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


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

Short title: Toronto Consensus for H. pylori Treatment

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Abbreviations
CAG: Canadian Association of Gastroenterology; CHSG: Canadian Helicobacter Study Group; CI: confidence interval; GRADE: Grading of Recommendation Assessment, Development and Evaluation; HR: hazard ratio; ITT: intention-to-treat; MALT: mucosa-associated lymphoid-tissue; NNT: number needed to treat; OR: odds ratio; PPI: proton pump inhibitor; P-CAB: potassium-competitive acid blocker; PUD: peptic ulcer disease; RCT: randomized controlled...
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**Trial**; RD: risk difference; RR: relative risk. *Abbreviations used in drug combinations*: A: amoxicillin; B: bismuth; C: clarithromycin; L: levofloxacin; M: metronidazole; P: proton pump inhibitor; Q: quinolone; R: rifabutin; T: tetracycline

**Disclosures**

NO, I do not have any industry or government relationships to report: (CR, GL, LF NC, NJ, RH)

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**Author contributions**

The steering committee (CF, NC, SVvZ), GL, and PM reviewed the literature and drafted the statements. GL 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. Subsequently it was made available to all CAG members for comments prior to submission for publication.

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ABSTRACT

Background & aims: *Helicobacter pylori* infection is increasingly difficult to treat. The purpose of these consensus statements is to review the literature and provide 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 recommended that all *H. pylori* eradication regimens now be given for 14 days. Recommended first-line strategies include concomitant non-bismuth 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 and either amoxicillin or metronidazole) was 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, PAL). Rifabutin regimens should be restricted to patients who fail at least 3 prior options.

Conclusions: Optimal treatment of *H. pylori* requires careful attention to local antibiotic resistance and eradication patterns. Quadruple therapies PAMC or PBMT should play a more prominent role in *H. pylori* eradication and all treatments should be given for 14 days.
Keywords: *Helicobacter pylori*, eradication, resistance, proton pump inhibitor, amoxicillin, bismuth, clarithromycin, metronidazole, tetracycline, levofloxacin, rifabutin
INTRODUCTION

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% to 75% of Alaskan or Canadian aboriginal populations).\(^2,3,5-8\)

*H. pylori* is implicated in the development of, and its eradication recommended in the treatment of duodenal or gastric ulcers, early gastric cancer, and gastric mucosa-associated lymphoid-tissue (MALT) 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. 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 employed first so as 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), non-bismuth 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; PPI + metronidazole + clarithromycin, 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 described 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 (CHSG) 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, since updated pediatric recommendations are currently in progress from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and North American Society for Paediatric 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 performed a systematic literature search of the Cochrane Register, MEDLINE, EMBASE, and CENTRAL for trials published from January 2008 through December 2013. The main focus of all literature searches was to identify data on cure rates of \textit{H. pylori} infection. We did not systematically search the literature prior to 2008 as 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 \textit{Helicobacter pylori}, eradication, bismuth, clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and rifabutin, among others in order to address each of the statements. Search strategies were limited to the English language and human studies, and further details are provided in Appendix 1, available online.

A formal systematic review was carried out for every statement. This included a literature search, and as described in more detail below, 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, Outcome), 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, and after removal of duplicates, 2372 citations remained. These were sorted into three separate lists: 1) results enriched with RCTs, systematic reviews/meta-analyses, and practice guidelines (1509 citations); 2) results enriched with Canadian studies (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 carried out to see if more current data altered the results and conclusions.

**Review and Assessment of Evidence**

Two non-voting methodologists (Dr. Grigorios Leontiadis and Dr. Paul Moayyedi) assessed the quality (certainty) of evidence using the GRADE (Grading of Recommendation Assessment, Development and Evaluation) method. The methodologists assessed the risk of bias (of individual studies and overall across studies), indirectness, inconsistency, imprecision, as well as other considerations (including publication bias) to determine the overall quality of evidence for each statement. GRADE assessments were then reviewed and agreed upon 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 and prior CAG consensus documents.
Approved product labeling from government regulatory agencies varies from country to country, and while 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 comprised of 8 voting members (5 participants and 3 steering committee members) including gastroenterologists, clinical epidemiologists (one of whom was not a gastroenterologist), and a microbiologist from Canada, the US, and Europe with expertise in managing *H. pylori* infection. There was representation from pediatric and community, non-academic gastroenterology (not a *H. pylori* expert), as well as a non-voting moderator for the meeting (Dr. John K. Marshall). Although there was no primary care representative, the impact of the recommendations on the primary care physician, as well as community resources and local availability, was discussed prior to voting for each statement.

Prior to the 2-day consensus meeting held in Toronto, Ontario, Canada in June 2015, the CAG facilitated the majority of the consensus process through the use of a web-based consensus platform (ECD solutions, Atlanta, Georgia, USA). The steering committee (CF, NC, SVvZ) developed the initial statements using PICO components (Population, Intervention, Comparator, Outcome) of the underlying research question for each statement (for example for statement #3 the PICO components were: 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 to a standard threshold for efficacy (e.g. > 80% 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 two individuals) through the web-based platform, and “tagged” (selected &
linked) all relevant references to a specific statement. Only one member was required to tag a
reference in order for it to remain linked to the statement. Subsequently, the tagged references
were again assessed by the steering committee, and 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 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. Two subsequent iterations of the
statements which 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, the 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 as per the GRADE approach for the statements were also reviewed, and all
panellists 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, so as to make the message clearer to the readers. Finally, participants were
asked to vote as to 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 being 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 the 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 CAG members for comments prior to submission for publication. As per CAG policy, all participants provided written disclosure of relevant potential conflicts of interest for the 24 months prior to meeting, which were made available to the other group members.

**Role of the Funding Sources**

The CAG administered all aspects of the meeting, which was co-funded by the CAG and the Canadian Helicobacter Study Group (CHSG) with no external funding sources.
RECOMMENDATION STATEMENTS

The individual recommendation statements are provided and include the quality of supporting evidence, as assessed by GRADE method and the voting results, after which, a discussion of the evidence considered for the specific statement, is presented. For some statements the quality of evidence was determined to be low, 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. In addition, success of eradication is highest with initial therapy and decreases with subsequent rescue therapy attempts. 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. Tables summarizing the most important evidence for each of the statements are provided in Appendix 2.

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, very low for PBMT, PAMC and PAL. Vote: strongly agree, 87.5%; agree, 12.5%
Key evidence (Appendix 2, summary of evidence table S1): 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 to shorter durations (intention-to-treat [ITT], 45 studies, 14 vs. 7 days, 82% vs. 73%; 12 studies, 14 vs. 10 days, 84% vs. 79%) (Table 4). A significant effect was seen in the subgroup of PAC (34 studies of 14 vs. 7 days; RR for *H. pylori* persistence, 0.65 [95% 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; RR, 0.37 [95% CI, 0.16–0.83]; NNT, 3 [95% CI, 2–10]). There was 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). A 14-day optimized PAMC combination also achieved higher eradication compared to 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.

Finally, for bismuth quadruple therapy, the Cochrane meta-analysis of RCTs did not find duration to have significant effect on therapeutic success for first-line therapy (Table 4), but very few studies exist for 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 had previously failed eradication. Overall, 51 RCT and cohort studies were included (see statement 8), and meta-analysis showed that the ITT eradication was
numerically but not statistically higher with the 14-day vs. the 10-day regimen (78.7% vs. 75.6%; \( P = .33 \)).

**Other issues and discussion:** 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, eradication success of resistant strains were 35% lower than those of sensitive strains.\(^{46}\) The impact was greatest among regimens of the shortest duration; eradication success of sensitive vs. resistant strains were 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 stains. The differences in efficacy between therapies in the studies presented are likely underestimated, since 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 compared to 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**

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 (Appendix 2, summary of evidence table S2):** Although no study directly examined the impact of tailoring first-line therapy to local antibiotic resistance patterns and eradication rates, a meta-analysis of five RCTs (n=701) found that culture-guided triple therapy resulted in a significantly lower risk of treatment failure compared to empiric standard triple therapy (ITT RR, 0.84; 95% CI, 0.77-0.90; \( P < .00001 \); eradication 85.4% vs. 71.5%).

**Other issues and discussion:** *H. pylori* resistant strains have become more prevalent over time. Studies from the 1990s showed a low prevalence of clarithromycin resistance ranging from 1% to 8%, which has risen to 16% to 24% in more recent studies from around the world. Primary resistance to metronidazole appears to have remained relatively stable over time at 20% to 40%. *H. pylori* resistance to amoxicillin generally remains low, at approximately 1% to 3%. In addition, prevalence of secondary resistance to clarithromycin and metronidazole are very high; up to 67% to 82% for clarithromycin and 52% to 77% for metronidazole. RCTs confirm that the proportion of successful eradication is significantly lower in resistant compared to sensitive strains, especially with triple therapy and therapy of shorter duration. 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. A meta-analysis of 12 studies found that...
success of eradication with bismuth quadruple therapy remained stable at approximately 80% in studies from 2006-2011 compared to those from 2000-2005, but the efficacy of clarithromycin-based triple therapy dropped from approximately 80% in studies from 2000-2005, to only 62% in more recent studies (2006-2011) (Figure 1).\textsuperscript{22}

Bismuth quadruple therapy is unaffected by clarithromycin resistance.\textsuperscript{22, 53} However, the eradication success with PBMT seems to be slightly lower in metronidazole-resistant vs. metronidazole-sensitive strains (92% vs. 80%; $P = .06$).\textsuperscript{53, 54} In one meta-analysis of triple and quadruple regimens, successful eradication 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%.\textsuperscript{56}

Similar effects of resistance were seen with levofloxacin triple therapy and bismuth quadruple levofloxacin-based therapy; among levofloxacin susceptible strains, eradication was 97% in both groups, but among resistant strains the proportion dropped to 71% with quadruple therapy, and 38% with triple therapy.\textsuperscript{52}

If one knows the susceptibility profile of a patient’s infection or an estimate of it from the population the patient is from, one can predict the efficacy of a proposed regimen.\textsuperscript{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 pre-treatment exposure to antibiotics can also aid in the identification of the regimen most likely to succeed.\textsuperscript{60}

**Decisions:** Evidence suggests that culture-guided therapy is associated with higher eradication success,\textsuperscript{47} and that both antibiotic-resistant \textit{H. pylori},\textsuperscript{18, 19, 48-50} and treatment failures,\textsuperscript{46, 52-55} are increasing. It is important, therefore, to encourage susceptibility testing to be
made available locally and performed if the patient is undergoing endoscopy. However, currently, it is not clinically practical, nor 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 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 percentage they obtain locally with treatments.

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, very low for duration. **Vote:** strongly agree, 75%; agree, 25%

**Key evidence (Appendix 2, summary of evidence table S3):** Two systematic reviews of RCTs have evaluated the efficacy of first-line bismuth quadruple therapy (PBMT) compared to triple therapy (PAC).\textsuperscript{21,22} The more recent meta-analysis of 12 RCTs found that the overall pooled eradication success 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 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).\textsuperscript{22} Although this analysis did not demonstrate a statistically significant difference, there was a trend toward greater eradication, with PBMT.\textsuperscript{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 10-14 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 found higher eradication success with bismuth quadruple therapy compared to triple therapy, but this was significant only in the per protocol analysis and not the ITT analysis. 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. resistance strains, 90.2% vs. 22.2%).

Other issues and discussion: As described in statements 1 and 8, a meta-analysis of observational data conducted for the meeting to evaluate duration of bismuth quadruple rescue therapy showed by regression analysis that ITT eradication success was numerically higher with the 14-day vs. the 10-day regimen, though 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®) being used most commonly in Europe, and bismuth subsalicylate (Pepto-Bismol®) in North America; however, whether the different formulations result in a different outcome is not clear. Although usually administered QID, some studies (from China) have suggested that giving double the bismuth dose twice daily is also effective.

There were no significant differences in proportions with adverse events or compliance between first-line PBMT compared to PAC in the meta-analyses. However, adherence tends to be higher in clinical trials compared to real-world settings. Data show that in many therapeutic areas, adherence is negatively impacted by dose frequency and regimen complexity (multiple medications, multiple doses, specific dietary or time requirements). 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 four-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 drop in eradication success in studies from 2006 and later, compared to those conducted in 2005 and earlier; the drop was much more pronounced with triple therapy, likely due to resistance development (Figure 1).\(^{21, 22}\) This finding and the efficacy data presented above 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 with 7- to 10-day regimens, is suboptimal at around 80% (usually for 7- to 10-day regimens), and that success rates are dropping over time.\(^{21, 22}\)

Therefore, despite the limitations of these data, the consensus group concluded that it does support the use of PBMT with the optimal duration of 14 days when given as first-line therapy. Because the proportion of eradication successes 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 BID and the other agents all QID vs. prescribing a combination of QID (for bismuth and tetracycline) and TID dosing (for metronidazole) (Table 2). Having the pharmacy prepare blister packs can also help. In some countries, a three-in-one 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 penicillin-allergic patients (ITT eradication, 75% and 59%; \( P < .05 \)).

4. In patients with \textit{H. pylori} infection, we recommend concomitant non-bismuth quadruple therapy (PAMC) for 14 days as one of the options for first-line therapy.

\textbf{GRADE:} Strong recommendation; quality of evidence moderate for efficacy, very low for duration. \textbf{Vote:} strongly agree, 87.5%; agree, 12.5%

\textbf{Key evidence (Appendix 2, summary of evidence table S4):} Meta-analyses of RCTs assessing the efficacy of concomitant non-bismuth quadruple therapy (PAMC) have generally reported pooled ITT eradication success of approximately 90%,\textsuperscript{44, 68, 69} although one meta-analysis reported 81% success with 5- to 10-day regimens.\textsuperscript{70} However, a trend toward better eradication with longer durations of treatment has been demonstrated: 85%/88%/89%/93%/92% for 3 days/4 days/5 days/7 days/10 days, respectively.\textsuperscript{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 with non-bismuth concomitant quadruple therapy of 88% (95% CI, 86%-89%).\textsuperscript{69} In sub-group analyses, concomitant was more effective than triple therapy (\( n=19 \) RCTs; risk difference [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).\textsuperscript{69} Concomitant therapy also performed better than sequential therapy in resistant
strains (clarithromycin resistance, 92% vs. 62%; \textsuperscript{55,71,72} metronidazole resistance, 97% vs. 82%; \textsuperscript{71-73} and dual clarithromycin and metronidazole resistance, 79% vs. 47%\textsuperscript{55,71-73}).\textsuperscript{69}

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

**Decisions:** Based on the evidence of acceptable eradication, and the trend toward increasing efficacy with longer durations, the consensus group agreed that concomitant quadruple therapy (PAMC) for 14 days should be considered a first-line option. For patients with penicillin allergy however, PBMT is the preferred first-line option (see statement 3).

**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 (>85%).**

**GRADE:** Strong recommendation; quality of evidence moderate for efficacy of PPI triple therapy for 14 days, low for restrictions. **Vote:** strongly agree, 12.5%; agree, 75%; disagree, 12.5%

**Key evidence (Appendix 2, summary of evidence table S5):** Although meta-analyses of RCTs (mainly published before 2008) have not demonstrated a significant difference in...
eradication with PPI triple therapies compared to bismuth and non-bismuth quadruple therapies (see statement 3),\textsuperscript{21, 22, 70} eradication success with triple therapies has been decreasing over time (Figure 1).\textsuperscript{21, 22, 75} As described under statement 2, the success of clarithromycin-based therapies is very dependent on the susceptibility profile of the organism to this antibiotic.\textsuperscript{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\%).\textsuperscript{22} In addition, as discussed in statement 1, a 14-day duration is associated with a superior success rate compared to shorter durations of this regimen.\textsuperscript{27, 28, 76}

**Other issues and discussion:**

PAM is a PPI triple therapy that avoids the issue of clarithromycin resistance, however, in early studies it was inferior to PAC and PMC,\textsuperscript{77} and therefore, it was concluded that use of PAM should also be restricted to areas with demonstrated high 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 (usually \( \geq 90\% \), 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, they recommended that clinicians err on the side of caution and avoid PPI triple therapy containing clarithromycin (PAC, PMC), unless they have evidence of high success (\( >85\% \)) in their community. In addition, contrary to prior recommendations,\textsuperscript{11, 12} if triple therapy is to be used at all, it should be given for 14 days.
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%

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**Key evidence (Appendix 2, summary of evidence table S6):** In RCTs, ITT eradication successes for the 7-day and 10-day levofloxacin-containing triple therapy regimen (PAL) for first-line therapy ranged from 74% to 85%. While this regimen was significantly more effective than PAC triple therapy for the same duration, eradication was generally inadequate (<80% in most studies). Several studies that assessed susceptibility found dramatically lower eradication with PAL in levofloxacin-resistant vs. levofloxacin-sensitive strains (37.5% vs. 97.3% and 50.0% vs. 84.4%).

**Other issues and discussion:** Levofloxacin is widely used for other types of infections, and as such, there is a high prevalence of background resistance to this and other quinolones (primary resistance 6% to 36%, secondary resistance 18% to 63%). There is also cross-resistance with other quinolones. Levofloxacin resistance among respiratory, urinary, and other pathogens is highly correlated with fluoroquinolone use, 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 non-bismuth quadruple therapy (PAMC), are preferred in this setting.
7. In patients with *H. pylori* infection, we recommend against the use of sequential non-bismuth 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%

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**Key evidence (Appendix 2, summary of evidence table S7):** Meta-analyses of early studies (up to 2009) with sequential therapy showed promising results, with eradication consistently higher than 90%. Several more recent meta-analyses have shown that 10-day sequential therapy was not superior to 14-day triple therapy, bismuth quadruple therapy, and concomitant non-bismuth quadruple therapy.

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

**Other issues and discussion:** Analyses of studies in patients with resistant strains found higher eradication with concomitant therapy vs. sequential therapy among resistant strains (clarithromycin resistance, 92% vs. 62%; metronidazole resistance, 97% vs. 82%; and dual clarithromycin and metronidazole resistance, 79% vs. 47%).

**Decisions:** The consensus group concluded these data strongly suggest that sequential therapy is inferior to concomitant therapy, with current successful eradication falling to <80% in more recent studies. Therefore, non-bismuth quadruple therapy should be administered via a concomitant, rather than sequential regimen.
PRIOR FAILURE

8. In patients who have previously failed *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 (Appendix 2, summary of evidence table S8):** A meta-analysis of data from 38 RCTs assessing bismuth quadruple therapy (PBMT) after failure of standard triple therapy (PAC) reported eradication success of 78% (95% CI, 75%-81%). There was a trend toward a higher eradication with longer duration of therapy (7-day, 76%; 10-day, 77%; 14-day 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 using ITT analyses were numerically higher (although not statistically significant) with the 14-day vs. 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 of 66.7%. In a Canadian study, PBMT rescue therapy after one to five prior treatment failures had an ITT eradication of 84%,
However, this was much lower in patients previously exposed to bismuth and tetracycline compared to patients without exposure (55% vs. 90%; risk difference, 35%; 95% CI, 10%–62%; $P < .01$).\textsuperscript{43}

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

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- vs. high-dose PPI, or twice-daily vs. more frequent dosing. However, the data allowed between-study comparisons for the dose of esomeprazole (20 mg BID in 9 studies; 40 mg BID in 6 studies). Meta-regression models adjusting for duration did suggest that regimens containing esomeprazole 40 mg bid were more effective than regimens containing esomeprazole 20 mg bid ($P = .005$).

A focused literature search was conducted for studies that assessed the role of metronidazole dose in eradication regimens. Metronidazole resistance has been shown in meta-analyses to be a predictor of failure of treatment with metronidazole-containing regimens.\textsuperscript{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%).\textsuperscript{26, 32, 101, 102} Increasing the dose and duration of metronidazole may, at least partially, overcome metronidazole resistance.\textsuperscript{32} Some data from triple therapy studies support the use of a higher metronidazole dose.\textsuperscript{103, 104} In the HOMER study, the eradication successes for metronidazole-resistant strains according to metronidazole dose in a PAM regimen were 54% with 800, 50% with 1200, and 75% with 1600 mg/day, although in this study the dose of amoxicillin also varied from 1.5 to 2-g/day.\textsuperscript{103} Similarly, a comparison of
metronidazole doses in a BMT regimen reported eradication of resistant strains in 64.2% of cases with 750 mg/day compared to 39-40% with 375 mg/day.  

**Decisions:** The consensus group concluded that for patients who have previously failed *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%, the consensus group recommended the metronidazole dose in the bismuth quadruple therapy regimen be at least 1500 mg/day (maximum 2000 mg/day) (Table 2).

Since existing data on the efficacy of PBMT as a rescue therapy comes primarily from studies conducted with patients who had previously failed 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 higher dose metronidazole and/or PPI in certain cases where options are very limited (eg, cases where the clinician wants an alternative to a rifabutin combination after PBMT and PAL have already failed).

9. In patients who have previously failed *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 (Appendix 2, summary of evidence table S9): A meta-analysis of five studies assessed PAL after failure of sequential non-bismuth quadruple therapy and yielded an overall eradication of 81% (95% CI, 71%-91%). Another meta-analysis reported eradication success with PAL of 81% after sequential (6 studies) and 78% after concomitant (3 studies) non-bismuth quadruple therapy. Meta-analyses of studies comparing PAL and PBMT as second-line therapy report no significant differences in overall eradication (77-79% with PAL vs. 67-69% for PBMT). One RCT found that 14-day PAL was as effective as 14-day PBMT, in patients who had failed 7-day triple therapy (ITT eradication: 86.3% and 86%, respectively). However, a recent real-world study demonstrated superior performance of PBMT over PAL in second- to sixth-line rescue therapy (ITT, 84% vs. 61%; risk difference, 24% [95% CI, 10%-37%]).

Eradication was significantly higher (88.7%; 95% CI, 56.1%-100%; P < .05) with 10-day compared to 7-day levofloxacin-containing regimens (70.6%; 95% CI, 40.2%-99.1%).

Other issues and discussion: A RCT showed that adding bismuth to a 14-day, first-line PAL (BPAL) regimen only marginally improved ITT eradication overall (87.5%; 95% CI, 78.5%-93.1 vs. 82.7%; 95% CI, 73%-89.4%; P = .39), but eradication was much higher among levofloxacin-resistant strains (70.6% vs. 37.5%). After prior treatment failure (including both standard triple and non-bismuth quadruple therapies), BPAL had an ITT eradication success of 90% (95% CI, 86%-94%) in a prospective, cohort study.

Decisions: The consensus group agreed that for patients who have previously failed H. pylori eradication therapy, levofloxacin-containing therapy (usually PAL) is an option. However, in light of evidence of higher eradication with longer treatment durations, the consensus group recommended a 14-day regimen.
10. In patients who have previously failed 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. **Vote:** strongly agree, 100%

**Key evidence (Appendix 2, summary of evidence table S10):** As discussed in statements 2 and 5, the efficacy of clarithromycin-containing regimens are highly impacted by clarithromycin resistance. More importantly, the prevalence of secondary resistance is very high (up to 70% in some series).  

**Decisions:** As a result of resistance concerns, the consensus group recommended against re-using clarithromycin in patients who had already failed a clarithromycin-containing regimen.

11. In patients who have previously failed 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 (Appendix 2, summary of evidence table S11):** As discussed in statement 6, the efficacy of levofloxacin-containing regimens is highly impacted by levofloxacin
resistance. Studies have shown that the prevalence of secondary levofloxacin resistance is very high (up to 63% in some series).

**Decisions:** As a result of resistance concerns, the consensus group recommended against re-using levofloxacin in patients who had already failed 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.

**12. In patients who have previously failed *H. pylori* eradication therapy, we recommend against the use of sequential non-bismuth 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 (Appendix 2, summary of evidence table S12):** Cohort data have suggested that sequential non-bismuth 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 is low quality. As discussed in statement 7, eradication success with this regimen was low (<80%) and it was inferior to concomitant administration when used in the first-line setting (Figure 2). In addition, this strategy was associated with very low eradication of clarithromycin and dual clarithromycin and metronidazole resistant strains (62% and 47%).

**Decisions:** The consensus group recommended that sequential non-bismuth quadruple therapy not be used as rescue therapy, as it is less efficacious than other therapies.
I3. We recommend restricting the use of rifabutin-containing regimens to cases where 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 (Appendix 2, summary of evidence table S13):** A systematic review of 21 studies assessing rescue therapy with rifabutin-containing regimens found that overall ITT eradication success was 73% (95% CI, 67%-79%).\(^{111}\) Success was 79% for second-line regimens, and 66-70% 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 about half of patients when used as fourth-line rescue therapy in a cohort of 190 patients, with ITT eradication of 52% (95% CI, 45%-59%).\(^{112,113}\)

**Other issues and discussion:** The most commonly studied rifabutin-containing regimen is PAR (PPI, amoxicillin, rifabutin), and 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 around 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.  

**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 (for example 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, ITT eradication with PAMC after failure of PAC triple therapy was 88.5% compared to 82.7% with PAM.  

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 *H. pylori* eradication. Successful eradication has been shown to be closely related to the degree of acid inhibition, with a cohort study using triple therapy (PAC) finding a significantly higher mean gastric pH in patients with vs. those without successful eradication (6.4 vs. 5.2; *P* = .013). It has been suggested that achieving more potent acid inhibition can improve treatment success. Meta-analyses of RCTs have shown higher eradication with triple therapy using standard-dose PPI twice daily vs. once daily (13 studies; 83.9% vs. 77.7%; *P* < .01), and with high-dose (eg, esomeprazole 40 mg BID) vs. standard-dose PPI (eg, esomeprazole 20 mg BID) (6 studies; 82% vs. 74%; *P* = .03). In addition, a meta-analysis of 35 studies showed higher eradication with esomeprazole (82.3% vs. 77.6%; OR, 1.32; 95% CI, 1.01-1.73) and rabeprazole...
(80.5% vs. 76.2%; OR, 1.21; 95% CI, 1.02-1.42) compared to first-generation PPIs (omeprazole-
lansoprazole-pantoprazole).\textsuperscript{119}

Another potential method to improve acid inhibition would be to use newer, more potent
antisecretory agents. Potassium-competitive acid blockers (P-CABs) inhibit the gastric $H^+/K^+$-
ATPase in a $K^+$ competitive but reversible manner, and thus do not require prior proton pump
activation to achieve their antisecretory effect.\textsuperscript{120, 121} One of these agents, vonoprazan, was
recently approved in Japan for a number of gastrointestinal diseases, including \textit{H. pylori}
eradication.\textsuperscript{121} Data suggest that the pH 4 holding time with this drug is equivalent to
esomeprazole 20 mg four times daily.\textsuperscript{122, 123} Superior clinical efficacy of this more potent acid
suppressant in triple therapy regimens has been demonstrated in first-line and second-line
settings.\textsuperscript{124} For example, vonoprazan-based triple therapy with amoxicillin and clarithromycin
had greater eradication success (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.\textsuperscript{124}

\textit{High dose dual therapy}: Further evidence for increased efficacy with greater acid suppression
comes from a study of high-dose PPI dual therapy.\textsuperscript{50} Despite the recognized inadequacy of
standard-dose PPI dual therapy,\textsuperscript{125} a large, RCT reported significantly higher ITT eradication
with high-dose PPI dual therapy (amoxicillin 750 mg QID and rabeprazole 20 mg QID for 14
days; 95.3%) as first-line treatment compared to either 10-day sequential (85.3%) or 7-day
standard triple therapy (80.7%), and as second-line treatment (89.3%) compared to sequential
(51.8%) but not levofloxacin-based triple therapy (78.6%).\textsuperscript{50} It is unknown how this regimen
would compare to 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 (for example compared to 14-day PBMT or PAMC first line therapy, compared to 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.

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. Vote: strongly agree, 87.5%; agree, 12.5%

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 (Appendix 2, summary of evidence table S14): 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. 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 with the addition of probiotics to quadruple therapy in adults.\textsuperscript{127,128} When added to sequential non-bismuth quadruple therapy there was no significant impact on eradication, but side effects and compliance were improved compared to placebo.\textsuperscript{127} When added to bismuth quadruple therapy, a multi-strain probiotic compound showed no beneficial effects on efficacy (ITT eradication, 76.6\% vs. 81.1\%; $P = .029$) or overall tolerability ($P = .851$) compared to placebo.\textsuperscript{128} There was a significant reduction in diarrhea, but an increase in abdominal pain.

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

\textbf{Decisions:} The consensus group concluded that the evidence does not convincingly demonstrate that probiotics will increase the efficacy of the recommended eradication therapies and they should not be used for this purpose. In contrast, while 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 \textit{C. difficile} infection.
FUTURE DIRECTIONS

The lack of availability of data on local susceptibility patterns and eradication successes 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. This 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 non-bismuth therapy vs. PBMT as first-line treatment, as well as studies on 10-day vs. 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 TID vs. 500 QID) for PBMT. The role of more potent acid suppression through higher or more frequent doses, or the use of newer anti-secretory agents, such as vonoprazan, requires further study.

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

Further study on high-dose PPI dual therapy (amoxicillin 750 mg QID and rabeprazole 20 mg QID for 14 days),\textsuperscript{50} and other high-dose dual regimens is required before they can be recommended.

In certain countries, some agents are not available, and hence 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 treatment failures.

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 before every vote, their potential viewpoints were discussed at the face-to-face meeting. In addition, it was decided not to search for data prior to 2008 to avoid confounding of data from earlier studies that had higher eradication success likely as a result of lower antibiotic resistance. This cut-off can however be viewed as a shortcoming especially in the rare instance when no new data was available. Older studies and meta-analyses were used as a discussion point when presenting newer studies and newer meta-analyses, as we did not want to completely ignore older data. The older data was only used in decision-making if newer data did not exist for that particular statement. We believe this approach was valid as it puts more emphasis on more recent data while not ignoring data published before 2008. Finally, the
systematic evaluation of evidence relied on studies where 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. Similarly, different studies may have used different doses, dosing intervals, relation to meals, etc, 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 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 traditional quadruple bismuth therapy (PBMT), concomitant non-bismuth 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 (Table 1, Figure 3). Levofloxacin triple therapy (PAL) and sequential non-bismuth quadruple therapy (PA followed by PMC) were not recommended for first-line treatment.

Potential strategies for subsequent therapy for patients who fail 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 QID could be considered as an option if the patient has previously failed regular PBMT and PAL, especially
if one wanted to avoid rifabutin. There is not, however, 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 at least 3 prior options. Regarding non-bismuth quadruple therapy, there was insufficient data to make a recommendation regarding concomitant PAMC as rescue therapy, but sequential therapy (PA followed by PMC) was not recommended.
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Canadian Association of Gastroenterology 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 the Canadian Association of Gastroenterology
(CAG) and under the direction of CAG Clinical Affairs. It has 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. It represents the consensus of a Canadian
and international panel comprised 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.
### Table 1. Recommendations for regimens used for the eradication of *H. pylori*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Regimen</th>
<th>Definition (see dose table)</th>
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</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
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<tr>
<td><strong>Recommended option</strong></td>
<td>Bismuth quadruple (PBMT)</td>
<td>PPI + bismuth + metronidazole + tetracycline</td>
</tr>
<tr>
<td><strong>Recommended option</strong></td>
<td>Concomitant non-bismuth quadruple (PAMC)</td>
<td>PPI + amoxicillin + metronidazole + clarithromycin</td>
</tr>
<tr>
<td><strong>Restricted option</strong></td>
<td>PPI triple (PAC, PMC or PAM)</td>
<td>PPI + amoxicillin + clarithromycin</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td>Levoﬂoxacin triple (PAL)</td>
<td>PPI + amoxicillin + levofloxacin</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td>Sequential non-bismuth quadruple (PA followed by PMC)</td>
<td>PPI + amoxicillin followed by PPI + metronidazole + clarithromycin</td>
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<tr>
<td><strong>Prior treatment failure</strong></td>
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<tr>
<td><strong>Recommended option</strong></td>
<td>Bismuth quadruple (PBMT)</td>
<td>PPI + bismuth + metronidazole + tetracycline</td>
</tr>
<tr>
<td><strong>Recommended option</strong></td>
<td>Levoﬂoxacin-containing therapy (usually PAL)</td>
<td>PPI + amoxicillin + levofloxacin</td>
</tr>
<tr>
<td><strong>Restricted option</strong></td>
<td>Rifabutin-containing therapy (usually PAR)</td>
<td>PPI + amoxicillin + rifabutin</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td>Sequential non-bismuth quadruple therapy (PA followed by PMC)</td>
<td>PPI + amoxicillin followed by PPI + metronidazole + clarithromycin</td>
</tr>
<tr>
<td><strong>Undetermined</strong></td>
<td>Concomitant non-bismuth quadruple therapy (PAMC)</td>
<td>PPI + amoxicillin + metronidazole + clarithromycin</td>
</tr>
</tbody>
</table>

*Tinidazole may be substituted for metronidazole; †Restricted to areas with known low clarithromycin resistance (≤15%) or proven high local eradication (>85%) (see Statement 5); ‡Some evidence that adding bismuth to this combination may improve outcomes; §Restricted to cases where at least 3 recommended options have failed (see Statement 13); PPI, proton pump inhibitor.*
Table 2. Recommendations for dose of agents used in *H. pylori* eradication therapies*

<table>
<thead>
<tr>
<th>Doses for agents in bismuth quadruple therapy</th>
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<tbody>
<tr>
<td>Bismuth</td>
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<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>PPI</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

*Doses for agents in all regimens other than bismuth quadruple therapy*  
(includes PPI triple, concomitant & sequential non-bismuth quadruple,  
levofloxacin and rifabutin therapies)

<table>
<thead>
<tr>
<th>Doses for agents in all regimens other than bismuth quadruple therapy</th>
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</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
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<tr>
<td>Clarithromycin</td>
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<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>PPI</td>
</tr>
<tr>
<td>Rifabutin</td>
</tr>
</tbody>
</table>

X: Dose depends on formulation used. In clinical trials the most common doses were: 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, and in Pylera® (Aptalis Pharma US, Inc.), the combination pill, bismuth subcitrate potassium (140 mg) 3 tablets QID.

Y: The dose depends on the PPI used. Standard doses are esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, 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.

*These doses are North American. They may vary in different parts of the world (for example 400 mg of metronidazole or 200 mg of clarithromycin may be the preferred doses in parts of Europe and Asia, respectively).

†Studies (from China) have suggested that giving double the bismuth dose twice daily is also effective; 62 Good evidence for QID dosing of metronidazole is lacking, however, some consensus group members 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 format is available); §In clinical trials eradication appears to be similar in studies that use levofloxacin 250 mg BID or 500 mg QD dosing. 138
Table 3. Summary of consensus recommendations for the treatment of *H. pylori* infection

<table>
<thead>
<tr>
<th>ALL PATIENTS</th>
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</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE THERAPY</strong></td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence low.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
</tr>
<tr>
<td><strong>SECOND-LINE THERAPY</strong></td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
</tr>
<tr>
<td><strong>SUPPLEMENTAL THERAPY</strong></td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence very low.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence very low.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence very low.</td>
</tr>
<tr>
<td><strong>PRIOR FAILURE</strong></td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
<td><strong>GRADE:</strong> Strong recommendation; quality of evidence moderate for efficacy, very low for duration.</td>
</tr>
</tbody>
</table>

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 there was insufficient evidence to make a recommendation on high-dose dual therapy with a PPI and amoxicillin.
Table 4. Relative risks (RR) for *H. pylori* persistence according to duration of regimens

<table>
<thead>
<tr>
<th>Studies (n=75)</th>
<th>14 vs. 7 days</th>
<th>10 vs. 7 days</th>
<th>14 vs. 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR for <em>H. pylori</em> persistence (95% CI); NNT (95% CI); studies (n)</td>
<td></td>
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<tr>
<td>PPI triple therapy</td>
<td>0.66 (0.60–0.74); NNT 11 (9–14); (n=59)</td>
<td>0.80 (0.72–0.89); NNT 21 (15–38); (n=24)</td>
<td>0.72 (0.58–0.90); NNT 17 (11–46); (n=12)</td>
</tr>
<tr>
<td>PAC (n=34)</td>
<td>0.65 (0.57–0.75); NNT 12 (9–16); (n=34)</td>
<td>0.80 (0.70–0.91); NNT 21 (14–48); (n=17)</td>
<td>0.69 (0.52–0.91); NNT 16 (10–54); (n=10)</td>
</tr>
<tr>
<td>PMC (n=4)</td>
<td>0.87 (0.71–1.07); NNT 3 (2–10); (n=4)</td>
<td>0.99 (0.55–1.79); NNT 2 (1–5); (n=2)</td>
<td>-</td>
</tr>
<tr>
<td>PAQ (n=2)</td>
<td>0.37 (0.16–0.83); NNT 3 (2–10); (n=2)</td>
<td>0.58 (0.36–0.95); NNT 7 (5–9); (n=2)</td>
<td>-</td>
</tr>
<tr>
<td>PPI bismuth quad therapy (n=6)</td>
<td>0.71 (0.44–1.15); (n=3)</td>
<td>0.70 (0.43–1.14); (n=2)</td>
<td>1.13 (0.59–2.18); (n=1)</td>
</tr>
</tbody>
</table>

NNT, number needed to treat; PAQ, PPI-amoxicillin-quinolone; PAC, PPI-amoxicillin-clarithromycin; PMC, PPI-metronidazole-clarithromycin; PPI, proton pump inhibitor; RR, risk ratio.

Based on data from meta-analysis by Yuan et al.\textsuperscript{28}
Figure 1: Pooled successful eradication (intention to treat) in subgroup analysis according to year of study publication.

Based on data from meta-analysis by Venerito et al. 2013.²²

RD, risk differences are shown as proportions rather than percentages.
Figure 2: Meta-analysis of eradication successes (intention to treat) with sequential vs. concomitant non-bismuth quadruple therapies.

Regimens using the same drugs at the same doses for equal durations. Risk differences are shown as proportions rather than percentages.

Updated meta-analysis conducted for the consensus meeting, based on reference 69.
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 in order to reserve rifabutin for 4th-line use (see statement 8). Optimized refers to using a higher dose of PPI or metronidazole.

PAC, PPI + amoxicillin + clarithromycin; PAL, PPI + amoxicillin + levofloxacin; PAMC, PPI + amoxicillin + metronidazole + clarithromycin; PAR, PPI + amoxicillin + rifabutin; PBMT, PPI + bismuth + metronidazole + tetracycline; PMC, PPI + metronidazole + clarithromycin; PPI, proton pump inhibitor. See tables 1 and 2 for more details on regimens and dosing.
APPENDICES

Online Appendix 1. Search strategies used for EMBASE and 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. eradicate*.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
### Online Appendix 2: Summary of evidence tables for each consensus statement for the treatment of H. pylori infection

#### Table S1: Evidence for statement 1 (In patients with H. pylori infection, we recommend a treatment-duration of 14 days)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk of bias</th>
<th>Inconsistencies</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality of evidence</th>
<th>Overall quality of evidence</th>
<th>Eradication rates (ITT)</th>
<th>Relative effect (95% CI)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>PPI-based triple regimens: 14 days vs. 7 days</td>
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<tr>
<td>1 SR&lt;sup&gt;c&lt;/sup&gt; (45 RCTs)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>MODERATE</td>
<td>MODERATE</td>
<td>81.9%</td>
<td>72.9%</td>
<td>NNT: 11 (9 to 14)</td>
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<td></td>
<td>The quality of evidence is moderate for PAC, but low for PMC</td>
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<td>PPI-based triple regimens: 14 days vs. 10 days</td>
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<tr>
<td>1 SR&lt;sup&gt;b&lt;/sup&gt; (12 RCTs)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>none</td>
<td>none</td>
<td>none</td>
<td>MODERATE</td>
<td>MODERATE</td>
<td>84.4%</td>
<td>78.5%</td>
<td>NNT: 17 (11 to 46)</td>
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<td>PPI-based triple regimens: 10 days vs. 7 days</td>
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<tr>
<td>1 SR&lt;sup&gt;c&lt;/sup&gt; (24 RCTs)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>none</td>
<td>MODERATE</td>
<td>MODERATE</td>
<td>79.9%</td>
<td>75.7%</td>
<td>NNT: 21 (13 to 38)</td>
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<td>PPI-based triple regimens: 14 days vs. 10 days vs. 7 days</td>
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<tr>
<td>1 RCT&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>1 SR&lt;sup&gt;a&lt;/sup&gt; (3 RCTs)</td>
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<td>none</td>
<td>none</td>
<td>none</td>
<td>very serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>77.9%</td>
<td>69.1%</td>
<td>Non-significant difference</td>
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<td>Trend favoring 14 or 10 vs 7 days but not statistically significant</td>
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<td>PBMT: 14 days vs. 10 days</td>
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<tr>
<td>1 SR&lt;sup&gt;b&lt;/sup&gt; (1 RCT)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>very serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>91.6%</td>
<td>92.6%</td>
<td>Non-significant difference</td>
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<tr>
<td>1 SR&lt;sup&gt;c&lt;/sup&gt; (cohort-type data from 51 studies)</td>
<td>none</td>
<td>serious</td>
<td>none</td>
<td>serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>VERY LOW</td>
<td>78.7%</td>
<td>75.6%</td>
<td>Non-significant difference</td>
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<td>PBMT: 10 days vs. 7 days</td>
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<tr>
<td>1 SR&lt;sup&gt;d&lt;/sup&gt; (2 RCTs)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>very serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>87.4%</td>
<td>81.9%</td>
<td>Non-significant difference</td>
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<tr>
<td>PAMC</td>
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<tr>
<td>1 SR&lt;sup&gt;e&lt;/sup&gt; (cohort-type data from 15 studies)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>VERY LOW</td>
<td>92% (10 days)</td>
<td>89% (5 days)</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>1 cohort study&lt;sup&gt;f&lt;/sup&gt;</td>
<td>serious</td>
<td>none</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>none</td>
<td>VERY LOW</td>
<td>VERY LOW</td>
<td>93.3% (14 days)</td>
<td>86.6% (10 days)</td>
<td>P&lt;0.05 Relative effect not reported</td>
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<td>PAL: 14 days vs. 7 days</td>
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<tr>
<td>1 SR&lt;sup&gt;e&lt;/sup&gt; (2 RCTs)</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>serious</td>
<td>none</td>
<td>VERY LOW</td>
<td>VERY LOW</td>
<td>78.5% (14 days)</td>
<td>42% (7 days)</td>
<td>NNT: 3 (2 to 10)</td>
</tr>
</tbody>
</table>
Fallone et al. CAG and CHSG consensus on H. pylori treatment

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 of bias; f One of the studies used ofloxacin (not levofloxacin).

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; NNT, number needed to treat; PAC, PPI + amoxicillin + clarithromycin; PAL, PPI + amoxicillin + levofloxacin; PAMC, PPI + amoxicillin + metronidazole + clarithromycin; PBMT, PPI + bismuth + metronidazole + tetracycline; PMC, PPI + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.

Table S2: 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)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Quality of evidence</td>
<td>Eradication rates (ITT)</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Overall quality of evidence</td>
<td>Relative effect (95% CI)</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>Regional antibiotic resistance patterns</td>
<td>Regiona l antibiotic resistance patterns not considered</td>
</tr>
<tr>
<td>Indirectness</td>
<td>considered</td>
<td></td>
</tr>
<tr>
<td>Imprecision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other considerations a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional antibiotic resistance patterns considered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication of H. pylori infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture-guided vs. empirical triple therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>⊕⊕⊝⊝ LOW</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1 SR (5 RCTs)</td>
<td></td>
<td>Culture-guided triple therapy resulted in a significantly lower risk of treatment failure compared to empiric standard triple therapy</td>
</tr>
<tr>
<td>Time trends for H. pylori antibiotic resistance and efficacy of eradication regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple reviews of observational studies a,b,c</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; RCT, randomized controlled trial; SR, systematic review.
Table S3: 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)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: relative to PPI-based triple regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR** (12 RCTs)</td>
<td>serious</td>
<td>none</td>
<td>serious</td>
</tr>
<tr>
<td>1 RCT***</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Efficacy: absolute rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR of observational studies and observational-type data from RCTs</td>
<td>serious</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Efficacy: metronidazole resistant strains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR** (2 RCTs)</td>
<td>none</td>
<td>none</td>
<td>serious</td>
</tr>
<tr>
<td>Duration: PBMT for 14 days vs. PBMT for 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR** (3 RCTs)</td>
<td>serious</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Duration: PBMT for 14 days vs. PBMT for 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR** (1 RCT)</td>
<td>serious</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>1 SR (cohort-type data from 51 studies)</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td>Duration: PBMT for 10 days vs. PBMT for 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR** (2 RCTs)</td>
<td>serious</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

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

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; NNT, number needed to treat; PAC, PPI + amoxicillin + clarithromycin; PBMT, PPI + bismuth + metronidazole + tetracycline; PP, per protocol; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
Fallone et al. CAG and CHSG consensus on *H. pylori* treatment

**Table S4: Evidence for statement 4 (In patients with *H. pylori* infection, we recommend concomitant non-bismuth quadruple therapy [PAMC] for 14 days as one of the options for first-line therapy)**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality of evidence</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SR<strong>6</strong> (6 RCTs)</td>
<td>serious[^a^]</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>⊕⊕⊕ ⊝ MODERATE</td>
<td>Eradication rates (ITT)</td>
<td>PAMC Comparator</td>
</tr>
<tr>
<td>1 SR* (19 RCTs)</td>
<td>serious[^a^]</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>⊕⊕⊕ ⊝ MODERATE</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>2 RCTs[^b^]</td>
<td>serious[^a^]</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>⊕⊕⊕ MODERATE</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Efficacy: relative to PPI triple regimens**

- **Eradication of *H. pylori* infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)**
- **Efficacy: relative to sequential regimen**
- **Efficacy: relative to hybrid regimen[^c^]**
- **Efficacy: absolute rates**
- **Duration: longer duration PAMC of shorter duration PAMC**

[^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.

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; PAMC, PPI + amoxicillin + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
### Table S5: 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 [>85%])

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
</tr>
<tr>
<td>1 SR(^a) (12 RCTs)</td>
<td>serious(^b)</td>
</tr>
<tr>
<td>1 RCT(^e)</td>
<td>none</td>
</tr>
</tbody>
</table>

Efficacy: relative to bismuth quadruple regimen (PBMT)

Efficacy: relative to sequential regimen

Efficacy: relative to concomitant regimen

Efficacy: absolute rates

Duration: 14 days vs. 7 days

Duration: 14 days vs. 10 days

Culture-guided vs. empirical triple therapy

Time trends for *H. pylori* resistance to clarithromycin and efficacy of eradication regimens

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\(^a\) 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 was at low risk of 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.

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; NNT, number needed to treat; PAC, PPI + amoxicillin + clarithromycin; PBMT, PPI + bismuth + metronidazole + tetracycline; PMC, PPI + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
Fallone et al. CAG and CHSG consensus on *H. pylori* treatment

**Table S6: 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)**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: relative to PAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RCTs[8, 9, 13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAL</td>
<td>Comparator</td>
<td></td>
</tr>
<tr>
<td>85%, 80%, and 81%, respectively</td>
<td>79%, 64%, and 87%, respectively</td>
<td>Overall, non-significant difference</td>
</tr>
<tr>
<td>Efficacy: levofloxacin-resistant strains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies (cohort-type data from 2 RCTs)[12, 13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table S7: Evidence for statement 7 (In patients with *H. pylori* infection, we recommend against the use of sequential non-bismuth quadruple therapy [PA followed by PMC] as a first-line therapy)**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANCE OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: relative to concomitant non-bismuth quadruple therapy (PAMC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR[89] (14 RCTs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>Comparator</td>
<td></td>
</tr>
<tr>
<td>79.7%</td>
<td>85.7%</td>
<td>RD 0.06 (0.03 to 0.09)</td>
</tr>
</tbody>
</table>

*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.*

*95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; PAC, PPI + amoxicillin + clarithromycin; PAL, PPI + amoxicillin + levofloxacin; PPI, proton pump inhibitor; RCT, randomized controlled trial.*

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Table S8: Evidence for statement 8 (In patients who have previously failed  
H. pylori eradication therapy, we recommend traditional  
bismuth quadruple therapy [PBMT] for 14 days as an option for subsequent therapy)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Studies</th>
<th>Risk of bias</th>
<th>Inconsistenc y</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideratio ns*</th>
<th>Quality of evidence</th>
<th>Overall quality of evidence</th>
<th>Eradication rates (ITT)</th>
<th>Relative effect (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy: absolute rates</td>
<td>1 SR (38 studies: observational studies and observational-type data from RCTs)**</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>⊕⊕⊝⊝ LOW</td>
<td>78%</td>
<td>NA</td>
<td>NA</td>
<td>Adequately high eradication rate after failure of PPI triple therapy</td>
</tr>
<tr>
<td>Duration: PBMT for 14 days vs. PBMT for 10 days</td>
<td>1 SR (14 studies: observational studies and observational-type data from RCTs)**</td>
<td>none</td>
<td>none</td>
<td>serious b</td>
<td>serious</td>
<td>none</td>
<td>⊗⊗ΟΓ VERY LOW</td>
<td>82%</td>
<td>77%</td>
<td>Non-significant difference</td>
<td>Trend favoring 14 days (not significant)</td>
</tr>
<tr>
<td></td>
<td>1 SR* (cohort-type data from 51 studies)</td>
<td>none</td>
<td>serious</td>
<td>serious b</td>
<td>serious</td>
<td>none</td>
<td>⊗⊗ΟΓ VERY LOW</td>
<td>78.7%</td>
<td>75.6%</td>
<td>Non-significant difference</td>
<td></td>
</tr>
</tbody>
</table>

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

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; PBMT, PPI + bismuth + metronidazole + tetracycline; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
Table S9: Evidence for statement 9 (In patients who have previously failed *H. pylori* eradication therapy, we suggest levofloxacin-containing therapy for 14 days as an option for subsequent therapy)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality of evidence</th>
<th>Overall quality of evidence</th>
<th>Eradication rates (ITT)</th>
<th>Relative effect (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy: relative to bismuth quadruple regimen (PBMT) after failure of PPI triple therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR(^a) (6 RCTs)</td>
<td>serious(^b)</td>
<td>none</td>
<td>none</td>
<td>serious</td>
<td>none</td>
<td>⊕⊕⊝⊝ LOW</td>
<td>79%(^c)</td>
<td>69%</td>
<td>Non-significant difference</td>
<td></td>
</tr>
<tr>
<td>Efficacy: absolute rates with 10-day PAL after failure of concomitant non-bismuth quadruple therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR(^d) (observational type data from 3 studies)</td>
<td>Not known(^e)</td>
<td>serious(^f)</td>
<td>none</td>
<td>serious</td>
<td>none</td>
<td>⊕⊕⊝⊝ LOW</td>
<td>78%</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: absolute rates after failure of sequential non-bismuth quadruple therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR(^g) (observational type data from 5 studies)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>⊕⊝⊝⊝⊝ VERY LOW</td>
<td>81%</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Duration: 10 days vs. 7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR(^h) (observational type data from 11 studies)</td>
<td>Not known(^i)</td>
<td>none</td>
<td>none</td>
<td>serious(^j)</td>
<td>none</td>
<td>⊕⊝⊝⊝⊝⊝ VERY LOW</td>
<td>88.7%</td>
<td>70.6%</td>
<td>P&lt;0.05</td>
<td>Superiority of longer duration</td>
</tr>
</tbody>
</table>

\(^a\) 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. 95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; PBMT, PPI + bismuth + metronidazole + tetracycline; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
Table S10: Evidence for statement 10 (In patients who have previously failed a clarithromycin-containing *H. pylori* eradication therapy, we recommend against the use of clarithromycin-containing regimens as subsequent therapy)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
</tbody>
</table>
| Prevalence of secondary resistance to clarithromycin | none | none | none | none | none | ☀ ☀ ☀ ☀ ☀ ☀ | ☀ ☀ ☀ ☀ ☀ ☀ | NA | NA | NA | Prevalence of secondary resistance to clarithromycin is very high (up to 70%)
| Impact of clarithromycin resistance | none | none | serious | none | none | ☀ ☀ ☀ ☀ ☀ ☀ | ☀ ☀ ☀ ☀ ☀ ☀ | NA | NA | NA | Efficacy of clarithromycin-containing regimens is highly impacted by clarithromycin resistance

Table S11: Evidence for statement 11 (In patients who have previously failed a levofloxacin-containing *H. pylori* eradication therapy, we recommend against the use of levofloxacin-containing regimens as subsequent therapy)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
</tbody>
</table>
| Prevalence of secondary resistance to levofloxacin | none | none | none | none | none | ☀ ☀ ☀ ☀ ☀ ☀ | ☀ ☀ ☀ ☀ ☀ ☀ | NA | NA | NA | The prevalence of secondary resistance to levofloxacin is very high (up to 60%)
| Impact of levofloxacin resistance | none | none | serious | none | none | ☀ ☀ ☀ ☀ ☀ ☀ | ☀ ☀ ☀ ☀ ☀ ☀ | NA | NA | NA | The efficacy of levofloxacin-containing regimens are highly impacted by levofloxacin resistance

a Including publication bias

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable.
Fallone et al. CAG and CHSG consensus on *H. pylori* treatment

**Table S12: Evidence for statement 12 (In patients who have previously failed *H. pylori* eradication therapy, we recommend against the use of sequential non-bismuth quadruple therapy (PA followed by PMC) as an option for subsequent therapy)**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Overall quality of evidence</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANT OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: absolute rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 cohort studies [106, 110]</td>
<td>none</td>
<td>none</td>
<td>very serious (^{a})</td>
</tr>
<tr>
<td>Efficacy: relative to concomitant non-bismuth quadruple therapy (PAMC), as first-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR (^{b}) (19 RCTs)</td>
<td>serious (^{c})</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

* Including publication bias; \(^{b}\) 40 and 2 patients, respectively; \(^{c}\) Mainly due to lack of blinding; \(^{d}\) These studies tested the regimens as first-line treatments.

**Table S13: Evidence for statement 13 (We recommend restricting the use of rifabutin-containing regimens to cases where at least 3 recommended options have failed)**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Overall quality of evidence</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication of <em>H. pylori</em> infection (IMPORTANT OF OUTCOME: CRITICAL for decision making)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy: absolute rates (overall)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR (^{e}) (21 studies: cohort studies and observational-type data from RCTs)</td>
<td>none</td>
<td>none</td>
<td>serious (^{b})</td>
</tr>
<tr>
<td>Efficacy: absolute rates (4th or 5th line treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR (^{f}) 7 studies: cohort studies and observational-type data from RCTs</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Duration: 10-12 days vs. 7 days (2nd line treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SR (^{g}) 8 studies: cohort studies and observational-type data from RCTs</td>
<td>none</td>
<td>none</td>
<td>very serious (^{c})</td>
</tr>
</tbody>
</table>

* Including publication bias; \(^{b}\) Included studies that tested the regimen as 1st, 2nd, 3rd, 4th or 5th-line treatment; \(^{c}\) Only 2nd line treatment; between-studies comparisons. 95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; RCT, randomized controlled trial; SR, systematic review.
Fallone et al. CAG and CHSG consensus on *H. pylori* treatment

**Table S14: 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)**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP, <em>H. pylori</em> infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>1 SR^2^ (10 RCTs)</td>
<td>serious^b^</td>
<td>serious^c^</td>
</tr>
</tbody>
</table>

| Effect on adverse effects | | |
| ERP, *H. pylori* infection | | |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of evidence | Overall quality of evidence | Eradication rates (ITT) | OR 0.3 | (0.1 - 0.8) | Very low evidence |
| 1 SR^2^ (10 RCTs) | serious^b^ | serious^c^ | serious^d^ | none | none | 🌟🌟🌟🌟 VERY LOW | Not reported | Not reported | OR 0.3 | (0.1 - 0.8) | Very low evidence |

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^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.

95% CI, 95% confidence interval; ITT, intention to treat; NA, not applicable; NNT, number needed to treat; PAC, PPI + amoxicillin + clarithromycin; PAL, PPI + amoxicillin + levofoxacin; PAMC, PPI + amoxicillin + metronidazole + clarithromycin; PBMT, PPI + bismuth + metronidazole + tetracycline; PMC, PPI + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; SR, systematic review.
REFERENCES


Fallone et al. CAG and CHSG consensus on *H. pylori* treatment


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.


Fallone et al. CAG and CHSG consensus on *H. pylori* treatment


