First-line therapies for Helicobacter pylori eradication: a critical reappraisal of updated guidelines

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Abstract
Helicobacter pylori (H. pylori) treatment remains a challenge for the clinician, as no available therapy is able to cure the infection in all treated patients. In the last two decades, several antibiotic combinations have been proposed, including triple therapies, bismuth-free therapies (sequential, concomitant, hybrid regimens), and bismuth-based quadruple therapy. Some national and international guidelines on H. pylori management have recently been updated, recommending or discouraging the use of each of these therapeutic approaches, based mainly on the presumed pattern of primary antibiotic resistance in different geographic areas. We examined the recommendations on first-line therapies in the most recently updated guidelines worldwide, taking into account other data affecting the efficacy of a therapy regimen beyond the primary resistance pattern. Although several guidelines highlighted that the results achieved by an eradication therapy are population-specific and not directly transferable, it emerged that some therapy regimens are recommended or discouraged with no mention of the vital need for national data.

Keywords Helicobacter pylori, therapy, sequential, concomitant, hybrid, bismuth salts, guidelines, bacterial resistance

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Introduction
Choosing a treatment for Helicobacter pylori (H. pylori) eradication in a definite geographic area relies on different factors, such as the local availability of antimicrobial agents, the pattern of primary antibiotic resistance, and the therapeutic cost [1]. In a specific patient, the probability of successful therapy is affected by several host and bacterial factors [2], but patient compliance and bacterial resistance to antibiotics play a major role. Compliance with an eradication therapy, in turn, depends on regimen complexity, tolerability, and the incidence of related side-effects. Good compliance, defined as a concordance of more than 90% between the prescribed and the ingested drugs, significantly increases the eradication rate [3]. The presence of H. pylori strains resistant towards a certain antibiotic is associated with its consumption in the general population, or its previous use in the same patient to treat other infections [4,5]. A high prevalence of resistance to primary clarithromycin (>15%) or metronidazole (>30%) in H. pylori isolates reduces the efficacy of standard first-line therapies that include these drugs [6,7]. This suggests that efforts in assessing local, regional, and national patterns of antimicrobial resistance should be performed to allow an appropriate selection of H. pylori therapies [8,9]. However, following standard therapies, bacterial eradication may be achieved in a definite number (up to 38.5%) of patients despite the presence of clarithromycin and/or metronidazole resistance [10]. Indeed, the combination of different synergic antibiotics may allow the resistance towards a specific molecule to be overcome. On the other hand, the infection is not cured in a distinct portion (19.6%) of patients even when susceptible H. pylori strains are present [10], as several other factors apart from the bacterial susceptibility status are involved [2]. These findings suggest a significant discordance between the expected eradication rate based on antimicrobial resistance assessment in vitro and the actual performance in vivo for each therapy regimen. Therefore, monitoring the efficacy of standard therapies in a particular area, irrespective of the prevalence of antibiotic resistance, is of paramount relevance before a still potentially successful therapy is abandoned [11].
Since the 1990s, different national and international guidelines for the management of patients with H. pylori infection have been introduced and periodically updated. Undeniably, recommendations on some issues are universally applicable to different geographic areas, such as those concerning the indications for treatment, or diagnostic procedures. For instance, H. pylori infection should be searched for in all patients with a peptic ulcer, irrespectively of the country where they are living. Likewise, the accuracy of noninvasive or invasive tests does not change among patients of different geographic areas. Therefore, guidelines on diagnosis and clinical issues may be applicable in all countries. In contrast, the efficacy of a therapy regimen may be affected by local or regional host/bacterial peculiarities [8,9]. Consequently, recommendations on therapeutic approaches are more appropriately addressed in national rather than international guidelines, provided that data from national studies are considered.

Based on all these considerations, we aimed to examine the most recently updated guidelines worldwide, focusing our attention on first-line therapy recommendations for H. pylori eradication. Specifically, we considered European [8], NICE [12], Italian [13], Spanish [14] American [9] and Canadian [15] guidelines for Western countries, and Asian [16], Australian [17], Japanese [18], and Chinese [19] guidelines for Eastern countries.

Clarithromycin-based triple therapies

In the last two decades, H. pylori treatment has been largely focused on triple therapies based on clarithromycin, which is the most powerful antibiotic against H. pylori strains [20]. To date, there is well documented evidence regarding the decreasing efficacy of these regimens as a result of the increased prevalence of primary resistance to clarithromycin and metronidazole. Following standard 7-day triple therapies, an eradication rate less than 80% has repeatedly been reported in several countries [21], so that a 14-day regimen has been proposed to improve the success rate. A recent Cochrane systematic review [22] and a large network meta-analysis [23] found that the prolonged 14-day regimen achieves a higher eradication rate compared to the 7- and 10-day schedules, although the therapeutic gain was only +8%. However, a 7-day triple therapy is still recommended in all Eastern guidelines apart from the Chinese, mainly depending on a particular prescriptive policy for antimicrobial drugs (Table 1). Conversely, among western guidelines, only one suggests the use of a 7-day triple therapy [12], whilst European, American and Canadian, but not Spanish, guidelines conditionally recommend a 14-day regimen, limiting its use in those geographic areas to low (<15%) clarithromycin resistance and for patients not previously exposed to macrolides (Table 2). Surprisingly, the use of a 14-day triple therapy is still suggested in the Italian guidelines, even though the primary clarithromycin resistance rate is definitely >15% in Italy [5,7]. Moreover, there are only 3 studies on 14-day triple therapy performed in Italy, which concordantly found that the success rate was lower than 75% and 80% in intention-to-treat (ITT) and per-protocol analyses, respectively (Table 3) [24-26]. Unfortunately, the eradication rate of 14-day triple therapy was not significantly increased even by using a double-dose proton-pump inhibitor (PPI) (i.e. esomeprazole 40 mg b.i.d.) [26]. Therefore, the recommendation for using a 14-day triple therapy in the updated Italian guidelines would appear at least questionable. For instance, based on the disappointing results of national studies [27], the Spanish guidelines wisely excluded 14-day triple therapies from the recommended treatments [14]. In contrast, in Latin America [28], the cure rate following the 14-day clarithromycin-aminocillin triple therapy (82.2%) was higher than that of either concomitant (73.6%) or sequential (76.5%) therapies, most probably because of the very high (>80%) prevalence of metronidazole resistance in the H. pylori strains. Therefore, the same therapy regimen may be more successful in a specific geographic area than in another.

Bismuth-free therapies

In order to overcome the decreasing efficacy of triple therapies, alternative regimens combining the few available antibiotics active against H. pylori strains have been pioneered during the last 15 years [29]. These include the sequential, concomitant and hybrid therapy regimens, schematically described in Table 4. In the current guidelines, the use of these treatments is recommended or not, based on different discriminating factors, such as regimen complexity, the impact of isolate or combined antimicrobial primary resistance, and the geographic variations in their efficacy. Each of these aspects could be susceptible to reappraisal.

The complexity of sequential therapy has been emphasized in different guidelines, and it relies on the need to change antibiotics during treatment, which, in turn, could result in low patient compliance. The same limitation has also been ascribed to the hybrid therapy regimen, the use of which is not recommended by any current guidelines, with only the US and Spanish guidelines advocating that further data are needed. Therefore, some opinion leaders criticized the concept of “sequential” administration of antibiotics, suggesting that a “concomitant” use of 3 antibiotics would favor patient compliance and increase therapeutic efficacy [30]. Nevertheless, we were unable to find any published data in the literature supporting a difference in compliance rate between sequential and concomitant therapies. On the contrary, the time needed for explaining the therapeutic regimen to the patients was specifically addressed in a large study, which found a similarly short (<5 min) time among sequential, concomitant and hybrid regimens, with no difference between patients with a high or low educational level [31]. In addition, a recent review network meta-analysis found that tolerability and compliance with sequential therapy were similar when compared to triple therapy, as well as to a concomitant therapy regimen, which is associated with even more side-effects [23]. After all, it is improbable that a 10-day therapy with a total of 50 tablets (sequential regimen) is associated with a lower compliance than that of a 14-day therapy with 112 tablets (concomitant regimen). Therefore, the emphasis on regimen complexity, which features in current guidelines as a discriminating factor for choosing a treatment, seems not to be supported by objective data.
The pattern of primary bacterial resistance towards different antibiotics may be a cause for concern. Indeed, different guidelines suggest choosing the first-line therapy according to regional or national prevalence of antimicrobial resistance in *H. pylori* isolates [8,9,15]. Specifically, a prevalence rate >15% for combined resistance towards clarithromycin and metronidazole is recognized as the major factor impairing efficacy of all bismuth-free therapies [6], whilst an isolate resistance rate >20% to clarithromycin undermines the efficacy of triple and sequential therapies, but not the concomitant regimen [8]. Nevertheless, at least three meta-analyses, including data from studies performed in areas with different prevalences of antibiotic resistance, have shown a similar efficacy of triple and sequential therapies, but not the concomitant regimen [8]. The eradication rate following 14-day triple therapies in Italy is shown in Table 3.

### Table 1 First-line therapies recommended in Eastern guidelines

| Therapy          | Asia 2009 [16] | Japan 2010 [18] | China 2013 [19] | Australia 2014 [17] |
|------------------|----------------|-----------------|-----------------|---------------------|
| Triple           | Recommended 7 days | Recommended 7 days | Not recommended | Recommended 7 days |
| Sequential       | Not recommended | Suspended judgment\(^1\) | No recommended | Suspended judgment\(^2\) |
| Concomitant      | Not contemplated | Suspended judgment\(^1\) | Suspended judgment\(^1\) | Not contemplated |
| Hybrid           | Not contemplated | Not contemplated | Not contemplated | Not contemplated |
| Bismuth-based    | Alternative option 14 days | No contemplated | Recommended 14 days | Recommended 14 days |

\(^1\) Lacking studies or evidences; [Ref]

### Table 2 First-line therapy recommended in Western guidelines

| Therapy          | NICE 2014 [12] | Italy 2015 [13] | Spain 2016 [14] | Europe 2016 [8] | Canada 2016 [15] | USA 2017 [9] |
|------------------|----------------|-----------------|-----------------|-----------------|-----------------|--------------|
| Triple           | Recommended 7 days | Recommended 14 days | Not recommended | Conditionally recommended 14 days\(^1\) | Conditionally recommended 14 days\(^2\) | Conditionally recommended 14 days\(^3\) |
| Sequential       | Not contemplated | Recommended | Not recommended | Not recommended | Not recommended | Conditionally recommended\(^4\) |
| Concomitant      | No contemplated | Recommended 14 days | Recommended 14 days | Recommended 14 days | Recommended 14 days | Recommended 10-14 days |
| Hybrid           | Not contemplated | Not contemplated | Suspended judgment\(^2\) | Not contemplated | Not contemplated | Suspended judgment\(^2\) |
| Bismuth-based    | Recommended 7 days | Suspended judgment\(^2\) | Recommended 14 days | Recommended 10 or 14 days | Recommended 14 days | Recommended 14 days |

\(^1\) Only in those area with a low (<15%) prevalence of primary clarithromycin resistance. \(^2\) Lacking studies or evidence; [Ref]

### Table 3 Eradication rate following 14-day triple therapies in Italy

| Study            | Year | Disease       | ITT eradication rate (%) | PP eradication rate (%) |
|------------------|------|---------------|--------------------------|-------------------------|
| Paoluzi et al [24] | 2006 | NUD/PUD       | 156/247 (63.1)           | 156/209 (74.6)          |
| Zagari et al [25] | 2007 | PUD           | 246/301 (81.7)           | 185/218 (84.9)          |
| De Francesco et al [26] | 2016 | NUD/PUD       | 54/73 (74)               | 54/69 (78.3)            |
| Total            |      |               | 456/621 (73.4)           | 395/496 (79.6)          |

ITT, intention to treat; PP, per protocol; NUD, non-ulcer dyspepsia; PUD, peptic ulcer disease.
Arab Emirates (88.6%) [49], suggesting that this therapy is still effective in several countries. Based on these findings, Italian, Slovenian, or Portuguese physicians could inopportune deprive their patients *a priori* of a still effective therapy by following the European guidelines. In contrast, unsatisfactory cure rates were observed in Greece [50], Spain [51], Ireland [52], Turkey [53], Iran [54], Korea [55], China [56], and Puerto Rico [57]. Notably, the difference among results achieved by sequential therapy in different geographic areas could be due, at least in part, to the type of nitroimidazole used. In several studies, metronidazole 400 mg b.i.d. has been administered instead of tinidazole 500 mg b.i.d., and it has been found that the tinidazole-based regimen achieved significantly higher cure rates than metronidazole-based sequential therapy [36]. Indeed, apart from the higher dose, tinidazole possesses a markedly higher half-life compared to metronidazole [36].

Considering the geographic variations in cure rate achieved by an eradication regimen it was astonishing to note that some national guidelines discourage the use of a certain therapy, despite no data from Italian trials, the first studies only now found that the tinidazole-based regimen achieved significantly higher cure rates than metronidazole-based sequential therapy [36]. Indeed, the interest in such a regimen has recently been renewed by the marketing of a novel, three-in-one capsule (Pylera®) that was first proposed in 2001, each pill containing bismuth subcitrate potassium (140 mg), metronidazole (125 mg) and tetracycline (125 mg) [62]. The bismuth-based quadruple therapy is included among the recommended first-line therapies in the current European, US, Canadian and Chinese guidelines [8,9,15,19]. Surprisingly, such a therapy was also suggested as an alternative first-line therapy in the Italian guidelines published in 2015, which was before the marketing of these tablets (2016 in Italy) and without any data from Italian trials, the first studies only now being available [41,63].

The ITT eradication rate following such a quadruple therapy was 86% (95% confidence interval [CI] 79-91%) in 299 patients in the US [64] and 80% (95%CI=74-85%) in 440 patients in

Table 4 Therapy regimens suggested for *Helicobacter pylori* eradication in the current guidelines

| Therapy regimen | Administration (daily) | Duration (days) | Number of tablets | Cost in Italy (euros) |
|-----------------|------------------------|-----------------|-------------------|----------------------|
| Standard triple therapy | b.i.d. | 14 | 84 | 49.72 |
| - PPI+ clarithromycin 500 mg+amoxicillin 1000 mg | b.i.d. | 14 | 84 | 57.28 |
| - PPI+clarithromycin 500 mg+tinidazole 500 mg | b.i.d. | 10 | 50 | 29.40 |
| Sequential | PPI+amoxicillin 1000 mg (5 days) followed by PPI+clarithromycin 500 mg+tinidazole 500 mg | b.i.d. | 14 | 112 | 68.32 |
| Concomitant | PPI+clarithromycin 500 mg+amoxicillin 1000 mg+tinidazole 500 mg | b.i.d. | 10 | 80 | 48.8 |
| Bismuth-based quadruple (three-in-one tablets; Pylera*) | PPI+3 Pylera* | b.i.d. + q.i.d. | 10 | 140 | 74.04 |
| | PPI+3 Pylera* | b.i.d. + q.i.d. | 14 | 196 | 103.04 |

*PPI: esomeprazole 20 mg (brand) or rabeprazole 20 mg (brand)
Concluding remarks

*Helicobacter pylori* is a strange bacterium with several peculiarities. It has been living in the human stomach for thousands of years, even though it is a pathogen. It is able to survive in the prohibitive low pH values of gastric juice, hidden in a peculiar ecological niche between the gastric mucosal layer and the epithelium. It causes various benign and malignant diseases in the gastroduodenal tract, as well as some extra-intestinal diseases. It is a Gram-negative germ, but highly sensitive to penicillin, which acts better on the wall of Gram-positive bacteria. No single antibiotic is able to cure the infection, and even a combination of three or more compounds may be ineffective in a substantial portion of patients. No effective vaccine is available, since the bacterium can survive different approaches. Consequently, the therapeutic battle against *H. pylori*, which started in the 1980s, is still ongoing and the ideal treatment is lacking.

According to the evidence-based medicine approach, guidelines represent an undeniable advantage for the management of *H. pylori* infection in clinical practice. However, several factors are involved in the efficacy of a specific therapy regimen, including some specific host-bacteria interactions, which may be peculiar to different geographic areas. Indeed, the European guidelines clearly highlighted that the results achieved by an eradication therapy are population-specific and not directly transferable [8]. Therefore, at least the therapeutic aspects are more appropriately addressed in national than in other guidelines, providing that data from national trials are opportunistically considered.

Undeniably, the role of primary resistance is relevant [71], but antimicrobial resistance *in vitro* does not always correlate with poor results from multi-drug treatment regimens [72]. Indeed, it should be considered that all therapy regimens include a combination of antibiotics with a potentially synergistic effect that can overcome the resistance to a single molecule. Unfortunately, the infection is not cured in all cases, even using only those antibiotics with a proven susceptibility, as demonstrated in bacterial culture-based studies [73]. A meta-analysis of 12 studies found an eradication rate of 89.2% (95% CI=87.1-91.3) in 860 patients, despite the use of a therapy tailored according to susceptibility testing results [74]. Therefore, even if primary resistance status towards clarithromycin or levofloxacin could be assessed prior to first-line therapy, using novel stool tests based on the polymerase chain reaction technique [75], bacterial eradication is not guaranteed. Similarly, under the empirical administration of a 14-day bismuth–tetracycline–amoxicillin combination, three drugs with no or a very low (<5%) primary resistance rate to *H. pylori* isolates, the eradication rate was as low as 43% [76].

Keeping in mind that novel antibiotics against *H. pylori* are not available, the use of those regimens with proven efficacy in a specific geographic area would appear judicious, before abandoning a therapy *a priori*, considering only the bacterial resistance pattern. Last but not least, the therapeutic cost of different regimens should be taken into account when considering the vast diffusion of *H. pylori* infection worldwide. In those areas where the efficacy of different therapies is similar (±5%) the cost of drugs may be a cause for concern (Table 4), and specific cost-effectiveness studies are needed.

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