Chapter 6.

Considerations for choice of *Helicobacter pylori* treatment regimens

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Summary

- The design of population-based *H. pylori* screen-and-treat programmes must consider the impact they could have on the selection of antibiotic-resistant strains of *H. pylori* and other species, both at the individual level and at the societal–ecological level.

- The most common causes of the failure of treatment are poor compliance with therapy and/or *H. pylori* antibiotic resistance. Patients should receive counselling about the anticipated (generally mild) adverse events. Resistance rates vary remarkably between different geographical areas, and therefore the selection of therapeutic regimens needs to be adjusted according to the local resistance pattern. Several recent reviews have confirmed an increase in clarithromycin resistance rates in different areas around the world.

- *H. pylori* infection is an infectious disease, and therefore regimens should ideally be selected on the basis of antibiotic susceptibility determined at the individual patient level; if this information is not available, empirical regimens should be used that avoid (or have minimal risk of) antibiotic resistance. Local population-based data from surveillance registries will be of great help in this respect. Ultimately, the recommendations stated in each country's guidelines on *H. pylori* treatment should be followed.

- The main available eradication treatments for *H. pylori* worldwide include (i) clarithromycin triple therapy, (ii) classic bismuth-containing quadruple therapy (or the three-in-one single capsule), (iii) high-dose proton pump inhibitor–amoxicillin dual therapy, (iv) vonoprazan–amoxicillin dual therapy, and (v) non-bismuth-containing quadruple concomitant therapy.

6.1 General principles for choosing *H. pylori* treatment regimens

Factors to take into account when considering population-based H. pylori *eradication treatment*

An effective first-line eradication therapy is desirable, to avoid supplementary treatments and testing and to prevent the development of secondary resistance. In the context of population-based screening for and eradication of *H. pylori*, the challenges include dealing with clinically apparently healthy subjects, which requires a simple, well-tolerated therapy with few adverse events to support their motivation and adherence to treatment. In addition to effectiveness and tolerability, other issues that affect the treatment, such as the local availability of the treatment, the cost of the treatment, and the type of health system responsible for treatment, will play a critical role. Awareness campaigns on global, national, and regional scales will have an essential supportive role in disseminating knowledge about *H. pylori* therapy.

The design of these population-based *H. pylori* screen-and-treat programmes must also consider the impact they could have on the selection of antibiotic-resistant strains of *H. pylori* and other species, both at the individual level (i.e. the direct selection of surviving strains) and at the societal–ecological level (i.e. the type and quantity of antibiotic compounds entering the ecosystem could increase widespread resistance).

Therefore, programme design and treatment recommendations for *H. pylori* screening must fit the narrow criteria of being an acceptable compromise between the aims of cancer prevention (cost–effectiveness) and infection prevention (because population-based eradication reduces the sources of infection) with the containment of antimicrobial resistance.

Antibiotic resistance

The most common causes of the failure of reliably good or excellent regimens are, in addition to poor compliance with therapy, the presence of organisms that are resistant to one or more of the antimicrobial agents used [1].

Several studies have suggested a variety of miscellaneous factors that may be important in *H. pylori* eradication, including age, presentation (e.g. functional dyspepsia vs duodenal ulcer), and CagA status. However, these factors have typically been discovered in data-dredging studies in which resistance was not assessed [2].

Resistance rates vary remarkably between different geographical areas [3], and therefore the selection of therapeutic regimens needs to be adjusted according to the local resistance pattern. The prevalence of antibiotic resistance (mainly to clarithromycin) in various regions is correlated with the general use of antibiotics in the region, i.e. for infectious diseases other than *H. pylori* infection [4]. For example, the long-term use of clarithromycin as monotherapy, mainly for respiratory tract infections, has led to high clarithromycin resistance rates of *H. pylori* [4]. Several recent reviews have confirmed an increase in clarithromycin resistance rates in different areas around the world [4, 5, 6, 7, 8]. Metronidazole resistance plays a subordinate role, because metronidazole is not included in most triple therapies and this resistance can be overcome by the use of bismuth-containing quadruple therapy and by increasing the dose and duration of treatment [9].

The goal of H. pylori *eradication treatment*

The goal of any antimicrobial therapy is to reliably cure *H. pylori* infection in most patients [10]. Currently, as a general rule, it has been recommended that a regimen should not be used unless it reliably produces an eradication rate > 90% [10]. However, in the context of population-based *H. pylori* screen-and-treat programmes, it would be worth considering the use of treatments that are slightly less effective but are simpler, less expensive, and better tolerated and have minimal issues related to antibiotic resistance.

The reliable cure of *H. pylori* infection requires the use of antimicrobials to which local infections are susceptible. Physicians gain knowledge about the characteristics of the antibiotics and population antimicrobial resistance; this can be achieved using invasive and non-invasive methods. Antimicrobial susceptibility testing can be performed on *H. pylori* strains from patients with *H. pylori* infection by molecular testing in gastric biopsies, gastric juice samples, and possibly stool samples (most relevant for clarithromycin and levofloxacin) or by culture followed by an antibiogram, which provides susceptibility information for all relevant antibiotics. Several commercial kits are available that enable testing for clarithromycin (and possibly quinolone) susceptibility using polymerase chain reaction (PCR).

Another alternative, which is widely available to all, is to examine and regularly monitor the results of the eradication therapy (this monitoring is recommended to be routinely performed for all patients) and to share the data. Treatment failure with an

otherwise optimized therapy provides a strong indication of the presence of resistance, and that therapy should no longer be recommended and used unless local susceptibility is proven by culture or molecular testing.

In summary, *H. pylori* infection is an infectious disease, and therefore regimens should ideally be selected on the basis of antibiotic susceptibility determined at the individual patient level or by using eradication regimens that avoid (or have minimal risk of) antibiotic resistance. Establishing the collection of local population-based data from surveillance registries will be of great help in selecting the most effective therapies in the region.

Tailored versus empirical treatment

Resistance of *H. pylori* to antibiotics has reached alarming rates worldwide [11]. Local surveillance networks are required to select appropriate eradication regimens for each region. Tailoring treatment of *H. pylori* infection based on systematic antimicrobial susceptibility testing is useful to limit the increase in local, regional, and global antibiotic resistance by avoiding the use of unnecessary antibiotics. However, there is still a contentious debate about whether patients should systematically undergo an upper endoscopy for bacterial culture (or molecular techniques such as PCR) or even molecular tests in stool samples before the administration of *H. pylori* eradication treatment in clinical practice [10].

Ideally, the treatment for a bacterial infectious disease should be chosen based on antibiotic susceptibility testing, but the case of the infected stomach is very specific. Pre-treatment *H. pylori* susceptibility testing enables the selection of a regimen tailored by antimicrobial susceptibility. However, this is not always feasible in patients with *H. pylori* infection because, until very recently, this has required an invasive procedure (i.e. gastroscopy), which obviously is not indicated in population-based programmes such as those aimed at preventing gastric cancer in the general population [12]. In the past few years it has been reported that the genotypic testing of clarithromycin resistance from stool samples is an accurate, convenient, non-invasive, and rapid detection technology, which provides a definitive diagnosis of clarithromycin resistance and guides the rational selection of antibiotics [13, 14, 15]. However, the studies are still limited, some of their accuracy results are heterogeneous, and diagnostic kits are not available widely or in all settings worldwide [10].

Although some meta-analyses have found that, overall, first-line tailored therapy achieved higher eradication rates than empirical regimens, more recent meta-analyses have concluded that the benefit of susceptibility-guided treatment over empirical treatment of *H. pylori* infection could not be demonstrated in first-line therapy if the most up-to-date and effective quadruple regimens are prescribed [12, 16]. Thus, especially when bismuth-containing quadruple therapy is used as a first-line empirical therapy, there seems to be little need for routine upfront susceptibility testing for tailored treatment, as long as the local eradication success rate is high.

Therefore, a strategy that is also reasonable is that the selection of any empirical regimen be guided by regimen-specific eradication success rates locally. Thus, in many geographical regions, one must empirically choose therapy, and in this instance the best approach is to use regimens that have been proven to be reliably effective in a given area [2, 12]. That choice should take advantage of the knowledge of resistance patterns, obtained from local or regional antimicrobial surveillance programmes or based on local clinical experience with regard to which regimens are effective in that region. Ultimately, the recommendations stated in each country's guidelines on *H. pylori* treatment should be followed.

Finally, the history of the patient's prior antibiotic use and any prior therapies will help to identify which antibiotics are likely to be successful and those for which resistance is probable [2].

6.2 Treatment options

First-line *H. pylori* eradication treatments that have been recommended in guidelines and consensus reports published worldwide are listed in Table 6.1. Table 6.2 summarizes the main available eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses. The key principles that should guide the choice of *H. pylori* eradication therapy, in accordance with the World Gastroenterology Organization Global Guideline [3], are summarized in Box 6.1.

The eradication treatments that are currently in use are described and assessed below, along with their effectiveness, availability, and cost in each geographical area.

Box 6.1. Key principles that should guide 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 outcomes are useful.
2. Treatment recommendations based on resistance patterns and outcome data from one region may not be applicable elsewhere, because of variations 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 pre-treatment 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 use 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 likelihood of treatment failure.
9. Primary clarithromycin resistance has been reported to have increased in many countries over relatively few years, although it has remained stable in other countries.
10. Primary or secondary resistance to amoxicillin and tetracycline are so rare that this does not affect treatment choices.
11. Because much treatment is given presumptively or after non-invasive *H. pylori* testing, the choice of therapy will be based on knowledge of the probable antimicrobial resistance patterns locally.
12. The availability of rapid, inexpensive point-of-care polymerase chain reaction (PCR) antimicrobial resistance testing may change individual treatment choices and facilitate surveillance of trends in resistance.
13. Compliance is a major modifiable determinant of eradication success and should be supported with clear verbal and written information.
14. Smoking has an adverse effect on eradication success.
15. Ideally, outcome assessment (confirmation of *H. pylori* eradication) should be done in all treated patients, although in practice this is not available in many places.
16. These key principles must be adapted regionally according to the available resources.

Source: Adapted from Katelaris et al. (2023) [3].

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a]

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
Africa [44]	2024	African Helicobacter and Microbiota Study Group	CTT (provided there was no previous exposure to macrolides and local resistance to clarithromycin is < 15%)
Belgium [45]	2023	Belgian *Helicobacter pylori* and Microbiota Study Group	Empirical treatment: BQT or CQT If clarithromycin has been excluded: CTT
Brazil [46]	2018	Núcleo Brasileiro para Estudo do *Helicobacter pylori* e Microbiota	First-line: CTT Alternatives: BQT, CQT
Canada [47]	2016	Canadian Association of Gastroenterology	In areas with high (> 15%) clarithromycin resistance: BQT or CQT In areas with low (< 15%) clarithromycin resistance: CTT
China [48]	2022	*Helicobacter pylori* Study Group of Chinese Society of Gastroenterology	BQT or HDDT
Egypt [49]	2019	Egyptian Association for Study of Gastrointestinal Diseases and Liver	CTT
Europe (Maastricht VI/Florence) [10]	2022	European Helicobacter and Microbiota Study Group	In areas with high (> 15%) or unknown clarithromycin resistance: BQT (if unavailable: CQT) In areas with low (< 15%) clarithromycin resistance: BQT or CTT
Germany [50]	2024	German Society of Gastroenterology, Digestive and Metabolic Diseases	BQT
Greece [51]	2020	Hellenic Society of Gastroenterology	CQT
Hong Kong Special Administrative Region, China [52]	2023	Hong Kong Society of Gastroenterology	CTT or BQT
India [53]	2022	Indian Society of Gastroenterology	In areas with high clarithromycin resistance: BQT In areas with low clarithromycin resistance: CTT

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a] (continued)

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
Indonesia [54]	2023	Directorate of Research and Community Service, Deputy for Strengthening Research and Development, Ministry of Research and Technology, Research Agency and National Innovation	CTT: this therapy should be implemented with caution in some regions in Indonesia with high (> 10%) clarithromycin resistance Alternatives: BQT and CQT
Ireland [55]	2024	Irish *Helicobacter pylori* Working Group	BQT (first-line treatment in the absence of clarithromycin susceptibility testing or where clarithromycin resistance has been confirmed) CTT (only if clarithromycin susceptibility has been confirmed)
Italy [56]	2022	Italian Working Group	BQT, CTT, or SEQ CTT only considered in areas with low (< 15%) clarithromycin resistance
Japan [57]	2019	Japanese Society for *Helicobacter* Research	CTT or PPI–amoxicillin–metronidazole or P-CAB–clarithromycin–amoxicillin or P-CAB–amoxicillin–metronidazole
Republic of Korea [58]	2021	Korean Society of Clinical Microbiology, Korean Society of Pathologists, and Korean Society of Gastroenterology	CTT, BQT, CQT, or SEQ
Latin America [59]	2014	Latin American Expert Group	CTT or SEQ
Malaysia [60]	2023	Expert panel	CTT Alternative: HDDT
Poland [61]	2023	Polish Society of Gastroenterology	BQT or CQT
Saudi Arabia [53]	2022	Saudi *H. pylori* Working Group	BQT Alternatives: CQT, SEQ with quinolones, hybrid therapy, HDDT, vonoprazan triple therapy
Spain [62]	2022	Spanish Association of Gastroenterology and Spanish Society of Digestive Pathology	BQT or CQT
Thailand [63]	2016	Expert panel	CTT Alternatives: CQT or SEQ

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a] (continued)

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
USA [64]	2024	American College of Gastroenterology	BQT when antibiotic susceptibility is unknown Rifabutin triple therapy or P-CAB dual therapy is a suitable empirical alternative
Viet Nam [53]	2022	Vietnam Association of Gastroenterology	BQT Alternative: PPI–amoxicillin–levofloxacin–bismuth
World Gastroenterology Organization [3]	2023	World Gastroenterology Organization	In areas with high clarithromycin resistance: BQT (or PPI–bismuth–amoxicillin–metronidazole) In areas with low clarithromycin resistance: CTT

BQT, classic bismuth-containing quadruple therapy (PPI, bismuth, tetracycline, metronidazole); CQT, non-bismuth-containing quadruple concomitant therapy (PPI, clarithromycin, amoxicillin, metronidazole); CTT, clarithromycin triple therapy (PPI, clarithromycin, amoxicillin); HDDT, high-dose dual therapy (PPI, amoxicillin); P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; SEQ, sequential therapy (PPI plus amoxicillin for 5–7 days followed by PPI plus clarithromycin and metronidazole for 5–7 days).

[a] Only guidelines published in English are included. Guidelines exclusively focused on children were excluded. If multiple guidelines have been published, only the most up-to-date publication was included.

Table 6.2. Main eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses

Treatment name	Components and dosing	Duration (days)	Strengths	Weaknesses
Standard clarithromycin triple therapy	PPI (omeprazole 40 mg or equivalent/12 h) Clarithromycin (500 mg/12 h) Amoxicillin (1000 mg/12 h)	14	Simplicity Widely available Recommended by most guidelines in case of low clarithromycin resistance	Effectiveness reduced by clarithromycin resistance Requires the administration of 3 different drugs
Classic bismuth-containing quadruple therapy	PPI (omeprazole 20–40 mg or equivalent/12 h) Bismuth (120 mg/6 h or 240 mg/12 h) Tetracycline (500 mg/6 h) Metronidazole (500 mg/8 h)	10–14	Wide experience Effectiveness has remained constant over time Unaffected by clarithromycin resistance Can overcome metronidazole resistance	Requires the administration of 4 different drugs Complexity of dosing regimen Occasional unavailability of bismuth and/or tetracycline

Table 6.2. Main eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses (continued)

Treatment name	Components and dosing	Duration (days)	Strengths	Weaknesses
			Low price	Three-in-one single capsule only available in a few countries High cost of three-in-one single capsule (in the USA)
High-dose PPI–amoxicillin dual therapy	PPI (omeprazole 40–80 mg or equivalent/6–8 h) Amoxicillin (750–1000 mg/6–8 h)	14	Simplicity Requires the administration of only 2 different drugs Widely available No resistance problems Good tolerance Low price	Heterogeneous results (Asian countries vs European countries) Potentially optimizable PPI and amoxicillin doses
Vonoprazan–amoxicillin dual therapy	Vonoprazan (20 mg/12 h) Amoxicillin (750–1000 mg/8–12 h)	7–14	Simplicity Requires the administration of only 2 different drugs No resistance problems Good tolerance Not dependent on the *CYP2C19* genotype	Heterogeneous results (Asian countries vs European countries) Pending optimization of the dosage and duration of both vonoprazan and amoxicillin Higher cost of vonoprazan vs PPI
Non-bismuth-containing quadruple concomitant therapy	PPI (omeprazole 20–40 mg or equivalent/12 h) Clarithromycin (500 mg/12 h) Amoxicillin (1000 mg/12 h) Metronidazole (500 mg/12 h)	14	Not clearly impaired by either clarithromycin or metronidazole isolated resistance Consistent good results in Europe	Effectiveness reduced by dual metronidazole–clarithromycin resistance Requires the administration of 4 different drugs Exposes the patient to at least 1 unnecessary antibiotic

h, hour or hours; PPI, proton pump inhibitor.

Standard clarithromycin triple therapy

Nowadays, the efficacy of the standard triple therapy that includes clarithromycin is seriously challenged in many parts of the world, where eradication rates have declined

to unacceptably low levels, largely related to the development of resistance to this antibiotic. This low efficacy compromises the design and development of any population-based screening and treatment programme for the prevention of gastric cancer. Moreover, the risk of causing a direct or ecological increase in the existing antibiotic resistance rates of *H. pylori* and other agents must be considered before implementing screening and treatment programmes.

The most recent data show that the triple therapy, which generally includes a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole, has lost some efficacy and often enables the cure of only a maximum of 70% of the patients, which is less than the generally recommended rate of 90% and far below what should be expected for a bacterial infection [10]. The most important explanation for this decrease in the efficacy of the standard triple therapy is the increase in *H. pylori* resistance to clarithromycin. Pooled data from 20 studies involving 1975 patients treated with standard triple therapy showed an eradication rate of 88% in clarithromycin-sensitive strains compared with only 18% in clarithromycin-resistant strains [17]. The global clarithromycin resistance rate in Europe has increased from 9% in 1998 [18] to > 20% in more recent years [4]. Resistance has increased in most parts of Europe, but it has now reached a prevalence of > 20% in most countries in central, western, and southern Europe, which is considered to be a high resistance rate [19].

A threshold of 15–20% was recommended to separate the regions of high and low clarithromycin resistance [10]. There are very few remaining areas with low clarithromycin resistance. Worldwide, with few exceptions, the presence of resistance prohibits the empirical use of triple therapies that contain clarithromycin. However, in the few areas with clarithromycin resistance rates of < 15% (and locally confirmed evidence of effectiveness of ≥ 90%), the standard PPI–clarithromycin-containing regimen may still be used as the first-line treatment (although bismuth-containing quadruple therapy is also a valid first-line alternative) [10]. In situations in which susceptibility testing is lacking or in areas with limited health-care resources, physicians must rely on evidence of local results (i.e. test-of-cure data).

In cases in which the clarithromycin-containing triple regimen has been selected to be used as the first-line treatment, different ways of improving its efficacy have been proposed. These include (i) increasing the dose of PPI (40 mg of omeprazole, or equivalent, twice a day) and (ii) increasing the duration of treatment (up to 14 days) [10].

However, these options will also increase the cost of treatment, which is a major issue in resource-constrained regions [3].

Finally, overall eradication rates with PPI–amoxicillin–clarithromycin and PPI–amoxicillin–metronidazole have been equivalent worldwide [20]. However, the combination with metronidazole instead of clarithromycin showed high efficacy in areas with a low incidence of metronidazole resistance (i.e. Japan), and could accordingly be recommended as a first-line therapy in these populations [20].

Classic bismuth-containing quadruple therapy

From a microbiological standpoint, the most rational way to overcome antibiotic resistance would be the use of a combination of drugs for which resistance does not appear to be a problem. Therefore, as previously mentioned, no clarithromycin-based regimens should be recommended in areas with increasing clarithromycin resistance rates. In the context of increased resistance to antibiotics, quadruple therapy has the advantage of using the following compounds: (i) bismuth, for which the mechanism of action appears to be more like an antiseptic than like an antibiotic, and for which no resistance has been described; (ii) tetracycline, an antibiotic for which resistance is rarely encountered; and (iii) metronidazole, for which resistance in vitro exists at a high prevalence in most countries around the world, but the clinical impact of this resistance is limited and can be overcome by increasing the dose and duration of treatment [9, 21]. Accordingly, classic bismuth-containing quadruple therapy has been recommended by most of the guidelines worldwide as an alternative first-line regimen to standard triple therapy in areas with low rates of clarithromycin resistance, and has been recommended as the first-line therapeutic option in areas with a high (> 15%) or unknown prevalence of clarithromycin resistance.

The major drawback of this therapy is the complex dosing regimen (some drugs are dosed 4 times a day). Thus, clinical trials of bismuth-containing quadruple therapy are needed to simplify the regimen to improve compliance. Several studies have shown that bismuth administered twice a day may be sufficient [22]. Subsequently, a bismuth-containing quadruple therapy using a three-in-one single capsule that contains bismuth subcitrate, metronidazole, and tetracycline has been demonstrated to decrease the pill burden and improve patient compliance [23].

In general, the treatment duration of bismuth-containing quadruple therapy should be 14 days. However, 10-day therapies have increasingly achieved very good and

consistent results in different geographical areas [24]. Furthermore, a meta-analysis [23] and several studies from the European Registry on *Helicobacter pylori* Management, including almost 4000 patients treated with 10-day single-capsule bismuth-containing quadruple therapy, demonstrated a cure rate of ≥ 90% [25, 26].

The safety and tolerability of the quadruple therapy have been similar to those of the standard triple therapy in several meta-analyses [27]. Finally, because the bismuth-containing quadruple therapy is an inexpensive regimen, it is often preferred in situations where the cost of therapy is the main concern, which may be the situation for organized programmes in the general population. However, the limitations of this quadruple regimen are the unavailability of bismuth subcitrate worldwide and the current general unavailability of tetracycline in many countries. In addition, the three-in-one single-capsule presentation (marketed under the name Pylera) is only available on the market in a few countries worldwide.

High-dose PPI–amoxicillin dual therapy

In areas with high dual resistance (> 15%), a high-dose PPI–amoxicillin dual therapy may be an option, because it overcomes the issue of clarithromycin (and metronidazole) resistance, especially where bismuth, tetracycline, or the three-in-one single capsule are not available. Dosing frequency is essential for the efficacy of PPI–amoxicillin dual therapy, because amoxicillin has a time-dependent bactericidal effect. A meta-analysis including 15 randomized clinical trials found that PPI–amoxicillin administered 4 times a day achieved a significantly higher eradication rate than doses administered less frequently [28]. Some meta-analyses have demonstrated high (~90%) cure rates, with high-dose PPI–amoxicillin dual therapy being as effective as bismuth-containing quadruple therapy (and associated with fewer adverse effects) [29]. However, these favourable results obtained mainly in Asian countries have not been replicated in European countries (even when bismuth was added to this dual regimen), so this dual regimen cannot be recommended universally [30, 31].

Vonoprazan–amoxicillin dual therapy

Optimal eradication of *H. pylori* infection requires predictable and long-lasting inhibition of gastric acid secretion, especially throughout the night-time hours. Potassium-competitive acid blockers (P-CABs), which have been recently introduced and have a unique pharmacological profile, are better suited to combination treatment with one or

more antimicrobial agents [32]. P-CABs, such as vonoprazan, are characterized by a rapid onset of action and a predictable antisecretory profile that is not dependent on the *CYP2C19* genotype or the activation of parietal cells. This profile provides the opportunity to improve the management of *H. pylori* eradication treatments, particularly by simplifying complex eradication regimens and by potentially developing a very effective dual therapy [32].

Several systematic reviews and meta-analyses of randomized controlled trials have demonstrated that vonoprazan triple therapy is superior to PPI triple therapy in first-line treatment, with similar safety and patient tolerance levels [33]. Furthermore, several studies have shown a similar, or even higher, efficacy of vonoprazan–amoxicillin dual therapy compared with bismuth-containing quadruple therapy, and with better tolerance [34, 35]. However, it should be emphasized that the clinical experience with vonoprazan-based eradication regimens has been largely limited to East Asian countries. The eradication success rates with the vonoprazan regimens observed in the landmark trial in Europe and the USA were lower (79–85% in susceptible strains) than those observed in randomized clinical trials and observational studies in East Asia, perhaps due to differences in body mass index or parietal cell mass, among other factors, between the trial populations [36]. The same has been observed in other countries, such as Thailand, where dual therapies based on vonoprazan have yielded poorer outcomes that those in the studies carried out in East Asian countries [37]. Future research should focus on optimizing the dosage and duration of both vonoprazan and amoxicillin, especially in Europe and the USA.

Non-bismuth-containing quadruple concomitant therapy

This regimen combines a PPI, clarithromycin, amoxicillin, and metronidazole, which are administered together for at least 10 days [38]. In head-to-head trials against clarithromycin-resistant strains, concomitant therapy had superior outcomes (92%) compared with sequential therapy (62%) [38]. Concomitant therapy also works well in metronidazole-resistant, clarithromycin-susceptible cases because of its PPI–amoxicillin–clarithromycin component. Indeed, concomitant therapy was the only therapy other than bismuth-containing quadruple therapy that consistently achieved an eradication success rate of ≥ 90% in all European regions in the European Registry on *Helicobacter pylori* Management [25, 39]. The Achilles heel of concomitant therapy is dual metronidazole–clarithromycin resistance. Thus, the efficacy of concomitant therapy

was not impaired by either clarithromycin or metronidazole isolated resistance, but it is expected to be < 90% when the prevalence of dual clarithromycin–metronidazole-resistant strains is > 15% [38]. Furthermore, with this regimen, all patients are exposed to at least one unnecessary antibiotic, whether it is clarithromycin in clarithromycin-resistant cases or metronidazole in metronidazole-resistant cases, which may contribute to global antimicrobial resistance. Thus, according to the Maastricht VI/Florence Consensus report and other consensus reports, in areas with high (> 15%) clarithromycin resistance, non-bismuth-containing quadruple concomitant therapy may be considered, but only if bismuth-containing quadruple therapy, and perhaps other treatments as well, is unavailable.

Other treatments

Rifabutin has generally been recommended as a rescue therapy after at least several *H. pylori* eradication failures [40]. Because of potential – although rare – severe adverse events with rifabutin-based regimens, these regimens should not be used as a first-line treatment [10].

Because of the high or rapidly rising prevalence of quinolone resistance in communities, and also because of the possible adverse events, fluoroquinolone-containing regimens should be reserved for rescue treatment [10].

6.3 The importance of compliance with and tolerance of treatment

Compliance is an important issue when *H. pylori* treatment is planned for inclusion in population-based screening. Therefore, for population-based screening, substantial efforts should be directed towards identifying a regimen that is easy for the participant to follow. Furthermore, adverse events are reported by ≥ 25% of patients [41]. The most frequent adverse events are taste disturbance (reported by 7% of patients), diarrhoea (7%), nausea (6%), and abdominal pain (3%) [41]. However, most of the adverse events are mild (< 1% are serious) and of limited duration, and their occurrence does not seem to interfere significantly with treatment compliance [41]. Nevertheless, patients should receive counselling about the anticipated adverse events, so that their occurrence does not cause cessation of therapy.

Adherence to a complex regimen is a particular problem when it is used in the general population, who are largely asymptomatic. They are less likely to adhere to the therapy if eradication treatment is not used to cure symptoms, and this could be a

challenge for a screening programme. If compliance with the regimen is poor, even the best-designed regimen will have a poor outcome. Therefore, another aspect of optimization is to identify the factors that determine compliance, such as dosing, duration, and adverse events. First, health-care providers must ensure that patients understand the rationale for treatment (principally to reduce the risk of gastric cancer). Second, because adherence to the therapy is associated with higher eradication rates [39], patients should receive counselling about the importance of completing the treatment regimen; taking a few extra minutes to provide patients with all the relevant information can prevent most of the issues associated with treatment failures [42]. The fact that *H. pylori* eradication therapy involves multiple drugs (and frequently multiple dosing intervals) makes patient education extremely important; therefore, written instructions with an appropriate language and literacy level should be provided. Finally, patients who smoke should be advised to stop, because active smoking is associated with *H. pylori* eradication failure [43].

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