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

**Vincenzo De Francesco[a], Annamaria Bellesia[a], Lorenzo Ridola[b], Raffaele Manta[c], Angelo Zullo[d]**

Riuniti Hospitals, Foggia; Sapienza University of Rome, Polo Pontino, Latina; Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena; Nuovo Regina Margherita Hospital, Rome, Italy

**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].

[a]Section of Gastroenterology, "Riuniti" Hospitals, Foggia (Vincenzo De Francesco, Annamaria Bellesia); [b]Gastroenterology Unit, "Sapienza" University of Rome, Polo Pontino, Latina (Lorenzo Ridola); [c]Gastroenterology Unit, Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena (Raffaele Manta); [d]Gastroenterology and Digestive Endoscopy, "Nuovo Regina Margherita" Hospital, Rome (Angelo Zullo), Italy

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Correspondence to: Dr. Vincenzo De Francesco, AOU Gastroenterologia, Ospedali Riuniti di Foggia, Viale Pinto, 71100 Foggia, Italy, Tel.: +39 0881 733776, Fax: +39 0881 736218, e-mail: vdefrancesco@alice.it

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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–amoxicillin 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.

**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[1] |
| 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[1] | Conditionally recommended 14 days[1] |
| Sequential | Not contemplated | Recommended | Not recommended | Not recommended | Not recommended | Conditionally recommended[2] |
| Concomitant | No contemplated | Recommended | 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*

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 between sequential and concomitant therapies [32-34]. Therefore, *a priori* discrimination with respect to a particular therapy based only on the presumed prevalence of bacterial resistance in a geographic area seems to be at least questionable, and local validation of each therapy regimen would be desirable. Indeed, factors beyond the antibiotic resistance pattern could play a role, causing different results in diverse geographic areas. For instance, primary resistance towards either clarithromycin or metronidazole in *H. pylori* isolates is as high as 30% in Italy [5,7], so that the sequential therapy should not be used according to the European guidelines [8]. However, in the last decade, an eradication rate of >90% has repeatedly been found in all multicenter Italian trials involving thousands of patients [35,36], apart from one study published in 2010 where the infection was cured in 83% of 122 patients [37]. When considering only data from studies published in the last 5 years, the cure rate following sequential therapy was still 90-92.6% in 5 Italian studies with more than 1000 patients [26,38-41], and 73% in another study with 100 cases [42]. A similarly high success rate of sequential therapy has been observed in studies recently performed in Slovenia (94.2%) [43], Portugal (90%) [44], Belgium (90%) [3], Israel (95.9%) [45], Thailand (94%) [46], Taiwan (91.9%) [47], Singapore (90.3%) [48], and the United

**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 | | | | |
| - PPI* + clarithromycin 500 mg+amoxicillin 1000 mg | b.i.d. | 14 | 84 | 49.72 |
| - PPI+clarithromycin 500 mg+tinidazole 500 mg | b.i.d. | 14 | 84 | 57.28 |
| Sequential | | | | |
| PPI+amoxicillin 1000 mg (5 days) followed by | b.i.d. | 10 | 50 | 29.40 |
| PPI+clarithromycin 500 mg+tinidazole 500 mg (5 days) | b.i.d. | | | |
| Concomitant | | | | |
| PPI+clarithromycin 500 mg+amoxicillin 1000 mg+tinidazole 500 mg | b.i.d. | 10 | 80 | 48.8 |
| PPI+clarithromycin 500 mg+amoxicillin 1000 mg+tinidazole 500 mg | b.i.d. | 14 | 112 | 68.32 |
| 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)

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 inopportunely 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 a lack of robust data coming from the same geographic area. For instance, the Canadian guidelines recommend against sequential therapy, although only one study was performed in that country [58]. Specifically, a total of 104 patients from Arctic aboriginal community were enrolled, with 51 cases in the sequential therapy and 49 in the triple therapy arm, showing disappointing results for both therapies. Irrespective of the efficacy, can the results of a single, small study of Canada's Arctic population be extended to the entire Canadian population? Notably, it has been demonstrated that compliance with either triple or sequential therapies in the studied population was perfect in only 64% and good in another 16% of patients [59]. Can a therapy regimen efficacy be reliably assessed when tablets are taken correctly by only half of the patients? Are we sure that the result observed in the Arctic circle population is the same achievable in Toronto or Vancouver? It could be suggested that greater caution should be adopted in the preparation of statements for guidelines when national data are limited or even lacking. Indeed, a guideline statement influences the decisions of thousands of physicians, with potential consequences for millions of patients. For instance, US and Japanese guidelines correctly suggest that no reliable evaluation of sequential therapy is possible, since there is a lack of specific data for their countries [9,18].

## Bismuth-based quadruple therapies

Undeniably, 14-day triple therapy with bismuth salts, tetracycline and metronidazole was the first therapy to achieve consistently high *H. pylori* eradication rates. This therapy was introduced and largely used in the second part of the 1980s. The decline of such a regimen was mainly due to its intrinsic complexity (large number of tablets, q.i.d. administration, frequent side-effects) and to the rise of simpler and more tolerable triple therapies. In order to improve compliance with the bismuth-based triple therapy, a PPI has been added, aiming to reduce side-effects and shortening therapy length to only 4-7 days, thus configuring the bismuth-based quadruple therapy [60,61]. Unfortunately, some delivery problems have arisen with bismuth salts in Europe and tetracycline in the US, so that the use of quadruple therapy in several countries has been greatly limited in the last decade. 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

Europe [65], whilst another international trial found an 89.3% eradication rate (modified ITT of 93%, 95%CI=85.4-100%), without any difference between patients with metronidazole-resistant or susceptible strains [66]. Unfortunately, despite the three-in-one capsule formulation, as many as 3 tablets q.i.d. for 10 days plus 2 PPI tablets are needed, that is a total of 14 tablets daily. Therefore, patients' compliance with this therapy needs to be opportunely assessed in real life, where several patients are already taking other drugs for frequent chronic diseases, such as hypertension, diabetes, cardiovascular diseases, etc. Moreover, some concerns may arise with bismuth toxicity, especially when considering the coadministration of PPIs. Although bismuth salts are scarcely absorbed (<1%), high doses, long-term consumption and the simultaneous use of PPIs may lead to high blood levels and potential toxicity. In the past, bismuth doses of 240, 300 or 480 mg daily were generally administered for 4-10 days [67-69]. When a 480 mg bismuth dose has been used with omeprazole for 14 days, 9% of patients have blood bismuth levels higher than 50 μg/L, which is over the safety threshold for potential bismuth neurotoxicity, according to Hillemand's scale [70]. Note that, when the novel three-in-one capsules are used, a dose as high as 1680 mg subcitrate potassium (corresponding to 560 mg bismuth) is administered daily. A study found that bismuth plasma concentrations increased in 22% of patients receiving this therapy, but levels (4-20 μg/L) were below the toxic threshold. However, further studies on blood bismuth concentrations are needed, particularly when double-dose PPI (i.e., esomeprazole 40 mg b.i.d.) is used [63]. For the same reason, the statement in the European guidelines suggesting that such a bismuth quadruple therapy should be extended to 14 days (unless 10-day therapies are proven effective locally) deserves at least a note of caution.

## Concluding remarks

*H. 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 muco-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 opportunely 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.

## References


1. Hunt RH, Xiao SD, Megraud F, et al; World Gastroenterology Organization. *Helicobacter pylori* in developing countries. World Gastroenterology Organisation Global Guideline. *J Gastrointestin Liver Dis* 2011;**20**:299-304.
2. Zullo A, De Francesco V, Hassan C. Predicting *Helicobacter pylori* eradication: How to teach an old dog new tricks! *J Clin Gastroenterol* 2012;**46**:259-261.
3. Kotilea K, Mekhael J, Salame A, et al. Eradication rate of *Helicobacter pylori* infection is directly influenced by adherence to therapy in children. *Helicobacter* 2017 Mar 17. doi: 10.1111/hel.12383 [Epub ahead of print].
4. Megraud F, Coenen S, Versporten A, et al; Study Group participants. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;**62**:34-42.
5. De Francesco V, Giorgio F, Hassan C, et al. Worldwide *H. pylori* antibiotic resistance: A systematic review. *J Gastrointestin Liver Dis* 2010;**19**:409-414.
6. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: Evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014;**12**:177-186.e3.
7. Thung I, Aramin H, Vavinskaya V, et al. Review article: The global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016;**43**:514-533.

8. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017;**66**:6-30.
9. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 2017;**112**:212-239.
10. Park JY, Dunbar KB, Mitui M, et al. *Helicobacter pylori* clarithromycin resistance and treatment failure are common in the USA. *Dig Dis Sci* 2016;**61**:2373-2380.
11. Losurdo G, Leandro G, Principi M, et al. Sequential vs. prolonged 14-day triple therapy for *Helicobacter pylori* eradication: The meta-analysis may be influenced by 'geographical weighting'. *Int J Clin Pract* 2015;**69**:1112-1120.
12. National Institute for Health and Care Excellence (NICE) guidelines: Gastro-eesophageal reflux disease and dyspepsia: Investigation and management (CG184). NICE 2014:1-41 [Internet]. Available from: www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-pdf-35109812699845.
13. Zagari RM, Romano M, Ojetti V, et al. Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015. *Dig Liver Dis* 2015;**47**:903-912.
14. Gisbert JP, Molina-Infante J, Amador J, et al. IV Spanish Consensus Conference on *Helicobacter pylori* infection treatment. *Gastroenterol Hepatol* 2016;**39**:697-721.
15. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto Consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016;**151**:51-69.
16. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection *J Gastroenterol Hepatol* 2009;**24**:1587-1600.
17. Yaxley J, Chakravarty B. *Helicobacter pylori* eradication – an update on the latest therapies. *Aust Fam Physician* 2014;**43**:301-305.
18. Asaka M, Kato M, Takahashi S, et al; Japanese Society for Helicobacter Research. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter* 2010;**15**:1-20.
19. Liu WZ, Xie Y, Cheng H, et al; Chinese Society of Gastroenterology, Chinese Study Group on *Helicobacter pylori*. Fourth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *J Dig Dis* 2013;**14**:211-221.
20. Mégraud F. Current recommendations for *Helicobacter pylori* therapies in a world of evolving resistance. *Gut Microbes* 2013;**4**:541-548.
21. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010;**59**:1143-1153.
22. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database Syst Rev* 2013;**(12)**:CD008337.
23. Li BZ, Threapleton DE, Wang JY, et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: Systematic review and network meta-analysis. *BMJ* 2015;**351**:h4052.
24. Paoluzi P, Iacopini F, Crispino P, et al. 2-week triple therapy for *Helicobacter pylori* infection is better than 1-week in clinical practice: A large prospective single-center randomized study. *Helicobacter* 2006;**11**:562-568.
25. Zagari RM, Bianchi-Porro G, Fiocca R, Gasbarrini G, Roda E, Bazzoli F. Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for *Helicobacter pylori* eradication: The HYPER Study. *Gut* 2007;**56**:475-479.
26. De Francesco V, Ridola L, Hassan C, et al. Two-week triple therapy with either standard or high-dose esomeprazole for first-line *H. pylori* eradication. *J Gastrointestin Liver Dis* 2016;**25**:147-150.
27. Molina-Infante J, Lucendo AJ, Angueira T, et al; European Registry on *H. pylori* management (Hp-EuReg). Optimised empiric triple and concomitant therapy for *Helicobacter pylori* eradication in clinical practice: The OPTRICON study. *Aliment Pharmacol Ther* 2015;**41**:581-589.
28. Greenberg ER, Anderson GL, Morgan DR, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: A randomised trial. *Lancet* 2011;**378**:507-514.
29. De Francesco V, Ierardi E, Hassan C, Zullo A. *Helicobacter pylori* therapy: Present and future. *World J Gastrointest Pharmacol Ther* 2012;**3**:68-73.
30. Graham DY, Shiotani A. Which therapy for *Helicobacter pylori* infection? *Gastroenterology* 2012;143:10-12.
31. De Francesco V, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for *Helicobacter pylori* eradication: A prospective randomized study. *J Med Microbiol* 2014;**63**:748-752.
32. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: Systematic review and meta-analysis of sequential therapy. *BMJ* 2013;**347**:f4587.
33. He L, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for *Helicobacter pylori* eradication. *Intern Med* 2015;**54**:703-710.
34. Kim JS, Park SM, Kim BW. Sequential or concomitant therapy for eradication of *Helicobacter pylori* infection: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2015;**30**:1338-1345.
35. Zullo A, De Francesco V, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: A pooled-data analysis. *Gut* 2007;**56**:1353-1357.
36. Vaira D, Zullo A, Hassan C, Fiorini G, Vakil N. Sequential therapy for *Helicobacter pylori* eradication: The time is now! *Therap Adv Gastroenterol* 2009;**2**:317-322.
37. Romano M, Cuomo A, Gravina AG, et al. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for *Helicobacter pylori* eradication: A randomised trial. *Gut* 2010;**59**:1465-1470.
38. Zullo A, Scaccianoce G, De Francesco V, et al. Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: A pilot study. *Clin Res Hepatol Gastroenterol* 2013;**37**:647-650.
39. Manfredi M, Bizzarri B, de'Angelis GL. *Helicobacter pylori* infection: Sequential therapy followed by levofloxacin-containing triple therapy provides a good cumulative eradication rate. *Helicobacter* 2012;**17**:246-253.
40. Manfredi M, Bizzarri B, Sacchero RI, et al. *Helicobacter pylori* infection in clinical practice: Probiotics and a combination of probiotics + lactoferrin improve compliance, but not eradication, in sequential therapy. *Helicobacter* 2012;**17**:254-263.
41. Di Ciaula A, Scaccianoce G, Venerito M, et al. Eradication rates in Italian subjects heterogeneously managed for *H. pylori* infection. Time to abandon empiric treatments in Southern Europe. *J Gastrointestin Liver Dis* 2017;**26**:129-137.
42. Franceschi F, Ojetti V, Gabrielli M, et al. High dose amoxicillin-based first line regimen is equivalent to sequential therapy in the eradication of *H. pylori* infection. *Eur Rev Med Pharmacol Sci* 2016;**20**:297-300.
43. Tepeš B, Vujasinović M, Šeruga M, Stefanovič M, Forte A, Jeverica S. Randomized clinical trial comparing 10-day sequential, 7-day concomitant and 7-day standard triple therapies for *Helicobacter pylori* eradication. *Eur J Gastroenterol Hepatol* 2016;**28**:676-683.
44. Branquinho D, Almeida N, Gregório C, et al. Levofloxacin or Clarithromycin-based quadruple regimens: What is the best alternative as first-line treatment for *Helicobacter pylori* eradication in a country with high resistance rates for both antibiotics? *BMC Gastroenterol* 2017;**17**:31.
45. Schmilovitz-Weiss H, Schmiloviz-Weiss H, Shalev T, et al. High eradication rates of *Helicobacter pylori* infection following sequential therapy: The Israeli experience treating naïve patients. *Helicobacter* 2011;**16**:229-233.

46. Phiphatpatthamaamphan K, Vilaichone RK, Siramolpiwat S, et al. Effect of IL-1 polymorphisms, CYP2C19 genotype and antibiotic resistance on *Helicobacter pylori* eradication comparing between 10-day sequential therapy and 14-day standard triple therapy with four-times-daily-dosing of amoxicillin in Thailand: A prospective randomized study. *Asian Pac J Cancer Prev* 2016;**17**:1903-1907.
47. Liou JM, Chen CC, Chang CY, et al; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of *Helicobacter pylori* in the community and hospital populations: A randomised trial. *Gut* 2016;**65**:1784-1792.
48. Ang TL, Fock KM, Song M, et al. Ten-day triple therapy versus sequential therapy versus concomitant therapy as first-line treatment for *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2015;**30**:1134-1139.
49. Abuhammour A, Dajani A, Nounou M, Zakaria M. Standard triple therapy versus sequential therapy for eradication of *Helicobacter pylori* in treatment naïve and retreat patients. *Arab J Gastroenterol* 2016;**17**:131-136.
50. Georgopoulos SD, Xirouchakis E, Martinez-Gonzales B, et al. Randomized clinical trial comparing ten day concomitant and sequential therapies for *Helicobacter pylori* eradication in a high clarithromycin resistance area. *Eur J Intern Med* 2016;**32**:84-90.
51. McNicholl AG, Marin AC, Molina-Infante J, et al; Participant Centres. Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. *Gut* 2014;**63**:244-249.
52. Haider RB, Brennan DE, Omorogbe J, et al. A randomized-controlled study to compare the efficacy of sequential therapy with standard triple therapy for *Helicobacter pylori* eradication in an Irish population. *Eur J Gastroenterol Hepatol* 2015;**27**:1265-1269.
53. Rakici H, Akdoğan RA, Bedir R, Copur A, Yilmaz A. Comparison of standard triple therapy, sequential therapy and moxifloxacin-based triple therapy for *Helicobacter pylori* infection: Patients' compliance and bacterial eradication rates. *J Dig Dis* 2014;**15**:508-513.
54. Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for *Helicobacter pylori* eradication in Iran: A prospective randomized trial. *Helicobacter* 2013;**18**:129-134.
55. Lee JW, Kim N, Kim JM, et al. A comparison between 15-day sequential, 10-day sequential and proton pump inhibitor-based triple therapy for *Helicobacter pylori* infection in Korea. *Scand J Gastroenterol* 2014;**49**:917-924.
56. Zhou L, Zhang J, Chen M, et al. A comparative study of sequential therapy and standard triple therapy for *Helicobacter pylori* infection: A randomized multicenter trial. *Am J Gastroenterol* 2014;**109**:535-541.
57. Warrington E, López-Román O, Tirado Montijo R, Urbina R, Cruz-Correa M, Toro DH. Neither 10- nor 14-day sequential treatment is better than standard triple therapy for *Helicobacter pylori* eradication. *P R Health Sci J* 2016;**35**:203-208.
58. Morse AL, Goodman KJ, Munday R, et al; CANHelp Working Group. A randomized controlled trial comparing sequential with triple therapy for *Helicobacter pylori* in an Aboriginal community in the Canadian North. *Can J Gastroenterol* 2013;**27**:701-706.
59. Lefebvre M, Chang HJ, Morse A, van Zanten SV, Goodman KJ; CANHelp Working Group. Adherence and barriers to *H. pylori* treatment in Arctic Canada. *Int J Circumpolar Health* 2013;**72**:22791.
60. de Boer WA, Driessen WM, Potters VP, Tytgat GN. Randomized study comparing 1 with 2 weeks of quadruple therapy for eradicating *Helicobacter pylori*. *Am J Gastroenterol* 1994;**89**:1993-1997.
61. de Boer WA, van Etten RJ, Schade RW, Ouwehand ME, Schneeberger PM, Tytgat GN. 4-day lansoprazole quadruple therapy: A highly effective cure for *Helicobacter pylori* infection. *Am J Gastroenterol* 1996;**91**:1778-1782.
62. de Boer WA. A novel therapeutic approach for *Helicobacter pylori* infection: The bismuth-based triple therapy monocapsule. *Expert Opin Investig Drugs* 2001;**10**:1559-1566.
63. Tursi A, Di Mario F, Franceschi M, et al. New bismuth-containing quadruple therapy in patients infected with *Helicobacter pylori*: A first Italian experience in clinical practice. *Helicobacter* 2017;**22**. doi: 10.1111/hel.12371.
64. Laine L, Hunt R, El-Zimaity H, Nguyen B, Osato M, Spénard J. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: A prospective, randomized, multicenter, North American trial. *Am J Gastroenterol* 2003;**98**:562-567.
65. Malfertheiner P, Bazzoli F, Delchier JC, et al; Pylera Study Group. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: A randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011;**377**:905-913.
66. O'Morain C, Borody T, Farley A, et al; International multicentre study. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of *Helicobacter pylori*: An international multicentre study. *Aliment Pharmacol Ther* 2003;**17**:415-420.
67. Lerang F, Moum B, Ragnhildstveit E, et al. A comparison between omeprazole-based triple therapy and bismuth-based triple therapy for the treatment of *Helicobacter pylori* infection: A prospective randomized 1-yr follow-up study. *Am J Gastroenterol* 1997;**92**:653-658.
68. de Boer SY, van der Meeberg PC, de Boer WA. Comparison of four-day and seven-day pantoprazole-based quadruple therapy as a routine treatment for *Helicobacter pylori* infection. *Netherland J Med* 2003;**61**:218-222.
69. Fallone CA, Loo V, Joseph L, Barkun J, Kostyk R, Barkun A. predictors of failure of *Helicobacter pylori* eradication and predictors of ulcer recurrence: A randomized controlled trial. *Clin Invest Med* 1999;**22**:185-194.
70. Phillips RH, Whitehead MW, Doig LA, et al. Is eradication of *Helicobacter pylori* with colloidal bismuth subcitrate quadruple therapy safe? *Helicobacter* 2001;**6**:151-156.
71. McNulty CA, Lasseter G, Shaw I, et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther* 2012;**35**:1221-1230.
72. Graham DY, de Boer WA, Tytgat GN. Choosing the best anti-*Helicobacter pylori* therapy: effect of antimicrobial resistance. *Am J Gastroenterol* 1996;**91**:1072-1076.
73. Romano M, Marmo R, Cuomo A, et al. Pretreatment antimicrobial susceptibility testing is cost saving in the eradication of *Helicobacter pylori*. *Clin Gastroenterol Hepatol* 2003;**1**:273-278.
74. López-Góngora S, Puig I, Calvet X, et al. Systematic review and meta-analysis: Susceptibility-guided versus empirical antibiotic treatment for *Helicobacter pylori* infection. *J Antimicrob Chemother* 2015;**70**:2447-2455.
75. Ierardi E, Giorgio F, Iannone A, et al. Noninvasive molecular analysis of *Helicobacter pylori*: Is it time for tailored first-line therapy? *World J Gastroenterol* 2017;**23**:2453-2458.
76. Graham DY, Lew GM, Ramirez FC, Genta RM, Klein PD, Malaty HM. Short report: A non-metronidazole triple therapy for eradication of *Helicobacter pylori* infection—tetracycline, amoxicillin, bismuth. *Aliment Pharmacol Ther* 1993;**7**:111-113.