World Gastroenterology Organisation Global Guidelines

Helicobacter pylori

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Guideline Update Team
Peter Katelaris (Co-Chair, Australia), Richard Hunt (Co-Chair, United Kingdom),
Franco Bazzoli (Italy), Henry Cohen (Uruguay), Kwong Ming Fock (Singapore),
Manik Gemilyan (Armenia), Peter Malfertheiner (Germany), Francis Mégraud (France),
Alejandro Piscoya (Peru), Duc Quach (Vietnam), Nimish Vakil (USA),
Louis G. Vaz Coelho (Brazil), Anton LeMair (Netherlands)

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1 Summary

Helicobacter pylori continues to be a major health problem worldwide, causing considerable morbidity and mortality due to peptic ulcer disease and gastric cancer.

The burden of disease falls disproportionately on less well-resourced populations. As with most infectious diseases, the greatest impact on reducing this burden comes from improvements in socioeconomic status, which interrupt transmission. This has been observed in many regions of the world, but the prevalence of infection remains high in many regions in which improvements in living standards are slow to occur.

Meanwhile, the optimal clinical management and treatment pathways remain unsettled and are evolving with changing antimicrobial resistance patterns. Despite decades of research and clinical practice, major challenges remain. The quest for the most effective, safe, and simple therapy is still a major issue for clinicians. An effective vaccine also still appears to be elusive.

Clinical guidelines not infrequently proffer discordant advice. It is very difficult for guidelines to achieve relevance across a variety of populations with varying spectrums of disease, antimicrobial resistance rates, and vastly different resources. As local factors are central to determining the impact and management strategies for *H. pylori* infection, it is important for pathways to be based on the best available local knowledge, rather than solely extrapolated from guidelines formulated in other regions, which may be less applicable. To this end, this revision of the WGO *H. pylori* guideline uses a "cascades" approach that seeks to summarize the principles of management and offer advice for pragmatic, relevant, and achievable diagnostic and treatment pathways based on established key treatment principles and using local knowledge and available resources to guide regional practice.

2 Introduction

Helicobacter pylori has been recognized as a major pathogen of humankind for nearly four decades. However, despite the impact of treatment of infected individuals and the reduced transmission of infection in communities in which socioeconomic living standards have improved, it continues to be the most common human bacterial pathogen, infecting perhaps half of the world's population [1]. As a result, it is still a major cause of morbidity and mortality worldwide.

H. pylori infection invariably causes active chronic gastritis. In most people, this may be clinically silent throughout life, but in a substantial minority it causes gastroduodenal diseases, most importantly peptic ulcer disease, noncardia gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. It also increases the risk of gastroduodenal ulceration and bleeding in patients who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and is responsible for symptoms in a subset of patients with functional dyspepsia.

H. pylori has been studied intensively. A literature search reveals more than 45,000 publications. A great deal has been learned about the epidemiology of infection, biology, genetics, pathophysiology, disease expression, diagnosis, and treatment. However, major gaps in our knowledge remain. The precise mode of transmission of infection remains unclear, despite many epidemiological studies that identify risk factors for infection. The determinants of disease expression are still incompletely understood, including many aspects of the host–pathogen interaction. The pathophysiology of this interaction is complex and has been reviewed in detail elsewhere [2,3]. The optimal clinical management pathways in different settings are still a matter of debate, and refinements in diagnostic modalities continue to be

sought. The quest for the most effective, safe, and simple treatment is still a major issue for clinicians, and the problem of antimicrobial resistance to therapy is a significant challenge. The best method for surveillance of adverse histological changes in the gastric mucosa has not been determined, and the quest for an effective vaccine is ongoing.

There have been many reviews and clinical guidelines on *H. pylori* [4–12]. As the field is changing rapidly, there is a need for periodic updating and revision of these position papers. In addition, it is very difficult for guidelines to achieve relevance across a wide variety of populations with varying spectrums of disease and often with vastly different resources with which to deal with it. Guidelines not infrequently proffer discordant advice. As local factors are central to determining the impact and management strategies for *H. pylori* infection, this is not surprising. It is important for clinical advice to be based on the best available local data, rather than extrapolated from guidelines formulated in other regions, which may be less applicable. However, in many areas in which the impact of *H. pylori* infection is greatest, there is a lack of high-quality data to determine the local best practice. Addressing this gap in knowledge is a significant challenge. In the meantime, decisions need to be based on the best available local evidence, extrapolation from higher-quality data from elsewhere, and expert opinion.

The purpose of this update to the WGO guideline is to summarize and review the evidence from a number of new guidelines that outline best practice and to suggest how these principles may be applied around the world using the "cascades" approach. This approach recognizes variations in the regional prevalence and impact of infection and the vast differences in health resources available to address the problem, which require pragmatic, tailored local approaches. The burden of disease wrought by *H. pylori* falls disproportionately on less well-resourced regions, which are insufficiently represented in epidemiological surveys and are often not the focus of clinical guidelines.

Key statement
It is a major challenge for guidelines to achieve relevance across a wide variety of populations with varying spectrums of disease and with vastly different resources with which to deal with it.

3 Natural history, transmission and epidemiology—global aspects

3.1 Natural history of infection

H. pylori infection usually persists for life, unless it is treated with antibiotics or autoeradication occurs when long-standing infection causes widespread gastric mucosal atrophy and metaplasia with achlorhydria. Transient infection may occur in some infants. Reinfection after treatment in adults is uncommon in both higher-prevalence and lower-prevalence regions. Reinfection may be confused with recrudescence, when infection is suppressed transiently, below the threshold of detection by tests, but has not been eradicated by antibiotics. There are variations in the virulence of different *H. pylori* strains globally. The interplay between host and environmental factors may result in differences in the expression of disease.

3.2 Transmission of infection

Although there are well-described risk factors for infection, and plausible hypotheses, the precise mode of transmission has not been definitively established. Most infection appears to occur in early childhood, with a minority of cases developing in adults. There is strong evidence from epidemiology and genetic studies of person-to-person transmission,

particularly within families. Mothers appear to be particularly important in transmission to their young children. Ingestion of the organism seems most plausible via the gastro–oral or oral–oral route. Fecal–oral transmission appears less likely, at least in developed countries. Whether transmission occurs via water, food, household pets, or flies is still a matter of speculation.

3.3 Epidemiology

Although half of the world's population are thought to be infected with *H. pylori*, there is widespread variation in the prevalence of infection, between and within countries (Fig. 1). In addition, the prevalence may vary within a single city and also between subgroups within a population (Fig. 2) [13]. For example, there may be wide variations in the prevalence between more affluent urban populations and rural populations.

Fig. **1** Global prevalence of *H. pylori.* From Hooi et al. 2017 [1].

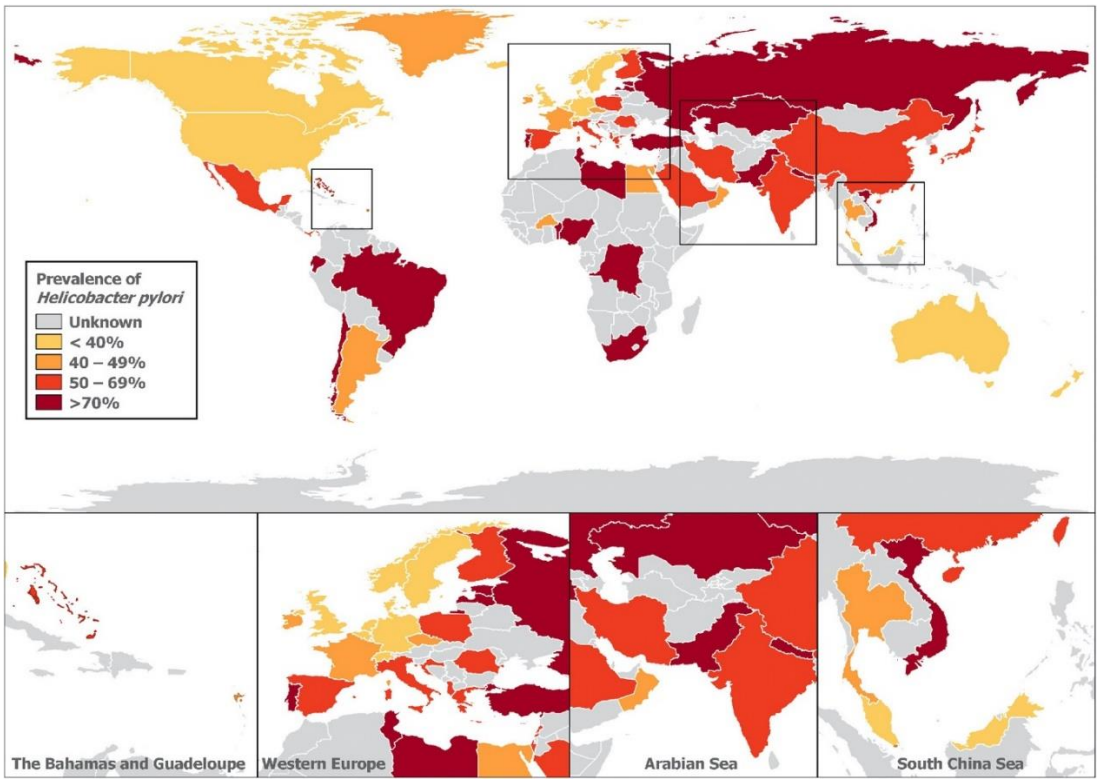
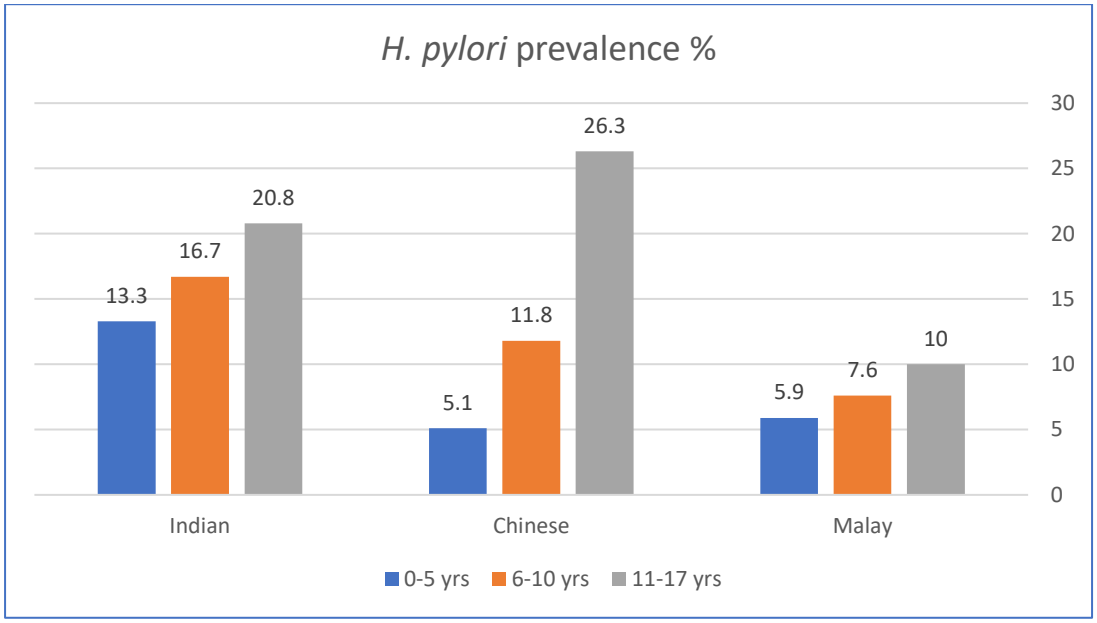


Fig. **2** Prevalence of *H. pylori* among children and young adults in Kuala Lumpur, Malaysia. From Goh [13].



The quality of prevalence data varies. Many studies are not true prevalence studies, but rather audits of clinical subsets. Other studies may not represent a valid cross-section of the population. Moreover, there is significant variability in the quality of reports. In some regions, diagnostic methods may be less reliable, while some countries are poorly represented as they lack any reliable data at all. For all these reasons, a single figure cannot be taken to summarize and represent the prevalence of infection in an entire country and must be applied with caution. For example, a prevalence study from one city in one region of a populous, multiethnic country with wide variation in socioeconomic standards is unlikely to represent the true prevalence across the entire country and cannot reflect high-risk and low-risk subsets. However, countries and regions can usually be characterized as high-prevalence, mid-prevalence, and low-prevalence locations [1].

The major determinant of the prevalence of infection is socioeconomic status in childhood. Socioeconomic factors reflect levels of hygiene, sanitation, density of living, and educational level.

A strong inverse relationship has been consistently reported. Thus, as expected, the prevalence of infection is generally higher in developing countries, and infection is almost ubiquitous in some of the most resource-poor subsets of these populations. Migrants from such regions are recognized as being a high-risk group in more developed, low-prevalence countries.

Key statement
The major determinant of the prevalence of infection is socioeconomic status in childhood.

The prevalence of *H. pylori* infection increases with age. This is mostly due to the cohort effect, in which the risk of acquiring infection was greater during the childhood of those born longer ago in comparison with more recently, rather than reflecting ongoing adult acquisition. Ethnicity has been described as a risk factor, but is most likely closely correlated with socioeconomic status or practices that may increase the risk of transmission, rather than having a genetic basis.

A striking observation has been the change in the prevalence of infection over time in some countries. Reports of rapidly falling infection rates, most marked in children and younger adults, are common from developed countries, and from countries that have undergone rapid

economic development that has led to raised socioeconomic standards. In these countries, the prevalence of infection is now low.

A gradual fall in the prevalence of peptic ulcer disease and noncardia gastric cancer is predicted by this observation, since in general the prevalence of peptic ulcer disease and gastric cancer reflects the prevalence of *H. pylori* in a population. Indeed, the prevalence of ulcer disease and gastric cancer have been falling for decades in developed countries. The fall in disease expression lags behind the fall in infection rates for many years. The declining prevalence of infection and disease occurred long before *H. pylori* was recognized and treatments were developed.

As with most endemic infectious diseases, a decline in prevalence has more to do with improvements in population hygiene and sanitation than with individual, case-by-case treatment, since in most countries, only a minority of infected individuals will ever receive therapy. Notable exceptions are well-resourced high-prevalence countries such as Japan, where screening and treatment is now done systematically in early adulthood. The prevalence of infection appears to be stable in countries in which standards have not improved or have deteriorated, and it is unlikely to fall substantially until improvements do occur. Peptic ulcer disease is still rampant in many of these countries. The burden of gastric cancer also falls disproportionately on these populations.

Key statement
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4 The impact of *H. pylori* infection and the effect of eradication

4.1 *H. pylori* and peptic ulcer disease

The recognition that *H. pylori* was the cause of most duodenal ulcers and about two-thirds of gastric ulcers was a seminal, Nobel Prize–winning medical breakthrough [14]. In many developed countries with a decreasing prevalence of infection and cure of ulcer patients, the proportion of all peptic ulcers due to *H. pylori* is falling. In less developed countries, where the prevalence of infection remains high and fewer ulcer sufferers receive curative treatment, peptic ulcer disease (PUD) continues to be a very common and important condition. *H. pylori* infection has been estimated to confer an individual lifetime risk of peptic ulcer disease of 15–20%. Untreated, PUD is a chronic relapsing and remitting disease that causes major mortality and morbidity due to pain, bleeding, and perforation. It also results in economic losses. Eradication of *H. pylori* heals most active peptic ulcers and prevents further relapses, thus effecting a cure. Eradication of *H. pylori* in patients with a history of ulcer disease prevents subsequent relapses.

NSAIDs and aspirin cause most other peptic ulcers. *H. pylori* and NSAIDs act synergistically to increase the risk of ulcers and bleeding. Eradication of *H. pylori* reduces this risk before the start of chronic NSAID therapy.

4.2 *H. pylori* and gastric cancer and MALT lymphoma

In susceptible infected hosts, long-standing active chronic gastritis may result in gastric mucosal atrophy with intestinal metaplasia. In a minority, these premalignant mucosal changes progress to dysplasia and clinically silent, early cancer, followed by advanced gastric cancer. Gastric cancer often presents at an advanced, symptomatic stage and it has a generally poor prognosis. *H. pylori* has been estimated to confer an individual lifetime risk of gastric

cancer of 1.5–2.0% in infected individuals. Despite the relatively low individual risk, as the global number of people infected is estimated in the billions, there is a global burden of gastric cancer of over one million per year, with a high fatality rate (Table 1) [15]. This burden is not distributed evenly. East Asia—Japan, Korea, and eastern China—has the highest prevalence of disease. China suffers 40% of world cases of gastric cancer. Most, but not all, gastric cancers are related to *H. pylori*. The risk of progression to gastric cancer varies and is related to host and pathogen factors. Host cofactors include smoking and diet. High salt intake, the consumption of pickled foods, and diets low in antioxidants are dietary cofactors. Genetic risk factors in the host that are associated with increased risk include the presence of polymorphisms in genes that determine the expression of interleukin-1 (IL-1; proinflammatory cytokines) and pathogen recognition receptors. Genotyping of strains of *H. pylori* has revealed differences in virulence factors that promote inflammation and are associated with an increased risk of cancer.

Table **1** Global burden of cancer in 2020

Most common cancers globally

- Breast (2.26 million cases)
- Lung (2.21 million cases)
- Colon and rectum (1.93 million cases)
- Prostate (1.41 million cases)
- Skin (nonmelanoma) (1.20 million cases)
- Stomach (1.09 million cases)

Most common causes of cancer deaths are cancers of the:

- Lung (1.80 million deaths)
- Colon and rectum (935,000 deaths)
- Liver (830,000 deaths)
- Stomach (769 000 deaths);
- Breast (685 000 deaths)

Source: World Health Organization [15].

Eradication of *H. pylori* before the occurrence of adverse, precancerous histological changes has been shown to prevent gastric cancer and is the rationale for mass test-and-treat screening programs in young adults in countries with a high burden of disease and with sufficient resources to devote to this endeavor. In less well-resourced regions with a high burden of gastric cancer, such a strategy remains aspirational rather than feasible, given cost constraints, logistical difficulties, and competing health-care needs.

Eradicating *H. pylori* after mucosal atrophy and/or intestinal metaplasia have developed may reduce the risk of gastric cancer, but does not eliminate it [16]. In any individual, the residual risk is related to the extent and severity of the mucosal changes, as well as other host risk factors. Endoscopic surveillance of intestinal metaplasia may be appropriate in some settings.

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is rare. Most cases are a consequence of *H. pylori* infection, and eradication of *H. pylori* when the lymphoma is at a low-grade stage results in regression and cure. Late recurrences after eradication have occasionally been reported.

Key statement

Eradication of *H. pylori* before the occurrence of adverse, precancerous histological changes has been shown to prevent gastric cancer and is the rationale for mass test-and-treat screening programs in young adults in countries with a high burden of disease and with sufficient resources to devote to this endeavor.

4.3 *H. pylori*–associated dyspepsia

Most *H. pylori* gastritis is asymptomatic, but it is commonly associated with upper gut symptoms in the absence of ulcer disease. However, only about one-third or less of infected patients with "functional dyspepsia" experience sustained relief of symptoms after eradication therapy. This is because functional dyspepsia is a heterogeneous condition that may be caused by different mechanisms. *H. pylori* may be causal in some patients with symptoms and may be present incidentally in others. However, the proportion of infected patients who improve after eradication therapy is greater than those who are given empirical acid-suppressive therapy. In addition, patients may benefit from a reduced lifetime risk of ulcer disease and cancer, especially if they are treated before adverse histological changes have developed in the gastric mucosa.

A recent revised classification of gastritis has recognized *H. pylori*–associated dyspepsia as a distinct entity, and it has been incorporated into the 11th revision of the International Classification of Diseases (ICD-11) [11]. The classification also highlights the significance of *H. pylori* gastritis as the precursor lesion that leads to peptic ulcer disease and gastric cancer, irrespective of whether symptoms are present.

H. pylori infection has been associated with a variety of other conditions. In most cases, the association has not been shown to be causal, and common conditions will inevitably coexist in some patients. There is modest evidence linking *H. pylori* to immune thrombocytopenic purpura, and eradication therapy has been tried, with variable results.

5 Diagnosis of *H. pylori* infection

5.1 Who to test and treat?

The decision on whether or not to treat *H. pylori* must be an active one that takes into account the individual patient's circumstances and risks. The decision to test for *H. pylori* should therefore only be made with therapeutic intent.

Good practice point
The decision to test for *H. pylori* should only be made with therapeutic intent.

Evidence-based indications for testing for and treating *H. pylori* are summarized in Table 2 [4,17]. The applicability of each indication in different regions will depend on the prevalence of infection and disease, resources, competing needs, and individual patient factors. Peptic ulcer disease is the prime indication in most of the world. The clinical and health-economic benefits of short-term curative therapy for a common, chronic, important disease have been amply demonstrated over many years. In resource-poor regions, this indication for therapy should be prioritized.

Table **2** Indications for treatment of *H. pylori* infection

- Past or present duodenal and/or gastric ulcer, with or without complications
- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- Gastric mucosal atrophy and/or intestinal metaplasia
- Following resection of gastric cancer
- Patients who are first-degree relatives of patients with gastric cancer

- Patients' wishes (after full consultation with their physician)
- Functional dyspepsia
- To reduce the risk of peptic ulcer and upper gastrointestinal bleeding in nonsteroidal anti-inflammatory drug-naive users
- Before starting long-term aspirin therapy for patients at high risk for ulcers and ulcer-related complications
- Patients receiving long-term low-dose aspirin therapy who have a history of upper gastrointestinal bleeding and perforation
- Patients with gastroesophageal reflux disease who require long-term proton-pump inhibitors
- As a strategy for gastric cancer prevention in communities with a high incidence
- Unexplained iron-deficiency anemia, or idiopathic thrombocytopenic purpura

Adapted from Fock et al. 2009 [4]. *Note:* the strength of indications may vary regionally and individually.

6 How to test for *H. pylori*

6.1 Endoscopic diagnostic tests

Diagnostic tests for *H. pylori* infection may be invasive (endoscopic) or noninvasive (nonendoscopic) (Table 3). Biopsies taken at endoscopy are most commonly for histological analysis and urease testing. Biopsies for culture are less often used for diagnosis, unless antimicrobial resistance testing is available and is needed to aid individual clinical decision-making or determine population resistance rates. A combination of two testing modalities taken from two topographic locations in the stomach is generally most effective for diagnosis. In practice, this usually means biopsies taken from the antrum and body of the stomach for histology and from the antrum for a urease test. More structured biopsy protocols may be used when there is an additional need for histological surveillance, as in the Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis/Intestinal-Metaplasia Assessment (OLGIM) protocols [18]. Histology is usually costly and very operator-dependent, and accuracy cannot be assumed except in comparison with other previous testing modalities.

Table **3** *Cascades:* Diagnostic tests for *H. pylori*—relative availability according to high, intermediate, or low levels of health-care resources

		High resources	Intermediate resources	Low resources
Endoscopic tests	Histology	Widely used	Usually used	Rarely used
	Commercial urease tests	Widely used	Widely used	Rarely used
	In-house urease tests	Widely used	Widely used	Widely used
	Culture	Many centers	Major centers	Rarely used
	PCR: diagnosis/culture	Major centers	Rarely used	Rarely used
Breath tests	C^{14} urea	Widely used	Usually used	Major centers
	C^{13} urea	Usually used	Major centers	Rarely used
Stool tests	Stool antigen	Usually used	Usually used	Major centers
	Stool PCR	Major centers	Rarely used	Rarely used
Serology	Venous	Widely used	Usually used	Usually used

	Fingerprick at point of care	Usually used	Rarely used	Rarely used
Clinical assessment	Symptoms	Widely used	Widely used	Widely used

PCR, polymerase chain reaction.

In resource-limited regions, reliance on urease tests is common. Most commercial urease tests appear to be accurate to a sensitivity of about 95%. Although they are much less expensive than histology, these tests may still incur a significant cost burden in resource-poor regions, especially when the cost is borne by the patient. A commercial test typically costs US$ 5. In regions where the average daily income for an unskilled worker may be $1–2, this may not be affordable. Fortunately, there are very inexpensive generic urease tests that have been available for many years and can be done on site, with a unit cost of about $0.20. These are usually unbuffered tests that give a very rapid result and have a sensitivity very similar to that of commercial tests [19]. They are in use in some countries in Africa, Asia, and the Pacific region.

Culturing *H. pylori* from biopsies requires specific transport conditions, laboratory skills, and equipment. Culture success rates may reach 90% in expert centers, but are often lower than that in less expert centers. Subculturing for antimicrobial testing may also not always be successful in less expert laboratories, so that results may not always be obtained when required. There are now commercially available real-time polymerase chain reaction (PCR) tests that allow the detection of *H. pylori* with high levels of sensitivity and specificity, and also of mutations that cause clarithromycin resistance [20–22]. These tests do not require strict preanalytic conditions and they can be performed in a few hours. The validation and implementation of these rapid, inexpensive kit-based point-of-care antimicrobial resistance tests promises to be a major advance in management. The availability of such tests in regions of high resistance may greatly aid the choice of therapy for individual patients, while also facilitating surveys of population prevalence.

Good practice point
The validation and implementation of rapid, inexpensive kit-based PCR diagnostic and antimicrobial resistance tests promises to be a major advance in management.

Endoscopic diagnosis of duodenal ulcer disease in a higher-prevalence, poorly resourced region, in a patient who is not taking NSAIDs, has an accuracy of 95% for predicting the presence of *H. pylori*. While a biopsy-based test to confirm infection is desirable, the presence of the duodenal ulcer has a predictive value similar to that of most tests, and so it is reasonable to treat without incurring further costs (unless inexpensive generic urease tests are available).

6.2 Noninvasive diagnostic tests

When endoscopy is not required or not available, noninvasive tests may be used. Urea breath tests (UBTs) are very useful and have higher diagnostic accuracy than other noninvasive tests for identifying *H. pylori* (in patients without a history of gastrectomy). Somewhat surprisingly, these are not widely available in many countries in which *H. pylori* and peptic ulcer disease are most common. The reasons for this are complex, and may include a lack of expertise or resources to set up and operate breath analysis laboratories, the relatively high cost of commercial kit tests, or overreliance on either empirical therapy or endoscopy. In many cases, valid anxiety about gastric cancer is a major driver of the use of endoscopy (although once they become symptomatic, gastric cancers are rarely curable). The costs of UBTs vary. In higher-resource countries, costs compare very favorably with endoscopy, although in regions in which endoscopy is relatively inexpensive, the cost advantage disappears unless low-cost UBTs are available. The stable isotope C^{13} UBT test has been validated in detail in multiple locations, and is often preferred in well-resourced regions. The C^{14} UBT uses a very low dose of radioactive isotope and usually has a shorter collection time,

but has not been as extensively validated. It may be somewhat less accurate. The laboratory set-up costs for C^{13} UBTs are higher, as a mass spectrometer is required, whereas a less expensive scintillation counter is needed for C^{14} UBTs. The real (rather than commercial) unit cost of the C^{14} isotope is low, so the test could be provided at a very low cost using a central laboratory "hub and spoke" model for service delivery, with remotely collected breath samples being delivered from throughout a region. Point-of-care commercial kits and analyzers are available. The accuracy varies, and the unit cost of these kits is often high.

Stool antigen testing is another option. These tests appear to be almost as accurate as UBTs, but patients and health-care and laboratory workers often have a lower preference for stool-based tests. Cost is an issue in some locations. Stool-based rapid PCR tests are also available [21]. Although these tests face the same acceptance barriers, as well as requiring laboratory equipment and skills, they have the potential to provide rapid diagnosis and antimicrobial resistance testing in a single noninvasive test.

Serological antibody tests are commonly available. Although they are useful as seroepidemiological surveys, these tests often lack the sensitivity and specificity required for decision-making in individual patients and are generally not very helpful. They need to be validated for specific locations, and the issue of false results due to cross-reactivity has rarely been addressed. In a community with moderate *H. pylori* prevalence, the accuracy of these tests may not exceed 50%.

6.3 Testing to assess the outcome after eradication therapy

As the success of eradication is very variable, outcome assessment should ideally be done in all patients, although this may not be feasible universally. Priority should be given to those who remain at highest risk for harm if the infection is ongoing, such as those who are being treated for complicated ulcer disease (bleeding or perforation).

Biopsy-based testing may be used to determine the outcome after eradication therapy when endoscopy is required (to assess gastric ulcer healing and exclude neoplasia, or to survey adverse histology, for example). Otherwise, noninvasive tests are preferred. UBTs and stool tests should be done not less than 1 month after the completion of eradication therapy. To minimize false-negative results, no antibiotics or bismuth compounds should be taken by the patient for at least a month before testing, and proton-pump inhibitor (PPI) use should be avoided for at least one and preferably two weeks. Serology is not useful for assessing the outcome, as antibody levels often persist for years after therapy. Despite the widespread validation of noninvasive diagnostic tests, and of breath tests in particular, they are still not available at low cost in many places around the world, and this remains a major unmet clinical need.

6.4 Diagnostic pathways

The choice of diagnostic test depends to a large extent on the clinical context, availability, expertise, and cost. If all modalities for diagnosis are available, the key issue is whether endoscopy is required to investigate symptoms or signs of upper gut disease. In low-prevalence, more developed countries, assessment for gastroesophageal reflux (GERD), functional dyspepsia, cardia and esophageal cancer concerns are common indications for endoscopy, and it is usual to biopsy the stomach for *H. pylori* at that time. *H. pylori* is still an issue in such regions, particularly in higher-risk subgroups such as older patients and those with lower socioeconomic status, or migrants from high-prevalence regions. In these countries, a noninvasive "test-and-treat" strategy using UBTs have been validated in younger patients and are cost-effective, although the use of this strategy may be declining. An empirical trial of PPI therapy is often done in primary care instead, with recourse to endoscopy if the symptoms are not relieved. Although popular, this is problematic when the symptoms are not typical of GERD, and the ideal duration of such a treatment trial is unclear. It may lead to failure to diagnose *H. pylori*. Although the organism may be incidental to the

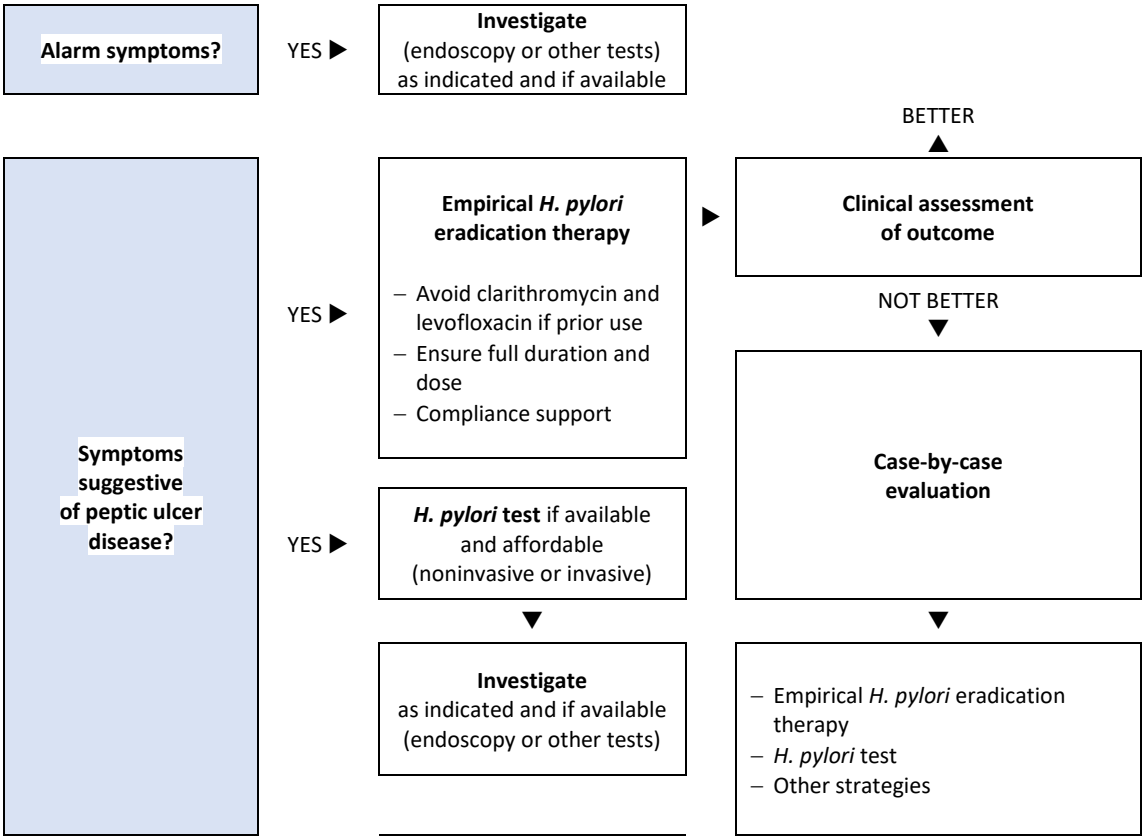
presentation, treatment in younger adults is associated with significant long-term risk reduction. The cost-effectiveness of management strategies for *H. pylori* in well-resourced, lower-prevalence countries varies with local health-care costs.

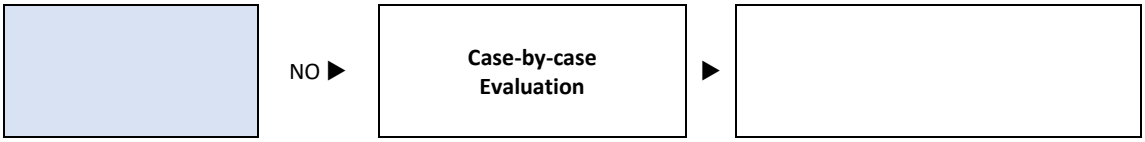
In higher-prevalence countries, there is often a distinct preference by both doctor and patient for prompt endoscopy, due to the fear of gastric cancer—although as noted, it is not certain whether this improves survival when patients present with symptoms. For individual decision-making, the pretest probability of infection, the patient's age, the nature of symptoms or signs, and the local prevalence of ulcer disease and gastric cancer must be considered.

6.5 Empirical therapy in low-resource regions

Where there is very limited access to endoscopic or noninvasive means of diagnosing *H. pylori* infection, decision-making must be empirical, based on the clinical setting. Peptic ulcer disease may be strongly suspected on clinical grounds when there is a clear history of periodic upper gut pain and/or any earlier or recent history of upper gastrointestinal bleeding. In regions in which it is known that the prevalence of *H. pylori* is high and peptic ulcer disease is common, it is reasonable to use empirical eradication therapy for the presumptive clinical diagnosis of peptic ulcer disease (Fig. 3). The cohort so treated will include many with peptic ulcer disease, who will gain major benefit. It will also include some who have *H. pylori*–associated gastritis but no active ulcer. In this group, symptom resolution occurs more frequently than with the use of any other therapy (commonly PPIs), and importantly, successful therapy reduces lifelong risks of peptic ulcer disease and gastric cancer. Treatment of both peptic ulcer disease and gastritis has also been shown to be cost-effective.

Fig. **3** *Cascades:* treatment pathways for upper gastrointestinal symptoms in regions with a high prevalence of *H. pylori* and with low health-care resources.





Note: Treatment for *H. pylori* in the context of possible ulcer disease dominates the clinical pathway, as the clinical and health economic benefits likely exceed those of other strategies.

With empirical symptom-based eradication therapy, there will be a subgroup treated who are not infected and may have other diagnoses. This group will not benefit from eradication therapy, and there are costs and the unnecessary use of antibiotics involved, but the likelihood of major harm is low and the overall benefit to the treated group justifies this approach. Indeed, the Asia–Pacific Consensus Group on *H. pylori* has specifically endorsed such an approach in regions in which *H. pylori* and peptic ulcer disease are common and many people have no access to investigations, for either economic or geographic reasons. Empirical use of PPI therapy is likely to be less beneficial than the initial treatment. Such an approach should be supported by programs for educating health-care workers to recognize symptoms that are more likely to be due to ulcer disease and to apply this strategy selectively. In these resource-poor regions, treating all upper gut symptoms with such an approach is harder to justify.

NSAID use is widespread, and NSAID-related peptic ulcer disease is common and may coexist with *H. pylori* infection. In an empirical setting of suspected ulcer disease, when NSAIDs (including aspirin) are being used, it is reasonable both to treat for *H. pylori* and to address the NSAID risk by ceasing the use of these agents and treating the patient with PPIs for a few weeks after the completion of eradication therapy.

Good practice point
In resource-poor, high-prevalence regions in which diagnostic testing is not available, a history suggesting chronic ulcer disease—periodic upper gut pain and/or past or present melena—suggests a high likelihood of *H. pylori* ulcer disease and justifies empirical eradication therapy, especially in patients with no history or NSAID or aspirin use.

7 Treatment of *H. pylori* infection

A vast number of studies have addressed therapy issues, and numerous expert guidelines recommending choices of therapy are available. However, much of the literature and advice derives from well-resourced countries, with relatively little coming from the poorly-resourced countries that bear the major burden of diseases caused by *H. pylori*. Principles for antibiotic therapy that apply universally have been established. However, there are key issues that must be addressed locally in order to determine the best local practice, as antimicrobial resistance patterns and therefore eradication rates vary regionally [23,24] and other local issues such as the cost and availability of drugs influence the choice of therapy. The key principles that guide the choice of eradication therapy are outlined in Table 4.

Table **4** Key principles guiding the choice of *H. pylori* eradication therapy

1. Randomized controlled treatment trials and meta-analyses provide the highest level of evidence, but are not available for many regions. Local audits of treatment outcome are useful.
2. Treatment recommendations based on resistance patterns and outcome data from one region may not be applicable elsewhere, due to variation in resistance rates and other factors.
3. Generating high-quality local data and monitoring antibiotic resistance and treatment outcomes are priorities.
4. Ad hoc, unproven therapies should be avoided.

5. The main determinant of eradication success is pretreatment antibiotic resistance.
6. Primary resistance to clarithromycin, metronidazole, and levofloxacin varies widely regionally.
7. Major determinants of primary resistance appear to be the magnitude and duration of community usage of these antibiotics as monotherapy for other indications.
8. Prior personal exposure of a patient to these drugs is likely to result in resistance and increases the chance of treatment failure.
9. Primary clarithromycin resistance (CR) is reported to have increased in many countries over relatively few years, while remaining stable in other countries.
10. Primary or secondary resistance to amoxicillin and tetracycline are so rare as to not affect treatment choices.
11. Since much treatment is given presumptively or after noninvasive *H. pylori* testing, the choice of therapy will be based on knowledge of likely local antimicrobial resistance patterns.
12. When endoscopy is carried out, culture is not often done routinely prior to first-line therapy in most places, but this will vary according to skills, resources, local knowledge of resistance rates, and outcomes. Ideally, culture should also be used to monitor local resistance trends over time.
13. The availability of rapid, inexpensive, point-of-care PCR antimicrobial resistance testing may change individual treatment choices and facilitate the surveillance of trends in resistance.
14. Secondary resistance after treatment failure is very common with clarithromycin, metronidazole, and perhaps levofloxacin.
15. Repeating the same therapy has a low likelihood of success and should be avoided.
16. The choice of second-line and subsequent therapies, if needed, should follow a logical decision path that involves using the most effective drugs first, avoiding repeating the same therapy, and using evidence-based choices of subsequent therapies.
17. Culture has a very limited role in determining the choice of salvage therapies.
18. The dosage and duration of therapy will influence outcomes.
19 Treatment should be preceded by an informed consent process that outlines the potential risks and benefits of therapy to the patient.
20. Compliance is a major modifiable determinant of eradication success and should be supported with clear verbal and written information.
21. Smoking has an adverse effect on eradication success.
22. Unmodifiable risk factors for treatment failure may include *CYP2C19* polymorphisms and the virulence factors of the organism.
23. The role and value of potassium-competitive acid blockers such as vonoprazan is still emerging. These drugs are not affected by *CYP2C19* polymorphisms and result in more uniform and potent inhibition of gastric acid secretion.
24. Costs may be minimized by using high-quality generic drugs, especially in resource-poor regions.
25. The drugs required should be on essential drug lists and be widely available.

These key principles must be adapted regionally according to the available resources.

8 Translating treatment principles into therapeutic choices

8.1 Choice of first-line eradication therapy

Application of these principles of therapy will ensure the best outcomes possible. In well-resourced regions, treatment may be based on high-quality trials and audit and culture data; in resource-poor regions, reliance on a knowledge of community or personal antibiotic usage and any local audit of outcomes will influence the use of therapies recommended in guidelines from elsewhere [4–12].

8.1.1 PPI, amoxicillin, clarithromycin triple therapy

In many parts of the world, triple therapy, comprising a proton-pump inhibitor (PPI) with amoxicillin and clarithromycin (PPI-AC), is still the most commonly used first-line therapy. This combination was the first very widely recommended therapy and superseded less effective triple therapies. It has been very well evaluated over the years. The major determinant of eradication success with this combination is pretreatment clarithromycin resistance (CR). The prevalence of antibiotic resistance, particularly CR, varies widely around the world (Table 5). Where clarithromycin has been and is used commonly as monotherapy for other infections, the level of CR is often high and increasing. There are views that this therapy should be abandoned in areas where the primary CR rates are known to be 15–20% or greater, because of the impact this has on eradication rates. A somewhat arbitrary minimum eradication rate of 80% on an intention-to-treat basis is often quoted as a benchmark for an acceptable therapy. This is a common eradication rate for PPI-AC in real-world studies in areas where CR rates are moderate or low (i.e., below 15–20%). Unacceptably lower eradication results may occur in countries in which the prevalence of CR is higher.

Table **5** Pooled prevalences of primary and secondary antibiotic resistance relative to World Health Organization region

WHO region	**Pooled prevalence of antibiotic resistance, % (95% CI)**					
Africa	Clarithromycin	Metronidazole	Levofloxacin	Cla+Met	Amoxicillin	Tetracycline
Overall	15 (0–30)	91 (87–94)	14 (12–28)	–	38 (32–45)	13 (9–17)
Americas	Clarithromycin [a]	Metronidazole	Levofloxacin	Cla+Met	Amoxicillin	Tetracycline
Primary	10 (4–16)	23 (2–44)	15 (5–16)	–	10 (2–19)	–
Secondary	18 (13–23)	30 (19–41)	22 (3–42)	–	7 (1–13)	–
Not specified [b]	–	–	–	3 (0–13) [c]	–	4 (1–11) [c]
Overall	14 (9–19)	27 (14–39)	14 (12–28)	3 (0–13) [c]	8 (3–13)	4 (1–11) [c]
Eastern Mediterranean	Clarithromycin	Metronidazole	Levofloxacin	Cla+Met	Amoxicillin	Tetracycline
Primary	33 (23–44)	56 (46–66)	19 (10–29)	19 (0–39)	14 (8–20)	10 (4–15)
Secondary	17 (10–27)	65 (54–74) [c]	30 (14–46)	11 (6–20)	10 (5–18) [c]	17 (8–26)
Not specified [b]	25 (17–32)	67 (61–72)	–	8 (4–11)	15 (8–22)	–
Overall	29 (23–25)	61 (55–67)	23 (14–32)	14 (5–23)	14 (10–18)	10 (8–13)
Europe	Clarithromycin [a]	Metronidazole [a]	Levofloxacin [a]	Cla+Met [a]	Amoxicillin	Tetracycline
Primary	18 (16–20)	32 (27–36)	11(9–13)	1 (0–2)	0 (0–0)	0 (0–0)
Secondary	48 (38–57)	48 (38–58)	19 (14–24)	18 (16–20)	0 (0–0)	0 (0–1)
Not specified [b]	33 (26–39)	47 (35–39)	14 (10–18)	7 (0–13)	1 (0–2)	1(0–2)
Overall	32 (25–31)	38 (33–42)	14 (12–16)	15 (12–18)	0 (0–0)	0 (0–0)

WHO region	Pooled prevalence of antibiotic resistance, % (95% CI)					
Southeast Asia	Clarithromycin	Metronidazole [a]	Levofloxacin [a]	Cla+Met	Amoxicillin	Tetracycline
Primary	10 (5–16)	51 (26–76)	30 (14–46)	–	2 (0–5)	0 (0–1)
Secondary	15 (8–27) [c]	44 (32–58) [c]	24 (15–37)	–	–	–
Not specified [b]	25 (0–55)	80 (57–100)	5 (3–11)	6 (1–10)	28 (0–62)	1 (1–2)
Overall	17 (6–28)	59 (40–78)	25 (13–28)	6 (1–10)	12 (6–17)	0 (0–12)
Western Pacific	Clarithromycin [a]	Metronidazole [a]	Levofloxacin	Cla+Met [a]	Amoxicillin	Tetracycline [a]
Primary	34 (30–38)	47 (37–57)	22 (17–28)	8 (6–10)	1 (1–1)	2 (1–2)
Secondary	67 (54–80)	62 (50–71)	30 (20–39)	13 (8–18)	1 (1–2)	0 (0–1)
Not specified [b]	25 (21–29)	69 (64–74)	19 (17–21)	14 (11–18)	1 (1 2)	10 (7–14)
Overall	34 (30–38)	55 (51–59)	24 (21–26)	11 (9–13)	1 (1–1)	2 (1–2)

From Savoldi et al. 2018 [23]. Cla+Met, combined resistance to clarithromycin and metronidazole.

Notes: [a] *P* value for subgroup comparison < 0.05. [b] Not specified: the study did not report the type of resistance. [c] Only one study contributed to the analysis.

Key statement
The major determinant of eradication success with PPI-AC is pretreatment clarithromycin resistance.

The optimal duration of therapy is a matter of contention. Recent calls for universal 14-day PPI-AC therapy usually originate from regions with higher CR. Initial studies were mostly for 7 days, although that duration may have been influenced by registration trial design. Proponents of the longer duration of therapy point to somewhat higher eradication rates in systematic reviews. However, there are other considerations that influence the duration of therapy, particularly in resource-poor countries. Adding a second week of therapy may increase eradication rates, typically by about 10%. This means that the number of patients needed to treat with an extra week of therapy in order to achieve one more treatment success is 10. The price of this higher eradication rate, if achieved, includes a doubling of the cost of treatment, which is a major issue in resource-poor regions. (It should be noted that the cost of a week of triple therapy in very resource-poor regions may be as much as weekly earnings for the lowest paid.) The risk of adverse effects increases considerably with protracted antibiotics, as does the likelihood of noncompliance. An alternative is to give shorter therapy where compliance is likely to be greater and adverse effects and costs fewer, with the understanding that 10% more patients may need a second-line salvage therapy. Overall antibiotic use will be much lower with the second strategy, as long as first-line eradication rates are at least moderately high. The longer therapy is usually recommended in some well-resourced countries, but more modeling of shorter courses in resource poor-regions is needed. It must also be noted that acceptable eradication rates with 1-week PPI-AC therapy have been reported from several countries, and the incremental benefit of a longer course has not been studied. The optimal dosage for the PPI (standard or high dose) and clarithromycin (250 mg or 500 mg twice daily) has not been determined in most locations. In high CR regions, neither one nor two weeks of this therapy may achieve acceptable eradication rates. In such places, the choice for first-line therapy varies.

The role and value of potassium-competitive acid blockers such as vonoprazan in place of PPIs in any eradication therapy is emerging. These drugs are not affected by *CYP2C19* polymorphisms and result in more uniform and potent inhibition of gastric acid secretion [25].

8.1.2 Bismuth-based quadruple therapies

The other core choice for first-line therapy, especially in regions with high primary CR, is still bismuth-based quadruple therapy. The best-studied regimen involves a PPI, bismuth, tetracycline, and metronidazole (PPI-BTM). This treatment has stood the test of time, since it leads to reliable and acceptable eradication rates irrespective of primary metronidazole resistance (MR), as the addition of a PPI to BTM appears to overcome MR. Good results have been achieved with 7-day therapy, although there are proponents of longer (10–14-day) treatments. The major drawbacks of this therapy are the clumsy dosage regimen (as it is usually dosed four times daily) and common but usually mild adverse effects, which may impair adherence. Reduced access to bismuth and tetracycline may limit the use of this treatment in some places. However, when these drugs are not readily available or not registered, it is often feasible to import generic drugs at low cost, with the permission of the relevant authorities.

A quadruple therapy substituting amoxicillin for tetracycline (PPI-BAM) has long been reported and is less used, but may provide acceptable outcomes.

More recently, converting standard PPI-AC triple therapy to a quadruple therapy by adding bismuth (B+PPI-AC) has been reported, with favorable results in some locations [26]. The value of this in overcoming CR has yet to be fully determined, but it merits detailed evaluation.

8.1.3 Nonbismuth quadruple therapies

There are advocates of nonbismuth quadruple therapies—usually meaning the addition of metronidazole to PPI-AC triple therapy (PPI-ACM). This may increase eradication rates if MR rates are low or moderate, but is unlikely to be very helpful in the many regions of the world where primary MR and/or CR are high. Moreover, patients in whom the treatment fails will often be found to have dual resistance. This type of concomitant therapy has been studied in well-resourced countries, but rarely in poorly resourced countries. Sequential or hybrid regimens are less well studied, appear not to offer superior eradication, are clumsy to prescribe, and pose particular challenges with adherence. As a result, they are not recommended.

Where metronidazole sensitivity is known from testing in a patient, PPI-AM may be used as a first-line treatment with reasonable outcomes. It is also suitable in locations where MR is known to be low in the population.

8.1.4 Levofloxacin triple therapy

Levofloxacin triple therapy (PPI, amoxicillin and levofloxacin, PPI-AL for 10–14 days) has been used in first-line therapy when levofloxacin resistance (LR) is known or presumed to be low, but the combination has not been studied extensively in this role, with most reports relating to second-line therapy. Reports of high levofloxacin resistance rates in some countries will limit the usefulness of this therapy in these locations. The treatment is generally well tolerated. There have been recent concerns about the risks of fluoroquinolone use. With levofloxacin, this is related to the rare risk of tendinitis or myositis. The precise prevalence of this adverse effect is not well documented, but it appears more common in the elderly and those with inflammatory arthritis or renal impairment and is best avoided in these high-risk subgroups if alternatives exist. A higher dose of levofloxacin and possibly high-dose PPI may be associated with superior eradication success. Moxifloxacin, a related quinolone, has also been used. It has been less studied and has a broader spectrum of activity, so is generally not preferred over levofloxacin.

There are a number of other less well studied treatments that have nonetheless been recommended in various reviews. Furazolidone, for example, has been used in locations

where CR and LR are high, but quality data attesting to its value are meager in comparison with established therapies, and its precise role remains to be defined.

When antimicrobial resistance by culture or rapid PCR testing is used, tailored therapy may be prescribed to individual patients. This is likely to have the most value in regions of higher primary CR, to allow avoidance of clarithromycin use in first-line therapy. Validation and acceptance of stool-based PCR testing offers the prospect of extending this benefit to primary care and in circumstances in which endoscopy is not required or accessible.

Tables 6 and 7 provide an overview and summary of first-line treatment regimens and their composition.

Table **6** Overview of first-line eradication therapies

Therapy	Application	Success	Dose and duration
PPI-AC	Widespread, when primary CR is low	Major determinant is primary CR	7–14 days Standard or high-dose PPI
PPI-BTM, PPI-BAM	Widespread, where available Useful when high primary CR Reduced access may limit use in some places	Reliable and acceptable eradication rates irrespective of primary MR Adherence may be challenging	7–14 days Standard or high-dose PPI Metronidazole > 1500 mg/day preferable
B+PPI-AC	Few data May help when CR high	Early data encouraging	Usually 14 days
PPI-ACM	Limited in high CR and MR regions	May increase eradication if low MR	Varies
PPI-AL	May be used first-line when LR is low especially if CR high, but most reports are for second-line therapy	Effective when LR low	For 10–14 days Standard or high-dose PPI
PPI-AM	In low MR regions or when there is known sensitivity	Low if MR high	7–14 days Standard or high-dose PPI
PPI-AR	Usually used third- or fourth-line, if at all	Moderate Risk of neutropenia an issue	Varies
PPI-A	Usually used third- or fourth-line, if at all	Moderate	Both in higher dose and longer duration
Other	If there is local evidence of efficacy, but usually little data	Usually low	Varies

A, amoxicillin; B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; PPI, proton-pump inhibitor; R, rifabutin; T, tetracycline.

Table **7** Triple therapies and quadruple-therapy combinations—typical composition, dosage, and duration

Triple therapies	**1**	**2**	**3**	
All twice daily for 7–14 days	PPI	Amoxicillin 1 g	Clarithromycin 500 mg	
	PPI	Metronidazole 400 mg	Clarithromycin 500 mg	
	PPI	Amoxicillin 1 g	Metronidazole 400 mg	
All twice daily for 10–14 days	PPI	Amoxicillin 1 g	Levofloxacin 500 mg	
All twice daily for 7–10 days	PPI	Amoxicillin 1 g	Rifabutin 150 mg	
Quadruple therapies	**1**	**2**	**3**	**4**
For 7–14 days	PPI twice daily	Bismuth 120 mg four times daily	Metronidazole 400–500 mg three times daily	Tetracycline 500 mg four times daily
	(Amoxicillin 500–1000 mg three times daily has been substituted for tetracycline)			
All twice daily for 7–14 days	Bismuth 240 mg	PPI	Amoxicillin 1 g	Clarithromycin 500 mg

Note: Published dosages and durations vary; see text.

8.2 Choice of second and subsequent eradication therapies

Second-line or salvage therapies after the failure of first-line eradication have been well studied in some locations, but there is a complete lack of data for many resource-poor regions [4–12].

8.2.1 Bismuth-based quadruple therapy and levofloxacin triple therapy

The most commonly studied and used second-line therapies include standard bismuth-based quadruple therapy for 7–14 days and levofloxacin triple therapy for 10–14 days, as described above. Both have been shown to achieve eradication rates above 80%. The choice between the two depends on whether or not there is knowledge of local primary levofloxacin resistance rates, availability, experience, adherence, and cost. A longer duration of therapy (i.e., 14 days) is often recommended, but data on local outcomes, costs and adherence are needed. When these treatments fail, the other therapy is the usual third choice. In experienced centers, overall eradication rates with judiciously chosen therapies after first-line failure should approach 98% after up to three treatments.

8.2.2 Other salvage therapies

Other salvage therapies that have been used include a rifabutin-based triple therapy (PPI-AR). It is generally less effective, and the risk of significant neutropenia may be as high as 1%, which tends to limit its use. It is usually avoided in regions with a high prevalence of tuberculosis. High-dose dual PPI with amoxicillin therapy (PPI-A) has been used with some success. Nonbismuth quadruple therapies are generally ineffective as salvage therapies, due to secondary CR and MR. Where metronidazole sensitivity is known after testing, PPI-AM may be used as a second-line treatment with reasonable outcomes, but it is generally not used for

second-line therapy empirically. Furazolidone has been used and is recommended as a component of therapy in some regions. There are few high-quality eradication studies that include this drug, and there is a dearth of randomized trials. Concern about its safety and use has led to it becoming unavailable in the United States and the European Union.

When appropriate treatment pathways have been followed and therapy has failed, ad hoc therapies at the whim of the prescriber should be avoided, and ongoing infection should be accepted unless subspecialty expertise or a clinical trial is available. In some patients—such as those with relapsing ulcer disease—eradication failure may result in a need for maintenance antisecretory therapy.

8.3 Treatment choices for patients with penicillin allergy

For patients with penicillin allergy, metronidazole may be substituted for amoxicillin and combined with a PPI and clarithromycin (PPI-MC). However, primary MR reduces the efficacy of this. Bismuth quadruple therapy is a very good alternative (PPI-BTM). If both of these therapies fail, there are limited further options. In patients who have a remote, uncertain, or unlikely history of penicillin allergy and when resources are available, formal assessment for type 1 penicillin allergy may be done. This involves measurement of penicillin antibodies, followed by skin-prick testing and if negative, a supervised oral challenge. When this is carried out in lower-risk patients, up to 80% of such patients have been shown not to be allergic to penicillin, and they may be treated safely with amoxicillin-containing therapies as required (usually PPI-AL or PPI-AC if clarithromycin was not used initially). Such a strategy has been shown to allow successful eradication therapy in most patients. Where there is a clear history of a type 1 reaction previously, allergy is assumed, and testing is not indicated.

8.4 Treatment pathways

In summary, in well-resourced regions in which local rates of CR and MR (and sometimes LR) are known, the evidence-based treatment choice in regions with lower CR is usually PPI-AC as the first line, with PPI-BTM or PPI-AL therapies as the second and third line, in either order. In regions with higher levels of CR, PPI-BTM may be used. B+PPI-AC or PPI-AL may be alternative first-line therapies. Second-line choices depend on what was used first: PPI-BTM or PPI-AL may be used if not used previously.

In resource-poor regions in which community CR and MR have not been established or are known to be high, the choice of therapy is based on empirical audits of outcomes, an individual patient's personal history of antibiotic exposure as monotherapy, known levels of community use of such drugs, availability and cost (Table 8). PPI-AC is still widely chosen with PPI-BTM or PPI-AL, or even nonbismuth quadruple therapies as alternative first-line or salvage therapies. However, when it is known that first-line therapy with clarithromycin results in poor outcomes, one of the other therapies described may be preferred. Data on the rates of levofloxacin resistance are sorely needed, as LR appears to be common in many regions, and the quality of some published data are uncertain. PPI-BTM quadruple therapy is therefore likely to be a good first and subsequent choice, as it avoids the issue of poor outcomes due to resistance. However, its use is sometimes limited by availability, compliance, and adverse effects. Whichever therapeutic pathway is chosen, it is crucial not to repeat the same therapy, as this is a very low-value strategy after first-line failure, due to secondary antibiotic resistance. The success rate for eradication with PPI-AC, for example, may be 80% or more in first-line treatment, but as low as 8% when the treatment is repeated after the first line has failed. Most of this is attributable to secondary CR. This practice is unfortunately still widespread in some places, but should be discouraged. Lastly, patients' access to inexpensive generic medications and medical education continue to be significant challenges that need to be overcome in many regions.

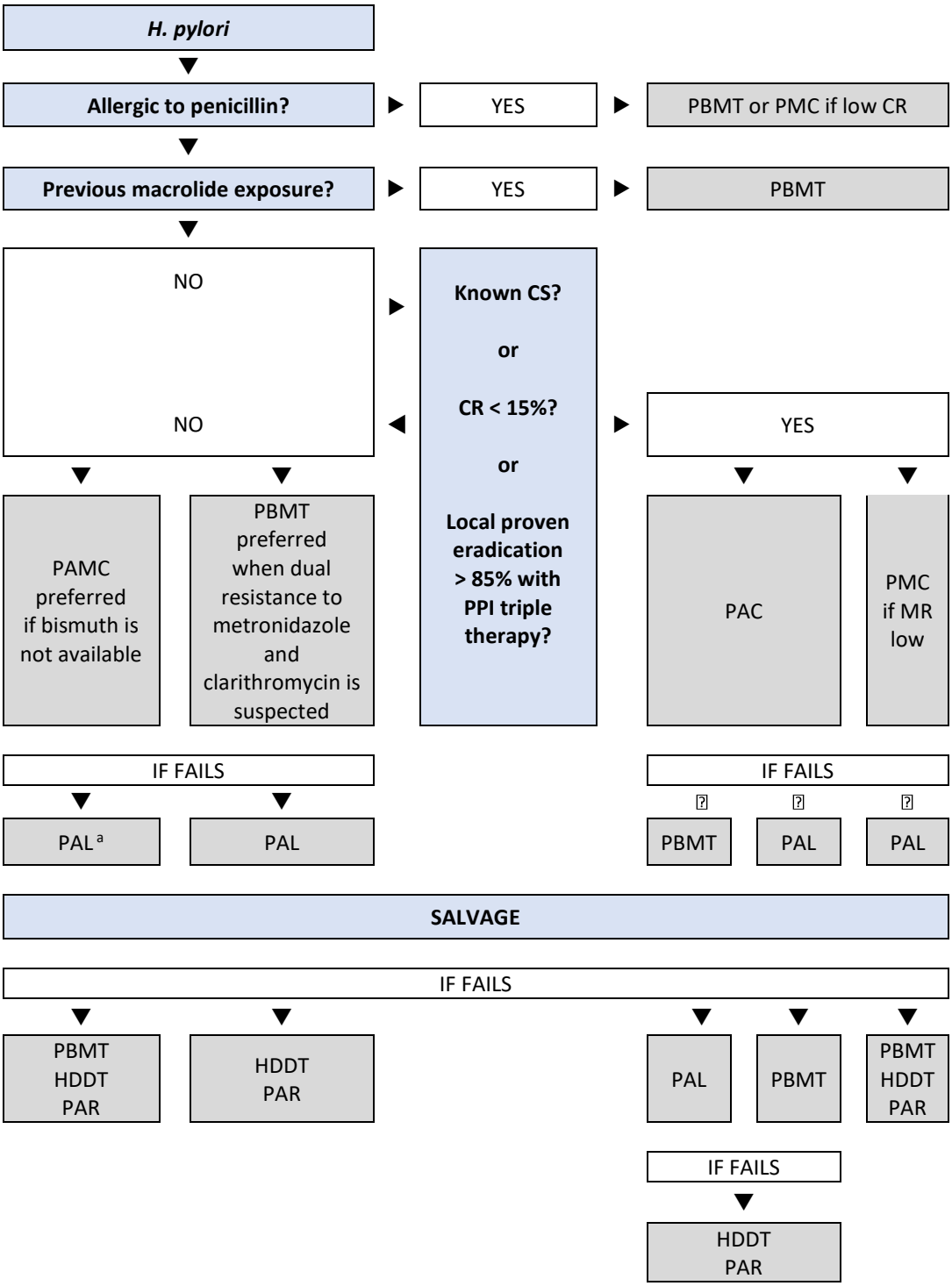
An appropriate pathway for choosing therapy is outlined in Fig. 4.

Table **8** *Cascades:* Treatment considerations when local resistance rates are not well defined, individual patient testing is not available, and there are low resources

First–line therapies		
• PPI-AC	In regions where clarithromycin resistance rate is thought to be low or moderate (< 20%)	If prior clarithromycin use in monotherapy or combination, assume resistance and avoid in first-line therapy 7-day minimum duration, likely higher eradication success with 10–14 days (consider costs) Use quality generic drugs to minimize costs Encourage compliance with full course
• Quadruple therapy	In regions where clarithromycin resistance rates are likely > 20%	Avoid PPI-AC first-line Quadruple therapy overcomes MR; unaffected by CR May be more difficult to take and "nuisance"; adverse effects are common Encourage compliance with full course Generic drugs may be less expensive than triple therapy
• PPI-AC or quadruple therapies	In regions with unknown clarithromycin resistance rates	Avoid clarithromycin if past personal patient exposure PPI-AC otherwise a reasonable choice Quadruple therapy also a good option
Second–line therapies		
• Quadruple therapy • Levofloxacin triple therapy	After failure of clarithromycin-containing regimen	Avoid repeating the same treatment Avoid using clarithromycin again, as secondary resistance will be high and eradication success very low Levofloxacin triple therapy a good option if no prior personal exposure and resistance thought to be low or moderate
• Clarithromycin or levofloxacin triple therapy	After failure of quadruple therapy	Check compliance Levofloxacin preferred if likely high CR region or past personal exposure

A, amoxicillin; C, clarithromycin; CR, clarithromycin resistance; MR, metronidazole resistance; PPI, proton-pump inhibitor.

Fig. **4** Treatment pathways for *H. pylori.* Adapted from Fallone et al. 2019 [8].



A, amoxicillin; B, bismuth; C, clarithromycin; CR, clarithromycin resistance; CS, clarithromycin sensitivity; HDDT, high-dose dual therapy; L, levofloxacin; M, metronidazole; MR, metronidazole resistance; P/PPI, proton-pump inhibitor; PAC, clarithromycin-based PPI triple therapy with amoxicillin; PAL, levofloxacin-based therapy; PAMC, concomitant nonbismuth quadruple therapy; PAR, rifabutin-containing triple therapy; PBMT, bismuth quadruple therapy; PMC, clarithromycin-based PPI triple therapy with metronidazole; R, rifabutin; T, tetracycline.

[a] Given the increasing resistance to levofloxacin in certain areas, susceptibility testing is recommended if available before using PAL.

8.5 The role of culture

Surveying *H. pylori* resistance patterns in order to define population prevalence and changes in prevalence will guide treatment choices. In some well-resourced countries, it is possible to tailor therapy on the basis of individual antimicrobial sensitivity testing of endoscopic biopsies prior to treatment. This is not the norm in clinical practice, however, and in any case, culture and subculture for resistance testing may fail in less expert laboratories. Moreover, much treatment is given in primary care, where noninvasive testing and treating is conducted. After treatment failure, antibiotic sensitivity testing from cultured biopsies is unlikely to play a major role in clinical decision-making. If clarithromycin has been used and failed, secondary CR is so common as to make testing for it unhelpful, and a different therapy should be chosen. Assessing MR is occasionally useful if PPI-AM might be an option, but it does not influence the choice of PPI-BTM, as that therapy is unaffected by MR. Levofloxacin is used empirically in most regions in which the prevalence of LR is known to be low. In addition, the in vitro sensitivity of *H. pylori* to other antibiotics does not imply therapeutic success, and ad hoc regimens should not be designed in this way.

If inexpensive point-of-care biopsy (or stool-based) molecular techniques (PCR) become widely available for rapid assessment of resistance, these may change practice by having a major impact on treatment selection. It is possible that such tests could replace urease tests by confirming the presence of infection and providing rapid antimicrobial resistance data to guide individualized therapy, at a cost only a little more than the current commercial urease tests. Stool-based tests would make it possible to carry out treatment tailored to the individual patient's antimicrobial sensitivity in primary care, without the need for endoscopy.

8.6 Compliance

Whichever therapy is prescribed, every effort must be made to maximize compliance. This means that the prescriber has to spend time with the patient to explain the importance of taking all of the therapy and not interrupting treatment. This is particularly important in regions in which regulations governing antibiotic use may be lax or not enforced, and where antibiotics can be obtained over the counter from pharmacies. Patients may buy drugs in small quantities for a day or two, with a risk of nonpersistence if symptoms are not immediately relieved or if any adverse effects occur. Clearly, the whole course of therapy should be prescribed and dispensed at the onset. Nuisance adverse effects—such as a transient taste disturbance, which is common with clarithromycin and metronidazole—should be anticipated and explained so that their occurrence does not lead to cessation of therapy. Providing printed material for dosage support and information has been found to be useful. As cigarette smoking is known to be an adverse predictive factor for the outcome, stopping smoking before and during therapy may improve outcomes, although this has not been well studied. Smoking cessation also aids ulcer healing. A role for probiotics in reducing adverse effects (and possibly improving outcomes) has been claimed, but this needs more and better-quality evidence.

Good practice point

Patients should always be advised that successful eradication depends on compliance with the treatment. Time should be taken to counsel the patient, explaining how to take the multidrug therapy and anticipating adverse side effects. The need to complete the treatment should be emphasized. Written or pictorial information may also aid compliance.

8.7 After treatment

Ideally, outcome assessment should be carried out in all treated patients, although in practice this is not available in many places. When endoscopy has been conducted initially and gastric atrophy and/or intestinal metaplasia was identified, a decision needs to be made about endoscopic mucosal surveillance [27]. This may benefit individual patients, but an overall

reduction in the mortality due to gastric cancer has yet to be clearly demonstrated. When focal high-grade gastric mucosal dysplasia is found, the areas may be removed endoscopically, but more advanced neoplasia requires surgery. Dysplasia may be detected using enhanced imaging, or by mapping biopsy specimens without discrete endoscopically visible lesions. These patients require endoscopic reassessment, preferably with image-enhanced and magnifying endoscopy, within 6 months for high-grade dysplasia and 12 months for low-grade dysplasia.

As atrophy and intestinal metaplasia are common, endoscopic surveillance will consume considerable endoscopy resources and will have an opportunity cost against other health-care needs. Generally only higher risk-individuals are therefore usually offered surveillance. High risk usually means the presence of more extensive gastric mucosal changes (involving the antrum and body of the stomach) and/or a family history of gastric cancer. The ideal strategy has yet to be determined. Accurate endoscopic detection and characterization of mucosal changes requires specific training and modern endoscopes, as well as skilled pathologists.

9 Regional views for best-practice eradication therapy based on local data and resources

9.1 Australia

Low rates of clarithromycin resistance (6–8%) and high rates of metronidazole resistance (45–50%) have been reported in Australia. Data on levofloxacin are sparse, but primary resistance seems to be very low, with the possible exception of rates in migrants from high-resistance regions. As a result, standard triple therapy with PPI, amoxicillin, and clarithromycin is still the recommended first-line therapy, unless and until evidence of rising clarithromycin resistance emerges. Reported 7-day eradication rates are 80–87%. Fourteen-day therapy has not been studied formally. Salvage therapies include levofloxacin triple therapy for 10 days (eradication rate 80–90%) and standard-dose quadruple therapy (PPI, bismuth, tetracycline, and metronidazole) for 7–14 days, with similar outcomes. Levofloxacin, tetracycline, and bismuth are not registered locally, so are not often used in first-line therapy. These drugs have to be obtained via a special-access scheme from abroad, or via compounding pharmacies, when required for salvage treatments. Rifabutin triple therapy has been used less commonly (76% eradication). Concomitant therapies have not been studied locally.

9.2 Pacific region

There is currently a lack of local resistance data, and there are few systematic data for assessing the outcome of therapy. The choice of therapy is therefore usually extrapolated from international guidelines and determined by drug availability. Clarithromycin triple therapy is commonly chosen, with PPI and amoxicillin or metronidazole, despite a clinical suspicion of high MR affecting the efficacy of the latter. Cost, availability, local expertise, and adherence to therapy are all barriers to effective treatment. There are no audited salvage therapy data. Ad hoc therapies and repeat clarithromycin therapy after first-line failure are discouraged.

9.3 Southeast Asia

There is good evidence that amoxicillin and tetracycline resistance is low and stable (< 5%), but MR is generally high (30–100%). CR has been increasing, but varies significantly across Southeast Asian countries (ranging from 2% to 43%). For most regimens, a 14-day duration should be used unless there is local evidence to prove reliable eradication rates with shorter

duration. Ideally, first-line regimens should be considered on the basis of local antibiotic resistance rates, due to the wide range of antibiotic resistance across countries. PPI-BTM has been reported consistently to have a success rate of > 90%. Second-line regimens should contain antibiotics not used previously, or those against which resistance is unlikely to develop, such as amoxicillin or tetracycline. PPI-BTM should be considered if it has not yet been used. Rifabutin should not be considered in regions with a high prevalence of *Mycobacterium tuberculosis*. If eradication treatment fails after a second attempt, antibiotic susceptibility tests should be considered.

9.4 Eurasia

On the basis of a pilot study, the prevalence of *H. pylori* seropositivity among healthy adults in Armenia is 41.5%, increasing with age (13.6% in the 18–25-year-old age group and 83.3% in those aged over 65). The rate of resistance to clarithromycin in 2018 was as low as 3.6%, and to fluoroquinolones 12.8%. However, new research is warranted, especially during the COVID-19 pandemic when there has been an unprecedented increase in the number of prescriptions for macrolides and respiratory fluoroquinolones by primary-care providers in the country. Tetracycline is only available in 100-mg tablets, making conventional quadruple regimen highly inconvenient. Local recommendations that are adapted from the Maastricht guidelines propose 14-day clarithromycin triple therapy as the first-line treatment and a modified bismuth quadruple therapy (PPI, bismuth, amoxicillin, and metronidazole) as an alternative first-line therapy. Second-line options include triple or quadruple treatment with levofloxacin. None of the eradication regimens has been studied locally for efficacy.

9.5 Western Europe

CR is highly relevant for the selection of first-line therapy. This varies among and within European countries. Monitoring of antibiotic resistance is therefore still essential at the population level. Recent European registry data, from > 30,000 patients in 27 countries [28], indicated pretreatment resistance rates of 23% for clarithromycin, 32% for metronidazole, and dual resistance in 13%. There is a dichotomy, with lower CR in central and northern Europe; in Germany, primary CR is still below the cut-off level of 15%. Triple therapy with amoxicillin and clarithromycin for 14 days is still effective in these conditions and is commonly used as first-line treatment. In areas where primary CR is > 15%, bismuth quadruple treatments for 10 days (or 14 days if components of this regimen are administered individually) is recommended as first-line treatment. Concomitant therapy, which includes three antibiotics instead of the two used in the bismuth-based quadruple treatment, is unpopular in most countries. Metronidazole in PPI triple therapies has been mostly abandoned and is now reserved for individual cases (e.g., in cases of amoxicillin allergy or proven susceptibility to metronidazole).

Increasing resistance to levofloxacin has excluded this antibiotic as a component in any first-line regimen. Its use is becoming increasingly worrisome, even if it is used as second-line treatment. Rifabutin is effective in third-line treatment and is recommended as a component of a rescue regimen after repeated treatment failure.

European recommendations put the emphasis on testing (^{13}C-UBT) for assessing the individual treatment response. Resistance testing of the commonly used antibiotics is encouraged after treatment failures.

9.6 Southern Europe

Rising antibiotic resistance is the main issue. Pretreatment antibiotic susceptibility for clarithromycin should be determined before first-line treatment, but is not currently feasible for most patients. The choice of treatment is therefore based on the local prevalence of CR. However, this information is lacking in most regions of Italy; high prevalence (30%) has been

reported in some central and southern regions. A 10- or 14-day bismuth-based quadruple therapy or nonbismuth concomitant quadruple therapy is recommended as the first-line treatment when CR is > 15% or unknown. The efficacy of these two regimens is not affected by CR or MR, and bismuth-based quadruple therapy performs well when there is dual resistance. Thus, bismuth quadruple therapy may be considered the best choice for empirical first-line treatment in Italy.

The standard triple therapy—PPI plus clarithromycin and amoxicillin or metronidazole/tinidazole—is effective in clarithromycin-sensitive strains, but fails when there is CR. A 14-day standard triple therapy should be used as the first-line treatment only in areas with a known low prevalence of CR (< 15%), in patients without previous use of macrolides, or in areas where this regimen has been proven to achieve high eradication rates.

Sequential therapy, with PPI plus amoxicillin for 5–7 days followed by PPI plus metronidazole and clarithromycin for 5–7 days, is a regimen designed to overcome the issue of clarithromycin resistance. However, data concerning its efficacy are contradictory. Recent guidelines have discouraged its use, despite some reports from Italy of eradication rates around 90%, even with CR. Second-line treatments include levofloxacin-containing triple therapy and bismuth quadruple therapy. Probiotic supplementation may be used in order to reduce antibiotic-related adverse events.

9.7 North America

North America has variable clarithromycin resistance (17–32% in different studies) and high metronidazole resistance (44%). Amoxicillin resistance was reported to be 6% in a recent study, and rifabutin resistance was 0%. U.S. guidelines recommend that for first-line treatment, clarithromycin triple therapy should be confined to patients with no previous history of macrolide exposure who live in areas in which clarithromycin resistance against *H. pylori* isolates is known to be low. Some suburban and rural areas of the country meet these criteria. First-line treatment with bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole is recommended as first-line therapy in most areas. A combination of rifabutin, amoxicillin, and omeprazole has been approved for *H. pylori* treatment in the United States. Its role in initial therapy remains to be determined.

9.8 South and Central America

Studies on clarithromycin resistance in South and Central America remain sparse, with some reported rates already exceeding 20%. The highest prevalences are described in Mexico, Colombia, Argentina, and Brazil. The indiscriminate use of azithromycin (a low-cost drug) may select macrolide-resistant mutants and aggravate CR rates. Low resistance rates for amoxicillin have been documented, but some studies show a high percentage in Brazil. If this trend is confirmed, it would be an alarming situation, due to the central role of these antibiotic therapies.

The classic triple regimen with PPI, amoxicillin, and clarithromycin for 7–14 days is still the most widely used regimen, followed by bismuth quadruple therapy as an alternative or second-line therapy and levofloxacin-based therapy as a salvage option. Resistance to levofloxacin is reported to be scarce, but high levels have been described in Peru. The associated use of metronidazole is common for first-line quadruple therapy, but the reported prevalence of resistance is above 50% in Central America, Mexico, and in some countries in South America such as Brazil and Colombia.

Recurrence rates of more than 3–5% per annum, with geographic variability, have been reported; data are lacking from many regions. Barriers that need to be overcome include the cost of medication, improving adherence to guidelines by physicians, a lack of UBTs in many regions, unavailability of bismuth salts, furazolidone, and rifabutin in some countries, and an

absence of high-quality local studies to validate anti-*H. pylori* regimens. Most health-care systems in the region are still operating suboptimally on these issues.

10 Abbreviations used in this WGO guideline

A	amoxicillin
B	bismuth
B+PPI-AC	bismuth with PPI, amoxicillin and clarithromycin
C	clarithromycin
CI	confidence interval(s)
CR	clarithromycin resistance
CS	clarithromycin sensitivity
GERD	gastroesophageal reflux disease
HDDT	high-dose dual therapy
ICD	International Classification of Diseases
IL	interleukin
L	levofloxacin
LR	levofloxacin resistance
M	metronidazole
MALT	mucosa-associated lymphoid tissue
MR	metronidazole resistance
NSAID	nonsteroidal anti-inflammatory drug
OLGA	Operative Link on Gastritis Assessment
OLGIM	Operative Link on Gastritis/Intestinal-Metaplasia Assessment
PAC	clarithromycin-based PPI triple therapy with amoxicillin
PAL	levofloxacin-based therapy
PAMC	concomitant nonbismuth quadruple therapy
PAR	rifabutin-containing triple therapy
PBMT	bismuth quadruple therapy
PCR	polymerase chain reaction
PMC	clarithromycin-based PPI triple therapy with metronidazole
PPI	proton-pump inhibitor
PPI-A	PPI with amoxicillin
PPI-AC	PPI with amoxicillin and clarithromycin
PPI-ACM	PPI with amoxicillin, clarithromycin, and metronidazole
PPI-AL	PPI with amoxicillin and levofloxacin
PPI-AM	PPI with amoxicillin and metronidazole
PPI-AR	PPI with amoxicillin and rifabutin

PPI-BAM	PPI with bismuth, amoxicillin, and metronidazole
PPI-BTM	PPI with bismuth, tetracycline, and metronidazole
PPI-MC	PPI with metronidazole and clarithromycin
PUD	peptic ulcer disease
R	rifabutin
T	tetracycline
UBT	urea breath test
WGO	World Gastroenterology Organisation
WHO	World Health Organization

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