy of clarithromycin-based triple therapy decreased from approximately 80% in studies from 2000 to 2005 to only 62% in more recent studies (2006–2011) (Figure 1).[22]

Bismuth quadruple therapy is unaffected by clarithromycin resistance.[22,53] However, the eradication success

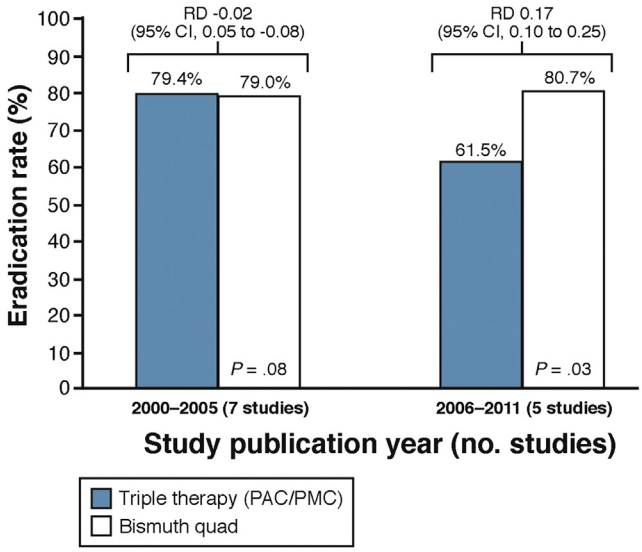

Figure 1. Pooled successful eradication (ITT) in subgroup analysis according to year of study publication. Based on data from a meta-analysis by Venerito et al.[22] RDs are shown as proportions rather than percentages.

rate with PBMT seems to be slightly lower in metronidazole-resistant versus metronidazole-sensitive strains (92% vs. 80%; $P = .06$).[53,54] In one meta-analysis of triple and quadruple regimens, the successful eradication rate was found to decrease by 0.5% for every 1% increase in the prevalence of metronidazole resistance, suggesting that when metronidazole resistance is 30%, treatment efficacy decreases by 15%.[56]

Similar effects of resistance have been seen with levofloxacin triple therapy and bismuth quadruple levofloxacin-based therapy; among levofloxacin-susceptible strains, the eradication rate was 97% in both groups; however, among resistant strains, the proportion dropped to 71% with quadruple therapy and 38% with triple therapy.[52]

If the susceptibility profile of a patient's infection or an estimate of it from the patient's population is known, the efficacy of a proposed regimen can be predicted.[57–59] Unfortunately, the resistance data required for these predictions is not available in most areas. Pragmatically, a combination of local experience of treatment success with different regimens and the patient's pretreatment exposure to antibiotics can also aid in the identification of the regimen most likely to succeed.[60]

Decisions. Evidence suggests that culture-guided therapy is associated with higher eradication success rates[47] and that both antibiotic-resistant *H pylori*[18,19,48–50] and treatment failures[46,52–55] are increasing. Therefore, it is important to encourage susceptibility testing to be made available locally and performed if the patient is undergoing endoscopy. However, it is not currently clinically practical or often possible to perform susceptibility testing in all patients. Therefore, the consensus group advised that local susceptibility patterns be used as a helpful surrogate when available. Studies to determine the local prevalence of primary antibiotic resistance patterns are essential to assist clinicians in selecting the most appropriate first-line treatment for their practice. When available, the actual proportion of patients with successful eradication after receiving a specific treatment can be used to guide future treatment selection. As such, clinicians are encouraged to maintain records of the eradication rates they obtain locally with treatments.

Statement 3. In patients with *H pylori* infection, we recommend traditional bismuth quadruple therapy (PBMT) for 14 days as one of the options for first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate for efficacy and very low for duration. Vote: strongly agree, 75%; agree, 25%.*

Key evidence (Supplementary Table 3). Two systematic reviews of RCTs have evaluated the efficacy of first-line bismuth quadruple therapy (PBMT) compared with triple therapy (PAC).[21,22] The more recent meta-analysis of 12 RCTs found that the overall pooled eradication success rate was 77.6% with PBMT and 68.9% with PAC (risk difference [RD], 6%; 95% CI, −1% to 13%; note that the mathematical difference in the eradication success rate is not the same as the RD because the latter statistic is more appropriately weighted for the study effect size and precision of each estimate).[22] Although this analysis did not show a statistically significant difference, there was a trend toward greater eradication rates with PBMT.[22] The subgroup analysis of duration showed that 10-day quadruple therapy was more effective than 7-day triple therapy, but no differences were noted between the therapies when given for the same duration for either 7 days or 10 to 14 days. Specific analyses for 14-day PBMT were not performed. Only one study was found that directly compared 14-day durations in first-line therapy, which showed higher eradication success rates with bismuth quadruple therapy compared with triple therapy; however, this was significant only in the per-protocol analysis and not the ITT analysis.[61] In addition, antimicrobial resistance has been shown to have less impact on the success of PBMT regimens (metronidazole-sensitive vs -resistant strains, 89.4% vs 80.6%) compared with PAC regimens (clarithromycin-sensitive vs -resistant strains, 90.2% vs 22.2%).[21]

Other issues and discussion. As described in statements 1 and 8, a meta-analysis of observational data conducted for the meeting to evaluate the duration of bismuth quadruple rescue therapy showed by regression analysis that the ITT eradication success rate was numerically higher with the 14-day versus the 10-day regimen, although this was not statistically different (78.7% vs 75.6%; $P = .33$).

The bismuth formulations used in these studies varied considerably, with colloidal bismuth subcitrate (De-Nol) used most commonly in Europe and bismuth subsalicylate (Pepto-Bismol) used most commonly in North America; however, whether the different formulations result in a different outcome is not clear. Although usually administered 4 times a day, some studies (from China) have suggested that giving double the dose of bismuth twice daily is also effective.[62]

There were no significant differences in proportions of adverse events or compliance between first-line PBMT and PAC in the meta-analyses.[21,22] However, adherence tends to be higher in clinical trials compared with real-world settings. Data show that in many therapeutic areas, adherence is negatively affected by dose frequency and regimen complexity (multiple medications, multiple doses, specific dietary or time requirements).[63] In one study, adherence to *H pylori* treatment was shown to decrease with increasing dose frequency and pill burden.[29] In the follow-up survey, 26% of patients reported that frequent dosing had reduced their ability to comply with a 4-drug treatment, while 22% reported that the number of pills required reduced their compliance.[29]

Decisions. As described in statement 2, meta-analyses show a substantial decrease in eradication success in studies from 2006 and later compared with those conducted in 2005 and earlier; the decrease was much more pronounced with triple therapy, likely due to development of resistance (Figure 1).[21,22] This finding and the efficacy data presented in the preceding text suggest that bismuth quadruple therapy is more effective than triple therapy, with longer durations of therapy resulting in more effective eradication. However, these analyses also show that eradication success rates with 7- to 10-day regimens are suboptimal at approximately 80% (usually for 7- to 10-day regimens) and that success rates are decreasing over time.[21,22]

Therefore, despite the limitations of these data, the consensus group supported the use of PBMT with the optimal duration of 14 days when given as first-line therapy. Because the proportion of eradication success decreases with subsequent rescue therapy attempts, this was voted a strong recommendation.[42,43]

The consensus group suggested steps that could be taken to minimize the impact of the more complex regimen on adherence. One strategy to improve compliance with PBMT might be prescribing the PPI twice daily and the other agents 4 times a day versus prescribing a combination of dosing 4 times a day (for bismuth and tetracycline) and 3 times a day (for metronidazole) (Table 2). Having the pharmacy prepare blister packs can also help. In some countries, a 3-in-1 pill is available, which simplifies dosing for patients.[54,64–66]

In patients with penicillin allergies, PBMT would be the preferred first-line option. This regimen was shown to be more effective than triple therapy (PMC) in a prospective study in patients allergic to penicillin (ITT eradication rate, 75% and 59%; $P < .05$).[67]

Statement 4. In patients with *H pylori* infection, we recommend concomitant nonbismuth quadruple therapy (PAMC) for 14 days as one of the options for first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate for efficacy and very low for duration. Vote: strongly agree, 87.5%; agree, 12.5%.*

Key evidence (Supplementary Table 4). Meta-analyses of RCTs assessing the efficacy of concomitant nonbismuth quadruple therapy (PAMC) have generally reported pooled ITT eradication success rates of approximately 90%,[44,68,69] although one meta-analysis reported 81% success with 5- to 10-day regimens.[70] However, a trend toward better eradication with longer durations of treatment has been shown: 85%/88%/89%/93%/92% for 3 days/4 days/5 days/7 days/10 days, respectively.[44] An updated meta-analysis of observational data extracted from RCTs, performed for the consensus meeting, included 57 RCTs as of 2015 and found an overall ITT eradication success rate with nonbismuth concomitant quadruple therapy of 88% (95% CI, 86%–89%).[69] In subgroup analyses, concomitant therapy was more effective than triple therapy (n = 19 RCTs; RD, 11%; 95% CI, 7%–16%; $P < .00001$) and more effective than sequential therapy in studies that compared the same drugs at the same dose and for the same duration (n= 14 RCTs; RD, 6%; 95% CI, 3%–9%; $P < .0001$) (Figure 2).[69] Concomitant therapy also performed better than sequential therapy in resistant strains (clarithromycin resistance, 92% vs 62%[55,71,72]; metronidazole resistance, 97% vs 82%[71–73]; dual clarithromycin and metronidazole resistance, 79% vs 47%[55,71–73]).[69]

Other issues and discussion. Two Spanish studies that assessed a regimen called optimized PAMC (increased PPI dose of esomeprazole 40 mg twice daily and extended duration from 10 to 14 days) found higher ITT eradication success rates compared with optimized triple therapy (PPI dose of esomeprazole 40 mg twice daily and 14-day duration) (90.4% vs 81.3%; $P < .001$)[74] and compared with standard concomitant therapy (93% vs 87%; $P < .01$).[45] Adverse events were significantly more common with the optimized PAMC therapy (~8%–15% more common), but compliance with therapy was similar between groups.[45,74]

Decisions. Based on the evidence of acceptable eradication rates and the trend toward increasing efficacy with longer durations, the consensus group agreed that concomitant quadruple therapy (PAMC) for 14 days should

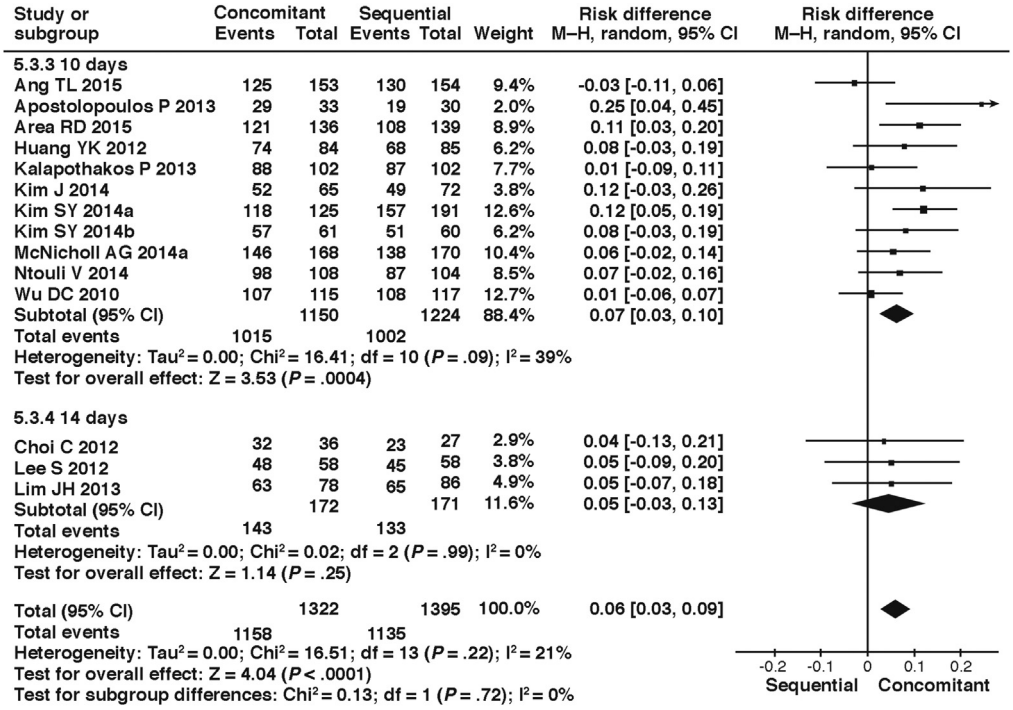

Figure 2. Meta-analysis of eradication successes (ITT) with sequential versus concomitant nonbismuth quadruple therapies. Regimens used the same drugs at the same doses for equal durations. RDs are shown as proportions rather than percentages. An updated meta-analysis conducted for the consensus meeting, based on Gisbert and McNicholl.[69]

be considered a first-line option. However, for patients allergic to penicillin, PBMT is the preferred first-line option (see statement 3).

Statement 5. In patients with *H pylori* infection, we recommend restricting the use of PPI triple therapy (PAC or PMC for 14 days) to areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%). *GRADE: Strong recommendation; quality of evidence moderate for efficacy of PPI triple therapy for 14 days and low for restrictions. Vote: strongly agree, 12.5%; agree, 75%; disagree, 12.5%.*

Key evidence (Supplementary Table 5). Although meta-analyses of RCTs (mainly published before 2008) have not shown a significant difference in eradication rates with PPI triple therapies compared with bismuth and nonbismuth quadruple therapies (see statement 3),[21,22,70] eradication success rates with triple therapies have been decreasing over time (Figure 1).[21,22,75] As described with statement 2, the success of clarithromycin-based therapies is very dependent on the susceptibility profile of the organism to this antibiotic.[21,22,46,52–55] In one meta-analysis, triple therapy achieved eradication in 88% of clarithromycin-sensitive strains but in only 14% of clarithromycin-resistant strains (RD, 75%; 95% CI, 63%–87%).[22] In addition, as discussed in statement 1, a 14-day duration is associated with a superior success rate compared with shorter durations of this regimen.[27,28,76]

Other issues and discussion. PAM is a PPI triple therapy that avoids the issue of clarithromycin resistance. However, it was inferior to PAC and PMC in earlier studies,[77] and therefore it was concluded that use of PAM should also be restricted to areas with demonstrated high rates of success.

Decisions. The dramatic impact of resistance on the efficacy of triple therapy reinforces the need to restrict this treatment to areas where it has demonstrated recent and ongoing high successful eradication rates (usually ≥90%; however, in the real-world setting, the consensus group decided >85% would be appropriate). The consensus group acknowledged that most clinicians may not know the prevalence of clarithromycin resistance in their local population (see statement 2). In such cases, given the evidence of inadequate eradication rates, they recommend that clinicians err on the side of caution and avoid PPI triple therapy containing clarithromycin (PAC, PMC) unless they have evidence of high success rates (>85%) in their community. In addition, contrary to prior recommendations,[11,12] if triple therapy is to be used at all, it should be given for 14 days.

Statement 6. In patients with *H pylori* infection, we recommend against the use of levofloxacin triple therapy (PAL) as a first-line therapy. *GRADE: Strong recommendation; quality of evidence very low. Vote: strongly agree, 87.5%; agree, 12.5%.*

Key evidence (Supplementary Table 6). In RCTs, ITT eradication success rates for the 7-day and 10-day levofloxacin-containing triple therapy regimen (PAL) for first-line therapy ranged from 74% to 85%.[52,78–81] Although this regimen was significantly more effective than PAC triple therapy for the same duration, eradication rates were generally inadequate (<80% in most studies). Several studies that assessed susceptibility found dramatically lower eradication rates with PAL in levofloxacin-resistant versus levofloxacin-sensitive strains (37.5% vs 97.3%[52] and 50.0% vs 84.4%[81]).

Other issues and discussion. Levofloxacin is widely used for other types of infections; as such, there is a high prevalence of background resistance to this and other quinolones (primary resistance, 6%–36%[48,52,82–85]; secondary resistance, 18%–63%).[83,84] There is also cross-resistance with other quinolones.[86] Levofloxacin resistance among respiratory, urinary, and other pathogens is highly correlated with use of fluoroquinolones,[87–90] and therefore its use should be limited.

Decisions. Based on the unacceptably low eradication rates of PAL for first-line therapy and the high prevalence of levofloxacin resistance, the consensus group agreed that other regimens, particularly bismuth quadruple therapy (PBMT) and concomitant nonbismuth quadruple therapy (PAMC), are preferred in this setting.

Statement 7. In patients with *H pylori* infection, we recommend against the use of sequential nonbismuth quadruple therapy (PA followed by PMC) as a first-line therapy. *GRADE: Strong recommendation; quality of evidence moderate. Vote: strongly agree, 50%; agree, 37.5%; uncertain 12.5%.*

Key evidence (Supplementary Table 7). Meta-analyses of early studies (up to 2009) with sequential therapy showed promising results, with eradication rates consistently higher than 90%.[91–93] Several more recent meta-analyses have shown that 10-day sequential therapy is not superior to 14-day triple therapy,[70,94,95] bismuth quadruple therapy,[70] and concomitant nonbismuth quadruple therapy.[70,96,97]

The updated meta-analysis of studies performed for this consensus meeting (as of 2015) included 14 RCTs comparing sequential and concomitant nonbismuth quadruple therapy using the same drugs at the same dose and for the same duration (see statement 4).[69] In this analysis, concomitant therapy was significantly more effective than sequential therapy (ITT eradication rate, 85.7% vs 79.7%; RD, 6%; 95% CI, 3%–9%; $P < .0001$) (Figure 2).[69]

Other issues and discussion. Analyses of studies in patients with resistant strains found higher eradication rates with concomitant therapy versus sequential therapy among resistant strains (clarithromycin resistance, 92% vs 62%[55,71,72]; metronidazole resistance, 97% vs 82%[71–73]; and dual clarithromycin and metronidazole resistance, 79% vs 47%[55,71–73]).[69]

Decisions. The consensus group concluded these data strongly suggest that sequential therapy is inferior to concomitant therapy, with current successful eradication rates decreasing to <80% in more recent studies.[69,98] Therefore, nonbismuth quadruple therapy should be administered via a concomitant rather than sequential regimen.

Prior Failure

Statement 8. In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend traditional bismuth quadruple therapy (PBMT) for 14 days as an option for subsequent

therapy. *GRADE: Strong recommendation; quality of evidence low. Vote: strongly agree, 62.5%; agree, 37.5%.*

Key evidence (Supplementary Table 8). A meta-analysis of data from 38 RCTs assessing bismuth quadruple therapy (PBMT) after failure of standard triple therapy (PAC) reported an eradication success rate of 78% (95% CI, 75%–81%).[99] There was a trend toward higher eradication rates with longer duration of therapy (7-day regimen, 76%; 10-day regimen, 77%; 14-day regimen, 82%).

A meta-analysis of RCTs and cohort studies was conducted for the meeting to assess the optimal duration of bismuth quadruple therapy as rescue therapy. Overall, 51 studies were included. No direct head-to-head studies comparing 10- and 14-day durations were found, but meta-regression showed that eradication rates using ITT analyses were numerically higher (although not statistically significant) with the 14-day regimen versus the 10-day regimen (78.7% vs 75.6%; $P = .33$).

There is little evidence for PBMT as rescue therapy after regimens other than standard triple therapy. In a small Korean cohort study (n = 45), third-line bismuth quadruple therapy after failure of second-line quadruple therapy had an ITT eradication rate of 66.7%.[42] In a Canadian study, PBMT rescue therapy after 1 to 5 prior treatment failures had an ITT eradication rate of 84%; however, this was much lower in patients previously exposed to bismuth and tetracycline compared with patients without exposure (55% vs 90%; RD, 35%; 95% CI, 10%–62%; $P < .01$).[43]

Other issues and discussion. The consensus group discussed different strategies to potentially improve or optimize bismuth quadruple therapy for use in patients who previously failed to respond to treatment, such as using more potent acid inhibition or higher doses of metronidazole.

The meta-analysis of 51 studies of PBMT rescue therapy that was conducted for the meeting found no direct head-to-head studies comparing low-dose versus high-dose PPI therapy or twice-daily versus more frequent dosing. However, the data allowed between-study comparisons for the dose of esomeprazole (20 mg twice daily in 9 studies and 40 mg twice daily in 6 studies). Meta-regression models adjusting for duration did suggest that regimens containing esomeprazole 40 mg twice daily were more effective than regimens containing esomeprazole 20 mg twice daily ($P = .005$).

A focused literature search was conducted for studies that assessed the role of the dose of metronidazole in eradication regimens. Metronidazole resistance has been shown in meta-analyses to be a predictor of failure of treatment with metronidazole-containing regimens.[26,56,100] In one meta-analysis of various regimens, metronidazole resistance reduced effectiveness by an average of 37.7% (95% CI, 29.6%–45.7%).[26,32,101,102] Increasing the dose and duration of metronidazole may at least partially overcome metronidazole resistance.[32] Some data from triple therapy studies support the use of a higher dose of metronidazole.[103,104] In the HOMER study, the eradication success rates for metronidazole-resistant strains according to dose of metronidazole in a PAM regimen were 54% with 800 mg/day, 50% with 1200 mg/day, and 75% with 1600 mg/day, although in this study the dose of amoxicillin also varied from 1.5 to 2 g/day.[103] Similarly, a comparison of doses of metronidazole in a BMT regimen showed eradication of resistant strains in 64.2% of cases with 750 mg/day compared with 39% to 40% with 375 mg/day.[104]

Decisions. The consensus group concluded that for patients who have previously failed to respond to *H pylori* eradication therapy, traditional bismuth quadruple therapy (PBMT) for 14 days is likely one of the more effective options for rescue therapy. However, more evidence is needed to determine whether PBMT is superior to other alternatives in the second-line setting. With the prevalence of metronidazole resistance reported at 20% to 77%,[4,18–20,40,51] the consensus group recommended a dose of metronidazole in the bismuth quadruple therapy regimen of at least 1500 mg/day (maximum of 2000 mg/day) (Table 2).

Because existing data on the efficacy of PBMT as rescue therapy come primarily from studies conducted in patients who previously failed to respond to a standard triple therapy regimen, there is some controversy as to whether PBMT can be used to re-treat patients after failure of the same regimen. Some members of the consensus group advocated against repeating this regimen, whereas others supported a role for repeat PBMT, perhaps with a higher dose of metronidazole and/or a PPI in certain cases in which options are very limited (eg, cases in which the clinician wants an alternative to a rifabutin combination after the patient has failed to respond to PBMT and PAL).

Statement 9. In patients who have previously failed to respond to *H pylori* eradication therapy, we suggest levofloxacin-containing therapy for 14 days as an option for subsequent therapy. *GRADE: Conditional recommendation; quality of evidence low. Vote: strongly agree, 12.5%; agree, 87.5%.*

Key evidence (Supplementary Table 9). A meta-analysis of 5 studies assessed PAL after failure of sequential nonbismuth quadruple therapy and yielded an overall eradication rate of 81% (95% CI, 71%–91%).[99] Another meta-analysis reported an eradication success rate with PAL of 81% after sequential (6 studies) and 78% after concomitant (3 studies) nonbismuth quadruple therapy.[105] Meta-analyses of studies comparing PAL and PBMT as second-line therapy showed no significant differences in overall eradication rates (77%–79% with PAL vs 67%–69% with PBMT).[99,106] One RCT found that 14-day PAL was as effective as 14-day PBMT in patients who failed to respond to 7-day triple therapy (ITT eradication rates of 86.3% and 86%, respectively).[107] However, a recent real-world study showed superior performance of PBMT over PAL in second- to sixth-line rescue therapy (ITT, 84% vs 61%; RD, 24% [95% CI, 10%–37%]).[43]

Eradication rates were significantly higher (88.7%; 95% CI, 56.1%–100%; $P < .05$) with 10-day compared with 7-day levofloxacin-containing regimens (70.6%; 95% CI, 40.2%–99.1%).[106]

Other issues and discussion. An RCT showed that adding bismuth to a 14-day, first-line PAL (BPAL) regimen only

marginally improved ITT eradication rates overall (87.5% [95% CI, 78.5%–93.1%] vs 82.7% [95% CI, 73%–89.4%]; $P = .39$), but eradication rates were much higher among levofloxacin-resistant strains (70.6% vs 37.5%).[52] After prior treatment failure (including both standard triple and nonbismuth quadruple therapies), BPAL had an ITT eradication success rate of 90% (95% CI, 86%–94%) in a prospective cohort study.[108]

Decisions. The consensus group agreed that for patients who have previously failed to respond to *H pylori* eradication therapy, levofloxacin-containing therapy (usually PAL) is an option. However, in light of evidence of higher eradication rates with longer treatment durations,[106] the consensus group recommended a 14-day regimen.

Statement 10. In patients who have previously failed to respond to clarithromycin-containing *H pylori* eradication therapy, we recommend against the use of clarithromycin-containing regimens as subsequent therapy. *GRADE: Strong recommendation; quality of evidence low. Vote: strongly agree, 100%.*

Key evidence (Supplementary Table 10). As discussed with statements 2 and 5, the efficacy of clarithromycin-containing regimens is highly affected by clarithromycin resistance.[19,22,46,52–55] More importantly, the prevalence of secondary resistance is very high (up to 70% in some series).[20,40]

Decisions. As a result of resistance concerns, the consensus group recommended against reuse of clarithromycin in patients who have already failed to respond to a clarithromycin-containing regimen.

Statement 11. In patients who have previously failed to respond to a levofloxacin-containing *H pylori* eradication therapy, we recommend against the use of levofloxacin-containing regimens as subsequent therapy. *GRADE: Strong recommendation; quality of evidence low. Vote: strongly agree, 62.5%; agree, 37.5%.*

Key evidence (Supplementary Table 11). As discussed in statement 6, the efficacy of levofloxacin-containing regimens is highly affected by levofloxacin resistance.[52,81] Studies have shown that the prevalence of secondary levofloxacin resistance is very high (up to 63% in some series).[83,84]

Decisions. As a result of resistance concerns, the consensus group recommended against reusing levofloxacin in patients who have already failed to respond to a levofloxacin-containing regimen. Previous quinolone use is also associated with levofloxacin-resistant *H pylori* and would be expected to reduce the therapeutic success of this agent.

Statement 12. In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend against the use of sequential nonbismuth quadruple therapy (PA followed by PMC) as an option for subsequent therapy. *GRADE: Strong recommendation; quality of evidence very low. Vote: strongly agree, 50%; agree, 50%.*

Key evidence (Supplementary Table 12). Cohort data have suggested that sequential nonbismuth quadruple therapy can be effective after failure of previous eradication therapy, but data are from a small number of patients (42 patients in total) and low quality.[109,110] As discussed in statement 7, eradication success rates with this regimen were low (<80%) and inferior to concomitant administration when used in the first-line setting (Figure 2).[69] In addition, this strategy was associated with very low eradication of clarithromycin and dual clarithromycin and metronidazole resistant strains (62% and 47%).[69]

Decisions. The consensus group recommended that sequential nonbismuth quadruple therapy not be used as rescue therapy, because it is less efficacious than other therapies.

Statement 13. We recommend restricting the use of rifabutin-containing regimens to cases in which at least 3 recommended options have failed. *GRADE: Strong recommendation; quality of evidence very low. Vote: strongly agree, 62.5%; agree, 37.5%.*

Key evidence (Supplementary Table 13). A systematic review of 21 studies assessing rescue therapy with rifabutin-containing regimens found that the overall ITT eradication success rate was 73% (95% CI, 67%–79%).[111] The success rate was 79% for second-line regimens and 66% to 70% for third-line or greater regimens. The prevalence of resistance was low at 1.3%. Rifabutin triple therapy for 10 days was shown to be effective in approximately one-half of patients when used as fourth-line rescue therapy in a cohort of 190 patients, with an ITT eradication rate of 52% (95% CI, 45%–59%).[112,113]

Other issues and discussion. The most commonly studied rifabutin-containing regimen is PPI + amoxicillin + rifabutin [PAR]; current evidence suggests that 10 days may be more effective than 7 days, but no additional benefit has been shown with 14 days, which may increase the side effect burden.[111,114] For this reason, this is the only regimen for which a duration of therapy of 10 days may be suggested; however, this suggestion is based on a small number of patients who were treated.

Rifabutin-containing regimens should be reserved for patients with multiple treatment failures. Because eradication in the rescue setting is low, there are concerns about adverse events, especially myelotoxicity, and cost is also an issue. In addition, although the prevalence of resistance is low, there are theoretical concerns that overuse may increase the prevalence of rifabutin-resistant mycobacteria in the community, for which this agent is currently very important.[111]

Decisions. The consensus group agreed that rifabutin-containing regimens may be useful in the rescue setting but appear to be less safe than other regimens and should be reserved for patients with multiple previous failures (eg, PBMT, PAMC, and PAL).

Other statements/comments. *PAMC as rescue therapy.* The consensus group concluded that there was insufficient evidence to support or refute the efficacy of PAMC as a second-line option and thus was unable to recommend for or against this regimen as a rescue therapy. In a small Japanese study, the ITT eradication rate with PAMC after failure of PAC triple therapy was 88.5%, compared with 82.7% with PAM.[115] No data were found assessing the use of this regimen after failure of bismuth quadruple therapy.

The role of acid suppression. Acid suppression plays an important role in eradication of *H pylori* infection. Successful eradication has been shown to be closely related to the degree of acid inhibition, with a cohort study using triple therapy (PAC) showing a significantly higher mean gastric pH in patients with versus without successful eradication (6.4 vs 5.2; $P = .013$).[116]

It has been suggested that achieving more potent acid inhibition can improve treatment success. Meta-analyses of RCTs have shown higher eradication rates with triple therapy using a standard-dose PPI twice daily versus once daily (13 studies; 83.9% vs 77.7%; $P < .01$)[117] and with a high-dose (eg, esomeprazole 40 mg twice daily) versus standard-dose PPI (eg, esomeprazole 20 mg twice daily) (6 studies; 82% vs 74%; $P = .03$).[118] In addition, a meta-analysis of 35 studies showed higher eradication rates with esomeprazole (82.3% vs 77.6%; odds ratio, 1.32; 95% CI, 1.01–1.73) and rabeprazole (80.5% vs 76.2%; odds ratio, 1.21; 95% CI, 1.02–1.42) compared with first-generation PPIs (omeprazole, lansoprazole, pantoprazole).[119]

Another potential method to improve acid inhibition would be to use newer, more potent antisecretory agents. Potassium-competitive acid blockers inhibit gastric H^+/K^+–adenosine triphosphatase in a K^+ competitive but reversible manner and thus do not require prior proton pump activation to achieve their antisecretory effect.[120,121] One of these agents, vonoprazan, was recently approved in Japan for a number of gastrointestinal diseases, including eradication of *H pylori* infection.[121] Data suggest that the pH 4 holding time with this drug is equivalent to esomeprazole 20 mg 4 times daily.[122,123] Superior clinical efficacy of this more potent acid suppressant in triple therapy regimens has been shown in first-line and second-line settings.[124] For example, vonoprazan-based triple therapy with amoxicillin and clarithromycin had greater eradication success rates (92.6% vs 75.9%; $P < .0001$) than the same lansoprazole-based treatment due to the difference in eradication of clarithromycin-resistant cases (82.0% vs 40.0%; $P < .0001$), although treatment success in the presence of clarithromycin resistance is still far from desirable.[124]

High-dose dual therapy. Further evidence for increased efficacy with greater acid suppression comes from a study of high-dose PPI dual therapy.[50] Despite the recognized inadequacy of standard-dose PPI dual therapy,[125] a large RCT reported significantly higher ITT eradication rates with high-dose PPI dual therapy (amoxicillin 750 mg 4 times a day and rabeprazole 20 mg 4 times a day for 14 days; 95.3%) as first-line treatment compared with either 10-day sequential (85.3%) or 7-day standard triple therapy (80.7%) and as second-line treatment (89.3%) compared with sequential (51.8%) but not levofloxacin-based triple therapy (78.6%).[50] It is unknown how this regimen would compare with PBMT. This regimen may prove to be advantageous given the low prevalence of amoxicillin resistance, but the consensus group felt that more evidence was needed (eg, compared with 14-day PBMT or PAMC first-line therapy, compared with PBMT in rescue therapy and in other countries) before a statement on this therapy could be developed. However, high-dose dual PPI therapy for 14 days may be an option when both dual metronidazole/clarithromycin resistance and levofloxacin resistance are suspected, such as in a patient with multiple previous failures to respond to therapy.

Supplemental Therapy

Statement 14. In patients with *H pylori* infection, we recommend against routinely adding probiotics to eradication therapy for the purpose of reducing adverse events. *GRADE: Strong recommendation; quality of evidence very low. Vote: strongly agree, 87.5%; agree, 12.5%.*

Statement 15. In patients with *H pylori* infection, we recommend against adding probiotics to eradication therapy for the purpose of increasing eradication rates. *GRADE: Strong recommendation; quality of evidence very low. Vote: strongly agree, 62.5%; agree, 37.5%.*

Key evidence (Supplementary Table 14). A meta-analysis of 10 trials concluded that Lactobacillus-containing and Bifidobacterium-containing probiotic preparations during *H pylori* eradication therapy may have beneficial effects on eradication rate and incidence of total side effects.[126] However, this analysis was rated low-quality evidence due to serious limitations, inconsistency, and indirectness (the majority of trials assessed the impact of probiotic supplementation when added to triple rather than quadruple therapy).

Two RCTs have reported no improvement in eradication rates with the addition of probiotics to quadruple therapy in adults.[127,128] When added to sequential nonbismuth quadruple therapy, there was no significant impact on eradication rates; however, side effects and compliance were improved compared with placebo.[127] When added to bismuth quadruple therapy, a multi-strain probiotic compound showed no beneficial effects on efficacy (ITT eradication rate, 76.6% vs 81.1%; $P = .029$) or overall tolerability ($P = .851$) compared with placebo.[128] There was a significant reduction in diarrhea but an increase in abdominal pain.

Other issues and discussion. Although some studies suggest possible beneficial effects, these results are inconsistent across studies and there are a number of concerns with use of probiotics.[129] Formulations are not standardized and contain different bacterial strains in different combinations and at different concentrations; therefore, studies are needed to determine which, if any, specific formulations may actually have beneficial effects. Use of probiotics also increases the cost and complexity of an already complex treatment regimen.

Decisions. The consensus group concluded that the evidence does not convincingly show that probiotics will increase the efficacy of the recommended eradication therapies and they should not be used for this purpose. In contrast, although not recommended routinely for the prevention of adverse events, they may be potentially useful, and unlikely harmful, in certain high-risk cases to prevent diarrhea or *Clostridium difficile* infection.

Future Directions

The lack of availability of data on local susceptibility patterns and eradication success rates was identified as a knowledge gap that has a major impact on the choice of therapy and hence best management. Periodic susceptibility testing should be considered by health authorities, and clinicians should be encouraged to record their successes. These data should be published or presented at conferences to help monitor susceptibility on an ongoing basis.

There is a need for well-conducted, head-to-head RCTs on the efficacy of concomitant nonbismuth therapy versus PBMT as first-line treatment, as well as studies on 10-day versus 14-day regimens. In addition, more data are needed on the efficacy of rescue therapies after failure of concomitant or PBMT first-line treatment.

As discussed in statement 8, there continues to be a need to determine the optimal doses of drugs included in the recommended regimens, including the effects of various doses of metronidazole (500 mg 3 times daily vs 500 mg 4 times a day) for PBMT. The role of more potent acid suppression through higher or more frequent doses, or the use of newer antisecretory agents such as vonoprazan, requires further study.

The increasing prevalence of resistance and increasing rates of failure of current therapies emphasize the need to continue developing and evaluating new regimens. Moxifloxacin-containing triple therapies have been studied in some parts of the world.[130–133] Several meta-analyses of RCTs have reported that this regimen is better tolerated than bismuth quadruple therapy and is as effective in the first-line setting[130] and more effective in the second-line setting.[130,131] However, moxifloxacin is affected by the same high prevalence of fluoroquinolone resistance as levofloxacin (see statement 6). Bismuth quadruple therapy with a PPI, amoxicillin, and clarithromycin (PBAC)[134–137] or levofloxacin (BPAL; see statement 9) may be an effective alternative to PBMT.[52,108] Eradication success rates with PBAC have been widely variable, ranging from 55% to 96% in RCTs.[134–137] In addition, this regimen will likely be affected by clarithromycin resistance.

Further study on high-dose PPI dual therapy (amoxicillin 750 mg 4 times a day and rabeprazole 20 mg 4 times a day for 14 days)[50] and other high-dose dual regimens is required before they can be recommended.

In certain countries, some agents are not available; therefore, alternative regimens may be required for treatment failure. For example, if bismuth and levofloxacin are not available, high-dose PPI dual therapy or PAM can be considered. Further studies on these and other alternatives are required for those who fail to respond to treatment.

Limitations of the Consensus

There are some limitations of this consensus that should be mentioned. It would have been ideal if the consensus panel also included primary care physicians, patients, or other stakeholders, although their potential viewpoints were discussed at the face-to-face meeting before every vote. In addition, it was decided not to search for data before 2008 to avoid confounding of data from earlier studies that had higher eradication success rates likely as a result of lower antibiotic resistance. However, this cutoff can be viewed as a shortcoming, especially in the rare instance when no new data were available. Older studies and meta-analyses were used as a discussion point when presenting newer studies and newer meta-analyses, because we did not want to completely ignore older data. The older data were only used in decision making if newer data did not exist for that particular statement. We believe this approach was valid because it puts more emphasis on more recent data while not ignoring data published before 2008. Finally, the systematic evaluation of evidence relied on studies in which the populations had variable percentages of antibiotic resistance. This would affect the success rates of the different regimens and conclusions may not be generalizable to specific practice populations.[57] Similarly, different studies may have used different doses, dosing intervals, and relationships to meals that are not taken into account when combining results from different studies. Some of these factors may also play a role in determining outcome and have not been addressed by this consensus.

Summary

Based on evidence of higher eradication rates with regimens of longer duration and increasing failure of shorter treatment durations, the consensus group strongly recommended that all *H pylori* eradication regimens be given for 14 days. Recommended first-line strategies include

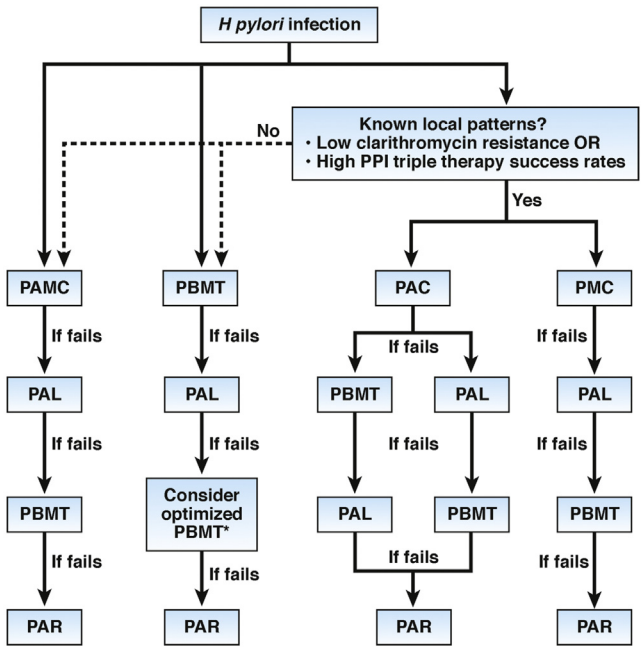

Figure 3. Algorithm for eradication therapies for first-line and rescue treatments. *Some members of the consensus group advocated against the repeat use of PBMT, whereas others suggested it may be useful to reserve rifabutin for fourth-line use (see statement 8). Optimized refers to using a higher dose of PPI or metronidazole. See Tables 1 and 2 for more details on regimens and dosing.

traditional quadruple bismuth therapy (PBMT), concomitant nonbismuth quadruple therapy (PAMC), and the restricted use of PPI triple therapy (PAC or PMC) to regions with known low clarithromycin resistance or high eradication success rates (Table 1 and Figure 3). Levofloxacin triple therapy (PAL) and sequential nonbismuth quadruple therapy (PA followed by PMC) were not recommended for first-line treatment.

Potential strategies for subsequent therapy for patients who fail to respond treatment are shown in Figure 3. The choice of second-line treatment depends on previous antibiotic exposure. If there is no previous metronidazole exposure, PBMT and levofloxacin-containing therapies are both options. If the patient was previously exposed to metronidazole, PAL is the preferred second-line option. If PAL has failed, then PBMT is the next option even if previously exposed to metronidazole. An optimized PBMT with higher-dose PPI and metronidazole 500 mg 4 times a day could be considered an option if the patient has previously failed to respond to regular PBMT and PAL, especially if one wanted to avoid rifabutin. However, there is not a large body of evidence for this, and some members of the group argued that repeating PBMT would not be useful. The use of rifabutin-containing regimens should be restricted to patients who have failed to respond to at least 3 prior options. Regarding nonbismuth quadruple therapy, there were insufficient data to make a recommendation regarding concomitant PAMC as rescue therapy, but sequential therapy (PA followed by PMC) was not recommended.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.04.006.

References

1. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter 2014;19(suppl 1):1–5.
2. Ford AC, Axon AT. Epidemiology of Helicobacter pylori infection and public health implications. Helicobacter 2010;15(suppl 1):1–6.
3. Goh KL, Chan WK, Shiota S, et al. Epidemiology of Helicobacter pylori infection and public health implications. Helicobacter 2011;16(suppl 1):1–9.
4. Wang AY, Peura DA. The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world. Gastrointest Endosc Clin North Am 2011;21:613–635.
5. Sethi A, Chaudhuri M, Kelly L, et al. Prevalence of Helicobacter pylori in a First Nations population in northwestern Ontario. Can Fam Physician 2013;59:e182–e187.
6. Cheung J, Goodman KJ, Girgis S, et al. Disease manifestations of Helicobacter pylori infection in Arctic Canada: using epidemiology to address community concerns. BMJ Open 2014;4:e003689.
7. Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of Helicobacter pylori in the Alaska native population and association with low serum ferritin levels in young adults. Clin Diagn Lab Immunol 2000;7:885–888.
8. Woodward M, Morrison C, McColl K. An investigation into factors associated with Helicobacter pylori infection. J Clin Epidemiol 2000;53:175–181.
9. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010;362:1597–1604.
10. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015;64:1353–1367.
11. Hunt R, Fallone C, Veldhuyzan van Zanten S, et al. Canadian Helicobacter Study Group Consensus Conference: 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;18:547–554.
12. Hunt RH, Fallone CA, Thomson AB. Canadian Helicobacter pylori Consensus Conference update: infections in adults. Canadian Helicobacter Study Group. Can J Gastroenterol 1999;13:213–217.
13. 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;56:772–781.
14. Gisbert JP, Calvet X. Review article: Helicobacter pylori-negative duodenal ulcer disease. Aliment Pharmacol Ther 2009;30:791–815.
15. Ford AC, Forman D, Hunt RH, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ 2014;348:g3174.
16. Chiba N, Van Zanten SJ, Sinclair P, et al. 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;324:1012–1016.
17. Moayyedi P, Soo S, Deeks JJ, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2011:CD002096.
18. Loo VG, Fallone CA, De Souza E, et al. In-vitro susceptibility of Helicobacter pylori to ampicillin, clarithromycin, metronidazole and omeprazole. J Antimicrob Chemother 1997;40:881–883.
19. Lahaie RG, Gaudreau C. Helicobacter pylori antibiotic resistance: trends over time. Can J Gastroenterol 2000;14:895–899.
20. Best L, Cooper-Lesins G, Haldane D, et al. Helicobacter pylori antibiotic resistance in Canadian populations (abstr S1293). Gastroenterology 2004;126:A-189.
21. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65–73.
22. Venerito M, Krieger T, Ecker T, et al. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple

therapy for empiric primary treatment of Helicobacter pylori infection. Digestion 2013;88:33–45.
23. McMahon BJ, Hennessy TW, Bensler JM, et al. The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for Helicobacter pylori infections. Ann Intern Med 2003; 139:463–469.
24. Saad RJ, Chey WD. Persistent Helicobacter pylori infection after a course of antimicrobial therapy—what's next? Clin Gastroenterol Hepatol 2008;6:1086–1090.
25. Peterson WL, Fendrick AM, Cave DR, et al. Helicobacter pylori-related disease: guidelines for testing and treatment. Arch Intern Med 2000;160:1285–1291.
26. Dore MP, Leandro G, Realdi G, et al. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of Helicobacter pylori therapy: a meta-analytical approach. Dig Dis Sci 2000; 45:68–76.
27. Chen Y-I, Fallone CA. A 14-day course of triple therapy is superior to a 10-day course for the eradication of Helicobacter pylori: A Canadian study conducted in a "real world" setting. Can J Gastroenterol Hepatol 2015; 29:e7–e10.
28. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev 2013;12:CD008337.
29. Lee M, Kemp JA, Canning A, et al. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. Arch Intern Med 1999;159:2312–2316.
30. O'Connor A, Gisbert JP, McNamara D, et al. Treatment of Helicobacter pylori infection 2010. Helicobacter 2010; 15(suppl 1):46–52.
31. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of Helicobacter pylori with triple therapy. Gastroenterology 1992;102:493–496.
32. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut 2010; 59:1143–1153.
33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
34. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
35. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. Gastroenterology 2014;146:835–848.e6.
36. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology 2015;148:1035–1058.e3.
37. Cook DJ, Greengold NL, Ellrodt AG, et al. The relation between systematic reviews and practice guidelines. Ann Intern Med 1997;127:210–216.
38. Dalkey N. An experimental study of group opinion: the Delphi method. Futures 1969;1:408–426.
39. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ 2008;336:1049–1051.
40. van Zanten SV, Desai S, Best L, et al. Rescue therapy using a rifabutin-based regimen is effective for cure of Helicobacter pylori infection. Can J Gastroenterol 2010; 24:303–306.
41. Megraud F, Coenen S, Versporten A, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34–42.
42. Lee SK, Lee SW, Park JY, et al. Effectiveness and safety of repeated quadruple therapy in Helicobacter pylori infection after failure of second-line quadruple therapy: repeated quadruple therapy as a third-line therapy. Helicobacter 2011;16:410–414.
43. Shaikh T, Fallone CA. Effectiveness of second- through sixth-line salvage Helicobacter pylori treatment: bismuth quadruple therapy is almost always a reasonable choice. Can J Gastroenterol Hepatol 2015 Nov 2. pii: 17152. http://dx.doi.org/10.1155/2016/7321574. [Epub ahead of print]
44. Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori. Aliment Pharmacol Ther 2011;34:604–617.
45. Gisbert JP, Molina-Infante J, Harb Y, et al. Nonbismuth quadruple (concomitant) therapy for eradication of H. pylori: standard vs. optimized (14-day, high-dose PPI) regimen (abstr Su1172). Gastroenterology 2014; 146:S394–S395.
46. Filipec Kanizaj T, Katicic M, Skurla B, et al. Helicobacter pylori eradication therapy success regarding different treatment period based on clarithromycin or metronidazole triple-therapy regimens. Helicobacter 2009; 14:29–35.
47. Wenzhen Y, Yumin L, Quanlin G, et al. Is antimicrobial susceptibility testing necessary before first-line treatment for Helicobacter pylori infection? Meta-analysis of randomized controlled trials. Intern Med 2010; 49:1103–1109.
48. Shiota S, Reddy R, Alsarraj A, et al. Antibiotic resistance of Helicobacter pylori among male United States veterans. Clin Gastroenterol Hepatol 2015;13:1616–1624.
49. Agudo S, Perez-Perez G, Alarcon T, et al. High prevalence of clarithromycin-resistant Helicobacter pylori strains and risk factors associated with resistance in Madrid. Spain. J Clin Microbiol 2010;48:3703–3707.
50. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for Helicobacter pylori infection. Clin Gastroenterol Hepatol 2015;13:895–905.e5.
51. Cheung J, Morse AL, Goodman KJ, et al. Prevalence of Helicobacter pylori and antibiotic resistance in an aboriginal population in Canada's arctic: preliminary results from the Aklavik H. pylori project (abstr M1058). Gastroenterology 2009;136:A341.
52. Liao J, Zheng Q, Liang X, et al. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. Helicobacter 2013; 18:373–377.
53. Katelaris PH, Forbes GM, Talley NJ, et al. A randomized comparison of quadruple and triple therapies for

Helicobacter pylori eradication: the QUADRATE Study. Gastroenterology 2002;123:1763–1769.
54. 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;98:562–567.
55. Molina-Infante J, Pazos-Pacheco C, Vinagre-Rodriguez G, et al. Nonbismuth quadruple (concomitant) therapy: empirical and tailored efficacy versus standard triple therapy for clarithromycin-susceptible Helicobacter pylori and versus sequential therapy for clarithromycin-resistant strains. Helicobacter 2012;17:269–276.
56. Fischbach LA, Goodman KJ, Feldman M, et al. Sources of variation of Helicobacter pylori treatment success in adults worldwide: a meta-analysis. Int J Epidemiol 2002; 31:128–139.
57. Wu JY, Liou JM, Graham DY. Evidence-based recommendations for successful Helicobacter pylori treatment. Expert Rev Gastroenterol Hepatol 2014;8:21–28.
58. Graham DY, Shiotani A. Which therapy for Helicobacter pylori infection? Gastroenterology 2012;143:10–12.
59. Graham DY. Hp-normogram (normo-graham) for assessing the outcome of H. pylori therapy: effect of resistance, duration, and CYP2C19 genotype. Helicobacter 2016;21:85–90.
60. Graham DY, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177–186.e3; discussion e12–e13.
61. Uygun A, Kadayifci A, Safali M, et al. The efficacy of bismuth containing quadruple therapy as a first-line treatment option for Helicobacter pylori. J Dig Dis 2007;8:211–215.
62. Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for Helicobacter pylori: lessons from China. Eur J Gastroenterol Hepatol 2013;25:1134–1140.
63. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008;31:213–224.
64. Malfertheiner P, Bazzoli F, Delchier JC, et al. Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet 2011;377:905–913.
65. Gisbert JP. Helicobacter pylori eradication: a new, single-capsule bismuth-containing quadruple therapy. Nat Rev Gastroenterol Hepatol 2011;8:307–309.
66. O'Morain C, Borody T, Farley A, et al. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of Helicobacter pylori: an international multicentre study. Aliment Pharmacol Ther 2003;17:415–420.
67. Gisbert JP, Barrio J, Modolell I, et al. Helicobacter pylori first-line and rescue treatments in the presence of penicillin allergy. Dig Dis Sci 2015;60:458–464.
68. Essa AS, Kramer JR, Graham DY, et al. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. Helicobacter 2009; 14:109–118.
69. Gisbert JP, McNicholl AG. Eradication of Helicobacter pylori infection with non-bismuth quadruple concomitant therapy. In: Talebi Bezmin Abadi A, ed. Helicobacter pylori: to be or not to be! Sharjah, UAE: Bentham, 2016.
70. Gatta L, Vakil N, Vaira D, et al. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. BMJ 2013; 347:f4587.
71. Huang YK, Wu MC, Wang SS, et al. Lansoprazole-based sequential and concomitant therapy for the first-line Helicobacter pylori eradication. J Dig Dis 2012; 13:232–238.
72. Wu DC, Hsu PI, Wu JY, et al. Sequential and concomitant therapy with four drugs is equally effective for eradication of H pylori infection. Clin Gastroenterol Hepatol 2010; 8:36–41.e1.
73. Georgopoulos SD, Xirouchakis E, Zampeli E, et al. A randomised study comparing 10 days concomitant and sequential treatments for the eradication of Helicobacter pylori, in a high clarithromycin resistance area (abstr Su1152). Gastroenterology 2015;148:S-422.
74. Molina-Infante J, Lucendo AJ, Angueira T, et al. Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: the OPTRICON study. Aliment Pharmacol Ther 2015; 41:581–589.
75. Rodgers C, van Zanten SV. A meta-analysis of the success rate of Helicobacter pylori therapy in Canada. Can J Gastroenterol 2007;21:295–300.
76. Fallone CA, Barkun AN, Szilagyi A, et al. Prolonged treatment duration is required for successful Helicobacter pylori eradication with proton pump inhibitor triple therapy in Canada. Can J Gastroenterol 2013; 27:397–402.
77. 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;1:138–144.
78. Assem M, El Azab G, Rasheed MA, et al. Efficacy and safety of levofloxacin, clarithromycin, and esomeprazol as first line triple therapy for Helicobacter pylori eradication in Middle East. Prospective, randomized, blind, comparative, multicenter study. Eur J Intern Med 2010; 21:310–314.
79. Molina-Infante J, Perez-Gallardo B, Fernandez-Bermejo M, et al. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. Aliment Pharmacol Ther 2010;31:1077–1084.
80. Qian J, Ye F, Zhang J, et al. Levofloxacin-containing triple and sequential therapy or standard sequential therapy as the first line treatment for Helicobacter pylori eradication in China. Helicobacter 2012;17:478–485.
81. Liou JM, Lin JT, Chang CY, et al. Levofloxacin-based and clarithromycin-based triple therapies as first-line and

second-line treatments for Helicobacter pylori infection: a randomised comparative trial with crossover design. Gut 2010;59:572–578.
82. O'Connor A, Taneike I, Nami A, et al. Helicobacter pylori resistance rates for levofloxacin, tetracycline and rifabutin among Irish isolates at a reference centre. Ir J Med Sci 2013;182:693–695.
83. Karczewska E, Klesiewicz K, Wojtas-Bonior I, et al. Levofloxacin resistance of Helicobacter pylori strains isolated from patients in southern Poland, between 2006-2012. Acta Pol Pharm 2014;71:477–483.
84. Phan TN, Santona A, Tran VH, et al. High rate of levofloxacin resistance in a background of clarithromycin- and metronidazole-resistant Helicobacter pylori in Vietnam. Int J Antimicrob Agents 2015;45:244–248.
85. Eng NF, Ybazeta G, Chapman K, et al. Antimicrobial susceptibility of Canadian isolates of Helicobacter pylori in Northeastern Ontario. Can J Infect Dis Med Microbiol 2015;26:137–144.
86. Berning M, Krasz S, Miehlke S. Should quinolones come first in Helicobacter pylori therapy? Therap Adv Gastroenterol 2011;4:103–114.
87. Khawcharoenporn T, Vasoo S, Ward E, et al. High rates of quinolone resistance among urinary tract infections in the ED. Am J Emerg Med 2012;30:68–74.
88. Lee YJ, Liu HY, Lin YC, et al. Fluoroquinolone resistance of Pseudomonas aeruginosa isolates causing nosocomial infection is correlated with levofloxacin but not ciprofloxacin use. Int J Antimicrob Agents 2010; 35:261–264.
89. Wu HH, Liu HY, Lin YC, et al. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant Escherichia coli. J Microbiol Immunol Infect 2012 May 4 [Epub ahead of print].
90. May L, Klein EY, Rothman RE, et al. Trends in antibiotic resistance in coagulase-negative staphylococci in the United States, 1999 to 2012. Antimicrob Agents Chemother 2014;58:1404–1409.
91. Gatta L, Vakil N, Leandro G, et al. Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children. Am J Gastroenterol 2009; 104:3069–3079; quiz 1080.
92. Jafri NS, 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;148:923–931.
93. Gisbert JP, Calvet X, O'Connor A, et al. Sequential therapy for Helicobacter pylori eradication: a critical review. J Clin Gastroenterol 2010;44:313–325.
94. Nyssen O, McNicholl A, Megraud F, et al. Sequential versus standard triple therapy for Helicobacter pylori eradication (protocol). Cochrane Database Syst Rev 2011:CD009034.
95. Nyssen OP, McNicholl AG, Megraud F, et al. Meta-analysis of sequential vs. standard triple therapy for Helicobacter pylori eradication: final results of a Cochrane systematic review (abstr Su1165). Gastroenterology 2014;146:S393.
96. Kim JS, Park SM, Kim BW. Sequential or concomitant therapy for eradication of H. pylori infection: a systematic review and meta-analysis. J Gastroenterol Hepatol 2015; 30:1338–1345.
97. He L, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for Helicobacter pylori eradication. Intern Med 2015;54:703–710.
98. Morse AL, Goodman KJ, Munday R, et al. A randomized controlled trial comparing sequential with triple therapy for Helicobacter pylori in an Aboriginal community in the Canadian North. Can J Gastroenterol 2013;27:701–706.
99. Marin AC, McNicholl AG, Gisbert JP. A review of rescue regimens after clarithromycin-containing triple therapy failure (for Helicobacter pylori eradication). Expert Opin Pharmacother 2013;14:843–861.
100. van der Wouden EJ, Thijs JC, van Zwet AA, et al. The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-Helicobacter pylori regimens: a meta-analysis. Am J Gastroenterol 1999; 94:1751–1759.
101. Graham DY, Osato MS, Hoffman J, et al. Metronidazole containing quadruple therapy for infection with metronidazole resistant Helicobacter pylori: a prospective study. Aliment Pharmacol Ther 2000;14:745–750.
102. van der Wouden EJ, Thijs JC, Kusters JG, et al. Mechanism and clinical significance of metronidazole resistance in Helicobacter pylori. Scand J Gastroenterol 2001; 36:10–14.
103. Bardhan K, Bayerdorffer E, Veldhuyzen Van Zanten SJ, et al. The HOMER Study: the effect of increasing the dose of metronidazole when given with omeprazole and amoxicillin to cure Helicobacter pylori infection. Helicobacter 2000;5:196–201.
104. Roghani HS, Massarrat S, Pahlewanzadeh MR, et al. Effect of two different doses of metronidazole and tetracycline in bismuth triple therapy on eradication of Helicobacter pylori and its resistant strains. Eur J Gastroenterol Hepatol 1999;11:709–712.
105. Marin AC, McNicholl AG, Gisbert JP. Efficacy of a second-line levofloxacin-containing triple therapy after the failure of the non-bismuth sequential or concomitant treatments: systematic review and meta-analysis (abstr P11.39). Helicobacter 2014;19(suppl 1):139–140.
106. Di Caro S, Fini L, Daoud Y, et al. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for Helicobacter pylori eradication in second-line. World J Gastroenterol 2012;18:5669–5678.
107. Chuah SK, Tai WC, Hsu PI, et al. The efficacy of second-line anti-Helicobacter pylori therapy using an extended 14-day levofloxacin/amoxicillin/proton-pump inhibitor treatment–a pilot study. Helicobacter 2012; 17:374–381.
108. Gisbert JP, Romano M, Gravina AG, et al. Helicobacter pylori second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. Aliment Pharmacol Ther 2015;41:768–775.
109. Urgesi R, Pelecca G, Cianci R, et al. Helicobacter pylori infection: is sequential therapy superior to standard triple therapy? A single-centre Italian study in treatment-naive

and non-treatment-naive patients. Can J Gastroenterol 2011;25:315–318.
110. Liu KS, Hung IF, Seto WK, et al. Ten day sequential versus 10 day modified bismuth quadruple therapy as empirical firstline and secondline treatment for Helicobacter pylori in Chinese patients: an open label, randomised, crossover trial. Gut 2014;63:1410–1415.
111. Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory Helicobacter pylori infection. Aliment Pharmacol Ther 2012;35:209–221.
112. Gisbert JP, Castro-Fernandez M, Perez-Aisa A, et al. Fourth-line rescue therapy with rifabutin in patients with three Helicobacter pylori eradication failures. Aliment Pharmacol Ther 2012;35:941–947.
113. Gisbert JP, Castro-Fernandez M, Aisa AP, et al. Fourth-line rescue therapy with rifabutin in patients with three H. pylori eradication failures (abstr Su1131). Gastroenterology 2015;148:S-416.
114. 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;26:1537–1542.
115. Ueki N, Miyake K, Kusunoki M, et al. Impact of quadruple regimen of clarithromycin added to metronidazole-containing triple therapy against Helicobacter pylori infection following clarithromycin-containing triple-therapy failure. Helicobacter 2009;14:91–99.
116. Sugimoto M, Furuta T, Shirai N, et al. Evidence that the degree and duration of acid suppression are related to Helicobacter pylori eradication by triple therapy. Helicobacter 2007;12:317–323.
117. Vallve M, Vergara M, Gisbert JP, et al. Single vs. double dose of a proton pump inhibitor in triple therapy for Helicobacter pylori eradication: a meta-analysis. Aliment Pharmacol Ther 2002;16:1149–1156.
118. Villoria A, Garcia P, Calvet X, et al. Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther 2008;28:868–877.
119. McNicholl AG, Linares PM, Nyssen OP, et al. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther 2012;36:414–425.
120. Maradey-Romero C, Fass R. New and future drug development for gastroesophageal reflux disease. J Neurogastroenterol Motil 2014;20:6–16.
121. Garnock-Jones KP. Vonoprazan: first global approval. Drugs 2015;75:439–443.
122. Scarpignato C, Hunt RH. Editorial: towards extended acid suppression - the search continues. Aliment Pharmacol Ther 2015;42:1027–1029.
123. Hunt R, Scarpignato C. Potassium-competitive acid blockers (P-CABs): Are they finally ready for prime time in acid-related disease? Clin Trans Gastroenterol 2015;6:e119.
124. Murakami K, Sakurai Y, Shiino M, et al. A phase 3, double-blind study of a triple therapy with TAK-438, amoxicillin, and clarithromycin as first line eradication of H. pylori and a triple therapy with TAK-438, amoxicillin, and metronidazole as second line eradication of H. pylori (abstr Tu1056). Gastroenterology 2014;5:S-740.
125. Chiba N. Chapter 5: Ulcer disease and Helicobacter pylori. In: McDonald J, Burroughs A, Feagan B, eds. Evidence-based gastroenterology and hepatology. 2nd ed. New Delhi: Blackwell Publishing Ltd, 2004:83–116.
126. Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. J Clin Gastroenterol 2013;47:25–32.
127. Manfredi M, Bizzarri B, Sacchero RI, et al. Helicobacter pylori infection in clinical practice: probiotics and a combination of probiotics + lactoferrin improve compliance, but not eradication, in sequential therapy. Helicobacter 2012;17:254–263.
128. Shavakhi A, Tabesh E, Yaghoutkar A, et al. The effects of multistrain probiotic compound on bismuth-containing quadruple therapy for Helicobacter pylori infection: a randomized placebo-controlled triple-blind study. Helicobacter 2013;18:280–284.
129. Molina-Infante J, Gisbert JP. Probiotics for Helicobacter pylori eradication therapy: not ready for prime time. Rev Esp Enferm Dig 2013;105:441–444.
130. Zhang G, Zou J, Liu F, et al. The efficacy of moxifloxacin-based triple therapy in treatment of Helicobacter pylori infection: a systematic review and meta-analysis of randomized clinical trials. Braz J Med Biol Res 2013;46:607–613.
131. Wu C, Chen X, Liu J, et al. Moxifloxacin-containing triple therapy versus bismuth-containing quadruple therapy for second-line treatment of Helicobacter pylori infection: a meta-analysis. Helicobacter 2011;16:131–138.
132. Wenzhen Y, Kehu Y, Bin M, et al. Moxifloxacin-based triple therapy versus clarithromycin-based triple therapy for first-line treatment of Helicobacter pylori infection: a meta-analysis of randomized controlled trials. Intern Med 2009;48:2069–2076.
133. Gisbert JP, Romano M, Molina-Infante J, et al. Two-week, high-dose proton pump inhibitor, moxifloxacin triple Helicobacter pylori therapy after failure of standard triple or non-bismuth quadruple treatments. Dig Liver Dis 2015;47:108–113.
134. Sezgin O, Altintas E, Ucbilek E, et al. Bismuth-based therapies for the first step eradication of Helicobacter pylori. Turk J Gastroenterol 2006;17:90–93.
135. Liang J, Li J, Han Y, et al. Helicobacter pylori eradication with ecabet sodium, omeprazole, amoxicillin, and clarithromycin versus bismuth, omeprazole, amoxicillin, and clarithromycin quadruple therapy: a randomized, open-label, phase IV trial. Helicobacter 2012;17:458–465.
136. Sun Q, Liang X, Zheng Q, et al. High efficacy of 14-day triple therapy-based, bismuth-containing quadruple therapy for initial Helicobacter pylori eradication. Helicobacter 2010;15:233–238.
137. Srinarong C, Siramolpiwat S, Wongcha-um A, et al. Improved eradication rate of standard triple therapy by adding bismuth and probiotic supplement for Helicobacter pylori treatment in Thailand. Asian Pac J Cancer Prev 2014;15:9909–9913.

138. 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.
139. Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance. Gastroenterology 2013;145:121–128.e1.
140. Zullo A, Scaccianoce G, De Francesco V, et al. Concomitant, sequential, and hybrid therapy for H. pylori eradication: a pilot study. Clin Res Hepatol Gastroenterol 2013;37:647–650.

Reprint requests
Address requests for reprints to: Carlo A. Fallone, MD, Division of Gastroenterology, McGill University Health Centre, Royal Victoria Hospital Site, 1001 Decarie Boulevard, Room D5.7154, Montréal, Quebec, Canada H4A 3J1. e-mail: carlo.fallone@mcgill.ca.

Acknowledgments
The consensus group thanks Paul Sinclair (Canadian Association of Gastroenterology [CAG] representative, administrative and technical support) and Louise Hope and Lesley Marshall (CAG, logistics assistance) as well as Pauline Lavigne and Steven Portelance (unaffiliated), who provided medical writing services supported entirely by funds from CAG and the Canadian *Helicobacter* Study Group.

The steering committee (CAF, NC, SVvZ), GIL, and PM reviewed the literature and drafted the statements. GIL and PM assessed the evidence and provided GRADE evaluations. All members of the CAG Treatment of *H pylori* Infection Consensus Group voted on the recommendations. The steering committee then drafted the initial manuscript, which was reviewed, revised, and approved by all members of the consensus group and all authors. It was subsequently made available to all CAG members for comments before submission for publication.

CAG Statement

These consensus statements on the treatment of *H pylori* infection were developed under the direction of Drs Carlo A. Fallone, Naoki Chiba, and Sander Veldhuyzen van Zanten, in accordance with the policies and procedures of CAG and under the direction of CAG Clinical Affairs. They have been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The consensus statements were developed following a thorough consideration of medical literature and the best available evidence and clinical experience. They represent the consensus of a Canadian and international panel composed of experts on this topic. The consensus aims to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. These consensus statements are not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Conflicts of interest

The authors disclose the following: Advisory Board: AbbVie (JPG), Allergan (JPG), Almirall (JPG), AstraZeneca (JPG), Casen Fleet (JPG), Casen Recordati (JPG), Chiesi (JPG), Dr Falk Pharma (JPG), Faes Farma (JPG), Ferring Pharmaceuticals (JPG), Gebro Pharma (JPG), Hospira (JPG), Janssen (JPG), Kern Pharma (JPG), MSD (JPG), Nycomed (JPG), Otsuka Pharmaceuticals (JPG), Pfizer (JPG), Shire Pharmaceuticals (JPG), Takeda (JPG), Vifor Pharma (JPG).

Consultation Fees: AbbVie (JKM, SVvZ), Actavis (CAF), AstraZeneca (JKM), Celltrion (JKM), Cubist (JKM), Ferring Pharmaceuticals (JKM), Forest (JKM), Hospira (JKM), Janssen (CAF, JKM, SVvZ), Procter & Gamble (JKM), Pendopharm (CAF), Shire (JKM, SVvZ), Takeda (CAF, JKM).

Educational Support: AstraZeneca (PM).

Research Grants/Clinical Trial Funding: AbbVie (JPG), Allergan (JPG), Almirall (JPG), AstraZeneca (JPG), Casen Fleet (JPG), Casen Recordati (JPG), Chiesi (JPG), Dr Falk Pharma (JPG), Faes Farma (JPG), Ferring Pharmaceuticals (JPG), Gebro Pharma (JPG), Hospira (JPG), Janssen (JPG), Kern Pharma (JPG), MSD (JPG), Nycomed (JPG), Otsuka Pharmaceutical (JPG), Pfizer (JPG), Shire Pharmaceuticals (JPG), Takeda (JPG), Vifor Pharma (JPG).

Speaker's Bureau: AbbVie (JPG, JKM), Allergan (JPG), Almirall (JPG), Aptalis (JKM), AstraZeneca (JPG), Casen Fleet (JPG), Casen Recordati (JPG), Chiesi (JPG), Dr. Falk Pharma (JPG), Faes Pharma (JPG), Ferring Pharmaceuticals (JPG, JKM), Forest (JKM), Gebro Pharma (JPG), Hospira (JPG), Janssen (JPG, JKM), Kern Pharma (JPG), MSD (JPG), Nycomed (JPG), Otsuka Pharmaceutical (JPG), Pfizer (JPG), Procter & Gamble (JKM), Purdue Pharma (SVvZ), Shire (JPG, JKM), Takeda (JPG, JKM, SVvZ), Warner Chilcott (JKM), Vifor Pharma (JPG).

Funding
Supported by the Canadian Association of Gastroenterology and the Canadian *Helicobacter* Study Group, with no external funding sources.

Supplementary Appendix 1. Search Strategies Used for EMBASE, MEDLINE, and CENTRAL

1. pylori.tw.
2. clarithromycin.tw.
3. (amoxicillin or amoxycillin).tw.
4. azithromycin.tw.
5. tetracycline.tw.
6. (roxithromycin or erythromycin).tw.
7. nitroimidazole.tw.
8. metronidazole.tw.
9. tinidazole.tw.
10. ranitidine-bismuth.tw
11. levofloxacin*.tw.
12. moxifloxacin*.tw.
13. furazolidone.tw.
14. rifabutin.tw.
15. or/2-14
16. 1 and 15
17. eradicat*.tw.
18. 1 and 17
19. 16 or 18
20. limit 19 to yr=2008-2013
21. exp animals/not humans.sh.
22. 20 not 21
23. limit 22 to english language

Supplementary Table 1. Evidence for Statement 1 (In patients with *H pylori* infection, we recommend a treatment duration of 14 days)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Longer duration	Shorter duration	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
PPI-based triple regimens: 14 days vs 7 days							⊕⊕⊕⊖				The quality of evidence is moderate for PAC but low for PMC
1 SR[28] (45 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate	Moderate	81.9	72.9	NNT: 11 (9–14)	
PPI-based triple regimens: 14 days vs 10 days											
1 SR[28] (12 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		84.4	78.5	NNT: 17 (11–46)	
PPI-based triple regimens: 10 days vs 7 days											
1 SR[28] (24 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		79.9	75.7	NNT: 21 (15–38)	
PPI-based triple regimens: 14 days vs 10 days vs 7 days											
1 RCT[46]	None	None	None	Serious	None	⊕⊕⊕⊖ Moderate		NA	NA	NA	Increased efficacy with longer durations of therapy in resistant strains
PBMT: 14 days vs 7 days							⊕⊖⊖⊖				Trend favoring 14 or 10 vs 7 days but not statistically significant
1 SR[28] (3 RCTs)	Serious[b]	None	None	Very serious	None	⊕⊖⊖⊖ Very low	Very low	77.9	69.1	Nonsignificant difference	
PBMT: 14 days vs 10 days											
1 SR[28] (1 RCT)	Serious[b]	None	None	Very serious	None	⊕⊖⊖⊖ Very low		91.6	92.6	Nonsignificant difference	
1 SR[c] (cohort-type data from 51 studies)	None	Serious	None	Serious	None	⊕⊖⊖⊖ Very low		78.7	75.6	Nonsignificant difference	
PBMT: 10 days vs 7 days											
1 SR[28] (2 RCTs)	Serious[b]	None	None	Very serious	None	⊕⊖⊖⊖ Very low		87.4	81.9	Nonsignificant difference	

Supplementary Table 1. Continued

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Longer duration	Shorter duration	Relative effect (95% CI)	Comments
PAMC							⊕⊖⊖⊖				
1 SR[44] (cohort-type data from 15 studies)	None	None	None	Serious	None	⊕⊖⊖⊖ Very low	Very low	92 (10 days)	89 (5 days)	Not statistically significant	
1 cohort study[45]	Serious	None	Serious[d]	None	None	⊕⊖⊖⊖ Very low		93.3 (14 days)	86.6 (10 days)	$P < .01$ Relative effect not reported	
PAL: 14 days vs 7 days							⊕⊖⊖⊖ Very low				
1 SR[28] (2 RCTs)	Serious[e]	None	Serious[f]	Serious	None	⊕⊖⊖⊖ Very low		78.5 (14 days)	42 (7 days)	NNT: 3 (2–10)	

SR, systematic review; NA, not applicable.
[a]Including publication bias.
[b]Most of the included RCTs were at high risk or unclear risk of bias.
[c]Unpublished data; SR conducted for the meeting.
[d]The longer regimen also included a higher PPI dose.
[e]Both studies were at high risk for bias.
[f]One of the studies used ofloxacin (not levofloxacin).

Supplementary Table 2. Evidence for Statement 2 (In patients with *H pylori* infection, we recommend that the choice of first-line therapy consider regional antibiotic resistance patterns and eradication rates)

Quality assessment								Summary of findings			
								Eradication rates (ITT)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Regional antibiotic resistance patterns considered	Regional antibiotic resistance patterns not considered	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Culture-guided vs empirical triple therapy							⊕⊕⊖⊖				
1 systematic review[47] (5 RCTs)	Serious[b]	None	Serious[c]	None	None	⊕⊕⊖⊖ Low	Low	NA	NA	NA	Culture-guided triple therapy resulted in a significantly lower risk of treatment failure compared with empirical standard triple therapy
Time trends for *H pylori* antibiotic resistance and efficacy of eradication regimens											
Multiple reviews of observational studies[19,22]	None	None	Serious	None	None	⊕⊖⊖⊖ Very low		NA	NA	NA	

[a]Including publication bias.
[b]Mainly due to inadequate sequence generation and unclear/inadequate allocation concealment.
[c]The research question is only indirectly related to this statement.

Supplementary Table 3. Evidence for Statement 3 (In patients with *H pylori* infection, we recommend traditional bismuth quadruple therapy [PBMT] for 14 days as one of the options for first-line therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)		Relative effect	
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PBMT	Comparator	(95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: relative to PPI-based triple regimens							⊕⊕⊕⊖				Trend toward higher eradication (~9%) found in the SR was significant only in the per-protocol analysis (not ITT)
1 SR[22] (12 RCTs)	Serious[b]	None	Serious[c]	None	None	⊕⊕⊖⊖ Low	Moderate	81.9	72.9 (PPI-based triple regimens)	Nonsignificant difference	
1 RCT[61]	None	None	None	Serious	None	⊕⊕⊕⊖ Moderate		70.0 (PBMT for 14 days)	57.5 (PAC for 14 days)	Nonsignificant difference	
Efficacy: absolute rates											Adequately high eradication rate
SR of observational studies and observational-type data from RCTs[22]	None	None	None	None	None	⊕⊕⊖⊖ Low		77.6	NA	NA	
Efficacy: metronidazole-resistant strains											Metronidazole resistance had less impact on the success of PBMT regimens compared with clarithromycin resistance on PAC regimens
1 SR[21] (2 RCTs)	None	None	Serious	Serious	None	⊕⊕⊖⊖ Low		NA	NA	NA	
Duration: PBMT for 14 days vs PBMT for 7 days							⊕⊖⊖⊖				Trends toward superiority of prolonged duration vs 7 days (not significant)
1 SR[28] (3 RCTs)	Serious	None	None	Very serious	None	⊕⊖⊖⊖ Very low	Very low	77.9	69.1	Nonsignificant difference	
Duration: PBMT for 14 days vs PBMT for 10 days											
1 SR[28] (1 RCT)	Serious	None	None	Very serious	None	⊕⊖⊖⊖ Very low		91.6	92.6	Nonsignificant difference	
1 SR[d] (cohort-type data from 51 studies)	None	Serious	Serious[e]	Serious	None	⊕⊖⊖⊖ Very low		78.7	75.6	Nonsignificant difference	
Duration: PBMT for 10 days vs PBMT for 7 days											
1 SR[28] (2 RCTs)	Serious	None	None	Very serious	None	⊕⊖⊖⊖ Very low		87.4	81.9	Nonsignificant difference	

[a]Including publication bias.
[b]Mainly due to lack of blinding.
[c]The studies have tested regimens of various durations (7, 10, 14 days). No subgroup analyses for 14-day regimens were performed.
[d]Unpublished data; SR conducted for the meeting.
[e]The comparisons were between studies, not within study.

Supplementary Table 4. Evidence for Statement 4 (In patients with *H pylori* infection, we recommend concomitant nonbismuth quadruple therapy [PAMC] for 14 days as one of the options for first-line therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PAMC	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: relative to PPI triple regimens							⊕⊕⊕⊖				PAMC was superior to PPI triple therapy
1 SR[44] (6 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate	Moderate	91.1	80.6	Odds ratio, 2.4 (1.63–3.55)	
Efficacy: relative to sequential regimen											PAMC was superior to sequential therapy
1 SR[69] (19 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		Not reported	Not reported	RD, 0.11 (0.07–0.16)	
Efficacy: relative to hybrid regimen[c]											
2 RCTs[139,140]	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		91.7 (for 14-day treatment)	90.0 (for 14-day treatment)	Nonsignificant difference	
Efficacy: absolute rates											Adequately high eradication rate
1 SR[44] (cohort-type data from 15 studies)	None	None	None	None	None	⊕⊕⊖⊖ Low		90	NA	NA	
Duration: longer-duration PAMC or shorter-duration PAMC							⊕⊖⊖⊖				Trend favoring longer duration in SR (not significant)
1 SR[44] (cohort-type data from 15 studies)	None	None	None	Serious	None	⊕⊖⊖⊖ Very low	Very low	92 (10 days)	89 (5 days)	Not statistically significant	
1 cohort study[45]	None	None	Serious[d]	Serious	None	⊕⊖⊖⊖ Very low		93.3 (14 days)	86.6 (10 days)	$P < .01$ Relative effect not reported	

[a] Including publication bias.
[b] Mainly due to lack of blinding.
[c] Hybrid regimen was omeprazole 40 mg and amoxicillin 1 g twice daily for 14 days plus clarithromycin 500 mg and nitroimidazole 500 mg twice daily for the final 7 days.
[d] The longer regimen also included a higher PPI dose.

Supplementary Table 5. Evidence for Statement 5 (In patients with *H pylori* infection, we recommend restricting the use of PPI triple therapy [PAC or PMC for 14 days] to areas with known low clarithromycin resistance [<15%] or proven high local eradication rates [>85%])

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PPI triple therapy	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (Importance of outcome: critical for decision making)											
Efficacy: relative to bismuth quadruple regimen (PBMT)							⊕⊕⊕⊖				Low success rates
1 SR[22] (12 RCTs)	Serious[b]	None	Serious[c]	None	None	⊕⊕⊖⊖ Low	Moderate	72.9	81.9	Nonsignificant difference	
1 RCT[61]	None	None	None	Serious	None	⊕⊕⊕⊖ Moderate		57.5 (PAC for 14 days)	70.0 (PBMT for 14 days)	Nonsignificant difference	Low success rates
Efficacy: relative to sequential regimen											
1 SR[70] (7 RCTs)	Serious[d]	Serious[e]	None	None	None	⊕⊕⊕⊖ Moderate		81.3	80.8	Nonsignificant difference	
Efficacy: relative to concomitant regimen											PPI triple therapy was inferior to concomitant therapy
1 SR[44] (6 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		80.6	91.1	Odds ratio, 2.4 (1.63–3.55)	
Efficacy: absolute rates											Low success rates
1 SR[22] (observational-type data from 5 RCTs published from 2006 to 2011)	None	None	None	None	None	⊕⊕⊖⊖ Low		61.5	NA		
Duration: 14 days vs 7 days							⊕⊕⊕⊖				The quality of evidence is moderate for PAC but low for PMC
1 SR[28] (45 RCTs)	Serious[f]	None	None	None	None	⊕⊕⊕⊖ Moderate	Moderate	81.9	72.9	NNT: 11 (9–14)	
Duration: 14 days vs 10 days											
1 SR[28] (12 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		84.4	78.5	NNT: 17 (11–46)	
Culture-guided vs empirical triple therapy							⊕⊕⊖⊖				Indirect evidence
1 SR[47] (5 RCTs)	Serious[g]	None	Serious[h]	None	None	⊕⊕⊖⊖ Low	Low	NA	NA	NA	
Time trends for *H pylori* resistance to clarithromycin and efficacy of eradication regimens											
Multiple reviews of observational studies[19,22]	None	None	Serious	None	None	⊕⊖⊖⊖ Very low		NA	NA	NA	

[a]Including publication bias.
[b]Mainly due to lack of blinding.
[c]The studies have tested regimens of various durations (7, 10, 14 days). No subgroup analyses for 14-day regimens were performed.
[d]None of the studies were at low risk for bias.
[e]Unexplained heterogeneity.
[f]Most of the included RCTs were at high risk or unclear risk of bias.
[g]Mainly due to inadequate sequence generation and unclear/inadequate allocation concealment.
[h]The research question is only indirectly related to this statement.

Supplementary Table 6. Evidence for Statement 6 (In patients with *H pylori* infection, we recommend against the use of levofloxacin triple therapy [PAL] as a first-line therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PAL	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)											
Efficacy: relative to PAC							⊕⊖⊖⊖				
3 RCTs[78,79,81]	Serious[b]	Serious[c]	None	Serious	None	⊕⊖⊖⊖ Very low	Very low	85, 80, and 81, respectively	79, 64, and 87, respectively	Overall, nonsignificant difference	
Efficacy: levofloxacin-resistant strains											
2 studies (cohort-type data from 2 RCTs)[52,81]	None	None	Serious	None	None	⊕⊖⊖⊖ Very low		NA	NA	NA	Significantly lower eradication rates with PAL in levofloxacin-resistant vs levofloxacin-sensitive strains

[a]Including publication bias.
[b]Mainly due to lack of blinding.
[c]Two of the RCTs showed better efficacy for PAL, but the third showed better efficacy for PAC.

Supplementary Table 7. Evidence for Statement 7 (In patients with *H pylori* infection, we recommend against the use of sequential nonbismuth quadruple therapy [PA followed by PMC] as a first-line therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Sequential therapy	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: relative to 14-day PPI triple regimens							⊕⊕⊕⊖				
1 SR[70] (7 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate	Moderate	81.3	80.8	Nonsignificant difference	
Efficacy: relative to concomitant nonbismuth quadruple therapy (PAMC)											
1 SR[69] (14 RCTs)	Serious[c]	None	None	None	None	⊕⊕⊕⊖ Moderate		79.7	85.7	RD, 0.06 (0.03–0.09)	Concomitant therapy superior to sequential therapy
Efficacy: relative to traditional bismuth quadruple therapy (PBMT)											
1 SR[70] (5 RCTs)	Serious[b]	None	None	None	None	⊕⊕⊕⊖ Moderate		84.9	86.2	Nonsignificant difference	

[a]Including publication bias.
[b]None of the studies was at low risk of bias.
[c]Mainly due to lack of blinding.

Supplementary Table 8. Evidence for Statement 8 (In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend traditional bismuth quadruple therapy [PBMT] for 14 days as an option for subsequent therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PBMT	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: absolute rates							⊕⊕⊖⊖				
1 SR (38 studies: observational studies and observational-type data from RCTs)[99]	None	None	None	None	None	⊕⊕⊖⊖ Low	Low	78	NA	NA	Adequately high eradication rate after failure of PPI triple therapy
Duration: PBMT for 14 days vs PBMT for 10 days											
1 SR (14 studies: observational studies and observational-type data from RCTs)[99]	None	None	Serious[b]	Serious	None	⊕⊖⊖⊖ Very low		82	77	Nonsignificant difference	Trend favoring 14 days (not significant)
1 SR[c] (cohort-type data from 51 studies)	None	Serious	Serious[b]	Serious	None	⊕⊖⊖⊖ Very low		78.7	75.6	Nonsignificant difference	

[a]Including publication bias.
[b]The comparisons were between studies, not within study.
[c]Unpublished data; SR conducted for the meeting.

Supplementary Table 9. Evidence for Statement 9 (In patients who have previously failed to respond to *H pylori* eradication therapy, we suggest levofloxacin-containing therapy for 14 days as an option for subsequent therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	PAL	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: relative to bismuth quadruple regimen (PBMT) after failure of PPI triple therapy							⊕⊕⊖⊖				Adequately high eradication rates for salvage treatment
1 SR[99] (6 RCTs)	Serious[b]	None	None	Serious	None	⊕⊕⊖⊖ Low	Low	79[c]	69	Nonsignificant difference	
Efficacy: absolute rates with 10-day PAL after failure of concomitant nonbismuth quadruple therapy											
1 SR[105] (observational type data from 3 studies)	Not known[d]	Serious[e]	None	Serious	None	⊕⊕⊖⊖ Low		78	NA		
Efficacy: absolute rates after failure of sequential nonbismuth quadruple therapy											
1 SR[99] (observational type data from 5 studies)	None	None	None	None	None	⊕⊕⊖⊖ Low		81	NA	NA	
Duration: 10 days vs 7 days							⊕⊖⊖⊖				Superiority of longer duration
1 SR[106] (observational type data from 11 studies)	Not known[d]	None	None	Serious[f]	None	⊕⊖⊖⊖ Very low	Very low	88.7	70.6	$P < .05$ Relative effect not reported	

[a] Including publication bias.
[b] Mainly due to lack of blinding.
[c] Calculated from unweighted means, but given that the weights of the included studies were very similar, it is likely that weighted estimates would produce similar results.
[d] The SR did not report assessments of risk of bias.
[e] Unexplained heterogeneity.
[f] The comparisons were between studies, not within study.

Supplementary Table 10. Evidence for Statement 10 (In patients who have previously failed to respond to a clarithromycin-containing *H pylori* eradication therapy, we recommend against the use of clarithromycin-containing regimens as subsequent therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	NA	NA	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Prevalence of secondary resistance to clarithromycin							⊕⊕⊖⊖				The prevalence of secondary resistance to clarithromycin is very high (up to 70%)
Multiple cohort studies and case series[20,40]	None	None	None	None	None	⊕⊕⊖⊖ Low	Low	NA	NA	NA	
Impact of clarithromycin resistance											The efficacy of clarithromycin-containing regimens is highly affected by clarithromycin resistance
Multiple reviews of observational studies[19,22]	None	None	Serious	None	None	⊕⊖⊖⊖ Very low		NA	NA	NA	

[a]Including publication bias.

Supplementary Table 11. Evidence for Statement 11 (In patients who have previously failed to respond to a levofloxacin-containing *H pylori* eradication therapy, we recommend against the use of levofloxacin-containing regimens as subsequent therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	NA	NA	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Prevalence of secondary resistance to levofloxacin							⊕⊕⊖⊖				The prevalence of secondary resistance to levofloxacin is very high (up to 60%)
2 cohort studies and case series[83,84]	None	None	None	None	None	⊕⊕⊖⊖ Low	Low	NA	NA	NA	
Impact of levofloxacin resistance											The efficacy of levofloxacin-containing regimens is highly affected by levofloxacin resistance
2 studies (cohort-type data from 2 RCTs)[52,81]	None	None	Serious	None	None	⊕⊖⊖⊖ Very low		NA	NA	NA	

[a]Including publication bias.

Supplementary Table 12. Evidence for Statement 12 (In patients who have previously failed to respond to *H pylori* eradication therapy, we recommend against the use of sequential nonbismuth quadruple therapy [PA followed by PMC] as an option for subsequent therapy)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Sequential therapy	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: absolute rates											
2 cohort studies[109,110]	None	None	None	Very serious[b]	None	⊕⊖⊖⊖ Very low	⊕⊖⊖⊖ Very low	93 and 100	NA		
Efficacy: relative to concomitant nonbismuth quadruple therapy (PAMC) as first-line treatment											
1 SR[69] (19 RCTs)	Serious[c]	None	None	Very serious[d]	None	⊕⊖⊖⊖ Very low		Not reported	Not reported	RD, 11% (0.7%–16%)	PAMC was superior to sequential therapy

[a]Including publication bias.
[b]Forty and 2 patients, respectively.
[c]Mainly due to lack of blinding.
[d]These studies tested the regimens as first-line treatments.

Supplementary Table 13. Evidence for Statement 13 (We recommend restricting the use of rifabutin-containing regimens to cases in which at least 3 recommended options have failed)

Quality assessment								Summary of findings			
								Eradication rates (ITT) (%)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Rifabutin-containing regimens	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Efficacy: absolute rates (overall)							⊕⊖⊖⊖				Reasonable eradication rate for those who previously failed to respond to therapy
1 SR[111] (21 studies: cohort studies and observational-type data from RCTs)	None	None	Serious[b]	None	None	⊕⊖⊖⊖ Very low	Very low	73	NA	NA	
Efficacy: absolute rates (4th- or 5th-line treatment)							⊕⊖⊖⊖				Eradication demonstrated when used as fourth- or fifth-line therapy
1 SR[111] (7 studies: cohort studies and observational-type data from RCTs)	None	None	None	None	Serious	⊕⊖⊖⊖ Very low	Very low	70	NA	NA	
Duration: 10–12 days vs 7 days (2nd-line treatment)							⊕⊖⊖⊖				Evidence suggests more than 7 days is preferred
1 SR[111] (8 studies: cohort studies and observational-type data from RCTs)	None	None	Very serious[c]	None	Serious	⊕⊖⊖⊖ Very low	Very low	92	69	Not reported	

[a]Including publication bias.
[b]Included studies that tested the regimen as first-, second-, third, fourth-, or fifth-line treatment.
[c]Only second-line treatment; between-studies comparisons.

Supplementary Table 14. Evidence for Statements 14 and 15 (In patients with *H pylori* infection, we recommend against routinely adding probiotics to eradication therapy for the purpose of reducing adverse events or increasing eradication rates)

Quality assessment								Summary of findings			
								Eradication rates (ITT)			
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Quality of evidence	Overall quality of evidence	Probiotic supplementation	Comparator	Relative effect (95% CI)	Comments
Eradication of *H pylori* infection (importance of outcome: critical for decision making)											
Effect on adverse effects 1 SR[126] (10 RCTs)	Serious[b]	Serious[c]	Serious[d]	None	None	⊕⊖⊖⊖ Very low	⊕⊖⊖⊖ Very low	Not reported	Not reported	Odds ratio, 2.1 (1.4–3.1)	Very low-quality evidence
Effect on eradication rates 1 SR[126] (10 RCTs)	Serious[b]	Serious[c]	Serious[d]	None	None	⊕⊖⊖⊖ Very low	⊕⊖⊖⊖ Very low	Not reported	Not reported	Odds ratio, 0.3 (0.1–0.8)	Very low-quality evidence

[a]Including publication bias.
[b]Mainly due to lack of blinding.
[c]Unexplained heterogeneity.
[d]Most of the studies assessed the impact of probiotic supplementation when added to triple rather than quadruple therapy.