

Management of *Helicobacter pylori* infection in Latin America: A Delphi technique-based consensus

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Abstract

AIM: To optimize diagnosis and treatment guidelines for this geographic region, a panel of gastroenterologists, epidemiologists, and basic scientists carried out a structured evaluation of available literature.

METHODS: Relevant questions were distributed among the experts, who generated draft statements for consideration by the entire panel. A modified three-round Delphi technique method was used to reach consensus. Critical input was also obtained from representatives of the concerned medical community. The quality of the evidence and level of recommendation supporting each statement was graded according to United States Preventive Services Task Force criteria.

RESULTS: A group of ten experts was established. The survey included 15 open-ended questions that were distributed among the experts, who assessed the articles associated with each question. The levels of agreement achieved by the panel were 50% in the first round, 73.3% in the second round and 100% in the third round. Main consensus recommendations included: (1) when available, urea breath and stool antigen test (HpSA) should be used for non-invasive diagnosis; (2) detect and eradicate *Helicobacter pylori* (*H. pylori*) in all gastroscopy patients to decrease risk of peptic ulcer disease, prevent or retard progression in patients with preneoplastic lesions, and to prevent recurrence in patients treated for gastric cancer; (3) further investigate implementation issues and health outcomes of *H. pylori*

eradication for primary prevention of gastric cancer in high-risk populations; (4) prescribe standard 14-d triple therapy or sequential therapy for first-line treatment; (5) routinely assess eradication success post-treatment in clinical settings; and (6) select second- and third-line therapies according to antibiotic susceptibility testing.

CONCLUSION: These achievable steps toward better region-specific management can be expected to improve clinical health outcomes.

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Key words: *Helicobacter pylori*; Consensus development conference; Delphi technique; Latin America

Core tip: By means of Delphi technique method, a multidisciplinary panel of Latin American experts releases a set of updated recommendations on diagnosis and treatment of *Helicobacter pylori* (*H. pylori*) infection for this region. Main recommendations include test and treat all symptomatic patients submitted to gastroscopy, use 14-d triple therapy or sequential therapy for first-line treatment, and to promote more information and demonstration projects to identify effective and safe strategies for control and prevention in areas with high prevalence of *H. pylori* infection and associated diseases.

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INTRODUCTION

Latin America has a high burden of *Helicobacter pylori* (*H. pylori*) infection and associated diseases, particularly gastric cancer (GC). Clinical and public health management of this common bacterial infection needs to be adapted to different epidemiological situations. The last (and only) Latin-American Consensus Conference on *H. pylori* infection, published more than a decade ago, provided regional guidance for diagnosis and treatment^[1]. Since then, important information has been gained on the role of *H. pylori* eradication in primary and secondary prevention of GC, availability of new diagnostic tests, decreasing efficacy of common antibiotic schemes and novel treatment approaches. A working group was convened to generate updated recommendations.

MATERIALS AND METHODS

Participants and evidence collection

Under the sponsorship of the Chilean Society of Gastroenterology (<http://sociedadgastro.cl>), the consensus

organizing committee assembled a multidisciplinary group of adult and pediatric gastroenterologists, epidemiologists and basic scientists with expertise in various aspects of *H. pylori* infection and associated diseases, and evidence-based medicine. They were selected from a group of regional investigators particularly interested on *H. pylori* infection that had previously participated in a series of International Latin American Symposia on this topic. The organizing committee generated a list of questions relevant for Latin American countries related to diagnosis, long-term consequences and treatment of *H. pylori* infection. To address these questions, a member of the panel (RC) performed separate searches in PubMed® (United States National Library of Medicine, Bethesda, Maryland), retrieving reports published in English or Spanish up to May 2013. Search results were distributed and further supplemented as appropriate by individual panelists with data from regional databases (LILACS®, Latin America and the Caribbean Literature on Health Sciences, and SciELO®, Scientific Electronic Library Online), and abstracts presented at Latin American meetings. Each expert was required to answer one to three questions and to provide draft recommendation statements with rationales for consideration by all of the panelists. The quality of the evidence (Table 1) and the level of recommendation (Table 2) were graded following United States Preventive Services Task Force criteria^[2,3].

Generation of the consensus

A modified three-round Delphi technique method^[4] was used to reach consensus. Initial draft recommendation statements were compiled by the committee and distributed to the entire panel for the first assessment of agreement. A Likert-type scale (1, totally disagree; 2, disagree; 3, uncertain or with objections; 4, agree; and 5, totally agree) was used to measure agreement. In cases of disagreement or uncertainty (*i.e.*, score less than or equal to 3), panelists were required to submit comments and proposed changes. Recommendations were revised incorporating these opinions and returned to topic area experts for confirmation or reformulation. The updated statements were then judged by the entire panel as the second-round. In order to allow critical input from representatives of the concerned medical community, the recommendations were also presented to the roughly 400 gastroenterologists attending the XXXIX Chilean Congress of Gastroenterology and V International Symposium on *H. pylori* Infection in Viña del Mar, Chile, November 2012. The audience voted in real-time and provided additional oral comments. Final recommendations were revised as necessary to incorporate the public feedback, and translated from Spanish into English, for the third-round vote by the expert panel. Approved recommendations (*i.e.*, those with average score ≥ 4 on the Likert scale) are presented below.

RESULTS

What is the best use of noninvasive tests for the diagnosis of *H. pylori* infection?

Urea breath test: The consensus statement as follows: (1)

Table 1 Levels of evidence according to the study design^[3]

Level of evidence	Description
Type I	Evidence obtained at least from one well-designed, randomized, controlled ¹ trial or from a systematic review of randomized clinical studies
Type II	II-1 Evidence obtained from non-randomized, prospective, controlled ¹ studies II-2 Evidence obtained from cohort observational studies ² or case-control studies, preferably multi-centric II-3 Evidence obtained from case series
Type III	Opinion of authorities on the subject matter based on expertise, expert committees, case reports, patho-physiological studies or basic science studies

¹A controlled study is a study where the intervention is managed by the researcher; ²An observational study is a study where the intervention is not controlled by the researcher.

Table 2 Levels of recommendation according to the available evidence^[3]

Recommendation	Description
A	The Consensus strongly recommends the mentioned intervention or service. This recommendation is based on high quality evidence, with a benefit that significantly exceeds the risks
B	The Consensus recommends the regular clinical use of the mentioned intervention or service. This recommendation is based on moderate quality evidence, with a benefit that exceeds the risks
C	The Consensus does not make any positive or negative recommendation regarding the mentioned intervention or service. A categorical recommendation is not provided, because the evidence (of at least moderate quality) does not show a satisfactory risk/benefit relationship. The decision has to be made on a case-by-case basis
D	The Consensus makes a negative recommendation against the mentioned intervention or service. The recommendation is based on at least moderate quality evidence, not showing any benefit or where the risk or damage exceeds the benefits of the intervention
I	The Consensus concludes that the evidence is insufficient, due to low-quality studies, heterogeneous results or because the risk/benefit balance cannot be determined

the urea breath test with ¹³C (¹³C-UBT) is a good non-invasive diagnostic test for *H. pylori* infection in adults, with high accuracy and easy implementation. (Evidence level II-1, grade of recommendation B; Agreement 4.7 ± 0.5); (2) in patients with peptic ulcer disease, when rapid urease test or histology is negative, a ¹³C-UBT can be used to assess the presence of *H. pylori*. (Evidence level II-2, grade of recommendation B; Agreement 4.7 ± 0.5); and (3) the ¹³C-UBT is a good method to confirm *H. pylori* eradication after treatment, both in adults and children, especially in those older than 6 years old. (Evidence level II-2, grade of recommendation B; Agreement 4.7 ± 0.5).

The rationale is that invasive methods are generally accepted to provide superior sensitivity and specificity for diagnosis for *H. pylori* infection. For non-invasive diagnosis, the ¹³C-UBT is well-suited in different clinical situations^[5,6]. Extensive reviews have consistently shown sensitivity between 88%-95% and specificity between 95%-100% using invasive methods as gold standard^[7,8]. Thus, UBT may be used as part of the test-and-treat strategy in adult patients with dyspepsia, and also in epidemiological studies. However, in patients with increased risk of GC, endoscopic diagnosis strategies should be preferred^[5].

Partial gastrectomy hampers the diagnostic accuracy of ¹³C-UBT, dropping the sensitivity to 77% (95%CI: 72%-82%) and specificity to 89% (95%CI: 85%-93%)^[9]. In contrast, the ¹³C-UBT performs well in patients with peptic ulcer bleeding, as suggested by a meta-analysis reporting a sensitivity of 93% (95%CI: 90%-95%) and specificity of 92% (95%CI: 87%-96%)^[10]. When direct endoscopic tests for *H. pylori* infection are negative in patients with ulcer bleeding, a ¹³C-UBT would be a suitable alternative. However, in areas with a high prevalence of *H. pylori* infection and rather low availability of diagnostic tests, such as the Latin American region, empirical *H. pylori* eradication immediately after bleeding would be appropriate and perhaps more cost-effective^[11].

In children with dyspepsia and/or abdominal pain, the test-and-treat strategy has not been validated^[12] and diagnosis of *H. pylori* infection is usually made by endoscopic methods. Moreover, performing UBT is relatively difficult in young children and its diagnostic accuracy is variable under 6 years old^[13]. In children < 2 years of age, the ¹³C-UBT may have false-positive results, requiring adjustments of the cutoff, pretest meal and urea dose. However, a recent meta-analysis^[14] showed good diagnostic accuracy of ¹³C-UBT in pediatric patients (sensitivity 96%, specificity 96%), especially in children > 6 years (sensitivity 97%, specificity 98%), but also in children ≤ 6 years (sensitivity 95%, specificity 94%).

There is extensive evidence from several high quality studies that ¹³C-UBT is an excellent method to confirm eradication of *H. pylori* after antibiotic treatment in both children^[10,13] and adults^[15], despite the variability in the dose of marker, type of food, fasting period, type of analysis and cutoff point.

***H. pylori* HpSA:** The consensus statement as follows: (1) the monoclonal HpSA is an alternative for non-invasive diagnosis of *H. pylori* infection in adults and children, either pre- or post-eradication (Evidence level II-2, grade of recommendation B; Agreement 4.6 ± 0.7); and (2) in patients with peptic ulcer bleeding, the polyclonal HpSA could be considered for diagnosis of *H. pylori* infection after a negative direct test (Evidence level II-2, grade of recommendation C; Agreement 4.6 ± 0.7).

The rationale is that a meta-analysis of 22 observational studies comprising 2499 patients evaluated the accuracy of monoclonal HpSA for the initial diagnosis

of *H. pylori*^[16]. Sensitivity was 94% (95%CI: 93%-95%), specificity 97% (95%CI: 96%-98%), positive likelihood ratio (LR+) 24 (95%CI: 15%-41%) and negative likelihood ratio (LR-) 0.07 (95%CI: 0.04-0.12) as compared to at least one independent diagnostic method^[16]. Performance was superior with monoclonal than with polyclonal antigen tests (sensitivity 95% *vs* 83%, respectively).

Twelve studies evaluated the performance of HpSA after *H. pylori* eradication. A pooled analysis of those studies showed sensitivity of 93% (95%CI: 89-96%), specificity of 96% (95%CI: 94-97%), LR+ of 17 (95%CI: 12-23) and LR- of 0.1 (95%CI: 0.07-0.15). Again, sensitivity with monoclonal test was superior than with polyclonal test (91% *vs* 76%, respectively). Subgroup analyses, considering different gold standards study populations or study quality showed no significant differences in results^[16].

Another meta-analysis, including 6 studies and 377 adult patients, evaluated the accuracy of HpSA in patients with upper gastrointestinal (GI) bleeding^[10]. Only polyclonal tests were analyzed. Sensitivity was 87% (95%CI: 82%-91%), specificity 70% (95%CI: 62%-78%), LR+ 2.3 (95%CI: 1.4-4) and LR- 0.2 (95%CI: 0.13-0.3), with high between-study heterogeneity. No subgroup analyses were performed.

A meta-analysis of HpSA in children included 48 case-control studies with 5799 patients. Monoclonal ELISA tests (6 studies, 445 patients) showed the best performance, with sensitivity and specificity both 97%, LR+ 29.9, and LR- 0.03. Polyclonal ELISA tests (29 studies, 2460 patients) had sensitivity of 92%, specificity of 93%, LR+ of 16.2, and LR- of 0.09, with high heterogeneity ($P < 0.0001$)^[17].

Serological tests: The consensus statement as follows: (1) serological tests are not recommended for clinical diagnosis of *H. pylori* in adults; either pre- or post-eradication (Evidence level II-3, grade of recommendation D; Agreement 4.5 ± 0.8). Western-blot might be considered as an alternative for non-invasive diagnosis of *H. pylori* infection in children (Evidence level II-2, grade of recommendation C; Agreement 4.5 ± 0.8); and (2) in areas with high risk of GC, serological tests are cost-effective for identification of asymptomatic *H. pylori*-infected individuals (Evidence level III, grade of recommendation C; Agreement 4.5 ± 0.8).

The rationale is that a number of different techniques exist for detection of antibodies against *H. pylori*, including solid phase assays (mostly in the ELISA format), agglutination tests (antigen binds to latex beads or gelatin), western blotting (useful for detection of response to different antigens) and immunochromatography tests. Performance of the different tests may vary in same population, and the same test will vary when tested on different populations^[18]. Rahman *et al*^[19] evaluated different kits in 82 patients from India. Current infection marker immunoblot showed the best accuracy, with sensitivity of 98% (95%CI: 91%-99%) and specificity of

90% (95%CI: 70%-99%). A study in 337 asymptomatic volunteers in China with the Assure[®] rapid test showed a sensitivity of 93% (95%CI: 89%-96%) and specificity of 91% (95%CI: 83%-95%), and six month after treatment the sensitivity was 86% and specificity 97%^[18].

A meta-analysis of serological tests in children included 58 studies and 8336 patients. The ELISA-IgG tests (42 studies, 5632 patients) showed sensitivity of 79% (95%CI: 77%-81%), specificity of 92% (95%CI: 92%-93%), LR+ of 10.2 (95%CI: 8.1-13) and LR- of 0.19 (95%CI: 0.15-0.25), while IgA tests showed a sensitivity of only 43% (95%CI: 36%-49%). Western-blot tests (10 studies, 1119 patients) showed sensitivity of 91% (95%CI: 89%-93%), specificity of 89% (95%CI: 86%-92%), LR+ of 8.2 (95%CI: 5.1-13.3) and LR- of 0.06 (95%CI: 0.02-0.16). There was evidence of considerable heterogeneity^[20].

Screening for *H. pylori* has been proposed as a cost-effective strategy in prevention of GC in high-risk populations^[21]. A number of screening strategies are currently available but it is unknown which approach is the best. Using a Markov model, a serologic testing was more cost-effective than the ¹³C-UBT in prevention of GC in Singapore Chinese males^[22].

Is it necessary to seek and eradicate *H. pylori* infection in all patients undergoing upper GI endoscopy?

Consensus statement: Testing and eradication of *H. pylori* infection in all symptomatic patients undergoing upper GI endoscopy decreases the risk of peptic ulcer disease and its complications and may improve functional dyspeptic symptoms, but does not modify the clinical course of gastroesophageal reflux disease (GERD) disease. (Evidence level I, grade of recommendation B; Agreement 4.1 ± 1.1).

Rationale: Chronic *H. pylori* infection is strongly associated with both benign and malignant outcomes^[23,24]. Universal testing and eradication of *H. pylori* infection in patients undergoing upper GI endoscopy, regardless of endoscopic findings, should be considered from both clinical and epidemiological perspectives. Main indications for upper GI endoscopy include dyspeptic or reflux symptoms. *H. pylori* eradication is justified in dyspeptic patients with normal endoscopy. A meta-analysis of 21 randomized controlled trials (RCT) suggested that *H. pylori* eradication is better than placebo to improve symptoms in patients with functional dyspepsia, with a relative risk (RR) reduction of 10% (95%CI: 6%-14%) and a number needed to treat (NNT) of 14 (95%CI: 10-25)^[25]. In patients with GERD, available evidence suggests that in most cases there is no clinically significant interaction between GERD and *H. pylori* infection^[5]. Current proton pump inhibitors (PPI) are able to compensate for any increase in acid secretion that might occur after eradication of *H. pylori*. A RCT of 231 *H. pylori*-positive patients with GERD, on long-term PPI therapy showed that *H. pylori* eradication did not worsen GERD

or require increased omeprazole maintenance dose^[26].

From an epidemiological perspective, the majority of patients with GERD may require long-term treatment with PPIs. It has been suggested that in the presence of *H. pylori* infection acid suppression may increase the risk of gastric atrophy^[27]. Although this intriguing hypothesis has not been confirmed^[28], some recent clinical guidelines still include long-term PPIs as an indication for *H. pylori* eradication^[5,6].

What is the role of *H. pylori* eradication in primary and secondary prevention of GC? What is the most appropriate age to eventually implement this action?

Primary prevention: The consensus statement is that the potential benefit of eradicating *H. pylori* in primary prevention of GC is highly suggested. However, there is insufficient evidence to justify large-scale implementation in the general population. Further studies should be performed on high-risk populations in Latin America to confirm the expected benefit and to evaluate potential adverse effects. (Evidence level I, grade of recommendation C; Agreement 4.5 ± 0.5).

The rationale is that the potential benefit of *H. pylori* eradication in primary prevention of GC has been evaluated as a secondary end-point in RCT of preneoplastic lesions, including individuals with and without gastric atrophy. The most recent meta-analysis of those studies suggests that *H. pylori* eradication significantly reduces the risk of GC^[29]. We updated this meta-analysis by including more recent data from two trials^[30,31], and excluding one of two reports that was based on the same sample^[32,33]. The updated summary RR was 0.6 (95%CI: 0.4-0.9), with low heterogeneity among trials ($PQ = 0.7$, $I^2 = 0\%$). Notably, the observed association was primarily driven by a single large study from China^[31].

Some international consensus reports^[5,6,34] consider a population intervention to “test and treat” for *H. pylori* an effective strategy for GC prevention in high-risk communities and some evidence supports the cost-effectiveness of *H. pylori* eradication for GC prevention at the population level^[21].

There are no empirical data addressing the most appropriate age for interventions to eradicate *H. pylori* infection. The trials described above have generally targeted older individuals because of their greater prevalence of preneoplastic lesions and faster progression to more advanced histologies. Nevertheless, a model projecting the potential reduction in lifetime GC risk and associated costs in a high-risk region in China, found that eradication at age 20 years is more cost-effective as compared to ages 30 or 40. The model assumed that new infections and reinfection are rare in adulthood, even in developing countries^[21].

Secondary prevention: The consensus statement is that the eradication of *H. pylori* infection is recommended as a routine measure to prevent recurrence in GC patients receiving either subtotal surgical gastrectomy or endo-

scopic resection. (Evidence level I, grade of recommendation A; Agreement 4.8 ± 0.5).

The rationale is that the potential benefit of *H. pylori* eradication in GC secondary prevention, defined as therapy in early stages of disease, has been mainly evaluated in patients with early GC who underwent subtotal surgical or endoscopic resection. Although observational studies have shown inconsistent results^[35-37], an open-label, RCT of prophylactic eradication in 544 patients found an OR of 0.4 (95%CI: 0.2-0.8) for metachronous GC and a NNT of 19^[38].

***H. pylori* infection and gastric premalignant lesions**

What is the effect of *H. pylori* eradication on gastric premalignant lesions?: The consensus statement is that in patients with gastric premalignant lesions, the eradication of *H. pylori* infection halts the progression of chronic atrophic gastritis and probably that of intestinal metaplasia. Although the evidence is still limited, current data favors the eradication of *H. pylori* infection in these patients. (Evidence level I for CAG and II-1 for IM, grade of recommendation B; Agreement 4.6 ± 0.5).

The rationale is that the effect of *H. pylori* eradication on the histologic improvement of premalignant lesions has not been fully elucidated and remains controversial. There are few RCT, usually with shorter follow-up than required to demonstrate effect^[39], and most reports and meta-analyses are based on prospective cohort studies. A RCT in Colombia included 795 adults with premalignant lesions, randomized to *H. pylori* eradication and/or antioxidants^[40]. After 12 years of follow-up, a composite histopathological score showed 15% more regression and 14% less progression in subjects who became *H. pylori* negative. The effect was more evident for subjects with CAG than with IM at baseline (total regression 66% vs 20%, respectively)^[30]. Another long-term RCT from China including 3365 subjects, showed a significant reduction in the combined prevalence of CAG, IM, dysplasia and GC, after 5 years (OR = 0.8; 95%CI: 0.6-0.95) and 9 years of follow-up (OR = 0.6; 95%CI: 0.5-0.8)^[41]. The most recent meta-analysis included 3 RCT and 8 observational studies, comprising 2,658 patients with CAG or IM, followed for 1 to 6.7 years. The summary mean difference on histological score before and after *H. pylori* eradication showed significant differences only for corpus CAG ($P = 0.006$), but not for antral CAG or IM in any anatomical site^[42]. The inclusion of mainly observational studies and the short mean follow up period may have influenced these results. There are several impediments to the proper assessment of reversibility of gastric premalignant lesions^[43]. Further well designed and properly executed studies are needed.

What is the most appropriate follow-up strategy for patients with premalignant conditions?:

The consensus statement is that high-risk gastric premalignant conditions, such as severe or extensive CAG, IM or dysplasia, require periodic follow-up. Endoscopic examina-

tion is recommended every 2-3 years for patients with moderate to severe CAG or IM, annually for those with low-grade dysplasia, and every 3-6 mo for those with high-grade dysplasia and no focal lesion on endoscopy. (Evidence level III, grade of recommendation B; Agreement 4.3 ± 0.8).

The rationale is that eradication of *H. pylori* may reduce GC incidence even in subjects with premalignant conditions^[29], albeit less clearly than in subjects without them^[44]. There is evidence from observational studies that GC risk of the intestinal type increases significantly with the severity of lesions^[45,46]. The existence of a 'point of no return' is a widely accepted concept, although its precise location in the carcinogenic continuum is still unknown. The more advanced the preneoplastic lesion, the more likely it is that development of GC cannot be halted. In subjects with severe or extensive CAG or IM further monitoring is necessary even after *H. pylori* eradication, but there are no prospective studies evaluating various monitoring schemes. Risk stratification of patients with premalignant lesions should be based on histological assessment. When endoscopy is appropriate, the Sydney biopsy sampling protocol should be applied because of its worldwide acceptance^[47]. The OLGA (Operative Link on Gastritis Assessment) histological staging is a recent proposal that considers the severity and distribution of gastric atrophy to assess the individual likelihood of progression to GC^[48]. There is preliminary evidence of its prognostic accuracy^[49]. More recently, the OLGIM histological staging, using IM instead of CAG because of its better interobserver agreement, has been shown to be of similar value^[50]. Prospective multicenter studies in different epidemiological contexts are needed to further validate this new reporting format.

The Maastricht IV Consensus Report 2012 recommends that regular follow-up should be considered at 2-3 year intervals in moderate to severe atrophy and 3-6 mo intervals where there is dysplasia^[5]. MAPS European guidelines recommend *H. pylori* eradication and endoscopic follow-up every 3 years for extensive CAG (corpus and antrum), annually for low-grade dysplasia, and immediate follow-up and then every 6-12 mo for high-grade dysplasia, with consideration of endoscopic or surgical resection of focal visible lesions^[51]. Prospective studies, that should include factors such as age and family history of gastric cancer, are needed to test and validate the correct timing of follow-up.

What is the effectiveness of current therapeutics schemes to eradicate *H. pylori*? Which scheme should be the first option in Latin America?

Short (7 d) *vs* long (10-14 d) standard triple therapy: The consensus statement is that standard triple therapy should be administered for 14 d and include high-dose PPI to achieve the best possible eradication rate (Evidence level I, grade of recommendation B; Agreement 4.5 ± 0.8).

The rationale is that seven to 14 d of triple therapy

(TT), including a PPI, clarithromycin and either amoxicillin or metronidazole, has been the standard eradication regimen for the last 10 to 15 years. Many studies have evaluated the optimal duration of treatment. A meta-analysis showed a benefit of 7%-9% in the cure rate when comparing 7 d *vs* 14 d, but no differences between 7 and 10 d, with a per protocol (PP) eradication rate of 90%^[52]. A more recent meta-analysis, including 21 studies showed no benefit in extending therapy over 7 d, although 14 d of treatment showed a favorable trend for the eradication rate in regimens including amoxicillin^[53]. Most included studies were of low quality. Another meta-analysis concluded that higher doses of the more potent second-generation PPIs -namely, 40 mg of esomeprazole or rabeprazole twice a day- may increase cure rates by 8%-12% in comparison with standard doses^[54]. The effectiveness of TT has shown a clear downward trend over the last years and in most recent studies eradication rates are below the 90% PP or 80% intention-to-treat (ITT) generally regarded as acceptable^[55-57]. Rising antibiotic resistance is the most important determinant of treatment failure^[58]. In Turkey, a small RCT showed 93% rate of PP eradication in patients infected with clarithromycin-susceptible strains treated for 14 d, compared to 63% in those treated for 7 d ($P = \text{NS}$), while in patients with clarithromycin-resistant strains, eradication rates were unacceptably low either after 14 or 7 d (60% and 27%, respectively)^[59]. In Pakistan, 110 subjects infected with clarithromycin-susceptible strains, were randomized to 7 or 14-d high-dose PPI triple therapy (lansoprazole 60 mg twice daily). The eradication rate was 100% with the 14-d regimen and 92.7% (with the 7-d regimen ($P = \text{NS}$)^[60].

Sequential therapy *vs* standard triple therapy: The consensus statement is that standard TT for 14 d is comparable to sequential therapy (ST) as empiric therapy for *H. pylori* infection in diverse Latin American populations. Sequential therapy is probably a better first-line alternative regimen in areas with high prevalence of clarithromycin-resistant strains (Evidence level I, grade of recommendation B; Agreement 4.6 ± 0.7).

The rationale is that the sequential therapy (ST), first introduced in Italy, consists of a 5-d dual therapy with a PPI (standard dose, bid.) and amoxicillin (1 g, bid) followed by a 5-d triple therapy with a PPI, clarithromycin (500 mg, bid) and metronidazole or tinidazole (500 mg, bid)^[61,62]. This regimen could be more effective in the setting of high clarithromycin resistance, although would fail in the presence of dual clarithromycin and metronidazole resistance^[63]. Many current clinical guidelines include both TT and ST as first-line regimens to treat *H. pylori* infection^[64,65], and it has been argued that standard TT should be abandoned when clarithromycin resistance is more than 15%-20%, because the ITT eradication rates are usually less than 80% in this setting^[5,66]. Both regimens have been compared in many RCT. A meta-analysis by Jafri *et al*^[67] comparing ST with TT (7 or 10

d), included 10 RCT and 2747 patients. Eradication rate was significantly higher for ST than TT (93.4% *vs* 76.9%, respectively; $P < 0.05$). A second meta-analysis by Gatta *et al*^[68] comprising 3006 patients also favored ST. The OR for *H. pylori* eradication was 3.0 (95%CI: 2.5-3.6), giving a NNT of 6. In patients with clarithromycin-resistant strains, the OR was 10 (95%CI: 3.0-35), but the numbers studied are small. The latest published meta-analysis by Tong *et al*^[69], including 11 RCT, demonstrated superiority of ST over 7-d or 10-d TT, with a RR of 1.2 (95%CI: 1.2-1.3), and 1.2 (95%CI: 1.1-1.2), respectively. Limitations of all of these meta-analyses are that most of the included studies were conducted in Italy, few patients had clarithromycin-resistant strains and 14-d TT was not used. Some RCTs conducted in Iran^[70], India^[71] and South Korea^[72] have failed to demonstrate superiority of ST over 10 or 14-d TT. In Taiwan, 900 adults were randomized to either 14-d or 10-d ST, or 14-d TT. The eradication rate was 91%, 87% and 82%, respectively. Treatment efficacy was significantly better for the ST-14 compared to TT-14 regimen (NNT of 12 on IIT analysis; $P = 0.003$)^[73]. Finally, a recent updated analysis added data from 10 recent RCT to the 3 previous meta-analyses, totaling more than 5000 patients. *H. pylori* infection was eradicated in 86% (95%CI: 84.7-87.3) of patients treated with ST and in 75.3% (95%CI: 73.8-76.9) of patients with TT ($P < 0.001$), corresponding to a NNT of 9. They concluded that comparison between ST and 14-d TT deserves further investigations^[74].

There are also relevant studies in pediatric populations. A study from Belgium showed superiority of ST only in patients with clarithromycin and metronidazole susceptible strains^[75]. In Poland, a RCT found higher eradication rates with ST over TT for 7 d, although with borderline significance^[76]. A meta-analysis including a total of 857 children aged 3-18 years, showed eradication rates of 78% with ST and 71% with TT (RR = 1.14, 95%CI: 1.06-1.23; NNT = 15). ST was superior to 7-d TT, but was not significantly better than 10-d or 14-d TT^[77].

Regarding treatment regimens, the most important Latin American study is a recent multicenter RCT comparing 14-d TT *vs* 5-d concomitant (lansoprazole, amoxicillin, clarithromycin and metronidazole) and 10-d ST in seven sites (Chile, Colombia, Costa Rica, Honduras, Nicaragua, and Mexico), including 1463 participants^[78]. The IIT eradication rate with TT and ST was similar (82.2% and 76.5%, respectively, $P = \text{NS}$). An updated evaluation showed that the estimated eradication success rate after 1 year of follow-up was virtually the same for both TT and ST (80.4% and 79.8%, respectively)^[79]. Because both regimens just border the acceptable efficacy limit (80% IIT), there is an important space for improvement, and more efficacious treatment schemes are clearly needed.

Levofloxacin-based triple therapy: The consensus statement as follows: (1) a quinolone-based regimen is

a good alternative second-line therapy, especially when bismuth is not easily available (Evidence level I, grade of recommendation A; Agreement 4.6 ± 0.5); and (2) a quinolone-based regimen might be considered as a first-line alternative regimen in areas with high prevalence of clarithromycin-resistance and low quinolone resistance (Evidence level I, grade of recommendation C; Agreement 4.6 ± 0.5).

The rationale is that both levofloxacin-based triple therapy (LBTT) (PPI, levofloxacin and amoxicillin) and the classical bismuth-based quadruple therapy (BBQT) (PPI, bismuth, tetracycline and metronidazole) have been recommended as second-line therapy by the Maastricht IV Consensus Report^[5] and other international clinical guidelines^[80,81]. Two meta-analyses evaluated the efficacy of LBTT as second-line therapy, showing higher eradication rates compared to 7-d BBQT with an OR of 1.80 (95%CI: 0.94-3.46)^[82] and less adverse events than BBQT^[82,83]. A subsequent meta-analysis including 13 RCT showed that the eradication rates of the two regimens were similar (OR = 1.43; 95%CI: 0.82-2.51) except for subgroup analysis comparing 10-d LBTT with 7-d BBQT (OR = 4.79, 95%CI: 2.95-7.79, $P < 0.00001$)^[84]. The more recent meta-analysis included 14 RCT comparing 7 or 10-d LBTT with 7-d BBQT. Both 7-d regimens showed comparable efficacy, with eradication rates of 70.6% and 67.4%, respectively, whereas the 10-d LBTT was significantly better than 7-d BBQT (eradication rate 88.7% *vs* 67.4%, $P < 0.001$). LBTT regimens were more effective in European than in Asian populations (78.3% *vs* 67.7%, $P = 0.05$)^[85]. All meta-analyses showed that LBTT for 10 d is more effective than for 7 d and better tolerance for LBTT than for BBQT.

Levofloxacin-based therapies have also been studied as first-line therapy, with inconsistent results. A non-randomized Dutch study compared two 7-d LBTT, with either amoxicillin or clarithromycin. IIT eradication rates were 96% and 93%, respectively, probably reflecting a very low local resistance to quinolones^[86]. A RCT from the Middle East compared the same two LBTT with 7-d standard TT. IIT eradication rates were of 84.7% and 90.6% for amoxicillin and clarithromycin LBTT respectively *vs* 78.6% with TT ($P < 0.001$)^[87]. Another RCT from Spain compared LBTT with standard TT, both for 10 d. IIT cure rates were similar (75.0% *vs* 82.8%, $P = \text{NS}$), perhaps reflecting the increasing levofloxacin resistance rate in this region. A RCT from South Korea, including 300 patients, compared 7-d LBTT with 7-d standard TT and with a quadruple regimen including PPI, levofloxacin, amoxicillin and rifaximin. The IIT eradication rate was higher with TT than with LBTT (77.8% and 65.3%, respectively, $P = 0.05$) while the rifaximin-based quadruple regimen was not inferior to TT^[88]. Levofloxacin-based sequential or quadruple regimens have also been tried as first-line options, with better results than standard TT^[89,90]. Based on this large body of clinical trial data, LBTT shows similar or better outcomes compared with other current first-line therapies. Under

exceptional circumstances, such as populations with low quinolone resistance (< 10%) and high clarithromycin resistance (> 15%-20%), this combination might be considered as a first-line treatment option for patients with no previous quinolone exposure^[64,91].

Concomitant quadruple therapy: The consensus statement is that concomitant quadruple therapy for 10 or 14 d should be studied in Latin America and may be a good first or second-line alternative in areas with high prevalence of dual resistance to clarithromycin and metronidazole (Evidence level II-1, grade of recommendation C; Agreement 4.3 ± 0.5).

The rationale is that the so-called “concomitant therapy” is a non-bismuth-containing quadruple regimen, including a PPI (standard dose, bid), clarithromycin (500 mg, bid), amoxicillin (1 g, bid) and metronidazole or tinidazole (500 mg, bid) and was designed primarily to overcome antibiotic resistance to TT. It has been used for 3 to 14 d but direct comparisons between variable durations of treatment are lacking^[63,92,93]. A meta-analysis including 5 RCTs and 576 subjects compared concomitant quadruple therapy (CQT) (3 to 5 d) with standard TT (5 to 10 d). Pooled estimates showed ITT eradication rate of 90.8% and 79% for CQT and TT, respectively. The OR was 2.86 (95%CI: 1.7-4.7)^[94]. Another meta-analysis suggested that CQT may overcome resistance to either clarithromycin or metronidazole^[95]. CQT is less complex than ST as this regimen does not involve changing drugs halfway through and may be assembled by adding metronidazole or tinidazole to standard TT. A head-to-head non-inferiority trial of 10-d ST and 10-d CQT showed that they were equivalent (ITT eradication rate of 92.3% and 93.0%, respectively)^[84]. Dual resistance to clarithromycin and metronidazole did not influence the level of eradication in the CQT group, but significantly affected efficacy of ST, although the low number of patients precludes a clear conclusion^[63].

A Turkish RCT compared a modified BBQT (PPI, bismuth, tetracycline and amoxicillin) with a modified CQT (PPI, tetracycline, amoxicillin and metronidazole), both for 10 d, as first-line therapy. The ITT eradication rates were similar and unsatisfactory (79% and 74%, respectively; *P* = NS) probably because of antibiotic resistance^[96]. In a Spanish RCT, patients with clarithromycin-susceptible strains were randomized to receive TT *vs* CQT, while those with clarithromycin-resistant strains were randomized to ST *vs* CQT^[97]. For clarithromycin-susceptible patients, CQT was significantly better than TT (ITT eradication rate 92% *vs* 70%, respectively; *P* = 0.02). For clarithromycin-resistant and dual-resistant strains (9 cases each), the eradication rates were non-significantly better with CQT. In the same study, 209 consecutive naive *H. pylori*-positive patients without susceptibility testing were empirically treated with 10-d CQT, with an ITT eradication rate of 87% (95%CI: 83%-92%).

In Latin America, the previously mentioned multi-

center RCT comparing some recommended first-line empirical regimens, included one arm with 5-d CQT^[78]. Although TT had appeared to be superior to ST and CQT at 6 to 8 wk, there were only modest and non-significant differences in 1-year outcomes among the 3 treatment groups^[79].

What is the clinical usefulness of assessing the susceptibility of *H. pylori* to antibiotics?

Consensus statement: Determination of antibiotic susceptibility of *H. pylori* before treatment may improve the effectiveness of therapy and should be used when available, particularly in populations with high prevalence of resistance (Evidence level I, grade of recommendation B; Agreement 4.0 ± 0.6).

Antibiotic resistance of *H. pylori* should be monitored by systematic surveillance in all countries throughout the region (Evidence level III, grade of recommendation B; Agreement 4.0 ± 0.6).

After a treatment failure, the design of second and third line therapies should be based on *H. pylori* antibiotic susceptibility to the greatest extent possible (Evidence level II-3, grade of recommendation B; Agreement 4.0 ± 0.6).

Rationale: Clarithromycin resistance is the most important factor in explaining the increasing failure of standard TT^[95], and has been correlated with the consumption of clarithromycin in the general population^[98].

In Latin America, there is no surveillance system of *H. pylori* antimicrobial susceptibility. A meta-analysis of observational studies evaluating *H. pylori* strains in Latin American populations found high frequencies of primary antibiotic resistance, including summary prevalences of 12% for clarithromycin, 53% for metronidazole, 4% for amoxicillin, 15% for fluoroquinolones, and 8% for dual clarithromycin and metronidazole^[99]. It has been suggested that standard TT should be used only when resistance of *H. pylori* to clarithromycin is less than 15%-20%^[5] or after susceptibility testing has confirmed clarithromycin sensitivity^[95].

Some studies have compared the effectiveness of empiric therapy *vs* therapy guided by antibiotic susceptibility (tailored therapy). A meta-analysis, comprising 5 RCT and 701 patients, showed that tailored TT had a higher ITT-eradication rate than empiric TT (RR = 0.84; 95%CI: 0.77-0.90) and suggested that tailored therapy may be cost-effective^[100]. Several methodological weaknesses may limit the validity and generalizability of this meta-analysis, including that 4 of the studies came from Italy and cost analysis is based in only one study^[101].

Culture of *H. pylori* may be difficult, even in expert hands^[102] and sensitivity values of 55%-73% have been reported in some trials^[103-106]. Few Latin American microbiological laboratories routinely perform culture and susceptibility studies of *H. pylori*, and standardization of culture media, culturing methods, and interpretative values for susceptibility testing of isolated strains is lacking.

The increasing availability of PCR-based approaches (not requiring culture) to evaluate antibiotic susceptibility may facilitate the implementation of these techniques^[107]. A systematic effort to monitor the regional frequency and evolution of *H. pylori* antibiotic resistance would be very helpful for designing the best options for empiric treatment.

After a treatment failure, culture and standard susceptibility testing of *H. pylori* has been recommended, while after a second failure it should be performed in all cases^[5]. However, there is limited evidence to sustain these recommendations. A study including 94 consecutive patients with 2 previous failures found resistance to metronidazole in 100%, to clarithromycin in 95%, to levofloxacin in 31% and to tetracycline in 5% of cases. Patients were treated with a culture-guided, third-line regimen, most with a 7-d BBQT including omeprazole, bismuth, doxycycline and amoxicillin. ITT eradication rate was 90%^[108]. Another open prospective, multicenter study included 41 patients with 2 previous failures. Despite the use of two-week, high-dose, quadruple and culture-guided combinations of drugs, overall eradication rate was only 60%^[109].

Recurrence of *H. pylori* infection after treatment

In which clinical situations eradication should be confirmed?: The consensus statement is that because of the declining efficacy of current therapies, *H. pylori* testing should be offered to all patients after eradication therapy, especially when persistent infection may be associated to clinically relevant disease risks, such as in patients with peptic ulcer disease, GC or mucosa-associated lymphoid tissue (MALT) lymphoma. (Evidence Level II-1, grade of recommendation B; Agreement 4.3 ± 0.7).

The rationale is that because of the declining efficacy of current therapies, *H. pylori* testing should be offered to all patients after treatment, but is mandatory when the treatment failure may be associated to clinically relevant risks, such as in patients with complicated ulcer disease, with gastric MALT lymphoma or after endoscopic or surgical resection of GC^[80,110-112]. However, cost-effectiveness of this strategy has not been determined. Testing should be done at least 4 wk after treatment, although proposals have been made to extend this period to 6 or 8 wk.

Peptic ulcer rebleeding virtually does not occur after *H. pylori* eradication^[113,114], and bleeding recurrence is related to persistent or recurrent infection or concurrent NSAIDs^[115]. Because persistent *H. pylori* infection poses a risk of a potentially serious complication, a second-line therapy is mandatory in this situation.

H. pylori play a causative role in the development of gastric MALT lymphoma and the eradication of *H. pylori* leads to a complete remission in 50%-90% of cases^[80]. In a systematic review, data from 32 studies and 1,408 patients with gastric MALT lymphoma treated only by *H. pylori* eradication, demonstrated a remission rate of 77.5% and a relapse rate of 7.2% after 10 to 75 mo of follow up. Only 17% of relapses were related to recurrence of *H. pylori*, but lymphoma was cured by additional

eradication therapy in all these patients^[116].

How to define reinfection? What is the reinfection rate in Latin America?: The consensus statement as follows: (1) recurrence of *H. pylori* infection after treatment is variable in Latin America, but considerably higher than in developed countries, probably due to a higher frequency of reinfection. (Evidence level I; grade of recommendation B; Agreement 4.0 ± 0.4); and (2) good-quality information about long-term risk of reinfection is lacking and should be addressed in future studies (Evidence level III, grade of recommendation C; Agreement 4.0 ± 0.4).

The rationale is that recurrent *H. pylori* infection following apparently successful eradication can be due to a recrudescence (defined as infection by the same strain) or reinfection (*i.e.*, infection with a new strain). Because culture of *H. pylori* is uncommon in clinical practice, reinfection has been conventionally defined as the situation where tests for *H. pylori* infection, which were negative for 12 mo after eradication treatment, later become positive^[117]. *H. pylori* recurrence within the first year after eradication seems likely to represent a mixture of recrudescence and reinfection, the former predominant^[118], whereas reinfection dominates in subsequent years, and the overall annual risk of recurrence tends to diminish^[119]. Recurrence risk is generally directly proportional to the frequency of infection in the population^[120,121] and inversely proportional to the efficacy of the initial treatment^[122]. In a review of more than 100 studies, the annual recurrence risk ranged from 3.4% (95%CI: 3.1%-3.7%), in high-income countries, to 8.7% (95%CI: 8.8%-9.6%) in lower-income countries^[123]. In a meta-analysis of 17 studies, comprising more than 5000 patients followed for at least one year, the annual recurrence rates were 2.7% and 13% for developed and developing countries, respectively. The recurrence during the first year was similar, while nested meta-analysis of cases with a negative 12-mo UBT and a longer follow-up revealed an annual recurrence rate of 1.45% in developed countries and 12% in developing countries^[15]. Only one of the studies came from Latin America^[118]. Latin American studies with at least 50 person-years of follow-up showed 1-year recurrence risk from 0% to 17.3%^[30,118,119,124,125]. A recent study evaluating the risk of recurrent *H. pylori* infection 1 year after successful therapy in 1091 subjects from 7 different Latin American communities found a recurrence risk of 11.5% (95%CI: 9.6%-13.5%). The recurrence rate significantly differed according to the study site, ranging from 6.8% in Costa Rica to 18.1% in Colombia ($P = 0.03$). Predictors of failed eradication were having more children in the household and poor adherence to initial therapy^[79], suggesting that both recrudescence and reinfection are components of 1-year recurrence in this study. There is little information regarding the long-term recurrence rate of *H. pylori* infection in Latin America. A Brazilian study of 115 patients followed during 2 to 5 years showed an annual reinfection rate of 1.8%^[124]. A

Chilean study of 96 patients followed for a mean of 37.2 mo showed a reinfection rate of 1.5% during the second and third year after treatment^[119].

DISCUSSION

The high burden of *H. pylori* associated diseases in Latin America demands the attention of the public health community. The consensus statements presented here represent locally adapted strategies to control this serious problem.

However, some limitations should be considered. First, there is a shortage of locally-generated evidence about some of the selected topics. Second, it is important to note that factors such as accessibility of UBT, HpSA and antibiotic susceptibility testing, affordability, and differences in clinical setting between rural and urban areas of Latin America, not addressed in our study, may also influence the applicability of our recommendations.

Finally, our systematic review indicated that future epidemiological and clinical research should focus on (1) potential benefits and adverse effects of population-based eradication for primary prevention; (2) appropriate follow-up strategies for patients with advanced premalignant lesions; (3) identification of alternative and superior first-line therapies; (4) estimating long-term risk of reinfection; and (5) periodic and representative assessment of resistance to first- and second-line antibiotics. Better region-specific evidence is needed to inform future management toward improving clinical and population health outcomes.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection affects more than 80% of adult population across the Latin American region. Gastric cancer, an associated disease, is common and has a poor prognosis. The optimal management of this bacterial infection is evolving and needs to be adapted to local epidemiological situations. A multidisciplinary panel of Latin American experts conducted a structured analysis of the current literature on some relevant topics about *H. pylori* infection.

Research frontiers

Indications of *H. pylori* eradication for epidemiological reasons are still uncertain and the efficacy of common antibiotic schemes shows a progressive decline. More studies are needed, but in the meantime, consensual evidence-based recommendations can help to guide clinical practice.

Innovations and breakthroughs

Using the Delphi technique method to reach a consensus among experts after assessing the quality of the available evidence is a reasonable approach for generating up-to-date practical recommendations on *H. pylori* infection.

Applications

The statements of the current evidence-based clinical practice review provide a rationale for current management of *H. pylori* infection in clinical practice.

Terminology

The Delphi technique is a method for gathering data from specialists within their domain of expertise to achieve a convergence of opinion on a specific real-world issue. The Delphi technique is well suited as a method of consensus building in scenarios where evidence-based recommendations are insufficient or uncertain.

Peer review

To optimize diagnosis and treatment guidelines for *H. pylori* infection in Latin American countries, a group of gastroenterologists, epidemiologists and basic

reviewed and discussed all relevant clinical data present in literature to arrive at recommendations for the clinical management of *H. pylori* infection. Fifteen key clinical questions were proposed and a modified Delphi method was used to reach consensus. The paper is well written and it is complete.

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