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CLINICAL PRACTICE GUIDELINES

Indications, diagnostic tests and *Helicobacter pylori* eradication therapy. Recommendations by the 2nd Spanish Consensus Conference

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ABSTRACT

The results of the 2nd Spanish Consensus Conference for appropriate practice regarding indications for eradication, diagnostic tests, and therapy regimens for *Helicobacter pylori* infection are summarized. The Conference was based on literature searches in Medline, abstracts from three international meetings, and abstracts from national meetings. Results were agreed upon and approved by the whole group. Results are supplemented by evidence grades and recommendation levels according to the classification used in the Clinical Practice Guidelines issued by Cochrane Collaboration.

Convincing indications (peptic ulcer, duodenal erosions with no history of ASA or NSAIDs, MALT lymphoma), and not so convincing indications (functional dyspepsia, patients receiving low-dose ASA for platelet aggregation, gastrectomy stump in patients operated on for gastric cancer, first-degree relatives of patients with gastric cancer, lymphocytic gastritis, and Ménétrier's disease) for *H. pylori* eradication are discussed.

Diagnostic recommendations for various clinical conditions (peptic ulcer, digestive hemorrhage secondary to ulcer, eradication control, patients currently or recently receiving antibiotic or antisecretory therapy), as well as diagnostic tests requiring biopsy collection (histology, urease fast test, and culture) when endoscopy is needed for clinical diagnosis, and non-invasive tests requiring no biopsy collection (^{13}C-urea breath test, serologic tests, and fecal antigen tests) when endoscopy is not needed are also discussed.

As regards treatment, first-choice therapies (triple therapy using a PPI and two antibiotics), therapy length, quadruple therapy, and a number of novel antibiotic options as "rescue" therapy are prioritized, the fact that prolonging PPI therapy following effective eradication is unnecessary for patients with duodenal ulcer but not for all gastric ulcers is documented, the fact that cultures and antibiograms are not needed for all eradicating therapies is indicated, and finally the test and treat strategy is considered adequate, however only under certain circumstances.

Key words: Amoxicillin. Clarithromycin. Diagnosis. Eradication. Esomeprazole. *Helicobacter pylori*. Indications for eradication. Proton pump inhibitors (PPIs). Lansoprazole. Metronidazole. Omeprazole. Pantoprazole. Rabeprazole. Ranitidine-bismuth citrate. Therapy.

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ABBREVIATIONS

Helicobacter pylori (H. pylori), Urea Breath Test (UBT), Proton Pump Inhibitor (PPI), 95% Confidence Interval (95% CI), Odds Ratio (OR), Ranitidine-Bismuth Citrate (RB), acetilsalicilic acid (ASA).

INTRODUCTION

Helicobacter pylori (H. pylori) infection plays a relevant role in a number of gastric conditions, and possibly a less convincing part in other diseases. It is for this reason that agreeing on indications for eradication, most appropriate diagnostic tests, and better eradicating drugs is of clinical significance. Therefore, it is only natural that various consensus conferences on these issues have been held in America (1-4), Europe (5) and Asia (6). In 1999, the "Club Español para el Estudio de *Helicobacter pylori*" organized the 1st Spanish Consensus Conference on this infection, and their conclusions have already been reported (7,8). Five years later, in November 2004, the 2nd Consensus Conference on *H. pylori* infection has taken place with the following aims:

1st. To establish accurate indications regarding diagnosis and therapy.

2nd. To rationalize the use of the various diagnostic tests for infection.

3rd. To evaluate the most appropriate therapy for *H. pylori* infection.

All this was based on a methodology similar to that used 5 years before, a systematic literature review, and a subsequent joint debriefing. Furthermore, evidence grades and recommendation levels have been established in this conference, which had not been considered in the previous consensus.

METHODOLOGY

A literature search was performed including the Medline database, and abstracts from the following international meetings: International Workshop on Gastroduodenal Pathology & *H. pylori,* United European Gastroenterology Week, and American Digestive Disease Week. To answer specific questions (efficacy of given therapy or possibilities for easier diagnosis in Spain), reports at national congresses and meetings were also reviewed. Since many of the questions posed had already been reviewed during the 1st Consensus Conference, new evidence supporting existing recommendations or modifications thereof will be emphasized.

Results from the systematic review will include a grading of scientific evidence supporting statements according to the categorization used in the Clinical Practice Guidelines jointly issued by the Cochrane Collaboration (9). In summary, evidence levels go from grade 1 –supported by multiple clinical trials with homogeneous results or at least a meta-analysis– to grade 5 –based only on expert views on the issue or studies of uncertain reliability (Table I). Recommendation grade A –the highest, considered highly recommendable– corresponds to level-1 studies. Recommendation grade B –meaning a favorable recommendation– corresponds to level-2 or -3 studies or evidence, or extrapolations from level-1 studies. Recommendation grade C –interpreted as an inconclusive favorable recommendation– corresponds to level-4 studies or extrapolations from level-2 or -3 studies. Finally, recommendation grade D –which neither recommends nor disapproves of an intervention– corresponds to level-5 studies, or to inconclusive or inconsistent studies at any level.

Table I. Scientific evidence levels and recommendation grades

Recommendation grade	*Evidence level*	*Source*
A	1a	Systematic review of randomized clinical trials, with homogeneity (including studies with comparable results in the same direction)
	1b	Individual randomized clinical trial (with narrow confidence intervals)
	1c	Efficacy demonstrated by clinical practice rather than by experimetation
B	2a	Systematic review of cohort studies, with homogeneity (including studies with comparable results in the same direction)
	2b	Individual cohort study and poor-quality randomized clinical trials (< 80% follow-up)
	2c	Health outcomes research, echological studies
	3a	Systematic review of case-control studies, with homogeneity (including studies with comparable results in the same direction)
	3b	Individual case-control study
C	4	Case series and poor-quality cohort and case-control studies
D	5	Expert opinions with no explicit critical assessment

PARTICIPANTS

Grupo Conferencia Española de Consenso sobre *Helicobacter pylori* included: J. I. Arenas (San Sebastián), F. Bermejo (Madrid), M. Bixquert (Valencia), D. Boixeda (Madrid), F. Borda (Pamplona), L. Bujanda (San Sebastián), A. Caballero (Granada), X. Calvet (Barcelona), R. Cantón (Madrid), F. Carballo (Murcia), M. Castro (Seville), M. Díaz-Rubio (Madrid), E. Domínguez-Muñoz (Santiago), J. Ducons (Huesca), I. Elizalde (Barcelona), M. Forné (Terrassa), E. Gené (Barcelona), J. P. Gisbert (Madrid), F. Gomollón (Saragossa), J. M. Herrerías (Seville), S. Khorrami (Madrid), A. Lanas (Saragossa), C. Martín de Argila (Madrid), M. J. Martínez (Madrid), J. Monés (Barcelona), C. Montalbán (Madrid), M. Montoro (Huesca), J. M. Pajares (Madrid), J.M. Piqué (Barcelona), M. Rodríguez-Téllez (Seville), R. Sáinz-Samitier (Saragossa), F. Sancho (Barcelona), S. Santolaria (Huesca), C. Taxonera (Madrid), J. Torrado (San Sebastián), J. Valdepérez (Saragossa).

CONSENSUS CONFERENCE STRUCTURE

The steering committee of "Spanish group for the study of *H. pylori* infection" appointed a general coordinator (Dr. Joan Monés) and three workgroups with their corresponding heads:

1st. Indications for diagnosis and eradication (Dr. Fernando Borda).

2nd. Infection diagnosis (Dr. Enrique Domínguez-Muñoz).

3rd. Infection therapy (Dr. Javier P. Gisbert).

All participants were included in one of the three groups; each group manager developed questions on their

corresponding topic, which were then answered via e-mail by all group members. The level of consensus required to directly proceed to the plenary session was greater than 80%. Answers failing to reach this level of accord were debated in a workshop prior to the plenary session and, eventually, their approval.

Each of the situations and questions posed in the aforementioned consensus meeting, together with their answers as approved during the plenary session, are discussed below.

1st INDICATIONS FOR DIAGNOSIS AND ERADICATION

Is *Helicobacter pylori* eradication indicated for functional dyspepsia?

Patients with dyspeptic symptoms in whom gastroscopy demonstrates no significant macroscopic condition are diagnosed with functional dyspepsia. The indication of *H. pylori* eradication is controversial in these subjects. Literature references are many, but contradictory (10-12). Meta-analyses only show a moderate 4-15% clinical benefit in patients undergoing eradication when compared to control subjects (12). The dyspeptic subgroup likely to benefit from eradicating therapy is poorly defined, and may in addition correspond to patients with ulcer in whom no lesion was identified at endoscopy. In dyspeptic patients failing to improve following a symptomatic therapy course using proton pump inhibitors (PPIs) and/or prokinetic agents, an indication of eradicating therapy is considered acceptable, which represents an extension of therapeutic criteria as agreed upon at the previous consensus meeting back in 1999.

In summary:
—Eradication is not indicated for patients with functional dyspepsia, but eradicating therapy is considered acceptable for patients with persisting manifestations following a symptomatic therapy course using PPIs and/or prokinetic agents.
(Recommendation grade: C; Evidence level: 4).

Is *Helicobacter pylori* eradication indicated for gastric and duodenal ulcer?

There is currently extensive scientific evidence available that in patients with gastric or duodenal ulcer *H. pylori* eradication results in lesion healing, and dramatically reduces both relapse (13) and complications (hemorrhage and perforation). An indication for eradication is recommended in both active and asymptomatic ulcers, provided they have been properly documented before. Such evidence will be dealt with in greater depth in the therapy section.

In summary:
—H. pylori eradication is indicated for all patients with well-documented, active or asymptomatic gastric or duodenal ulcer, both with and without complications.
(Recommendation grade: A; Evidence level: 1a).

Is *Helicobacter pylori* eradication indicated for patients with duodenal and gastric erosions receiving no ASA or NSAIDs?

In patients not receiving aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) erosive duodenitis may be considered within the spectrum of duodenal ulcerative disease, and eradication is therefore recommended (7,8). Gastric erosions may represent a heterogeneous group of lesions varying in extension, number and even underlying histologic changes, and scientific evidence available is insufficient to support an indication for eradication.

In summary:
—Eradicating therapy is indicated for duodenal but not gastric erosions.
(Recommendation grade: B; Evidence level: 2b).

Is *Helicobacter pylori* eradication indicated for patients receiving non-steroidal anti-inflammatory drugs (NSAIDs), aspirin (ASA) or COX-2 specific inhibitors (coxibs)?

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used in the treatment of rheumatic disease (arthritis and osteoarthritis), and sporadically for headaches and menstrual pain as well. NSAIDs are highly effective in these indications, and give rise to 100 million prescriptions/year in the USA. However, their use is clearly restricted –particularly in the long run– by side effects, specifically gastrointestinal and renal toxicity (14).

A meta-analysis of 18 epidemiologic studies (15) demonstrated that patients receiving NSAIDs have a 3.8% relative risk (RR) of severe gastrointestinal complications. Differences exist depending on age (patients with 65-80 years of age have a 4-5-fold increased risk *versus* patients with 25-50 years of age), and a history of peptic ulcer entails a 6-fold increased risk, this risk growing to 15 times higher for complicated ulcers (hemorrhage or perforation). Another study (16) recorded gastrointestinal symptoms in patients receiving celecoxib (n = 68,939), ibuprofen (n = 71,456) or naproxen (n = 50,014) for the first time, with an incidence of gastrointestinal symptoms equal to 0.46 patients-day for celecoxib, 0.70 for ibuprofen, and 0.62 for naproxen. However, as recently noted, increased cardiologic problems in relation to coxibs must be considered.

Most peptic ulcers are associated with *H. pylori* infection or NSAIDs, and synergy has been suggested for these factors (17), which raises a possibility that eradication be protective regarding NSAID aggression. A group of patients with *H. pylori* + arthritis and no peptic ulcer received diclofenac, and gastric mucosal integrity was assessed at 1 month using endoscopy. *H. pylori* was eradicated in 161 patients, and 171 patients were treated with placebo. In the eradication group 2 (1.2%) ulcers were seen, *versus* 10 (5.8%) ulcers in the placebo group ($p = 0.03$). However, in a similarly designed subsequent study (18) no differences were seen (7% NSAID-related ulcers in eradicated patients *versus* 9% in the placebo group).

A limited but properly performed study (19) evaluates the protection of the eradicating effect *versus* omeprazole 20 mg/day for the prevention of hemorrhagic relapse in patients with a previous UGB episode undergoing therapy with naproxen 500 mg/12 hours for 6 months. Bleeding relapsed in 17% of the eradicated group *versus* 4% of the omeprazole group, with significant differences favoring omeprazole therpay. However, eradication was effective and showed no differences *versus* omeprazole in patients treated with low-dose aspirin (bleeding relapse in around 1% for both groups).

In summary:

—Non-selective NSAIDs: eradication for gastroprotection in not recommended. Once therapy with NSAIDs has been completed, eradication will follow in patients with a history of ulcer or who developed ulcer during the course of their therapy with NSAIDs.

(Recommendation grade: A; Evidence level: 1c).

—Low-dose ASA and COXIB: eradication is recommended for patients with risk factors such as a previous history of ulcer or of gastrointestinal bleeding.

(Recommendation grade: B; Evidence level: 3a).

Is eradication indicated for patients with gastroesophageal reflux disease (GERD)?

H. pylori infection is less prevalent in patients with GERD than in controls (20), and eradication increases reflux in a number of patients, both *"de novo"* and by worsening pre-existing levels (21). Therefore, H. pylori eradication is not advisable for patients with GERD in the absence of other gastroduodenal condition. When a patient with GERD also has a gastric or bulbar ulcer, the benefit of eradication for his or her ulcer is far greater than the potential but unproven adverse effect on reflux.

It was postulated that patients with GERD and *H. pylori* infection undergoing long-term maintenance therapy with a PPI developed more severe gastric mucosal atrophy (22) (a manifestation with pre-malignant connotations), and hence eradication was suggested. However, subsequent studies would not confirm this (23), and a clear stance on this topic remains to be taken (24).

In summary:

—Eradication is not indicated for patients with GERD and H. pylori infection in the absence of other gastroduodenal condition.

—Eradication is indicated for the association of GERD with peptic ulcer.

(Recommendation grade: A; Evidence level: 1b).

—Maintenance therapy with PPIs is not an indication for eradicating therapy.

(Recommendation grade: B; Evidence level: 1c).

Is *Helicobacter pylori* eradication indicated for gastritis or the prevention of gastric cancer?

H. pylori infection leads to chronic gastritis, and the following usually incomplete sequence is widely accepted: superficial chronic gastritis –atrophic chronic gastritis– intestinal metaplasia –dysplasia– cancer. Eradicating therapy causes a regression of histologic lesions, and hence it would be theoretically possible to prophylactically target gastric cancer by eradicating this germ in infected patients, most of them asymptomatic (25). Given the prevalence of *H. pylori* worldwide, this measure to prevent gastric cancer is simply not feasible, with an unadvisable yield in terms of its cost-benefit ratio. Regarding the possibility of treating only patients with atrophic gastritis and intestinal metaplasia, data suggesting that pre-neoplastic lesions may regress following eradication remain inconclusive (26). In view of this lack of evidence and the high number of therapies needed, systematic eradication cannot be recommended. In contrast, eradication might be indicated for some uncommon conditions (lymphocytic gastritis or Ménétrier's disease) despite evidence on its scarce usefulness. Eradication is also recommended for patients undergoing partial gastrectomy for gastric cancer and *H. pylori* infection to prevent recurrence in the stump.

An excellent study (27) posed a new indication for eradication. First-grade relatives of patients with gastric cancer have a higher hypochlorhydria rate when compared to controls (27 *vs.* 3%), and a similar *H. pylori* prevalence (63%). They also have a greater prevalence of mucosal atrophy (34%) when compared to patients with functional dyspepsia (5%). Germ eradication solved mucosal inflammation, and both hypochlorhydria and atrophy resolved in 50% of patients. The conclusion was that first-grade relatives of patients with gastric cancer had a greater prevalence of mucosal abnormalities with a well-known malignant potential, but only those infected by *H. pylori.* Indicating eradication in this set of subjects seems only logical for the prevention of gastric cancer.

In summary:

—Eradication is not recommended for chronic gastritis. Regarding atrophic gastritis and intestinal metaplasia no evidence supports eradication, but this would seem a reasonable option for intestinal metaplasia with high-risk histological criteria.
(Recommendation grade: C; Evidence level: 4).

—Eradication may be recommended for lymphocytic gastritis and Ménétrier's disease.
(Recommendation grade: C; Evidence level: 4).

—Eradication is recommended for gastrectomy stumps in patients operated on for gastric cancer, and for first-grade relatives of patients with gastric cancer.
(Recommendation grade: C; Evidence level: 4).

Is *Helicobacter pylori* eradication indicated for gastric MALT lymphoma?

In controlled studies, patients with low-grade MALT lymphoma (*H. pylori* has been found in more than 90% of these lymphomas) had tumor regression following eradication. In one study (28) up to 80% of patients were healed provided the mucosa alone is involved, with this figure reaching up to 50% for submucosal involvement and 25% for cases with muscular or serosal disease, involvement depth being diagnosed in all cases by endoscopy. Therefore, endoscopy is important before an eradicating therapy is indicated, since eradication is likely to cure the malignancy when the mucosa and submucosa alone are involved. Patients with added muscular involvement will also need oncologic therapy.

Thus, *H. pylori* eradication results in total histological remission in most early, low-grade gastric MALT lymphomas (29). Treatment should be administered in specialized centers where echoendoscopy is available, and an extension study, the confirmation of total regression, and adequate long-term follow-up are ensured. For the remaining gastric MALT lymphomas (high-grade, advanced disease), eradication is only a therapy component, and other adjuvant therapies should be used.

In summary:

—Therapy with only H. pylori eradication should be reserved for low-grade, IE-1 stage MALT lymphomas within specialized centers. For the remaining MALT lymphomas other therapies should be used in addition to eradication.
(Recommendation grade: A; Evidence level: 1a).

Is eradication indicated for extraintestinal conditions in relation to *Helicobacter pylori* infection?

A wide number of extraintestinal conditions have been related to *H. pylori* infection –ischemic heart disease, rosacea, idiopathic chronic urticaria, alopecia areata, diabetes mellitus, autoimmune thyroiditis, Sjögren's syndrome, Raynaud's syndrome, Schönlein-Henoch syndrome, migraine, cholelithiasis, hepatic encephalopathy, developmental delay, and/or recurring abdominal pain in children. Results regarding *H. pylori* eradication are in disagreement among studies, and eradication is not recommended by most.

In summary:

—Eradication is not recommended for extraintestinal conditions, that had been related to H. pylori infection.
(Recommendation grade: B; Evidence level: 1c).

2nd DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION

It is presumed that *H. pylori* infection should only be diagnosed when an eradicating therapy is indicated. We currently have a wide variety of methods for the diagnosis of this infection. Since the last Spanish Consensus Conference a great number of papers have been published gaining insight into the understanding, usefulness, and clinical applicability of known diagnostic modalities, while others have dealt with new, recently introduced methods.

The present Consensus Conference has considered two viewpoints regarding diagnostic modalities for *H. pylori* infection: on the one hand, the diagnostic method to use in varying clinical situations; on the other hand, the current role of each individual diagnostic modality.

A. *Regarding diagnosis, agreed-upon recommendations for the following clinical settings will be discussed:*

a) Endoscopic diagnosis of normality and dyspepsia symptoms.
b) Diagnosis of gastric or duodenal ulcer.
c) In gastrointestinal bleeding secondary to peptic ulcer.
d) In patients with a history of peptic ulcer.
e) In the control of infection eradication.
f) In patients currently or recently on antibiotics or antisecretory agents.

B. *Regarding diagnostic modalities, consensus has been reached on the current role of methods based on:*

a) Biopsy collection (histology, rapid urease test, and culture) when endoscopy is required for clinical diagnosis (30,31).
b) Non-invasive methods (^{13}C-urea breath test, serology tests, and fecal antigens test) when endoscopy is not required (32).

A) Diagnosis of *Helicobacter pylori* infection in various clinical situations

a) Should infection be diagnosed in patients with dyspeptic symptoms and a normal endoscopy?

In this situation systematic biopsy collection is not indicated for the diagnosis of *H. pylori* infection.

In summary:
—Diagnostic tests for infection are not indicated in patients with dyspepsia and a normal endoscopy.
(Recommendation grade: A, Evidence level: 1b).

b) How and when should Helicobacter pylori infection be identified in the presence of an endoscopically diagnosed gastric or duodenal ulcer?

The finding of a gastric or duodenal ulcer during upper gastrointestinal endoscopy requires that the presence of *H. pylori* be ruled out. In such situation, it is accepted that the diagnosis of infection be based on modalities performed on biopsy samples (33,34). Endoscopists must take two biopsy samples from the antrum and one from the body.

—Urease test. Rapid urease testing should be first choice because of its simplicity, reliability, economy, and results in just a few hours. It requires a biopsy sample collected from the gastric antrum. A positive rapid urease test confirms infection (35,36).

In summary:
—Rapid urease testing is the modality of choice because of its simplicity, reliability, convenience, and economy.
(Recommendation grade: A; Evidence level: 1b).

—Pathology diagnosis. In case of a negative urease test or because of a study for gastritis, the two remaining biopsy samples (one antral and one from the gastric body) should be sent to the Pathology Dept. for histology (32-34). Naturally, and regardless of *H. pylori* infection, the presence of a gastric ulcer calls for biopsy collection in order to rule out a potential neoplastic nature.

In summary:
—In case of a negative urease test, a study of biopsy samples for the diagnosis of infection is recommended.
(Recommendation grade: A; Evidence level: 1b).

—Breath test. Lastly, given the relevance of *H. pylori* infection in the etiopathogenesis of gastroduodenal peptic ulcer and the effectiveness of eradicating therapy regarding its cure, a negative result in the two aforementioned tests (rapid urease test and histology) requires the use of a ^{13}C-urea breath test before the ulcer's infectious origin can be definitely excluded (37,38).

In summary:
—In case of negative results in the aforementioned diagnostic tests, and due to the clinical relevance of this diagnosis in peptic ulcer, a subsequent breath test is recommended
(Recommendation grade: A; Evidence level: 1c).

c) Which diagnostic methods are to be recommended for upper digestive bleeding secondary to either gastric or duodenal ulcer?

For upper digestive hemorrhage, when endoscopy demonstrates the presence of a gastric or duodenal ulcer, the diagnosis of *H. pylori* infection should be performed during that same endoscopy using the procedure described in the previous section (rapid urease test on an antral biopsy sample, histologic study of an antral sample and a sample from the gastric body), provided the patient's clinical status and blood remnants within the gastric chamber allow it (39-41). Otherwise the diagnosis of infection will be arrived at later using the ^{13}C-urea breath test (42). For gastric ulcer this diagnosis may be performed using biopsy-based methods in any of the necessary subsequent endoscopic monitorings.

In summary:
—Whenever possible (patient status or technical feasibility), acting as in non-bleeding ulcer is recommended. In compromised clinical settings or in case of technical inability (high-volume blood remnants), the diagnosis of infection will be subsequently reached using a breath test for duodenal ulcer, or a biopsy study for gastric ulcer during the mandatory endoscopic monitoring.
(Recommendation grade: A; Evidence level: 1b).

d) What is recommended for the diagnosis of infection in patients with a history of peptic ulcer?

In any patients with a history of previously diagnosed peptic ulcer using adequate modalities, with or without symptoms, the potential presence of *H. pylori* infection should be investigated. Given the fact that no endoscopy is usually needed in this setting, the method of choice for the diagnosis of *H. pylori* is the ^{13}C-urea breath test (31-34,38, 43-45). Should this test be unavailable, *H. pylori* stool antigen quantitation testing is considered an adequate alternative (46-49). Serologic tests are not recommended in view of their scarce positive predictive value (50,51). On the other hand, despite the high prevalence of *H. pylori* infection in peptic ulcer disease, the increasing relevance of other etiologic factors such as ASA and NSAID ingestion ren-

ders the administration of eradicating therapy inappropriate when infection is not confirmed.

In summary:
—In patients with a proven history of peptic ulcer disease, symptomatic or otherwise, H. pylori should be identified using a breath test or, if unavailable, fecal antigen quantitation.
(Recommendation grade: A; Evidence level: 1a).

e) Is the monitoring of eradication results necessary, and which methods should be used?

Effectiveness should be confirmed in all patients undergoing eradication therapy. This monitoring should be performed at least 6 weeks after treatment completion (31-34,44-46,52,53). The test of choice in such cases is the ^{13}C-urea breath test (31-33,45). If unavailable, *H. pylori* stool antigen quantitation may be used alternatively, bearing in mind that only monoclonal tests have shown adequate sensitivity and positive predictive value in this setting (47).

In summary:
—It is recommended that eradication be confirmed by using a breath test or alternatively Helicobacter pylori stool antigen quantitation.
(Recommendation grade: A; Evidence level: 1b).

f) May a diagnosis of Helicobacter pylori infection be reached in patients currently or recently subjected to treatment with antibiotics or antisecretory agents?

Treatment with antibiotics on any grounds entails a significant reduction of *H. pylori* numbers (without reaching eradication, though) in the gastric mucosa, and hence diminished sensitivity for diagnostic tests. On the other hand, PPIs are known to exert an inhibitory effect on the germ's urease activity, which also leads to reduced sensitivity regarding *H. pylori*-related diagnostic tests. Similarly, PPIs cause a migration of germs towards more proximal segments within the stomach. As a result, the diagnosis of infection in patients currently or recently on PPIs or antibiotics requires that this treatment be discontinued for at least 2 and 4 weeks, respectively, beforehand (54,55). Such therapy discontinuation is not required for H_2 antagonists.

In summary:
—In the presence of PPIs or antibiotics diagnostic tests have a reduced sensitivity, and their discontinuation is required within 2 weeks (PPIs) or 4 weeks (antibiotics). Discontinuation is not required for H_2 antagonists.
(Recommendation grade: A; Evidence level: 1b).

B) Diagnostic methods

—Rapid urease test. This is first-choice for the diagnosis of *H. pylori* infection in patients requiring upper gastrointestinal endoscopy (31-36). Rapid urease testing should be performed on a single biopsy sample, preferably from the gastric antrum.

In summary:
—A first-choice test for patients requiring endoscopy.
(Recommendation grade: A; Evidence level: 1b).

—Histology. A histological study of biopsy samples to diagnose infection is indicated for all patients requiring upper digestive endoscopy with a negative urease test. This circumstance takes place mainly in the presence of blood and in patients on antibiotic or antisecretory therapy. The histological diagnosis of *H. pylori* infection should be performed on two biopsy samples, one from the antrum and one from the gastric body. Because of its greater sensitivity, a Giemsa stain is recommended for negative studies using hematoxillin-eosin (31-34,37).

In summary:
—May be recommended for the diagnosis of H. pylori in subjects with negative urease tests.
(Recommendation grade: A; Evidence level: 1b).

—Culture. The culturing of biopsy specimens is most specific, but its complexity, cost, and diagnostic delay have relegated this method from clinical practice (32-34,53). Cultures and antibiograms may be performed on gastric mucosal biopsies when two eradication regimens (primary and salvage treatments) fail in order to study antibiotic resistance. However, this procedure has an uncertain impact in practice (32-34,53), and its use is then restricted to the setting of epidemiologic or clinical investigation trials. Sample collection using the so-called "thread test" is not recommended in view of its higher complexity and risk of contamination by oropharyngeal bacteria (30).

In summary:
—Use not recommended except for investigational studies.
(Recommendation grade: B; Evidence level: 1c).

—^{13}C-urea breath test. ^{13}C-urea breath test has a high diagnostic sensitivity and specificity, as well as a high predictive value, all of them above 95% at any rate (37,38,43-46). It is a simple, non-invasive, low-cost test that may be easily used in clinical practice. It is therefore the test of choice for the diagnosis of *H. pylori* infection in every clinical setting not requiring gastrointestinal endoscopy (primary diagnosis and control following eradication), as well as in patients having undergone endoscopy with a negative rapid urease test and histological

study. Efficacy is limited in patients with low-density colonization (treated with PPIs or antibiotics) (54,55) or gastrectomized, as contact between labelled urea and the gastric mucosa is less likely (56,57).

In summary:
—Test of choice in patients not requiring endoscopy.
(Recommendation grade: A; Evidence level: 1a).

—Serology. The predictive value of serologic tests is very limited, and their application in clinical practice is therefore not recommended (50,51,58). However, its use may be considered for patients not requiring endoscopy as an alternative to the breath and stool antigen tests, when both these tests are unavailable. The primary utility of serologic tests lies in population-based epidemiologic studies. Rapid serologic tests have a low diagnostic yield, and are therefore not recommended (59,60).

In summary:
—Serologic tests are not to be recommended for the diagnosis of Helicobacter pylori infection, except for epidemiologic studies.
(Recommendation grade: C; Evidence level: 1b).

—H. pylori stool antigen test. The diagnostic efficacy of this stool antigen test is high for both the primary diagnosis of *H. pylori* infection and eradication monitoring (sensitivity and specificity of 80-95%). Results are better with monoclonal *versus* polyclonal tests (47-49). Efficacy, as with the ^{13}C-urea breath test, is influenced by low-density colonization as a result of PPI or antibiotic therapy, or of the presence of blood in cases of upper digestive bleeding. The stool antigen test is simple and easy to use in clinical practice, its only limitation being fecal manipulation. As a result, it is considered the most appropriate alternative to ^{13}C-urea breath testing in the diagnosis of *H. pylori* infection.

In summary:
—Stool antigen testing is reliable and appropriate for the diagnosis of H. pylori infection, and is recommended as a second-line option for patients unable to undergo a breath test.
(Recommendation grade: A; Evidence level: 1a).

3rd MANAGEMENT OF *HELICOBACTER PYLORI* INFECTION

May combined ranitidin-bismuth citrate be included among first-choice eradicating therapies as a replacement for PPIs together with two antibiotics?

A recent systematic review of the literature showed a mean *H. pylori* eradication rate of 82% on the intent-to-treat analysis when ranitidin-bismuth citrate (R-BC) was associated with clarithromycin and a nitroimidazole. To date, 15 randomized studies comparing proton pump inhibitors (PPIs) *versus* R-BC together with clarithromycin and amoxicillin have been carried out, and both alternatives have been shown to be equivalent (61). However, when antibiotics used include clarithromycin and a nitroimidazole, a strategy evaluated in 13 studies, a meta-analysis of said studies showed that R-BC is superior to PPIs (61).

In summary:
—The combination R-BC together with two antibiotics may be included among first-choice eradicating therapies.
(Recommendation grade: A; Evidence level: 1a).

What eradicating therapies are considered first-choice in Spain?

The combination of a PPI with clarithromycin and amoxicillin has been most common in Spain. Since the 1st Spanish Consensus Conference numerous data have been reported supporting its first-choice role (62-69). Similarly, as previously suggested, combined R-BC together with two antibiotics may be included among first-choice eradicating therapies. Regarding antibiotics to be combined with both PPIs and R-BC, a recommendation that these should be clarithromycin and amoxicillin is currently favored. Few authors advocate for 1 week of quadruple therapy as first-line treatment (70).

In summary, first-choice regimens recommended in Spain include:
—A PPI (standard dose)/12 h + amoxicillin 1 g/12 h + clarithromycin 500 mg/12 h.
—R-BC 400 mg/12 h together with same antibiotics at same doses.
(Recommendation grade: A; Evidence level: 1a).

—In cases with allergy to penicillin amoxicillin should be replaced by metronidazole 500 mg/12 h; here R-BC should be probably used instead of a PPI.

Are all PPIs equally effective within triple therapies?

The 1st Spanish Consensus Conference concluded that both lansoprazole and pantoprazole were equivalent to omeprazole and therefore may be indistinctly used in triple therapies with two antibiotics. Various studies have been published since then evaluating pantoprazole in greater detail, and considerable experience has been acquired with other, more recent PPIs such as rabeprazole and esomeprazole. Regarding the latter three PPIs, various meta-analyses demonstrating an efficacy similar to that of omeprazole have been reported (71-73).

In summary:

—All PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are equivalent together with two antibiotics for the eradication of H. pylori infection.

(Recommendation grade: A; Evidence level: 1a).

Does previous treatment with a proton pump inhibitor reduce the effectiveness of subsequent triple therapy?

In dual therapy (a PPI plus one antibiotic), which was dropped because of ineffectiveness, a previous treatment with omeprazole was said to be a predictor of failed eradication. However, a previous PPI does not seem to influence eradication rates with triple therapies (74-77).

In summary:

—Previous treatment with a PPI does not reduce the effectiveness of subsequent triple therapies using this antisecretory agent together with two antibiotics.

(Recommendation grade: A; Evidence level: 1a).

Is it necessary to prolong PPI administration in duodenal ulcer following the completion of antibiotic therapy for 7 days?

In initial eradicating therapies PPIs were prolonged for 2-4 additional weeks. However, a high rate of duodenal ulcer healing has been detected with the use of a PPI (plus antibiotics) for one week (78-84). Furthermore, triple therapy for one week not only results in a high healing rate early during treatment, but this rate rises up to virtually 100% on subsequent endoscopic monitoring (a few weeks later), with no need to add any antisecretory agents whatsoever (80, 81, 83-86).

In summary:

—To obtain a high healing rate for duodenal ulcer the use of a PPI (plus two antibiotics) for one week suffices.

(Recommendation grade: A; Evidence level: 1a).

—Despite this, it seems prudent to prescribe a PPI for complicated ulcers (e.g, digestive bleeding) until H. pylori eradication is confirmed.

(Recommendation grade: D; Evidence level: 5).

Is it necessary to prolong PPI administration in gastric ulcer following the completion of antibiotic therapy for 7 days?

It should be highlighted that, in contrast with duodenal ulcer, no studies directly comparing eradicating therapy alone *versus* eradicating therapy followed by PPIs are available for gastric ulcer (87,88). One of the few studies providing relevant information on this topic assessed gastric ulcer healing as a function of ulcer size upon the administration of a PPI plus two antibiotics for one week, and reported that said therapy was enough to promote healing in approximately 90% of small gastric ulcers (smaller than 1 cm) (89). However, the healing rate exponentially decreased with ulcer size increases (89).

In summary:

—The small evidence available suggests that following eradicating therapy completion antisecretory therapy should be prolonged (e.g., between 4 and 8 additional weeks) in large-size gastric ulcers (> 1 cm). However, eradicating therapy without prolonged antisecretory treatment afterwards may suffice for small-size (≤ 1 cm) gastric ulcers.

(Recommendation grade: C; Evidence level: 4).

How long should eradicating therapy last when a proton pump inhibitor and two antibiotics are used?

It has been recently suggested that eradicating therapy is more effective in patients with ulcer, which could bring up the sufficiency of shorter therapy regimens (90-93). On the contrary, patients with functional dyspepsia seem to respond worse to eradicating therapy, and hence could benefit from prolonged therapy regimens (91-93). In this regard a Spanish multicenter study has just been completed where eradicating therapy with a PPI, clarithromycin and amoxicillin for 7 *versus* 10 days has been compared in a large group of patients using a randomized design (94). In patients with ulcer differences seen between both regimens were minimal, whereas the longest regimen proved obviously superior in patients with functional dyspepsia (94). On the other hand a financial analysis showed that therapy for 10 days is more cost-effective in patients with functional dyspepsia; however, prolonged therapy is no cost-effective strategy for patients with ulcer (95).

In summary:

—Seven days is the most cost-effective duration for triple therapies (PPI, clarithromycin, amoxicillin) in the eradication of H. pylori in patients with gastric or duodenal ulcer.

(Recommendation grade: B; Evidence level: 2c).

—Lengthy regimens (10 days) have proven more cost-effective in our setting for the treatment of H. pylori infection in patients with functional dyspepsia.

(Recommendation grades: B; Evidence level: 2c).

Are cultures (and antibiograms) necessary prior to the administration of a first course of eradicating therapy?

Prior cultures are not necessary in clinical practice, since empirical treatment (i.e., with no antibiogram) achieves *H. pylori* eradication in a high percentage of patients, namely 80-90% (96).

In summary:
—Cultures are not necessary in standard clinical practice before a first course of eradicating therapy.
(Recommendation grade: A; Evidence level: 1a).

Are cultures (and antibiograms) neccessary prior to a second course of eradicating therapy following a failed initial attempt?

Cultures are also unnecessary before a second course of eradicating therapy following a failed initial regimen because of the high effectiveness of empirical quadruple therapy (97-110). Therefore, considering overall results following this second attempt, a cumulative eradication rate approaching 100% is obtained (97), a percentage resulting from the addition of the mean eradication rate –85%– achieved by the first course of eradicating therapy to that of the quadruple salvage therapy –around 80%.

In summary:
—Cultures do not seem systematically necessary before a second course of therapy is administered following a failed initial attempt.
(Recommendation grade: A; Evidence level: 1c).

It is recommended that a number of specially devoted centers routinely perform cultures, in order to study the incidence of resistance following failed eradication, and to assess the influence of resistance on salvage therapy.

What salvage therapy should be used following a failed first attempt with a PPI, claritromycin and amoxicillin?

Various studies have assessed quadruple therapy using a PPI, bismuth, tetracycline and metronidazole in view of failed attempts with a PPI, clarithromycin and amoxicillin (98-110). Results with this strategy are promising, with a mean eradicating efficacy of 80%. More recently the substitution of R-BC for the PPI and bismuth compound in the quadruple salvage regimen has been seen to be associated with encouraging results (103,111-113), with the advantage that fewer drugs are required and dosage is simpler.

In summary:
—Following a failed attempt with a PPI, clarithromycin and amoxicillin a quadruple regimen is recommended for 7 days using: a PPI (at standard doses every 12 hours); bismuth subcitrate, 120 mg every 6 hours; tetracycline, 500 mg every 6 hours; and metronidazole, 500 mg every 8 hours. Substituting R-BC for the PPI and bismuth compound in the quadruple regimen is a valid option.
(Recommendation grade: A; Evidence level: 1a).

What is to be done when two eradication attempts fail (the first one using a PPI, clarithromycin and amoxicillin; the second attempt using quadruple therapy)? Are cultures necessary prior to a third eradicating attempt?

When two eradicating treatments fail a first option is obviously to perform cultures and an antibiogram, in order to select the most appropriate antibiotic regimen according to bacterial susceptibility. While this "targeted" treatment option is most recommended, its usefulness has not been sufficiently confirmed in clinical practice. On the other hand, there are reasons to hold back cultures before a third eradicating therapy course, and to recommend a new empirical treatment instead (114). No antibiotics previously used should be repeated for empirical treatment, since resistance to clarithromycin and metronidazole is known to arise in most cases when a combination including these two drugs fails. Therefore, none of the antibiotics to which *H. pylori* may have developed resistance should be used.

Thus, when a third empirical therapy course –bar clarithromycin and metronidazole– is to be administered, the following options are available:

—Rifabutin: combinations based on rifabutin represent a promising alternative, since *H. pylori* has proven highly susceptible to this antibiotic *in vitro* (115-120). On the other hand, and even more importantly, no *H. pylori* strains resistant to rifabutin have been isolated so far (121). However, a number of isolated myelotoxicity events have been reported, which underscores the need to be on the alert when this novel drug is administered.

—Levofloxacin: it is highly active against *H. pylori in vitro,* and primary resistance to this antibiotic is very rare (122,123).

—Furazolidone: it has shown a high antimicrobial activity against *H. pylori* in monotherapy, and resistance to furazolidone is almost non-existant (124). However, since experience with drugs used in third-line combinations is still limited and somehow relevant adverse effects have already been reported, it seems advisable that their assessment be performed by experienced teams specializing in this subject.

In summary:
—Although cultures and antibiograms have been usually recommended to select an appropriate antimi-

crobial combination following the failure of two eradicating treatments, another equally valid option is the use of a new empirical therapy with no prior culture, provided antibiotics not used in the two previous attempts are again employed.

(Recommendation grade: C; Evidence level: 4).

In patients having suffered from gastroduodenal ulcer-related bleeding, should a maintenance therapy course with antisecretory agents be used following the eradication of *Helicobacter pylori* infection?

Peptic ulcer is the main cause of upper gastrointestinal bleeding, and *H. pylori* infection is the main etiologic factor of gastroduodenal ulcer disease. Long-term maintenance antisecretory therapy has been a standard for the prevention of hemorrhagic recurrence in patients with a prior digestive bleeding episode from peptic ulcer. A systematic review and a meta-analysis have been published of late according to the Cochrane Collaboration's methodology, and they show that treatment for *H. pylori* infection is more effective than antisecretory therapy (either with or without maintenance antisecretory agents) for the prevention of bleeding recurrence from peptic ulcer (125,126). Based on the studies assessing the incidence of hemorrhagic recurrence following successful *H. pylori* eradication –with no subsequent maintenance antisecretory therapy– a yearly recurrence rate of only 0.78% (per patient and year of follow-up) may be estimated (125,126).

In summary:

—Eradicating therapy is more effective than antisecretory therapy for the prevention of bleeding recurrence from peptic ulcer. The presence of H. pylori infection should be therefore evaluated in all patients with peptic ulcer-related digestive bleeding, and an eradicating therapy course should be prescribed for those infected.

—Once eradication is confirmed, maintenance therapy with antisecretory agents is not required (if the patient receives no NSAIDs), as H. pylori eradication prevents nearly all bleeding recurrences.

(Recommendation grade: A; Evidence level: 1a).

May the "test and treat" strategy be recommended for dyspeptic patients in our setting?

There is no consensus regarding the initial diagnostic or therapeutic alternative of choice for young patients (cut-off age is usually 50 years) with dyspepsia and no symptoms or alert signs. Three strategies may be considered:

a) Initial endoscopy.

b) Empirical antisecretory therapy, or

c) *"Test and treat"* strategy.

The latter option entails an "indirect" test not requiring endoscopy (preferentially a breath test) for the diagnosis of *H. pylori* infection, and subsequent eradicating therapy when *H. pylori* is demonstrated (127). The *"test and treat"* strategy has been recommended by most Clinical Practice Guidelines and Consensus Conferences in young dyspeptic patients (younger than 50 years) with no symptoms or alert signs (128-131).

—"Test and treat" versus *initial endoscopy:* a recent review by the Cochrane Collaboration (132) identified four studies comparing the *"test and treat"* strategy *versus* initial endoscopy (133-136). A meta-analysis of these studies showed that therapeutic effectiveness was similar with both strategies, and the saving of endoscopies with the former option was around 70% (132). Following this review other authors confirmed these findings (137-139). It may be then concluded that the "test and treat" strategy is as effective as initial endoscopy in the management of uninvestigated dyspepsia, and reduces the number of endoscopies. In addition, a considerable number of cost-effectiveness analyses have been reported, which compared the *"test and treat"* strategy *versus* endoscopy; all of them agree that the former is notably more cost-effective than the latter (140). In summary, it may be concluded that the "test and treat" strategy is more cost-effective than initial endoscopy.

In summary:

—The "test and treat" strategy is as effective as initial endoscopy in patients with dyspepsia and no symptoms or alert signs, and reduces the number of endoscopies.

(Recommendation grade: A; Evidence level: 1b).

—The "test and treat" strategy is as effective as initial endoscopy in patients with dyspepsia and no symptoms or alert signs, and has a better cost-effectiveness ratio.

(Recommendation grade: B; Evidence level: 2c).

—"Test and treat" versus antisecretory therapy: three clinical trials of randomized design compared eradicating therapy *versus* antisecretory therapy in patients with dyspepsia and *H. pylori* infection. All of them showed a decrease in symptoms recurrence, as well as reduced dyspeptic symptoms and improved quality of life following the first treatment (141-143). One study (144) compared the *"test and treat"* strategy *versus* empirical antisecretory therapy in patients with uninvestigated dyspepsia, and concluded that the former option is more effective than the latter.

In summary:

—The "test and treat" strategy is more effective than antisecretory therapy in patients with dyspepsia and H. pylori infection.

(Recommendation grade: A; Evidence level: 1b).

Breath testing is to be preferred to serology for the study of *H. pylori* in the *"test and treat"* strategy. *H. pylori* stool antigen testing, a procedure that has demonstrated high accuracy in the diagnosis of infection before eradicating therapy, may represent a valid alternative, but further studies to validate it within the "test and treat" strategy are needed.

Multiple cost-effectiveness studies have shown that, under conditions of moderate to high *H. pylori* prevalence, the *"test and treat"* strategy is more cost-effective than antisecretory therapy (140). In contrast, initial empirical antisecretory therapy is more cost-effective when the prevalence of *H. pylori* infection falls below 15-20% (145). In our country, the prevalence of *H. pylori* infection in dyspeptic patients is around 60% (146), approximately 20% of patients undergoing early endoscopy for dyspepsia have ulcer disease, and this ratio goes up to 30% when only those infected with *H. pylori* are considered (140). Under such conditions, it may be obviously concluded that in our setting the "test and treat" strategy would be more cost-effective than empirical antisecretory therapy. Results obtained in other countries are difficult to extrapolate, notwithstanding, and factors on which the conclusion of whether this novel approach is appropriate for individual geographic areas are many (127).

In summary:

It may be concluded that, despite a need for further studies in our setting, the "test and treat" *strategy may be recommended as a reasonable, valid option for Spanish dyspeptic patients. However, an initial endoscopy needs to be performed in all patients with alert signs or symptoms, or in patients older than a certain age (e.g., 50 years) with new-onset dyspepsia* (127,140,147,148).

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