

Appendix 2

Quality of evidence as per GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Question 1: What is known about the epidemiology of *H. pylori* infection in North America? Which are the high risk groups?

H. pylori infection is chronic and is usually acquired in childhood. The exact means of acquisition is not always clear. The incidence and prevalence of *H. pylori* infection are higher among people born outside North America than among people born here. Within North America, the prevalence of the infection is higher in certain racial and ethnic groups, the socially disadvantaged, and people who have immigrated to North America.

Strength of recommendation not applicable (factual statement); low quality of evidence

Quality of Evidence

- **Low QoE.** Evidence from observational studies.

Question 2: What are the indications to test for, and to treat, *H. pylori* infection?

Since all patients with a positive test of active infection with *H. pylori* should be offered treatment, the critical issue is which patients should be tested for the infection. **Strong** recommendation; quality of evidence not applicable (good practice (motherhood) statement).

All patients with active peptic ulcer disease (PUD), a past history of PUD (unless previous cure of *H. pylori* infection has been documented), low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) should be tested for *H. pylori* infection. Those who test positive should be offered treatment for the infection.

Strong recommendation; quality of evidence: **high** for active or history of PUD, **low** for MALT lymphoma, **low** for history of endoscopic resection of EGC

Quality of Evidence

- **For active or history of PUD: High QoE.** Evidence from systematic reviews of RCTs without serious limitations.
- **For MALT lymphoma: Low QoE.** Evidence from systematic reviews of observational studies.
- **For history of endoscopic resection of EGC: Low QoE.** Evidence from systematic reviews of observational studies.

In patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, non-endoscopic testing for *H. pylori* infection is a consideration. Those who test positive should be offered eradication therapy.

Conditional recommendation; quality of evidence: **high** for efficacy, **low** for the age cut-off point

Quality of Evidence

- **For efficacy: high QoE.** Evidence from systematic reviews of RCTs without serious limitations.
- **For the age cut-off point: Low QoE.** Evidence from observational studies.

When upper endoscopy is undertaken in patients with dyspepsia, gastric biopsies should be taken to evaluate for *H. pylori* infection. Infected patients should be offered eradication therapy.

Strong recommendation; High quality of evidence

Quality of Evidence

- **High QoE.** Evidence from systematic reviews of RCTs without serious limitations.

Patients with typical symptoms of gastroesophageal reflux disease (GERD) who do not have a history of PUD need not be tested for *H. pylori* infection. However, for those who are tested and found to be infected, treatment should be offered acknowledging that effects on GERD symptoms are unpredictable.

Strong recommendation; High quality of evidence

Quality of Evidence

- **High QoE.** Evidence from systematic reviews of RCTs and systematic reviews of observational studies and cohort-type data from RCTs.

In patients taking long-term low-dose aspirin, testing for *H. pylori* infection could be considered. Those who test positive should be offered eradication therapy to reduce the risk of ulcer bleeding.

Conditional recommendation; Moderate quality of evidence

Quality of Evidence

- **Moderate QoE.** Evidence from RCTs, downgraded for indirectness (the studies included high-risk patients with recent peptic ulcer bleeding). Evidence from observational studies, upgraded for large effect size.

Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy. The benefits of testing and treating *H. pylori* in patients already taking NSAIDs remains unclear.

For patients initiating chronic treatment with NSAIDs: Strong recommendation; Moderate quality of evidence

Quality of Evidence

- **Moderate QoE.** Evidence from systematic reviews of RCTs, downgraded for indirectness (the outcome was endoscopic ulcers; limited data on symptomatic ulcers and ulcer complications).

For patients already on chronic treatment with NSAIDs: Conditional recommendation; Low quality of evidence

- **Low QoE.** Evidence from systematic reviews of RCTs, downgraded for indirectness (the outcome was endoscopic ulcers; limited info on symptomatic ulcers and ulcer complications) and imprecision (wide confidence intervals, small number of events)

Patients with unexplained iron deficiency anemia despite an appropriate evaluation should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy.

Conditional recommendation; Low quality of evidence

Quality of Evidence

- **Low QoE.** Evidence from systematic reviews of RCTs, downgraded for study limitations (unclear sequence generation process and concealment of allocation) and inconsistency (heterogeneity among studies, with larger effect size in studies outside of North America). Also, evidence from systematic reviews of observational studies.

Adults with idiopathic thrombocytopenic purpura (ITP) should be tested for *H. pylori* infection. Those who test positive

should be offered eradication therapy.

Conditional recommendation; Very Low quality of evidence

Quality of Evidence

- **Very low QoE.** Evidence from two RCTs, downgraded for very serious imprecision (very small number of events, very wide confidence intervals), study limitations (unclear sequence generation process and concealment of allocation, non-blinded assessors) and indirectness (short follow up). Also, evidence from systematic reviews of several observational studies with study limitations (mainly selection bias).

There is insufficient evidence to support routine testing for and treatment of *H. pylori* in patients with lymphocytic gastritis, hyperplastic gastric polyps and hyperemesis gravidarum (HG).

Strength of recommendation not applicable No recommendation; Very Low quality of evidence

Quality of Evidence

- **Very Low QoE.** Evidence from observational studies and non-randomized trials with study limitations

Question 3: What are evidence-based first-line treatment strategies for providers in North America?

Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen.

Conditional recommendation; moderate quality of evidence

Quality of Evidence

- **Moderate QoE.** Evidence from multiple cohort studies and subgroup analyses from RCTs, upgraded for large effect size.

Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment option in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason.

Conditional recommendation; low quality of evidence (for duration: moderate quality of evidence)

Quality of Evidence

- **Efficacy of clarithromycin triple therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from 3 recent RCTs from North America that compared PAC with sequential treatment and bismuth based quadruple treatment, downgraded for imprecision (small number of events; wide 95% CIs) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy clarithromycin triple therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs from North America.
- **Duration 14 days for clarithromycin triple therapy as first-line treatment: Moderate QoE.** Evidence from a meta-analysis of RCTs that compared regimens of different durations, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).

Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10-14 days is a recommended first line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin.

Strong recommendation; low quality of evidence

Quality of Evidence

- **Efficacy of bismuth quadruple therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from 2 RCTs from North America, downgraded for imprecision (small number of events; very wide 95% CIs) and

study limitations (performance bias due to lack of blinding; attrition bias in one of the studies). Evidence from multiple RCTs from other regions, downgraded for indirectness, and study limitations.

- **Absolute efficacy of bismuth quadruple therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs (from North America and elsewhere)
- **Duration 14 days for bismuth quadruple therapy as first-line treatment: Low QoE.** Evidence from a meta-analysis of 6 RCTs comparing different durations of PBMT regimens downgraded for imprecision (small number of events, wide 95% CIs), indirectness (studies conducted in Asia), and study limitations.

Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 7-14 days is a recommended first line treatment option.

Strong recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of concomitant therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from RCTs, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment) and indirectness (no studies from North America).
- **Absolute efficacy of concomitant therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs
- **Duration for concomitant therapy as first-line treatment: Very low QoE.** Evidence from subgroup analyses (between-study comparisons) from meta-analyses of cohort studies and cohort-type data, downgraded for indirectness, imprecision and study limitations.

Sequential therapy consisting of a PPI and amoxicillin for 5-7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5-7 days is a suggested first line treatment option.

Conditional recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of sequential therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from 2 RCTs from North America, downgraded for imprecision (small number of events; wide 95% CIs) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment; attrition bias in one of the RCTs). Multiple RCTs from Europe, Asia and Central America, further downgraded for indirectness.
- **Absolute efficacy of sequential therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs
- **Duration for sequential therapy as first-line treatment: Very low QoE.** Evidence one RCT from Asia, downgraded for imprecision, indirectness and study limitations (performance bias due to lack of blinding). Also, evidence from subgroup analyses from meta-analyses of cohort studies and cohort-type data from RCTs, downgraded for indirectness, and study limitations.

Hybrid therapy consisting of a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first line treatment option.

Conditional recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of hybrid therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from meta-analyses of 6 RCTs downgraded for indirectness (conducted outside North America) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of hybrid therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs.
- **Duration for hybrid therapy as first-line treatment: Very low QoE.** No RCTs have evaluated hybrid therapy of

duration other than 14 days.

Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10-14 days is a suggested first-line treatment option.

Conditional recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of levofloxacin triple therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from RCTs, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment) and indirectness (the studies were conducted outside of North America).
- **Absolute efficacy of levofloxacin triple therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs.
- **Duration for levofloxacin triple therapy as first-line treatment: Very low QoE.** Evidence from subgroup analyses (between-study comparisons) from meta-analyses of cohort studies and cohort-type data, downgraded for indirectness, imprecision and study limitations.

Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5-7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5-7 days is a recommended first line treatment option.

Conditional recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of fluoroquinolone sequential therapy as first-line treatment compared to other regimens: Low QoE.** Evidence from RCTs, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment) and indirectness (the studies were conducted outside of North America).
- **Absolute efficacy of fluoroquinolone sequential therapy as first-line treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs
- **Duration for fluoroquinolone sequential therapy as first-line treatment: Very low QoE.** Evidence from subgroup analyses (between-study comparisons) from meta-analyses of cohort studies and cohort-type data, downgraded for indirectness, imprecision and study limitations.

Question 4: What factors predict successful eradication when treating *H. pylori* infection?

The main determinants of successful *H. pylori* eradication are the choice of regimen, the patient's adherence to a multi-drug regimen with frequent side-effects, and the sensitivity of the *H. pylori* strain to the combination of antibiotics administered.

Strength of recommendation not applicable (factual statement); Moderate quality of evidence

Quality of Evidence

- **Moderate QoE.** Evidence from RCTs without limitations. Also, evidence from observational studies and cohort-type data from RCTs, upgraded due to large effect size.

PICO 5: What do we know about *H. pylori* antimicrobial resistance in the North America?

Data regarding antibiotic resistance among *H. pylori* strains from North America remain scarce.

Organized efforts are needed to document local, regional and national patterns of resistance in order to guide the appropriate selection of *H. pylori* therapy.

Strong recommendation; Low quality of evidence

Quality of Evidence

- **Low QoE.** Evidence from observational studies, upgraded due to large effect size, showing that sensitivity of the *H. pylori* strain to the combination of antibiotics administered is one of the main determinants of successful *H. pylori* eradication. However, this evidence is downgraded for indirectness because no study has directly assessed if knowledge of local, regional and national patterns of resistance actually improves eradication rates.

Question 6: What methods can be used to evaluate for *H. pylori* antibiotic resistance and when should testing be performed?

Although *H. pylori* antimicrobial resistance can be determined by culture and/or molecular testing (**Strong recommendation; Moderate quality of evidence**), these tests are currently not widely available in the US (*strength of recommendation: not applicable*)

Quality of Evidence

- **Moderate QoE.** Evidence from studies of diagnostic test accuracy. Downgraded for indirectness (imperfect concordance with clinical efficacy).

Question 7: Should we test for treatment success after *H. pylori* eradication therapy?

Whenever *H. pylori* infection is identified and treated, testing to prove eradication should be performed using a urea breath test, fecal antigen test or biopsy based testing at least 4 weeks after the completion of antibiotic therapy.
Strong recommendation; Low quality of evidence (for the choice of methods to test for eradication: Moderate quality of evidence)

Quality of Evidence

- **Testing vs. not testing to prove eradication: Low QoE.** Evidence from observational studies. Also, evidence from RCTs downgraded for very serious indirectness.
- **Choice of methods to test for eradication: Moderate QoE.** Evidence from systematic reviews of diagnostic accuracy studies

Question 8: When primary therapy fails, what are the options for salvage therapy?

In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline).
Strong recommendation; moderate quality of evidence

Quality of Evidence

- **Sensitivity of *H. pylori* to the antibiotics used is the most important determinant of the success of the eradication therapy: Moderate QoE:** evidence from cohort studies and observational-type data (eradication results stratified by pre-treatment sensitivity of *H. pylori* to antibiotics) from RCTs, upgraded for large effect size.

Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options, if a patient received a first-line treatment containing clarithromycin,. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.

Conditional recommendation; overarching statement (for quality of evidence see individual statements below)

Clarithromycin or levofloxacin containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.

Conditional recommendation; overarching statement (for quality of evidence see individual statements below)

The following regimens can be considered for use as salvage treatment:

a. Bismuth quadruple therapy for 14 days is a recommended salvage regimen.

Strong recommendation; low quality of evidence

Quality of Evidence

- **Efficacy of bismuth quadruple therapy as salvage treatment compared to other regimens: Low QoE.** Evidence from 4 RCTs (from North America and Europe), downgraded for imprecision (small number of events; wide 95% CIs) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of bismuth quadruple therapy as salvage treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs
- **Duration 14 days for bismuth quadruple therapy as salvage treatment: Low QoE.** Evidence from a meta-analysis of 4 RCTs (2 from Asia and 2 from Europe) comparing 14-day and 7-day regimens, downgraded for imprecision (small number of events, 95% CI crossing the line of minimal clinically important difference). Also downgraded for indirectness (for the difference between 14-day and 10 day regimens there is only indirect evidence from observational-type data).

b. Levofloxacin triple regimen for 14 days is a recommended salvage regimen.

Strong recommendation; moderate quality of evidence (for duration: low quality of evidence)

Quality of Evidence

- **Efficacy of levofloxacin triple salvage therapy compared to other regimens: Moderate QoE.** Evidence from several RCTs, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of levofloxacin triple therapy as salvage treatment: Low QoE.** Evidence from cohort-type data from several RCTs
- **Duration of 14 days for levofloxacin triple therapy as salvage treatment: Low QoE.** Evidence from one RCT downgraded for imprecision (small number of events) and indirectness (compared 7-day to 10-day regimens), and a second RCT downgraded for imprecision (small number of events) and indirectness (conducted in Asia). Also, evidence from subgroup analyses in proportion meta-analysis of cohort-type data from RCTs, downgraded for indirectness (between-study comparisons).

c. Concomitant therapy for 10-14 days is a suggested salvage regimen.

Conditional recommendation; very low quality of evidence

Quality of Evidence

- **Efficacy of concomitant therapy as salvage treatment compared to other regimens: Very Low QoE.** Evidence from 2 RCTs (from Asia), downgraded for indirectness (different population), imprecision (small number of events) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation

concealment).

- **Absolute efficacy of concomitant therapy as salvage treatment: Very Low QoE.** Evidence from cohort-type data from 2 RCTs (from Asia), downgraded for indirectness (different population). Evidence from systematic reviews of cohort-type data from RCTs on 1st-line treatment downgraded for indirectness (not salvage treatment). Evidence from cohort-type data from RCTs on 1st-line treatment showing limited reduction in efficacy in patients with stains with dual resistance, downgraded for indirectness (not salvage treatment) and imprecision (very small numbers).
- **Duration 14 days for concomitant therapy as salvage treatment: Very Low QoE.** Evidence from one RCT (from Asia) on 1st line treatment), downgraded for imprecision (small number of events, wide 95% CI) and very serious indirectness (different population, not salvage therapy, compared 5-day to 10-day regimens)

d. Clarithromycin triple therapy for 14 days is a suggested salvage regimen.

Conditional recommendation; low quality of evidence (for duration: moderate quality of evidence)

Quality of Evidence

- **Efficacy of clarithromycin triple therapy as salvage treatment compared to other regimens: Low QoE.** Evidence from 3 RCTs (from North America and Europe), downgraded for imprecision (small number of events; wide 95% confidence intervals) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of clarithromycin triple therapy as salvage treatment: Low QoE.** Evidence from cohort studies and cohort-type data from RCTs
- **Duration 14 days for clarithromycin triple therapy as salvage treatment: Moderate QoE.** Evidence from a meta-analysis of RCTs comparing different durations of clarithromycin triple therapy, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment). The quality of evidence was not downgraded for indirectness (the RCTs assessed 1st line treatments), because it is implausible that salvage clarithromycin triple therapy treatment should be used in shorter durations than 1st line clarithromycin triple therapy treatment.

e. Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen.

Conditional recommendation; moderate quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of rifabutin triple therapy as salvage treatment compared to other regimens: Moderate QoE.** Evidence from several RCTs, downgraded for study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of rifabutin triple therapy as salvage treatment: Low QoE.** Evidence from cohort-type data from several RCTs
- **Duration for rifabutin triple therapy as salvage treatment: Very Low QoE.** Evidence from subgroup analyses in proportion meta-analysis of cohort-type data from RCTs, downgraded for indirectness (between-study comparisons)

f. High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.

Conditional recommendation; low quality of evidence (for duration: very low quality of evidence)

Quality of Evidence

- **Efficacy of high-dose dual therapy as salvage treatment compared to other regimens: Low QoE.** Evidence from 2 RCTs from Europe, downgraded for imprecision (small number of events) and study limitations (performance bias due to lack of blinding; selection bias due to unclear allocation concealment).
- **Absolute efficacy of high-dose dual therapy as salvage treatment: Low QoE.** Evidence from cohort-type data from 2 RCTs
- **Duration of 14 days for high-dose dual therapy as salvage treatment: Very Low QoE.** Evidence from cohort-type

data from 2 RCTs, downgraded for indirectness (both studies assessed 14-day regimens)

Question 9: When should penicillin allergy testing be considered in patients with *H. pylori* infection?

Most patients with a history of penicillin allergy do not have true penicillin hypersensitivity. After failure of first-line therapy, such patients should be considered for referral for allergy testing since the vast majority can ultimately be safely given amoxicillin-containing salvage regimens.

Strong recommendation; Low quality of evidence

Quality of Evidence

- **Low** QoE. Evidence from observational studies