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Guidelines

Management of *Helicobacter pylori* infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED)

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ABSTRACT

Helicobacter pylori infection is very common and affects more than one-third of adults in Italy. *Helicobacter pylori* causes several gastro-duodenal diseases, such as gastritis, peptic ulcer and gastric malignancy, and extra-gastric diseases. The eradication of the bacteria is becoming complex to achieve due to increasing antimicrobial resistance. To address clinical questions related to the diagnosis and treatment of *Helicobacter pylori* infection, three working groups examined the following topics: (1) non-invasive and invasive diagnostic tests, (2) first-line treatment, and (3) rescue therapies for *Helicobacter pylori* infection. Recommendations are based on the best available evidence to help physicians manage *Helicobacter pylori* infection in Italy, and have been endorsed by the Italian Society of Gastroenterology and the Italian Society of Digestive Endoscopy.

1. Introduction

Helicobacter (H.) pylori infection is a widespread disease with more than one-third of adults infected in Italy [1]. *H. pylori* may cause chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, or MALT-lymphoma. Therefore, it is important to obtain the diagnosis of infection in the appropriate clinical setting, and once the diagnosis has been achieved, eradication is mandatory. National recommendations on the management of *H. pylori* infection are thus needed to allow gastroenterologists and general practitioners to have similar evidence-based approach.

While the diagnosis of *H. pylori* infection is based on well-established tests, there is still some debate as to when it is more appropriate to search for the infection. On the other side, due to the increase of *H. pylori* strains resistant to antimicrobials generally used for treating the infection, eradication of the bacterium is becoming more and more complex, involving an increasing number of antimicrobials, with a reduction in the compliance to the therapy and a higher rate of adverse events related to the treatment. Antimicrobial resistance, in particular to clarithromycin and fluoroquinolones, may be vary between different countries and, even in the same country, a regional variability may be present. Therefore, guidelines which may be appropriate for one country, may not be adequate for another. It is very important to adapt recommendations to the needs of the various geographical areas which strictly depend upon the different rates of

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clarithromycin, fluoroquinolones, metronidazole, or dual (i.e., clarithromycin and metronidazole) antibiotic resistance [2]. Based on this, under the auspices of the Italian Society of Gastroenterology (SIGE) and together with the Italian Society of Gastrointestinal Endoscopy (SIED), a group of experts has issued this consensus to support clinical practice guidelines for general practitioners and gastroenterologists who deal with patients with *H. pylori* infection.

2. Methods

This position paper is endorsed by the Italian Society of Gastroenterology and the Italian Society of Digestive Endoscopy. Representatives from SIGE (Marco Romano, Antonietta Gerarda Gravina, Raffaele Pellegrino and Giovanna Palladino) and SIED (Rocco Maurizio Zagari and Leonardo Henry Eusebi), members of the SIGE and SIED National Committee, as well as Antonio Gasbarrini and Francesco Di Mario as external reviewers, participated to the Consensus process. They agreed on a set of key questions to be addressed and on preliminary statements to guide literature research. The following topics were examined: (1) when to search for *H. pylori* infection, (2) how to search for *H. pylori* infection, (3) first-line treatment of *H. pylori* infection, (4) how to deal with *H. pylori* eradication after the failure of first-line therapy or multiple unsuccessful eradication attempts. The panel performed a systematic search of the literature, reviewed statements based on the best available evidence, and reported graded statements and recommendations. The working group produced statements reporting the quality of available evidence and the strength of the recommendation, graded according to the GRADE system [3,4].

The databases queried for the data search were MEDLINE, EMBASE, and Web of science. The search was not restricted by specific chronological filters, and the terms for the literature search were selected so that they were functional for the topic sought. Researchers prioritized data from systematic reviews and meta-analyses of randomized controlled trials (RCTs) when available, or individual RCTs with narrow 95% confidence intervals (CIs). If the clinical question was related to a specific population, the selection of studies was limited with filters to the target population to identify evidence related to that specific subgroup.

The clinical applicability of the statements and recommendations and their implementation in primary care were also considered. Both data from European publications, representative of an epidemiological situation similar to the Italian one, and, of course, from studies carried out in Italy were considered. The statements and recommendations with the supporting evidence were edited and discussed in a 1-day telematic plenary session. After an in-depth discussion, all participants were asked to vote on their agreement with the statements based on the available evidence as well as on the balance between benefits and risks of the same, and the consensus was defined according to the GRADE method. The final document was then submitted for external review to improve the quality of the guidelines, both in terms of expositional quality but also in terms of applicability, feasibility and strength of evidence of the recommendations.

To assess the strength of the recommendations, the following assessment was used: strong (desirable effects outweigh undesirable effects) or conditional (trade-offs are less certain). In addition, to evaluate the quality of evidence, the following definitions were used: strong (further research is unlikely to change confidence in the estimate), moderate (further research is likely to change confidence in the estimate), low (further research is very likely to change confidence in the estimate), or very low (the estimate of the effect is very uncertain).

3. Statements

3.1. Diagnosis

3.1.1. When to search for H. pylori infection?

***Statement 1: H. pylori* should be searched for and eradicated in patients with uninvestigated dyspepsia, in patients younger than 50 years of age, without alarm symptoms.**

Evidence level: moderate; Grade of recommendation: strong

Dyspepsia is a condition characterized by chronic symptoms, including epigastric pain, burning, early satiety, and postprandial fullness, localized in the central upper quadrant of the abdomen. It is well established that dyspeptic patients of 50 years of age or less without alarm symptoms (i.e., unintentional weight loss, iron-deficiency anemia, gastrointestinal bleeding, dysphagia) should not undergo esophagogastroduodenoscopy (EGDS) and should be non-invasively tested and eventually treated for *H. pylori* infection [5]. This approach is supported by several studies as reported by European and American guidelines [3,6]. Furthermore, this strategy has been demonstrated to be also cost-effective [7].

***Statement 2: H. pylori* should be searched for and eradicated in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) with a history of peptic ulcer. The eradication is more beneficial before starting NSAIDs or ASA therapy in preventing complicated and uncomplicated gastroduodenal peptic ulcers.**

Evidence level: moderate; Grade of recommendation: strong

The use of either NSAIDs or ASA increases the risk of uncomplicated gastroduodenal ulcers and bleeding in patients with *H. pylori* infection [3]. The presence of several factors such as anticoagulant use, advanced age, and history of peptic ulcer, further increases the risk [8,9]. NSAIDs, ASA, and *H. pylori* infection not only are independent risk factors for peptic ulcers [10] and for bleeding, but also have an additive effect on peptic ulcer bleeding [11]. The interaction between *H. pylori* infection and low-dose ASA remains controversial, although *H. pylori* eradication reduces peptic ulcer bleeding in ASA users [11]. Therefore, *H. pylori* should be non-invasively searched for and eradicated in NSAIDs and ASA users with a history of peptic ulcers, according to international guidelines [3,6]. *H. pylori* eradication is more beneficial before starting NSAIDs and ASA therapy [3].

***Statement 3: H. pylori* should be searched for and eradicated in patients with iron or vitamin B12 deficiency anemia, and in patients with idiopathic thrombocytopenia**

Evidence level: very low; Grade of recommendation: weak

Iron deficiency anemia (IDA) is well known to be associated with *H. pylori* infection, as demonstrated by several reviews and meta-analyses [12–18].

Several pathophysiological mechanisms are involved in this association: chronic blood loss due to the presence of gastric erosions or ulcers [18]; iron absorption deficiency at the duodenum due to increased gastric pH in *H. pylori*-associated corpus-predominant chronic gastritis which may impair the transformation of dietary Fe^{3+} to Fe^{2+} [19]; altered expression of hepcidin, a protein that regulates iron absorption by enterocytes, in patients with *H. pylori* infection [20,21]; the ability of *H. pylori* to acquire iron from host glycoproteins as transferrin and lactoferrin [19]; the ability of *H. pylori* to cause up-regulation of TNF-α, a pro-inflammatory cytokine that may cause IDA [23]. Indeed, eradication of *H. pylori* infection leads to a reversal of IDA in up to 75% of patients [22].

H. pylori infection is also associated with low levels of vitamin B12 (Vit. B12) [23,24], thus possibly leading to Vit. B12 deficiency anemia. Low levels of Vit. B12 are associated with an increase in homocysteine, a metabolic product of Vit. B12 [2,24]. Levels of Vit. B12 and homocysteine return to normal values after eradication

of *H. pylori* infection [24,25]. The mechanism of *H. pylori*-induced Vit. B12 deficiency could be related to the failure of gastric parietal cells to produce intrinsic factor in patients with *H. pylori*-associated corpus-predominant chronic gastritis [26].

Primary immune thrombocytopenia (ITP) is an autoimmune disorder, linked to *H. pylori* infection [26]. The putative pathogenic mechanism of this association is a molecular mimicry between platelet surface glycoproteins and amino acid sequences of *H. pylori* virulence factors, such as *H. pylori* lipopolysaccharide (LPS), Vac A, CagA, and urease B [25,27]. Also, *H. pylori* up-regulates Fcγ receptor expression, thus increasing the phagocytic capacity and down-regulating inhibitory receptors FcγRIIB that in turn enhance monocyte activity and autoreactivity in B and T lymphocytes [27–30]. As a result, B-lymphocytes produce autoantibodies against circulating platelets [25,28–30]. The potential causative role of *H. pylori* is suggested by many studies, showing that successful *H. pylori* eradication leads to a rise of the platelet count [31,32]. IDA, Vit. B12 deficiency and ITP are the only extra-gastric disorders associated with *H. pylori* infection for which the European Guidelines recommend searching for and eradicating *H. pylori* infection in a non-invasive manner [2]. *H. pylori* infection has been associated with other extra-gastric conditions, such as neurologic diseases (i.e. Alzheimer's disease, Multiple sclerosis, Parkinson's disease, Guillain-Barrè syndrome), ocular diseases (i.e. open-angle glaucoma, central serous chorioretinitis, blepharitis), metabolic diseases (i.e. diabetes mellitus, insulin resistance syndrome, metabolic syndrome), cardiovascular diseases (i.e. coronary atherosclerotic disease, myocardial infarction), dermatologic diseases (i.e. rosacea, psoriasis, chronic urticarial, alopecia areata, autoimmune bullous disease, Schoenlein-Henoch purpura). However, the causality of most of these associations has not been proven [17,18], and although a clinical improvement following *H. pylori* eradication has been shown in many studies, to date we do not have enough strong evidence to suggest testing for and treating *H. pylori* for extra-gastric diseases, except for the aforementioned hematological manifestations [17,18].

Statement 4: **In patients with gastroesophageal reflux disease (GERD) on PPI therapy, eradication of *H. pylori* is recommended.**

Evidence level: low; Grade of recommendation: weak

Several studies have suggested a protective role of *H. pylori* against GERD and its complications through a reduction in gastric acid secretion [3,33–35]. Eradication of the bacterium does not appear to be associated with worsening of preexisting GERD nor does it alter the response to proton pump inhibitors. Therefore, the change in gastric acid secretion after eradication of *H. pylori* infection should not be used as a decisive argument for treating or not treating the infection [3,36–39]. However, long-term treatment with proton pump inhibitors (PPIs), used for chronic GERD, in infected individuals has been shown to facilitate the migration of the bacterium from the antrum to the gastric body, leading to the development of body gastritis that is more associated with the development of gastric cancer [40–43].

The prevalence of *H. pylori* infection in family members or sexual partners of *H. pylori*-infected individuals has not been widely studied. A recent prospective study described a 74.5% prevalence of *H. pylori* infection in sexual partners of *H. pylori*-infected individuals compared with 32.3% in the control group [44]. The risk of both partners being infected was higher in those who had lived together for a long period and in couples with at least one member with GERD. However, major international guidelines do not recommend testing family contacts or sexual partners of infected individuals for *H. pylori* infection, and such research could be performed only if the patient explicitly requested it.

3.1.2. Which tests should be used for the diagnosis of H. pylori infection?

3.1.2.1. Non-invasive tests. ***Statement 5:*** **^{13}C-urea breath test and monoclonal ELISA stool antigen test have high accuracy for non-invasive diagnosis of *H. pylori* infection, both in pre- and post-therapy settings.**

Evidence level: high; Grade of recommendation: strong

The preferred non-invasive diagnostic method for *H. pylori* infection is the ^{13}C Urea Breath test (^{13}C UBT) which has a sensitivity of 96% and a specificity of 93% [45,46]. The ELISA stool antigen test (SAT) that detects *H. pylori* antigens in the feces, has a diagnostic performance similar to 13C-UBT, with a sensitivity and specificity of 93.3% and 93.2%, respectively [47–49].

The Rapid monophase HpSA test, based on an immunochromatographic technique, is an alternative to the ELISA SAT for an immediate evaluation of the *H. pylori* status but is less accurate than the ELISA test, in particular for the evaluation of treatment success after eradication therapy [50]. None of the stool antigen detecting tests can be performed in patients with diarrhea, nevertheless SATs appear to be an alternative to the UBT in elderly patients, pregnant women, and children, in whom performing a breath test may be troublesome [49,50].

To minimize the probability of false-negative results, each of the above-mentioned tests should be performed at least 4 weeks after stopping antibiotic or bismuth compounds use, and 2 weeks after proton pump inhibitors (PPIs) suspension [45,48,51,52]. Antiacids do not impair UBT and SAT sensitivity [3], whereas H2-receptor antagonists have only a minimal effect on the sensitivity of 13C-UBT since they do not have an anti-*H.pylori* activity, differently than PPIs. Bleeding peptic ulcers reduce the sensitivity of both UBT and SAT. Moreover, these non-invasive tests may also have a lower sensitivity in patients with gastric precancerous lesions, gastric cancer, and partial gastrectomy [53].

Statement 6: **Positive IgG serology is an indicator of past infection, but not necessarily of an ongoing infection. Serum IgG antibodies should not be used after eradication treatment.**

Evidence level: moderate; Grade of recommendation: strong

Serology (i.e., detection of anti-*H. pylori* IgG) does not discriminate between ongoing versus past infection and, therefore, its use to diagnose *H. pylori* infection should be discouraged. This test has a high negative predictive value but a low positive predictive value. Serum IgG may however represent the method of choice for diagnosing *H. pylori* infection in patients with bleeding ulcers, atrophic gastropathy, MALToma, gastric cancer, recent antibiotics, and PPIs use, as well as in cases when it is not possible to stop PPI treatments for at least 2 weeks or antibiotics for 4 weeks before testing [47,51,52]. The sensitivity and specificity of serum IgG anti-*H. pylori* test is 85% and 79%, respectively, highest in case of monoclonal antibodies [3,46,52].

The detection of CagA antibodies cannot be used as *H. pylori* diagnostic test [6], but it may be useful for the evaluation of the risk of gastric cancer. In Western countries, the seroprevalence of anti-CagA antibodies is less than 50% in infected individuals.

Serum IgG should not be used to assess the eradication of *H. pylori* since the antibodies continue to be detectable for 6-12 months after *H. pylori* eradication [54,55].

3.1.2.2. Invasive tests. ***Statement 7:*** **When there is an indication to perform upper endoscopy with gastric biopsies, histology should be used for the diagnosis of *H. pylori* infection both pre- and post-eradication treatment. Immunohistochemical analysis should be performed only in rare cases, such as when chronic or atrophic gastritis are present.**

Evidence level: moderate; Grade of recommendation: strong

Endoscopic tools, such as narrow-band imaging, linked color imaging, and blue laser imaging, do not allow an accurate *H. pylori* status evaluation, but are recommended by MAPS II guide-

lines for targeted biopsy sampling that efficiently improves the likelihood of diagnosing precancerous gastric lesions related to *H. pylori* infection [56]. Histology remains the gold standard for diagnosing *H. pylori* infection. Hematoxylin and eosin (H&E) staining was found to be 94% accurate compared to complementary staining immunohistochemistry (IHC), whereas the latter is preferred over H&E only in the presence of active chronic gastritis without *H. pylori* identification by standard staining, mainly due to low bacterial density or atypical localization of the pathogen [3,47,57]. Moreover, IHC could be useful in patients with chronic gastritis in which the suspicion of infection is high, such as in patients with atrophic gastritis when no bacteria are identified by standard histological examination [56]. However, IHC is not available in all laboratories, and it is more expensive than H&E [3].

According to the updated Sydney System, biopsies should be taken from the antrum and the corpus (lesser and greater curvature), and from the *incisura angularis* [3,58]. In particular, according to MAPS 2 guidelines, 2 biopsies should be taken from the antrum and two from the body of the stomach [56].

Statement 8: **Rapid urease test (RUT) should be performed in patients who undergo an upper endoscopy to prescribe immediately an eradication treatment for those *H. pylori*-positive. RUT should not be used after eradication treatment as the sensitivity is lower in this setting.**

Evidence level: low; Grade of recommendation: weak

The rapid urease test (RUT) showed a sensitivity of approximately 90% and specificity of 95-100% [59,60]. Sensitivity is lower in case of recent gastrointestinal bleeding or in patients recently treated with PPIs, antibiotics, bismuth-containing compounds, or when diffuse atrophy and intestinal metaplasia are present. For RUT, one biopsy from the antrum and one biopsy from the corpus should be taken to minimize false-negative results [61]. False-positive tests are unusual but may occur when urease-containing bacteria, such as *Proteus mirabilis, Citrobacter freundii, Klebsiella pneumoniae, Enterobacter cloacae,* and *Staphylococcus aureus*, are present in the stomach [3,62]. RUT can give quick information about *H. pylori* status and allows to prescribe an eradication therapy immediately [3].

Statement 9: **The accuracy of molecular methods on gastric biopsies should be better defined.**

Evidence level: very low; Grade of recommendation: weak

Molecular methods, such as real-time PCR, allow to define the *H. pylori* status of a patient as well as to evaluate if the clinical isolate carries genes that confer resistance against clarithromycin or levofloxacin, thus allowing a targeted therapy. More studies are needed to evaluate the accuracy of commercially available kits which find a large application in clinical practice [3]. Interestingly, recent studies on noninvasive molecular analysis of stool specimens for the detection of point mutations in *H. pylori* DNA, have reported an overall high sensitivity and specificity for clarithromycin and levofloxacin genotypic resistance comparable to that obtained with culture or PCR on gastric biopsies [63,64].

Statement 10: **Culture cannot be considered a routine diagnostic test, but should be used only after multiple treatment failures to choose the most appropriate therapy.**

Evidence level: very low; Grade of recommendation: weak

Culture is not currently used to diagnose *H. pylori* infection as it is complex, costly, and requires dedicated personnel. In addition, *H. pylori* culture showed poorer sensitivity in patients who underwent previous eradication treatment compared to naïve ones [3,54]. Thus, culture and *in vitro* anti-microbial sensitivity testing should be restricted to patients who are resistant to at least two eradication treatments, allowing targeted therapy.

3.2. Treatment

3.2.1. Which eradication regimen should be used as first-line therapy in Italy?

Statement 11: **Bismuth-based quadruple therapy, concomitant therapy, or sequential therapy should be used as first-line treatment for *H. pylori*. A 14-day standard triple therapy may only be considered in areas with proven low clarithromycin resistance (<15%).**

Evidence level: moderate; Grade of recommendation: strong.

The increasing resistance to antibiotics is the main issue in the treatment of *H. pylori* infection. There is unanimous consensus that the choice of the first-line therapy should be driven by the local prevalence of clarithromycin resistance; however, this information is often lacking [2].

The antibiotic susceptibility profile of *H. pylori* in most regions of Italy is unknown; however, there is evidence of a high prevalence, around 30%, of clarithromycin resistance in some areas of the Center and South of Italy [65]. International guidelines recommend a 10- or 14-day quadruple therapy, the bismuth-based quadruple therapy or the non-bismuth concomitant quadruple therapy, as first-line therapy in countries with high (>15%) or unknown prevalence of clarithromycin resistance. The efficacy of these two regimens is not affected by clarithromycin and metronidazole resistance, and bismuth-based quadruple therapy performs well also against dual clarithromycin and metronidazole resistance.

The bismuth-based quadruple therapy is a complex 20-year-old regimen including PPI, bismuth, tetracycline, and metronidazole [64]. To overcome the complexity of this regimen, a new galenic formulation of the "3-in-1" capsule (Pylera®) is available in many European countries including Italy [66]. In a meta-analysis of 21 studies, Pylera® yielded a pooled intention-to-treat eradication rate of about 90% as first-line therapy [67]. Several studies carried out in Italy have confirmed the high efficacy of Pylera® across different regions, including those with a high prevalence of clarithromycin resistance [68–70].

The concomitant therapy includes PPI, clarithromycin, amoxicillin, and metronidazole or tinidazole, all given together. Although single clarithromycin and metronidazole resistance do not undermine the therapeutic performance of this regimen, the effectiveness of concomitant therapy drops to a suboptimal 75% eradication rate in patients with dual clarithromycin and metronidazole resistance. Thus, this regimen is not recommended in areas with a known high prevalence (>15%) of dual clarithromycin and metronidazole resistance. A recent randomized controlled trial carried out in Italy showed that concomitant therapy was not inferior to bismuth-based quadruple therapy with eradication rates of around 90% as first-line treatment for *H. pylori* infection [71]. Similar results have been reported from another study from an area of Southern Italy with a high prevalence of clarithromycin resistance [72]. Therefore, there is consistent evidence that both bismuth-based quadruple therapy and concomitant therapy can be considered good options for the first-line treatment of *H. pylori* in Italy. Bismuth-based quadruple therapy has the advantage that bismuth is not used against other infectious diseases and that the use of tetracycline is minimal in clinical practice. On the other hand, it has been suggested that with concomitant therapy each patient may receive one unnecessary antibiotic. Thus, bismuth quadruple therapy may be considered the best choice for the empirical first-line treatment of *H. pylori* in Italy, especially in subjects who have previously received clarithromycin for conditions other than *H. pylori* infection [68].

Sequential therapy, which includes PPI plus amoxicillin for 5-7 days followed by PPI plus metronidazole and clarithromycin for another 5-7 days, is a regimen designed to overcome the issue of clarithromycin resistance. However, data on the efficacy of this reg-

imen against clarithromycin-resistant *H. pylori* strains are contradictory. Two systematic reviews with meta-analysis showed that sequential therapy was not better than 14-day standard triple therapy in the first-line treatment of *H. pylori,* with pooled eradication rates around 80% for both regimens [73,74]; in addition, the subgroup analysis that included subjects with clarithromycin-resistant *H. pylori* strains showed that eradication rate decreased to a suboptimal 70% with sequential therapy. Based on these data, international guidelines and a review reconciling guidelines have discouraged the use of sequential therapy for the treatment of *H. pylori*. However, sequential therapy seems to perform well in Italy providing eradication rates of around 90%, also in the presence of clarithromycin resistance. Two randomized controlled trials showed that sequential therapy achieved eradication rates similar to those of bismuth-based and concomitant quadruple therapies as first first-line treatment of *H. pylori* in clinical practice in Italy [71,75]. Thus, according to previous Italian guidelines, sequential therapy appears to be a valid option in Italy. National registries reporting the efficacy and side effects of the different regimens in clinical practice should be encouraged to improve the empirical first-line treatment of *H. pylori* infection in Italy.

The standard triple therapy, including a proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole/tinidazole, is highly effective in subjects with clarithromycin sensitive *H. pylori* strains, but fails against strains resistant to clarithromycin, with eradication rates lower than 70% [76]. Due to the paucity of data on the prevalence of clarithromycin resistance in many areas worldwide, it has been proposed that a high local eradication rate (> 85%) with this regimen should be considered a surrogate marker of the low prevalence of clarithromycin resistance. A meta-analysis of 45 randomized clinical trials has shown that 14 days is the optimal duration of this regimen achieving significantly higher eradication rates than 7- and 10-day treatment [77]. A 14-day standard triple therapy should be used in Italy as first-line treatment only in areas with a known low prevalence of clarithromycin resistance (<15%), in patients without previous use of macrolide, or where this regimen has been proven to achieve high eradication rates.

The choice between single capsule, bismuth-containing quadruple therapy, or a clarithromycin-containing regimen as first-line eradication regimens should be based on patients' previous antibiotic exposure and the presence of allergy to amoxicillin. It is well known that previous use of macrolides, even for infections other than *H. pylori*, may increase the likelihood that a patient harbors an *H. pylori* strain resistant to this class of antibiotics [78]. Also, single capsule, bismuth-containing quadruple therapy should be preferred in a geographical area with a well-known high prevalence of dual resistance to clarithromycin and metronidazole (>15%). In such areas, high-dose PPI-amoxicillin dual therapy can be considered as an alternative to bismuth quadruple therapy, in particular where bismuth, tetracycline, or Pylera® are not available, as this therapy avoids the issue of clarithromycin and metronidazole resistance all together [79]. Generally speaking, bismuth quadruple therapy should be preferred over a clarithromycin-containing regimen, in particular in the setting of a high rate of dual resistance.

Acid-suppressive drugs play a crucial role in eradication therapy by increasing the gastric bioavailability of antimicrobials and by increasing the number of dividing *H. pylori,* making the bacteria more susceptible to the action of antibiotics [80]. A meta-analysis has demonstrated that new-generation PPIs (i.e., esomeprazole or rabeprazole) are associated with significantly higher eradication rates than those obtained with first-generation PPIs (i.e., omeprazole, lansoprazole, or pantoprazole) [81]. Moreover, the eradication regimen is optimized by doubling the dose of PPI [82]. To further strengthen the role of acid suppression in *H. pylori* eradication, recent studies from Japan have shown that triple regimens based on the use of vonoprazan, a potassium-competitive acid blocker (P-CAB) achieve higher eradication rates than those obtained with PPIs [83]. This occurs because P-CABs achieve stronger, longer-lasting suppression of gastric acid secretion compared to PPIs [83].

Table 1 summarizes the available eradication regimens currently used with doses and indications. Recommended options for first-line therapy are indicated in Fig. 1.

3.2.2. Which eradication regimen should be used following first-line therapy failure in Italy?

Statement 12: **If first-line therapy with single-capsule bismuth quadruple regimen failed, levofloxacin containing regimen should be used as second line treatment, particularly in patients previously exposed to clarithromycin or in a geographical area of known high dual resistance. If a clarithromycin-containing regimen was used as the first line, single-capsule bismuth quadruple therapy should be used as a second-line treatment.**

Evidence level: low; Grade of recommendation: strong

Treating *H. pylori* infection following therapy failures is increasingly more complex, mainly due to the development of bacterial resistance to antibiotics. In particular, not only the rate but also the MIC values of resistance have been found to affect therapy success [84]. Bacterial resistance easily develops towards clarithromycin, metronidazole, and levofloxacin, whilst it remains distinctly low for amoxicillin and tetracycline, even after repeated use [85]. Therefore, when prescribing retreatment, there is a rationale for changing the antibiotics used previously, with the exception of amoxicillin and tetracycline. If the first-line therapy was a clarithromycin-containing regimen (concomitant or sequential), single capsule bismuth quadruple therapy should be the preferred second-line treatment (Fig. 1). On the other side, if the single capsule bismuth concomitant therapy was the first-line therapy, a 14-day levofloxacin-containing regimen should represent the preferred second-line therapeutic option [86,87] (Fig. 1). The levofloxacin-containing regimen should only be used as rescue treatment given the rapidly rising prevalence of quinolone resistance and the recent warnings about possible serious adverse events of fluoroquinolones. However, if the patients have never been exposed to clarithromycin previously, a second attempt should include a clarithromycin-containing regimen [84,85,88] (Fig. 1).

3.2.3. Which eradication regimen should be used in case the second-line, or third-line therapy fails in Italy?

Statement 13: **In case of second-line treatment failure, a 14-day levofloxacin-containing triple therapy, if not used already as a second-line regimen, or a 14 day high dose dual therapy may be used as an empirical third-line regimen.**

Evidence level: low; Grade of recommendation: weak

Statement 14: **In the case of third-line treatment failure, tailored therapy based on EGDS followed by culture and antimicrobial susceptibility testing should be the recommended procedure.**

Evidence level: very low; Grade of recommendation: weak

3.2.4. What should be the preferred rescue therapy after multiple eradication failures?

Statement 15: **Rifabutin based 12-days triple therapy or 14-day high dose dual therapy should be used in the case of multiple eradication failures**

Evidence level: very low; Grade of recommendation: weak

If the second-line therapy (quadruple bismuth or clarithromycin-containing regimen) also fails, a triple levofloxacin-containing regimen, preferably for 14 days, is suggested as

Table 1
Eradication regimens used in clinical practice in Italy: their duration and when should they be used.

Type	Regimen	Duration	When
Concomitant therapy	PPI high dose bid + amoxicillin 1 g bid + clarithromycin 500 mg bid + tinidazole 500 mg bid	14 days	First line. *Second line (if Pylera fails)
Single capsule (Pylera) bismuth therapy	PP high dose I bid + Pylera 3 tablets qid	10 days	First line. Second line (if concomitant fails)
Sequential Therapy	PPI high dose bid + amoxicillin 1 g bid for 5 days followed by PPI bid + clarithromycin 500 mg bid + tinidazole 500 mg bid for 5 more days	10 days	First line. *Second line (if Pylera fails)
Triple therapy	PPI high dose bid + amoxicillin 1g bid + clarithromycin 500 mg bid	14 days	First line (only if known <15% clarithromycin resistance)
Levofloxacin-containing triple therapy	PPI high dose bid + amoxicillin 1 g bid + levofloxacin 250 mg bid	14 days	Second line (if Pylera fails). Third line (if Pylera and concomitant therapy fail)
Rifabutin containing triple therapy	PPI high dose bid + amoxicillin 1 g bid + rifabutin 150 mg bid	12 days	Rescue therapy
High dose PPI amoxicillin dual therapy	PPI high dose tid + amoxicillin 1 g tid	14 days	Third line (if Pylera and levofloxacin triple therapy fail). Rescue therapy

bid: twice a day; **tid**: three times a day; **qid**: four times a day, **PPI**: proton pump inhibitor, **mg**:milligrams, **g**: grams.
* Only if no previous exposure to clarithromycin and/or well known low (i.e. <15%) prevalence of dual resistance.

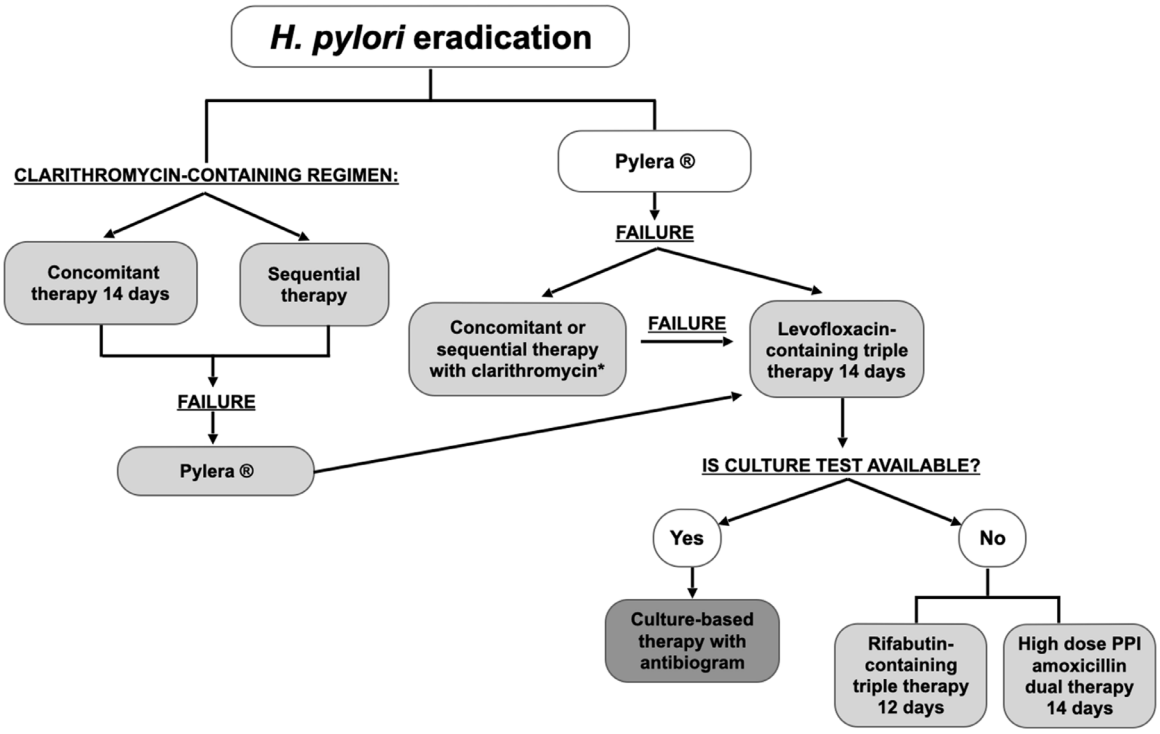

Fig. 1. Therapeutic algorithm for *H. pylori* eradication.
*only if no previous exposure to clarithromycin or knowledge of low prevalence of dual resistance.

third-line therapy, if not used before [89–91] (Fig. 1). A triple regimen with levofloxacin could be used as second-line treatment only if a quadruple therapy with bismuth has been used as first-line therapy in an area with high prevalence of *H. pylori* strains with dual resistance to clarithromycin and metronidazole [6,87] (Fig. 1).

Several consensus groups have, over time, recommended "tailored" therapy for refractory *H. pylori* infection based on in vitro antimicrobial susceptibility testing. Despite this, the strength of the recommendations has never been particularly strong [3,92]. The efficacy of "tailored" therapy has shown inconsistent results in the literature, with eradication rates ranging from 74% to 98.7% in areas with resistance rates to clarithromycin ranging from 51% to 95%, levofloxacin from 6% to 52%, and metronidazole from 43% to 100% [93–101].

Moreover, a recent meta-analysis showed that therapy based on antimicrobial susceptibility assessment was superior to empiric therapy only in the first line of treatment, whereas for the second and third line of treatments the evidence was less strong [102].

Overall, in cases of failure with three lines of treatment, this panel argues in favor of targeted therapy based on culture and *in vitro* antimicrobial susceptibility testing, where available (Fig. 1). However, careful empiric therapy, based on the epidemiology and on the patient's medical history, may be an alternative if culture testing is not available.

After multiple treatment failures, several salvage therapies have been suggested (Fig. 1). In particular, there is renewed interest in dual therapy with PPIs and high-dose amoxicillin for 14 days (i.e., omeprazole or esomeprazole 40 mg and amoxicillin 1 g, both three times daily), which has been shown to achieve cure rates similar

to those of other more complex and less safe therapies [103]. Two recent meta-analyses showed that high-dose dual therapy achieved similar eradication rates compared with bismuth-based quadruple therapies [104] or other salvage therapies [105]. Further favoring this therapeutic approach are both the low rate of side effects and the lower cost (52.36 euros in Italy) compared to Pylera® (74.04 euros) [106].

Another salvage therapy that has proven to be effective after multiple therapeutic failures is the 12-day rifabutin-amoxicillin triple therapy (i.e., PPI standard dose b.i.d. + amoxicillin 1 g b.i.d. + rifabutin 150 mg b.i.d.) [107,108]. A recent large study found that this regimen achieves eradication rates greater than 80% when used in patients with three or more treatment failures [109]. Based on potential bone marrow toxicity, the utility for treating mycobacterial infection in patients with HIV, and a very high cost, the expert panel suggests that rifabutin therapy should be used only after failure of all other regimens and in selected patients with severe gastric diseases (i.e., MALT-lymphoma, bleeding peptic ulcer). It is also suggested to perform tests for tuberculosis such as Mantoux, Quantiferon, or ELISPOT (Enzyme-Linked ImmunoSpot) tests before starting therapy with rifabutin because this drug can promote the emergence of *M. tuberculosis* strains resistant to common anti-tuberculosis. Finally, given the potential myelotoxicity, performing blood counts is also recommended.

3.3. What is the role of probiotics in the therapeutic management of H. pylori *infection?*

Statement 16: **In patients with *H. pylori* infection, supplementation with probiotics in addition to eradication therapy should be considered to reduce the rate of side effects associated with the eradication therapy.**

Evidence level: low; Grade of recommendation: weak

Probiotic supplementation in the treatment of *H. pylori* infection has been proposed to increase eradication rates and/or decrease adverse events related to antibiotics used in eradication treatment regimens [110]. The effect of probiotics on the eradication rate remains, to date, controversial due to inconsistent data and the reduced quality of available studies. A meta-analysis of 19 randomized controlled trials including 2,730 patients evaluated the impact of six probiotic mixtures on the efficacy of *H. pylori* eradication regimens, consisting mainly of triple therapy containing clarithromycin [111]. The eradication rate was significantly higher in patients who had used probiotics than in those who had not (86% vs 77%, respectively). In addition, probiotic use was associated with a decrease in adverse events (particularly diarrhea) of 14%. On the other hand, a prospective multicenter study in Italy showed no benefit from probiotic supplementation in patients receiving quadruple therapy with bismuth [66].

More high-quality studies are certainly needed to better clarify which strains are effective and in which contexts. European guidelines, in any case, suggest the use of probiotics only to reduce antibiotic-related adverse events [3].

Tools facilitating the implementation of the current guideline are provided at the end of this position paper, namely Fig. 1 (Therapeutic algorithm for *H. pylori* eradication) and Table 1 (Eradication regimens used in clinical practice in Italy).

Conflict of interest

None declared.

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