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Special Article

Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015

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ABSTRACT

Knowledge on the role of *Helicobacter pylori* (HP) infection is continually evolving, and treatment is becoming more challenging due to increasing bacterial resistance. Since the management of HP infection is changing, an update of the national Italian guidelines delivered in 2007 was needed. In the III Working Group Consensus Report 2015, a panel of 17 experts from several Italian regions reviewed current evidence on different topics relating to HP infection. Four working groups examined the following topics: (1) "open questions" on HP diagnosis and treatment (focusing on dyspepsia, gastro-oesophageal reflux disease, non-steroidal anti-inflammatory drugs or aspirin use and extra-gastric diseases); (2) non-invasive and invasive diagnostic tests; (3) treatment of HP infection; (4) role of HP in the prevention of gastric cancer. Statements and recommendations were discussed and a consensus reached in a final plenary session held in February 2015 in Bologna. Recommendations are based on the best current evidence to help physicians manage HP infection in Italy. The guidelines have been endorsed by the Italian Society of Gastroenterology and the Italian Society of Digestive Endoscopy.

1. Introduction

Our knowledge on the role of *Helicobacter pylori* (HP) in different clinical conditions has improved over the last decade, whereas the treatment of infection has become more challenging. According to the European guidelines the management of HP may differ among European countries (i.e. indications for a test- and- treat strategy, the regimen to choose for first-line treatment) in parallel with different prevalence rates of infection and levels of antimicrobial resistance, in particular to clarithromycin [1]. Attempts to standardize HP management within countries have led to the publication of several national guidelines, and Gastroenterologists and referring physicians have been shown to comply with these guidelines [2]. This is the third time a group of Italian experts convenes to review and discuss the relevant evidence concerning the clinical management of HP infection in Italy [3,4]. As HP testing and

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treatment should be managed in close cooperation between specialists and general practitioners, it is particularly important that data on diagnostic tools and therapeutic approaches be applied appropriately in clinical practice in specific national settings.

This consensus project aimed to summarize current evidence on the management of HP infection and update the Italian guidelines produced in the II Working Group Report 2006 [4]. At the III Working Group Consensus Report 2015, 17 experts from different Italian regions, chosen for their expertise and research contribution on HP and/or guideline methodology, convened at an official meeting by the coordinator (MC) of the two previous working group meetings [3,4]. Italian experts focused on updating indications, diagnosis and treatment of HP and its relationship with gastric cancer.

2. Methodology and consensus meeting structure

The guidelines are endorsed by the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED), which were not however promoters of the Consensus. Representatives from both SIGE (MR and FDM) and SIED (RMZ and CC) participated to the Consensus process. A panel of Italian gastroenterologists and pathologists met in April 2014 in Ferrara, where current European guidelines – Maastricht IV/Florence – [1] were reviewed at the introductory plenary session. The panel further agreed on the "Maastricht methodology" to be applied [1], on a set of key questions to be addressed and on preliminary statements to guide literature research. The panel worked in subgroups (working groups) to perform a systematic literature search, review statements on the basis of best available evidence and report graded statements and recommendations. Four working groups examined the following topics:

(1) "Open questions" for HP diagnosis and treatment, focusing on dyspepsia, gastro-oesophageal reflux disease (GORD), use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (acetylsalicylic acid – ASA) and extra-gastric diseases
(2) Non-invasive and invasive diagnostic tests
(3) Treatment of HP
(4) Role of HP treatment in the prevention of gastric cancer

For each topic, individual key questions were addressed. The quality level of evidence and the strength of recommendation were graded according to the same system used in the Maastricht IV/Florence report (Table 1) [1]. After discussion, the working group produced statements with the level of available evidence and the strength of the recommendation. Researchers prioritized data from systematic reviews and meta-analyses of randomized controlled trials (RCTs) when available, or individual RCTs with narrow 95% confidence intervals (CI). The clinical applicability of statements and recommendations and their implementations in primary care were also taken into account.

Statements and recommendations with supporting evidence were edited and discussed at a one-day final plenary session in February 2015 in Bologna. After a thorough discussion, all participants were asked to vote on their agreement with evidence-based statements, and consensus was defined when at least 70% of participants agreed with the statement. Recommendations are based on the best current evidence to aid physicians manage HP infection in Italy. Previous strong indications for HP eradication, such as peptic ulcer and gastric mucosa associated lymphoid tissue (MALT) [4], have been reconfirmed.

Table 1
Grades of recommendation and levels of evidence [1].

Grade of recommendation	Level of evidence		Type of study
A	1	1a	Systematic review of RCTs of good methodological quality and with homogeneity
		1b	Individual RCT with narrow 95% confidence interval
		1c	Individual RCT with risk of bias
B	2	2a	Systematic review of cohort studies
		2b	Individual cohort studies (including low quality RCT, <80% follow-up)
		2c	Non-controlled cohort studies or ecological studies
	3	3a	Systematic review of case-control studies
		3b	Individual case-control study
C	4		Case series or poor quality cohort or case-control studies
D	5		Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

RCT, randomized controlled trial.

3. Statements

3.1. Open questions for diagnosis and treatment

3.1.1. HP and dyspepsia

Several well-designed studies support the use of the HP test-and-treat for the initial management of uninvestigated dyspepsia in young patients without alarm signs or symptoms (i.e. unintentional weight loss, iron-deficiency anaemia, gastrointestinal bleeding, dysphagia) [5]. European guidelines recommend this strategy in countries where HP prevalence is higher than 20% [1]. In Italy, as well as in other Southern European countries, such as Greece and Spain, HP prevalence in adults is around 50% [6,7]. Thus, a test-and-treat strategy is still recommended in Italy. The specific cut-off age for referring patients with uninvestigated dyspepsia without alarm symptoms to endoscopy is controversial; it depends on the local age-specific incidence of gastric cancer [1]. The Italian cancer registry shows that the incidence of gastric cancer increases in subjects over 50 years of age [8]. In addition, a recent Italian survey reported a very low prevalence of gastric cancer (0.3%) in approximately one thousand patients referred for upper endoscopy [9]. Based on these data, a cut-off age of 50 years in Italy should be appropriate. Therefore, all dyspeptic patients older than 50 years or with alarm signs or symptoms should be referred for upper endoscopy [10]. When the test-and-treat strategy is applied, an accurate diagnosis is mandatory using a non-invasive test, either the ^{13}C-urea breath test (UBT) or the monoclonal stool antigen test (SAT) [1].

Many dyspeptic patients have no major lesions at endoscopy [6] and some of these are HP-infected (functional dyspepsia). A recent meta-analysis demonstrated that 1 out of 13 HP-infected patients with functional dyspepsia benefit from eradication [11]. Therefore, HP eradication is recommended in this setting.

Statement: HP test-and-treat strategy is appropriate for the initial management of uninvestigated dyspepsia as HP prevalence in adults in Italy is over 20%. This approach is applicable to patients younger than 50 years without alarm symptoms.
Evidence level: 1a; Grade of recommendation: A

3.1.2. HP and gastro-oesophageal reflux disease

An increasing body of evidence supports the suggestion of a protective role of HP against GORD by reducing gastric acid secretion. Several meta-analyses showed a statistically significant lower prevalence of HP in GORD patients [12], including those with Barrett's oesophagus [13] or oesophageal adenocarcinoma [14], than in controls. In addition, a recent RCT in Asia reported an increased prevalence of reflux oesophagitis after HP eradication [15]. This data are in contrast with a previous meta-analysis showing no association between HP eradication and development of new cases of GORD in dyspeptic patients [16]. However, the short follow-up after eradication may account for the discrepancy between studies. HP eradication does not seem to exacerbate the disease in patients with GORD, thus HP infection in GORD patients may be eradicated [17]. Further supporting HP eradication in GORD patients is the need for long-term proton pump inhibitor (PPI) therapy that seems to be associated with an increased risk of developing gastric precancerous conditions, such as corpus atrophic gastritis [18,19].

Statement: Increasing evidence supports a negative association between HP infection and GORD, including its complications (oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma). However, HP eradication does not worsen pre-existing GORD nor does it affect proton pump inhibitor treatment efficacy.
Evidence level: 1b; Grade of recommendation: A

3.1.3. HP and NSAIDs/ASA

HP infection is associated with an increased risk of uncomplicated and complicated gastro-duodenal ulcers in NSAID and ASA users [1]. There are no relevant additional studies addressing the role of HP in NSAIDs or ASA users, and data concerning the role of HP in patients taking low dose of ASA are still scarce. In agreement with international guidelines [1,20], HP should be searched and eradicated in all NSAID or ASA users with a history of peptic ulcer disease. In addition, as the combination of NSAID/ASA therapy with other risks factors for gastrointestinal (GI) bleeding increases the risk of upper gastrointestinal events [20] an HP test-and-treat may also be considered in NSAID/ASA users with multiple risk factors for upper gastrointestinal bleeding: combined NSAIDs and ASA, or concomitant anticoagulant therapy (i.e., un-fractionated or low-molecular-weight heparin and warfarin), clopidogrel or corticosteroids.

HP eradication seems to be more beneficial before starting long-term NSAIDs/ASA treatment [1]. However, after HP eradication these patients still require continuous PPI treatment [1,20].

There are no recent studies on subjects who chronically use corticosteroids (i.e., patients with inflammatory bowel disease or rheumatologic diseases). The problem whether this subgroup of patients could benefit from HP eradication remains open. In recent years, new anticoagulant drugs with a high risk of GI bleeding have been introduced for the prevention and treatment of myocardial infarction, stroke, and atrial fibrillation [21,22]. The absence of randomized controlled trials does not allow to provide recommendations for these patients.

Statements:
HP eradication reduces the risk of complicated and uncomplicated gastro-duodenal ulcers associated with either NSAID or low-dose ASA use. HP eradication is more beneficial before starting NSAID treatment.
Evidence level: 1b; Grade of recommendation: A
HP eradication is mandatory in chronic NSAID/ASA users with a peptic ulcer history.
Evidence level: 2b; Grade of recommendation: B
Eradication of HP may be considered in chronic NSAID/ASA users with multiple risk factors (both NSAID and ASA use or concomitant anticoagulant, clopidogrel or corticosteroid use) for upper GI bleeding.
Evidence level: 5; Grade of recommendation: D

3.1.4. HP and extra-gastric diseases

The association of HP with otherwise unexplained iron-deficiency anaemia, diagnosed after endoscopic exclusion of the most common bleeding (i.e. cancer, peptic ulcer) and non-bleeding (i.e. celiac disease, previous gastric surgery) GI diseases [23,24], has been well ascertained and demonstrated in a recent meta-analysis (Odds Ratio [OR]: 2.2; 95%CI, 1.52–3.24) [25]. Two further meta-analyses showed that HP eradication combined with oral iron supplementation is superior to iron supplementation alone for moderate to severe unexplained iron-deficiency anaemia [26,27]. However, it should be noted that only corpus mucosa involvement and development of corpus gastritis links HP infection to iron-deficiency anaemia [28].

Regarding idiopathic thrombocytopenic purpura (ITP), a meta-analysis [29] and two systematic reviews [30,31] demonstrated that HP eradication induced a significant increase in platelet count. For example, Arnold et al. showed an increase in platelet count in 51% of eradicated patients vs. 8.8% of non-eradicated patients with ITP [30].

A recent systematic review of 17 studies, including 2454 subjects, addressed the association between HP and cobalamin levels in patients with unexplained vitamin B_{12} deficiency. HP-positive subjects showed significantly lower cobalamin levels than HP-negative ones (mean difference: −0.74, 95% CI: −1.15 to −0.34) [32]. Moreover, a sub-group analysis on the effect of eradication on cobalamin levels showed significantly lower levels before eradication [32].

Recent data showed an association between CagA-positive HP strains and ischaemic heart disease [33,34]. In addition, it has been suggested that HP might be playing a pathogenic role in rosacea [35]. However, there is not enough evidence to suggest HP testing in these clinical settings.

Statements:
There is substantial evidence in favour of an association between HP infection and unexplained iron-deficiency anaemia, ITP and vitamin B_{12} deficiency. Therefore, in these conditions HP should be sought and treated.
Evidence level: 1a; Grade of recommendation: A (Unexplained iron-deficiency anaemia)
Evidence level: 1b; Grade of recommendation: A (ITP)
Evidence level: 1b; Grade of recommendation: A (Vitamin B_{12} deficiency)

3.2. Diagnosis

3.2.1. Non-invasive tests

Several meta-analyses confirmed that ^{13}C-UBT is the best test for the non-invasive HP diagnosis with a 96% sensitivity and a 93%

specificity [36]. A meta-analysis showed that the laboratory ELISA monoclonal SAT has a similar high accuracy for both the initial and post-treatment diagnosis [37]. The rapid in-office monoclonal SAT, based on an immunochromatographic technique, seems to be less accurate [38].

However, the recent use of PPIs (within 2 weeks) or antimicrobials (within 4 weeks) may lead to a decrease in the gastric bacterial load causing false-negative results [39–41]. Bleeding can also reduce the sensitivity of both UBT and SAT [39,40]. Data from a systematic review suggests repeating diagnostic tests in patients with bleeding ulcer after at least 4 weeks in case of a negative result [42]. In patients with precancerous conditions or gastric cancer, as well as in patients with partial gastrectomy, diagnostic tests may have lower accuracy [42].

Statements:

Both ^{13}C-UBT and monoclonal SAT have shown high diagnostic accuracy in both the pre- and post-HP treatment setting.

Evidence level: 1a; Grade of recommendation: A

The following conditions reduce the sensitivity of ^{13}C-urea UBT and SAT: use of antibiotics during the previous month, inability to stop proton pump inhibitors for at least 2 weeks, bleeding ulcer, atrophic gastritis and gastric malignancies.

Evidence level: 1b; Grade of recommendation: B

Serology is commonly used for the diagnosis of HP infection. When ^{13}C-UBT or SAT cannot be used (i.e. current anti-secretory or antibiotic use) or are unavailable, a validated IgG serology test with antibodies against whole HP bacterial body can be used. However, although anti-HP IgG titre is not affected by conditions reducing HP bacterial load, it cannot discriminate between active or past infection. Anti-HP IgG titre usually remains elevated for long periods after clearance or eradication [1].

Determination of anti-CagA antibodies alone is not appropriate to diagnose HP infection. In Western countries, the seroprevalence of anti-CagA antibodies is less than 50% in infected individuals and anti-CagA antibodies are detectable for years after eradication [43].

Statement: Positive IgG serology with antibodies against whole HP bacteria only indicates past, but not necessarily ongoing, infection.

Evidence level: 1b; Grade of recommendation: A

3.2.2. Invasive endoscopy-based tests

The working group did not deem it useful to draw up new statements on histology and rapid urease test, as no relevant new data are available. Culture allows performing standard susceptibility testing to antimicrobial agents; however the technique is complex and is performed in very few centres in Italy. Thus, in Italy culture cannot be recommended in clinical practice before first-line treatment. When endoscopy is otherwise clinically indicated, culture and standard susceptibility testing should be considered, before second-line treatment, and when second-line treatment has failed [1]

Molecular tests, which can be performed directly on gastric samples, allow obtaining data on both clarithromycin and fluoroquinolone resistance by polymerase chain reaction (PCR) analysis of HP DNA point mutations, such as 23S rRNA for clarithromycin and *gyrA* gene for levofloxacin [44,45]. Molecular tests have high accuracy, in particular for assessing HP clarithromycin susceptibility, compared to culture with standard susceptibility testing, with the advantage of a superior feasibility [46]. However, in a recent study carried out in Korea the sensitivity of this method in detecting antimicrobial resistance was not satisfactory [47]. Local validation studies assessing the accuracy of commercially available kits on representative sample of patients in Italy are certainly needed. Molecular methods have the potential limitation of a decreasing sensitivity in detecting resistance rates in relation to progressive occurrence of novel point mutations [48]. Molecular tests are a promising tool that may find a larger application in clinical practice in the future, if culture with standard susceptibility testing is not available, even before a first-line treatment [49].

Statements:

Culture with antimicrobial susceptibility testing is limited to few centres. Therefore, it cannot be considered a routine investigation.

Evidence level: 1b; Grade of recommendation: A

Molecular tests may be a valid alternative for detecting clarithromycin and/or fluoroquinolone resistance on gastric biopsies.

Evidence level: 1b; Grade of recommendation: B

3.3. Treatment

3.3.1. Basic principles

Proton pump inhibitor dose. High dose PPI (twice a day) is more effective than standard dose for eradicating HP infection. Often PPI is under-dosed in therapeutic regimens in primary care. “In vitro” studies show that antibiotic minimum inhibitory concentration is affected by intragastric pH [50]. An Italian study [51] and a meta-analysis [52] clearly state that PPIs need to be administered at a high dose to obtain the optimal outcome.

Retreatment after a previously failed regimen. Retreatment is required when treatment failure is demonstrated, and cannot be performed on the sole basis of symptoms persistence. The failure of a clarithromycin-containing first-line therapy is very likely to be associated with a primary or acquired clarithromycin resistance. Therefore, in these cases the use of clarithromycin in a second-line treatment is strongly discouraged for the high probability of failure [53].

Use of other antibiotics. Cephalosporins, quinolones other than levofloxacin (i.e. moxifloxacin), some tetracyclines (doxycyclin) should not be used in HP treatment for their poor effectiveness (<80%). [54,55]. Their use is, therefore, discouraged.

3.3.2. First-line treatment

Over the last decade the efficacy of standard 7-day PPI-based triple therapy (PPI + clarithromycin + amoxicillin or metronidazole/) has fallen to unacceptably low rates [1] due to the increased prevalence of clarithromycin resistance [56]. A recent Cochrane systematic review and meta-analysis of RCTs including 45 studies showed that a 14-day clarithromycin-containing triple therapy was more effective than 10- and 7-day regimens yielding an overall eradication rate >80% [57]. This finding confirmed the results of a previous meta-analysis showing that 14-day triple therapy was significantly more effective than 7-day triple therapy [58].

The standard 10-day sequential therapy has shown high efficacy in first-line HP treatment yielding eradication rates of about 90% [59]. Sequential therapy has been the most studied regimen in Italy and its high efficacy was also confirmed in clinical practice [60]. This regimen seems to be able to overcome the issue of clarithromycin resistance [59]. A recent systematic review and meta-analysis of 46 RCTs showed that sequential therapy was superior to 7- and 10-day triple therapy, but similar to 14-day triple therapy [61]. The efficacy of sequential therapy was also similar to 10-day concomitant

(non-bismuth quadruple) therapy [61]. In Italy, a study confirmed the good performance of concomitant therapy with an eradication rate of 90% [62]. This study also reported a high eradication rate with so-called "hybrid" therapy, which includes a 14-day treatment with PPI and amoxicillin and the addition of clarithromycin and metronidazole during the second week. However, data on hybrid therapies need to be confirmed in larger studies. No difference was found in terms of adverse events between 14-day standard triple, 10-day sequential and 10-day concomitant therapies [61].

According to the European guidelines, the choice of first-line regimen in a given country should be driven by the local prevalence of HP strains with clarithromycin resistance; a threshold of 15–20% has been recommended to define countries with low and high clarithromycin resistance rates [1]. The European guidelines recommend standard clarithromycin triple therapy with an extended duration to 10–14 days in low clarithromycin resistance areas; in alternative to a bismuth-containing quadruple therapy (PPI + bismuth + tetracycline + metronidazole), a sequential or a concomitant therapy in high clarithromycin resistance areas [1]. Unfortunately, Italy lacks a national monitoring of clarithromycin resistance rates. Studies carried out in selected patients showed clarithromycin resistance rates ranging between 10% and 35% across the country [56,63,64], with resistance rates varying in different Italian regions [63]. Therefore, a first-line regimen cannot be identified based on clarithromycin resistance rates. The standard 14-day clarithromycin-containing triple therapy as well as the 10-day sequential or concomitant therapies can all be considered effective first-line regimens in Italy (Table 2). However, recent evidence would discourage the use of a 10-day clarithromycin-containing triple therapy in view of sub-optimal eradication rates [57,61].

Sequential therapy is less expensive than both 14-day triple and concomitant therapies. However, studies specifically addressing cost-effectiveness of sequential therapy compared with other eradication regimens are lacking.

When available in Italy, an alternative first-line treatment may be the '3-drug pill' (i.e., bismuth, metronidazole and tetracycline). A large multicentre European RCT with this regimen (including Italy) reported eradication rates >90%, even in patients harbouring clarithromycin-resistant strains [65].

In case of penicillin allergy, both sequential and concomitant therapies are not feasible, and a 14-day PPI-clarithromycin-metronidazole triple regimen should be used.

The use of levofloxacin in first-line therapy should be discouraged, due to its important role in second-line regimens. Indeed, the strategy using a clarithromycin-containing therapy as initial treatment and a levofloxacin-containing therapy as rescue regimen achieved higher eradication rates than the opposite sequence [66].

When choosing an empirical first-line regimen among those recommended, Italian physicians should take into account what works best in their clinical practice and in their region, as well as the patient's preference [67].

Statements:

One of the following regimens should be used as first-line treatment in Italy:

- **standard 14-day PPI-based clarithromycin-containing triple therapy**
- **10-day sequential therapy**
- **10-day concomitant therapy (non-bismuth quadruple).**

Evidence level: 1a; Grade of recommendation: A

The "3-drug pill" (bismuth, metronidazole and tetracycline) may represent a valid alternative, when available.

Evidence level: 1b; Grade of recommendation: A

3.3.3. Second-line treatment

Current European guidelines recommend as second-line treatment either bismuth-containing quadruple therapy or 10-day levofloxacin-containing triple therapy [1]. A recent meta-analysis of RCTs, including those performed in Italy, supports the use of a 10-day levofloxacin-containing triple therapy as a simple second-line therapy for HP eradication (Table 2) [68]. This meta-analysis showed that triple therapy with PPI + levofloxacin + amoxicillin was not inferior in terms of efficacy to the more complex bismuth-containing quadruple therapy, providing cure rates of 88%. On the other hand, the incidence of side effects was lower with levofloxacin-containing triple therapy than with bismuth-containing quadruple therapy. When considering levofloxacin dosage, a sub-group analysis showed no significant difference in effectiveness between 500 mg (either once a day or 250 mg twice a day) and 1000 mg (500 mg twice a day) regimens, so that the low-dose regimen should be preferred [68]. Two different levofloxacin-containing regimens, a 10-day sequential and a 5-day concomitant, have both shown high eradication rates in a region of Southern Italy [69,70]. Whether these regimens may represent an alternative to levofloxacin-containing triple therapy needs to be confirmed. However, an increased prevalence of primary levofloxacin resistance has been recently reported in Italy and this may affect the efficacy of levofloxacin-based regimens [64]. Approaches to improve HP eradication may include extending therapy duration.

Bismuth salts are no longer available in most Italian areas. However, when available, bismuth-containing quadruple therapy represents a valid alternative second-line treatment for HP infection (Table 2) [1]. With respect to duration, 14-day treatment seems to provide higher eradication rates than 7-day treatment (Intention to treat analysis: 85.6% vs 81.6%; Per protocol analysis: 96.2% vs 89.6%, respectively) [71]. A potential role for quadruple therapy with the novel '3-drug pill" is foreseeable in this setting [65].

Statement: After failure of first-line therapy, 10-day levofloxacin-amoxicillin triple therapy should be used as second-line treatment. Bismuth-containing quadruple therapy is an alternative, if available.

Evidence level: 1a; Grade of recommendation: A

3.3.4. Third-line treatment

After two treatment failures, the European guidelines recommend HP culture and susceptibility testing [1] to allow a better choice of rescue antibacterial treatment based on the antimicrobial resistance pattern of the specific HP strain. Therefore, after two HP treatment failures, patients should be referred to a specialist setting. However, in clinical practice a culture-based approach is often unfeasible in Italy. Although data on empirical third-line therapy are very scanty, there is evidence in clinical practice of a cumulative 90–95% HP eradication rate using levofloxacin-amoxicillin triple therapy and bismuth-containing quadruple therapy as second- and third-line regimens [72]. Therefore, after a failure of second-line treatment with 10-day levofloxacin triple therapy, bismuth-containing quadruple therapy should be used as third-line treatment whenever bismuth salts are available. A rifabutin-based regimen should be used in the treatment of refractory HP infection, namely in patients in whom all previous treatments failed. Rifabutin is an antimycobacterial drug generally used to cure or prevent *Mycobacterium avium*- and *Mycobacterium intracellular*-related diseases. For this reason, the resistance of HP to rifabutin is very low in the general health population [1]. In most studies rifabutin was prescribed at a dose of 300 mg daily (either 150 mg twice a day or 300 mg once a day) for 10 days,

Table 2
Treatment regimens recommended for first- and second-line therapy of *Helicobater pylori* infection in Italy.

Therapeutic regimen	Duration	Drugs and doses
First-line therapy		
Clarithromycin-containing triple therapy	14 days	- PPI, standard dose twice a day - Clarithromycin, 500 mg twice a day - Amoxicillin, 1000 mg twice a day, or - Metronidazole or tinidazole, 500 mg twice a day
Sequential therapy	10 days: First 5 days Followed by 5 days	- PPI, standard dose twice a day - Amoxicillin, 1000 mg twice a day, - PPI, standard dose twice a day - Clarithromycin, 500 mg twice a day - Metronidazole or tinidazole, 500 mg twice a day
Concomitant therapy (non-bismuth quadruple)	10 days	- PPI, standard dose twice a day - Clarithromycin, 500 mg twice a day - Amoxicillin, 1000 mg twice a day - Metronidazole or tinidazole, 500 mg twice a day
Second-line therapy		
Levofloxacin-containing triple therapy	10 days	- PPI, standard dose twice a day - Levofloxacin, 500 mg once a day or 250 mg twice a day - Amoxicillin, 1000 mg twice a day
Bismuth-containing quadruple therapy (when bismuth is available)	7–14 days	- PPI, standard dose twice a day - Bismuth salts, four times a day - Tetracycline, 500 mg three times a day - Metronidazole, 500 mg three times a day

PPI, proton pump inhibitor.

providing eradication rates of about 70% [73]. An Italian study recently confirmed the efficacy of rifabutin in patients with strains resistant to single or multiple antibiotics [74]. However, both the cost and side effects of rifabutin should be taken into account before starting this regimen [73].

Statement: After failure of a second-line regimen, treatment should be guided by antimicrobial susceptibility testing. Nonetheless, referral to specialist setting is strongly advised.
Evidence level: 3a; Grade of recommendation: A

3.3.5. Adjuvant treatment with probiotics

In recent years, the use of probiotics as adjuvant therapies in HP eradication has been extensively studied. Certain probiotics, such as *Lactobacilli*, *Bifidobacteri* and *Saccaromyces boulardii*, exert in vitro anti-HP activity and are helpful in reducing adverse effects associated with antibiotics [75,76].

Three recent meta-analyses have better clarified the role of probiotics in the treatment of HP infection [77–79]. Whang et al. performed a meta-analysis including 10 clinical trials comparing *Lactobacillus*- and *Bifidobacterium*-containing probiotics with no intervention during standard triple therapy [77]. They showed a reduced incidence of side effects in the probiotics supplementation group compared to the group without probiotics (OR: 0.30, 95% CI: 0.11–0.79). Another meta-analysis, including 9 RCTs, evaluated the use of *Lactobacilli* as adjuvant to triple therapy. This meta-analysis showed a reduction of overall adverse effects, although this was not statistically significant [78]. Five RCTs comparing *Saccaromyces boulardii* administered concurrently to triple therapy with placebo or no intervention were selected by the third meta-analysis [79]. The use of probiotics significantly reduced adverse events, especially diarrhoea. All three meta-analyses also reported an increased eradication rate with probiotics supplementation [77–79].

However, standard 7-day clarithromycin-containing triple therapy was used in the majority of the trials included in these meta-analyses [77–79]. Recent studies confirmed the beneficial effect of probiotics in reducing side effects even when added to 14-day triple therapy [80] or to sequential therapy [81], but no benefit on eradication rate was shown with these regimens. More studies are needed to better define the effect of probiotics on eradication rate when added to regimens currently used in clinical practice.

Statement: Some probiotics reduce adverse effects during HP eradication therapy.
Evidence level: 3a; Grade of recommendation: B

3.4. HP and prevention of gastric cancer

Two recent meta-analyses confirmed HP as a strong risk factor for gastric cancer [82,83], reporting that HP eradication significantly reduced the risk of developing gastric cancer.

There is strong evidence that HP exerts a direct mutagenic effects in animal models and cell lines [84,85]. The bacterium has developed strategies to damage the DNA of gastric epithelium cells, thus contributing to the development of gastric neoplasia. The genotoxic properties of HP are the result of inflammatory cells chronically infiltrating the gastric mucosa generating reactive oxygen and nitrogen species that may damage cell DNA, involving the activation of bacterial virulent factors, such as urease, CagA and VacA [84,85]. In this respect, the gastric tumourigenic pathway is similar to that of other tumours caused by chronic inflammation. Although the risk of gastric cancer is influenced by bacterial virulence factors, their identification cannot currently be recommended in clinical practice [1].

Extensive epidemiological research, especially from Asia, has shown that the interplay between HP infection, host genetic conditions and environmental factors result in a wide variability of gastric cancer incidence among different regions [67,86,87]. In the Hehuang valley in China, the prevalence of HP-infected gastric cancers is astonishingly low and environmental factors could be associated with this malignancy [88]. To the contrary, in a study from Bhutan, 86% of the gastric cancer population was HP-infected while environmental factors seemed to play a minor role, thus

leading to the conclusion that the high gastric cancer incidence in this country was mainly due to HP infection [89]. Therefore, a multifactorial view of the diversity in gastric cancer aetiology (HP, host genetic factors and environment) should be accepted, further analyzed and used for an adequate prevention of this malignancy [90].

Statement: HP infection is the most consistent risk factor for gastric cancer.
Evidence level: 1a; Grade of recommendation: A

Gastric mucosal inflammation may result in mucosal atrophy, defined as "loss of appropriate glands" [91]. Histologically proven atrophic gastritis with or without intestinal metaplasia is an unequivocal gastric precancerous condition. Both the atrophy score and the atrophy-topography are strictly related to the risk of 'intestinal type' gastric cancer and this is the biological rationale for gastritis staging [92]. The gold standard in atrophy scoring is the combination of endoscopic and histological findings. Appropriate gastric biopsy sampling with two biopsy samples from the antrum, one biopsy sample from the "incisura angularis" and two biopsy samples from the corpus mucosa is mandatory for atrophy assessment [92].

One of the functional consequences of severe corpus atrophic gastritis is hypochlorhydria. A decrease in acid secretion allows the overgrowth of non-HP bacterial flora, which produces metabolites with carcinogenic potential [93]. HP eradication abolishes the inflammatory response and slows down or may arrest the progression of atrophy; in some cases, it may even reverse atrophy [1].

Statement: The risk of gastric cancer is associated with long-standing gastritis and severity of gastric atrophy/intestinal metaplasia.
Evidence level: 1c; Grade of recommendation: A

HP eradication for gastric cancer prevention may be cost-effective in certain communities at high risk for gastric cancer [1]. The meta-analysis by Ford et al. shows that the number of patients needed to be treated for preventing a single case of gastric cancer is 15 in China compared to 245 in USA [83]. A strong effort is required to identify communities at high risk for gastric cancer, where a test-and-treat "policy" would be indicated; for instance in areas with gastric cancer incidence rates above 10/100.000 subjects per year, such as Asia and Central America, or Marche and Umbria in Italy, where incidence is over 15/100.000 subjects per year [86]. Since HP eradication offers clinical and financial benefits in addition to gastric cancer prevention, the analysis should also consider local eradication costs and antibiotic resistance prevalence in a classic cost/effectiveness analysis.

In this context, attention should always be given to other causative (co)factors of gastric cancer (i.e., smoking and dietary factors) [94].

Statement: HP eradication is the most promising strategy to reduce the incidence of gastric cancer, particularly in high-incidence countries. However, the preventive value of this strategy has to be fully evaluated in Western countries.
Evidence level: 1a; Grade of recommendation: A

Among the possible serological tests, pepsinogens I and II (PgI and PgII), Gastrin-17 and HP serology are considered potential markers for gastric mucosal atrophy. PgI, PgII and the PgI/PgII ratio are the most widely applied gastric atrophy markers with excellent negative predictive value [95]. A PgI/PgII ratio lower than 3 strongly suggests clinically relevant gastric mucosal atrophy and prompts gastroscopy with multiple biopsies [95,96]. A recent meta-analysis showed that a panel test based on serum assay of PgI and PgII, Gastrin-17 and anti-HP IgG has a high sensitivity (80%) and specificity (90%) for the non-invasive diagnosis of atrophic gastritis [97].

Statement: Validated serological tests are available to identify extensive gastric mucosal atrophy. This enables to avoid invasive diagnostic procedures in patients without other indications and to select candidates for endoscopy for adequate gastric biopsy sampling.
Evidence level: 1a; Grade of recommendation: B

HP should be searched and eradicated in individuals with increased risk for gastric cancer, including: patients with a history of gastric cancer previously treated by endoscopic or subtotal gastric resection [98]; first-degree relatives of gastric cancer patients [99]; patients treated with proton pump inhibitors for more than one year [100]; subjects exposed to environmental risk factors (i.e. heavy smokers, individuals with high exposure to dust, coal, quartz, cement) [101,102].

Statement: HP testing and eradication should be considered in the following groups to prevent gastric cancer:
- **Patients with previous gastric neoplasia after endoscopic or surgical therapy**
- **First-degree relatives of patients with gastric cancer**
- **Patients with chronic gastric acid inhibition for more than one year**
- **Patients with strong environmental risk factors for gastric cancer (heavy smoking, high exposure to dust, coal, quartz, cement)**

Evidence level: 1a-4; Grade of recommendation: A

Gastric atrophy is the "field" in which intestinal-type gastric cancer develops. The European guidelines recommend endoscopic surveillance with multiple gastric biopsies every three years, even if *HP* infection was eradicated in patients with extensive (both in the antrum and corpus) atrophic gastritis and/or intestinal metaplasia [92].

However, both mucosal atrophy extent (i.e. topography) and severity (i.e. histology score) parallel gastric cancer risk [92]. Internationally validated trials consistently recognize the reliability of gastritis staging based on topography and severity of the atrophic changes in predicting the risk of gastric cancer. Two staging systems have been proposed: (i) the operative link for gastritis assessment (OLGA) staging, based on the global assessment of atrophy; (ii) the operative link for gastric intestinal metaplasia (OLGIM) staging, scoring the mucosal topography of intestinal metaplasia only. OLGA staging is more sensitive than OLGIM in predicting gastric cancer risk [102]. OLGA staging stratifies atrophic gastritis in 5 stages (0-IV) and identifies Stages III and IV (patients with severe antrum or corpus atrophy or moderate atrophy in both antrum and corpus) as those with high-risk for gastric cancer [103,104] eligible for surveillance (Fig. 1). Atrophic gastritis stages significantly correlate with serological PgI/PgII ratio [103]. The risk of gastric cancer is significantly higher in patients with dysplasia (also defined intra-epithelial neoplasia [IEN]), whose management should be based on the severity of dysplasia. Surveillance should be performed every year with extensive biopsy sampling of the gastric mucosa in case of low-grade dysplasia/IEN,

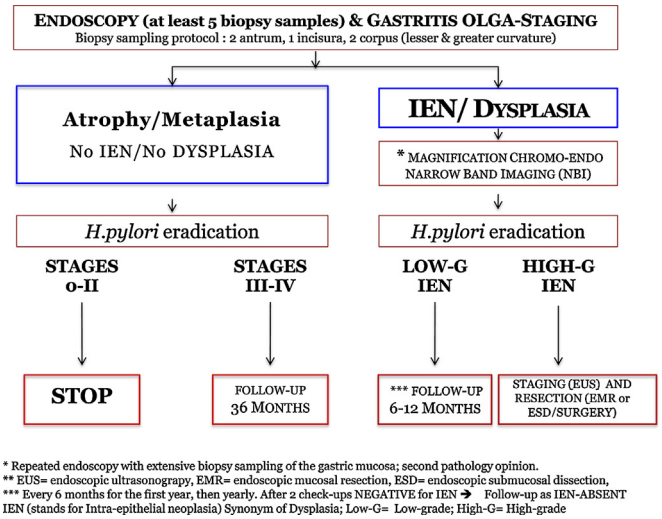

Fig. 1. Summary of proposed management of patients with atrophic gastritis/intestinal metaplasia or gastric dysplasia.

while high-grade dysplasia/IEN should be best removed with endoscopic submucosal dissection (ESD). Histologically complete resection at ESD does not require further surgery.

Statement: Gastric precancerous conditions (atrophic gastritis and/or intestinal metaplasia) require endoscopic surveillance.
Evidence level: 2a; Grade of recommendation: A

Conflict of interest

None declared.

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