World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i45.8168

World J Gastroenterol 2013 December 7; 19(45): 8168-8180
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography?

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Received: September 23, 2013 Revised: October 18, 2013
Accepted: November 3, 2013
Published online: December 7, 2013

Abstract

Therapeutic management of *Helicobacter pylori* (*H. pylori*) remains an unsolved issue. Indeed, no therapeutic regimen is able to cure the infection in all treated patients, and in many the infection persists despite the administration of several consecutive standard therapies. Although antibiotic resistance reports describe alarming results, the outcome of therapeutic regimens does not seem to parallel this scenario in most cases, since a successful performance is often reached in more than 80% of cases. However, the phenomenon of increasing antibiotic resistance is being closely studied, and the results show controversial aspects even in the same geographic area. For the continents of Europe, America, Asia, Africa, and Oceania, minimal and maximal values of resistance to the main antibiotics (clarithromycin, amoxicillin, metronidazole, and levofloxacin) feature wide ranges in different countries. The real enigma is therefore linked to the several different therapeutic regimens, which show results that often do not parallel the in vitro findings even in the same areas. A first aspect to be emphasized is that some regimens are limited by their use in very small geographic districts. Moreover, not all therapeutic trials have considered bacterial and host factors affecting the therapeutic outcome. The additional use of probiotics may help to reduce adverse events, but their therapeutic impact is doubtful. In conclusion, the "ideal therapy", paradoxically, appears to be a "utopia", despite the unprecedented volume of studies in the field and the real breakthrough in medical practice made by the discovery and treatment of *H. pylori*. The ample discrepancies observed in the different areas do not encourage the development of therapeutic guidelines that could be valid worldwide. On these bases, one of the main challenges for the future might be identifying a successful solution to overcome antibiotic resistances. In this context, geography must be considered a relevant matter.

Key words: *Helicobacter pylori*; Antibiotic resistance; Geography; Therapeutic regimens; Therapeutic outcome

Core tip: The present topic outlines the main data regarding antibiotic resistances, paying particular attention to the discrepant results obtained in different geographic areas worldwide, and even in the same districts. Discordances between *in vitro* and *in vivo* studies are detailed and the possible factors explaining this phenomenon are analyzed. Finally, the challenge for the future of devising a successful solution to overcome antibiotic resistances is highlighted, and geography is suggested as a relevant matter.

Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? *World J Gastroenterol* 2013;

19(45): 8168-8180 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i45/8168.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i45.8168

INTRODUCTION

Helicobacter pylori (*H. pylori*) eradication has undoubted benefits. The bacterium's diffusion worldwide, even if it is decreasing, especially in developed countries, still dictates the treatment of all infected subjects, and the possible legal implications that denial of treatment could have must also be considered. In Table 1, epidemiological studies of the last five years from five continents of the world (Europe, America, Asia, Africa, and Oceania) are reported[1-14]. Different infection rates depend on the type of study population (pediatric, adult, or geriatric patients), since increasing age, as well as poor hygienic environmental factors, are well known to have a strong influence. Arresting the bacterium's diffusion still has not been achieved.

Treatment of the infection nowadays is both a simple and, at the same time, complex problem. Alongside the conventional first-line regimen (triple therapy), others have been proposed (sequential, concomitant, quadruple, and miscellaneous) to face the growing problem of antibiotic resistance. For no other infection have so large a number of therapeutic proposals been reported by different working groups. The results, however, often appear conflicting and the same regimen may be extremely effective in one geographic area and deliver disappointing results in another. Finally, although many experts believe that there is no such thing as untreatable *H. pylori*, only ill-treated *H. pylori*, no clinical trial has yielded a successful 100% eradication. We must therefore conclude that "the infallible therapy" does not exist at present. Therefore, the aim of this review is to analyze the different results of therapeutic schemes in different geographic regions, as well as their relationship with the diffusion of antibiotic resistances in the same areas.

ANTIBIOTIC RESISTANCES

H. pylori antibiotic resistances are defined as primary (no previous treatment for bacterium eradication) and secondary (a susceptible strain acquires resistance during a treatment)[15]. The main reason for this phenomenon is point mutations of *H. pylori* DNA, often associated with inappropriate antibiotic use[15]. Heteroresistance is a condition characterized by the coexistence of susceptible and resistant strains in the same patient. Resistances are currently detected by culture-based and molecular methods. Different tests for both techniques have been described. The main culture-based techniques are the agar dilution method, *E*-test, breakpoint susceptibility test, and modified disk diffusion method. Molecular techniques include polymerase chain reaction (PCR), restriction fragment length polymorphism, allele-specific PCR, sequencing, real-time PCR, and fluorescent *in situ* hybridization[16-22]. Although these tests require sophisticated tools, their performance before starting a treatment for *H. pylori* will undoubtedly significantly improve the therapeutic outcome. However, this strategy is hard to apply in clinical practice owing to the long period necessary before obtaining results, as well as the high costs of routine performance of such methods.

GEOGRAPHIC DIFFERENCES IN ANTIBIOTIC RESISTANCES

A large number of reports from different geographic areas are available in the literature, showing heterogeneous results. Firstly, we will consider the geographic rates of resistance to each antibiotic, thus underlining differences and consequent clinical implications.

Clarithromycin

Clarithromycin is a drug that belongs to the macrolide family, and its mechanism of action is the inhibition of protein synthesis by binding and slowing down the activity of the bacterial ribosomal unit[23]. The mutations that may cause resistances are point mutations in the 23SrRNA component of ribosomes[24]: the three most frequent mutations that may occur are A2143G, A2142G, and A2142C, which are responsible for 90% of cases of primary clarithromycin resistance in *H. pylori* strains isolated in Western countries[25,26]. In particular, the A2143G mutation has a much stronger impact on conferring resistance than the other two[27]. In Eastern countries (*e.g.*, South Korea) additional mutations, such as T2183C and A2223G, have been frequently found to justify the observed clarithromycin resistance, while A2143G accounted only for 23% of resistant strains[26]. This finding, if confirmed in other Asian countries, suggests that point mutations inducing clarithromycin resistance might differ in this continent as compared to those in Europe and North America. In conclusion, resistance to clarithromycin is considered as the cause of most eradication regimen failures[28], as its prevalence is continuously increasing. Moreover, new point mutations have also emerged in South America[29]. However, isolated reports may not reflect the real scenario; therefore, it would be more useful to consider epidemiological data about resistance region by region.

In Eastern Asian countries, very high clarithromycin resistances have been recorded. The highest rate of resistance was found in Japan (86.4%) in a study on the efficacy of this antibiotic in a third line regimen[30]. Interestingly, in the same country, a lower percentage of 15.2% was detected in another study of first line therapy[31]. In any case, in every region of the Far East, the rates of resistance were at least 15%, a percentage that often determines the failure of clarithromycin-based therapy. In another two Japanese studies the rates were 32.4%[32] and 18.9%[33], respectively. In China, resistances ranged between 21.5% and 23.8%[34,35], while in Viet-

Table 1 Epidemiological studies of the last five years from five world continents regarding *Helicobacter pylori* infection prevalence

Country	Ref.	*Helicobacter pylori* positivity	Test	Population
Southern Europe				
Italy	Dore *et al*[1], 2012	13.3%	Serology	Children
Portugal	Bastos *et al*[2], 2013	84.2%	Serology	Adults
Northern Europe				
Sweden	Thjodleifsson *et al*[3], 2007	11%	Serology	Adults
Norway	Bakkevold[4], 2010	51%	Serology	Adults
Eastern Europe				
Czech Republic	Bureš[5], 2012	23.5%	Urea breath test	Combined data
Russia	Svarval' *et al*[6], 2011	40.48%	Serology	Children-adolescents
America				
United States	Patterson *et al*[7], 2012	17.1%	Serology	Adults
South America (combined data)	Porras *et al*[8], 2013	79.4%	Urea breath test	Adults
Asia				
Saudi Arabia	Hanafi *et al*[9], 2013	28.3%	Serology	Children, adolescents
South Korea	Baik *et al*[10], 2012	55.7%	Serology	Adults
Africa				
Nigeria	Etukudo *et al*[11], 2012	30.9%	Serology	Children
Morocco	Benajah *et al*[12], 2013	75.5%	Biopsy	Adults
Oceania				
Australia	Pandeya *et al*[13], 2011	15.5%	Serology	Combined data
New Zealand	Fawcett *et al*[14], 2005	6.2%	Serology	Children, adolescents

nam they were considerably higher (33%)[36]. A South Korean study revealed, in a pediatric population, tripled resistance rates within 20 years. Surprisingly, a Malaysian study carried out on 90 gastric samples did not show any strain resistant to clarithromycin: this is the only discordant value in this geographical area[37].

A similar pattern is observed in the Near East, where the percentages range between 14.3% (Iran)[38] and 37% (Pakistan)[39]. Interestingly, it is noticeable that in the same area, another study found a much lower resistance (17.1%)[40], emphasizing that even in the same geographical region, relevant differences may occur.

In Southern America, the most recent studies report a resistance rate that ranges between 13.6% and 19.5%, illustrating a more homogeneous distribution of resistant strains[41,42]. In the United States the continuous migration flows from Mexico and other Latin American countries are causing rapid changes in local *H. pylori* strains, as witnessed by the need for new regimens[43]. If we consider that in a 2011 randomized study the success rate of a therapy including levofloxacin, amoxicillin, and clarithromycin was only 73.3%[44], whereas in 1995 a clarithromycin-based therapy achieved eradication in more than 90%[45], this is a remarkable difference.

In Europe, there are ample variations between Northern Europe and Mediterranean countries, where the resistances to clarithromycin are considerably more widespread. Finland and Sweden recorded a rate of 2% and 1.5%[46,47], respectively, whilst in Germany and Norway the rates were 7.5% and 5.9%, respectively[48,49].

Resistance is higher in Central/Eastern Europe [9.3% (95%CI: 0-22)], and is at its highest in Southern Europe [18% (95%CI: 2.1-34.8)][50]. In Italy, the trend is continually on the increase; while in the year 2000 the percentages ranged between 1.8% and 14%[51-53], a few years later resistance had increased up to 24.1%, and will likely have doubled within 15 years[54,55]. As in all of Europe, primary clarithromycin resistance in Italy is highly variable in different geographic areas: 0%-6% in the north, 7%-15% in central areas, and 10%-25% in the south[56]. Other Mediterranean countries with high rates of clarithromycin resistance are Greece (40%), Spain (15%-20%), France (17.5%), and Portugal (34.7%)[57-60]. In Eastern Europe, the situation is similar to that in Southern Europe; several Bulgarian studies have reported a resistance rate of 18.4%-23.4%[15,61,62]. An isolated phenomenon has been observed in Poland; in 2013, resistance is around 22%, with a trend toward a perceptible decrease (it was 34% in 2008)[63]. Another strong diffusion of resistant strains has been shown in Lithuania (24.7%)[64].

In Oceania, resistance rates range between 8.7%[65] and 15.7%[66], suggesting that there is still a fair option for the use of the antibiotic in those areas.

Finally, the main data about the prevalence of resistance to clarithromycin in Africa show very low values in Gambia and Senegal (0% and 1%, respectively)[67,68], but not in South Africa (15.3%)[69].

Metronidazole

Metronidazole is a nitroimidazole antibiotic used particularly against anaerobic bacteria and protozoa. It works as a pro-drug: it is non-enzymatically reduced by reacting with reduced ferredoxin, which is generated by pyruvate oxidoreductase, and then the reduced molecule is taken up into bacterial DNA and forms unstable molecules that cause the death of the organism[70]. The resistance mechanism to metronidazole is not entirely straightforward[71,72]. Clearly, alterations of the rdxA gene are of primary relevance, but it has not been possible to identify a clear panel of point mutations which could explain the phenomenon. Moreover, other genes such as frxA seem to be involved[73].

Eastern Asian countries are the geographical area where it is possible to detect the highest percentages of resistance: 56.6%-95.4% in China[34,35], 57% in Japan[30], 27.3%-52.9% in South Korea[74,75], 69.9% in Vietnam[36], and 75.5% in Malaysia[37]. A very similar pattern has been detected in Africa, where the rates vary between 68.8% and 85%[67,68]. Indeed, it is well known that the prevalence is much higher in developing countries (50%-80%) like Mexico (76.3%)[76], Colombia (75.5%)[41], and Brazil (40%)[42]. In the Near East, a 69.5% resistance was reported in Saudi Arabia[77], 64.5% in Pakistan [40], and 76.8% in Iran[38].

The scenario appears to be slightly different in Europe, where in a multicenter study the global resistance rate to metronidazole was 33.1% (95%CI: 7.5-58.9), with no significant difference between the north [33% (95%CI: 7.1-69.2)] and south [40.8% (95%CI: 27.3-54.3)], but with a significantly lower prevalence in central and eastern areas [29.2% (95%CI: 17.9-41.5)][78]. However, this report was dated 2001, and in the last ten years the situation appears to have changed surprisingly, featuring a decreasing rate of resistance in northern countries (22.5% in Norway[49], 1.1% in Lithuania[63], 19.9% in the Netherlands[79], and 13% in the United Kingdom[51]). In Southern and Central-Eastern Europe however, rates of resistance are much higher (34.9% in France[59], 63.6% in Croatia[80], 37.2% in Germany[48], and 23.3% in Bulgaria[15]).

Several Italian studies[81] have described a resistance rate of 20%-23.9%[82-84], but the resistant strain could be undergoing a dizzying growth, if we consider that only five years later a single group reported a more than doubled rate (59.3%)[85].

In Oceania, three recent studies reported values of 20%[86], 36%[87], and 43.5%[65], suggesting an overall high rate of resistances.

Amoxicillin

Amoxicillin is a β-lactam antibiotic included in all current therapeutic regimens for *H. pylori* eradication[88]. Amoxicillin acts by interfering with peptidoglycan synthesis, in particular by blocking transporters named penicillin binding proteins[16]. This drug was the first antibiotic used for *H. pylori* therapy due to a presumed absence of resistance[89]. In almost all studies, percentages of resistance are quite low, and these data seem homogeneous worldwide. No resistances have been detected in Croatia, France, Germany, the Netherlands, Portugal, Spain, or Sweden[90-96]. In Italy, resistances range from 0% to 0.2%[97], while in the United Kingdom they range from 0% to 0.4%[98,99]. Almost negligible resistances have also been reported in America and Oceania. Data in contrast with this trend have been described in Iran and Japan, with a resistance prevalence of 28.6%[38] and 8.2%-15.2%[30,33], respectively. Surprisingly, an extremely high resistance rate (85.6%) has been observed in Cameroon[81].

Levofloxacin

Levofloxacin is a broad spectrum antibiotic of the fluoroquinolone drug class which is active against both Gram-positive and Gram-negative bacteria[100,101]. It acts by inhibiting DNA gyrase, type Ⅱ topoisomerase, and topoisomerase Ⅳ, an enzyme which is necessary to separate replicated DNA and block cell division[102]. Resistance of *H. pylori* to fluoroquinolones is due to point mutations in the quinolone resistance determining regions of gyrA[103].

Levofloxacin has recently appeared in therapeutic regimens for *H. pylori* eradication: in the Maastricht-Florence Ⅳ consensus for *H. pylori* treatment, a levofloxacin-containing regimen was proposed as second-line treatment when classical first-line therapy containing clarithromycin failed[88]. However, in the last three years, resistant strains are increasing, because of plasmid-mediated horizontally transferable genes encoding quinolone resistance[104], so that more and more levofloxacin-based treatments will likely be ineffective in the future.

An example of this unfavorable trend is evident in Asian countries, where the rates of resistance exceed 10%: 18.4% in Vietnam[36], 20.6% in China[34], and are as high as 63.3% in Pakistan[39]. Only Malaysia registered 0%[37], although Japan was also low at 8.2%[30].

In Europe, the overall resistance to levofloxacin, detected in a recent multicentric epidemiologic study, is 14.1%[105], with values ranging between 11.7% in Ireland[106] and 29.1% in Germany[107]: these last percentages must set the clinician on guard, if we consider that only a few years before, in 2003, a resistance rate of 3.3% was detected in France[108]. In Italy, a single study found resistance in 10.6% of strains[81], data confirmed by a recent overview that noted a rate of 11.8% in already treated patients[109]. In Africa, resistant strains are also not very widespread: 15% in Senegal and 10.2% in South Africa[68,69].

In America, a rate of 19% was found in Alaska[110], while in South America percentages are higher (23% in Brazil, where a clarithromycin resistance of only 8% means that this last drug is still a good therapeutic option)[111]. Surprisingly, no report about levofloxacin resistance in Oceania has yet been made, to the best of our knowledge.

Other antibiotics

Resistance to tetracycline is very low, or even absent, in most countries. Very low rates have been reported in Spain (0.7%[95]), the United Kingdom (0.5%[98]), and Hong Kong (0.5%[112]). Values lower than 5% are recorded in Germany[48] and Lithuania[64]. The highest prevalence rates are found in Korea (5.3%[113]), Iran[38] (18.7%), and Vietnam[36] (5.8%). The resistance mechanism has been described as a change in three contiguous nucleotides in the 16S rRNA gene (AGA 926-928RTTC)[114,115].

Rifabutin is a bactericidal antibiotic drug primarily used in the treatment of tuberculosis, and its effect on bacteria is based on DNA-dependent RNA polymerase blockage[116]. When it was firstly used in the late '90s, the prevalence of *H. pylori* resistance to this group of antibiotics was extremely low, as these drugs were used

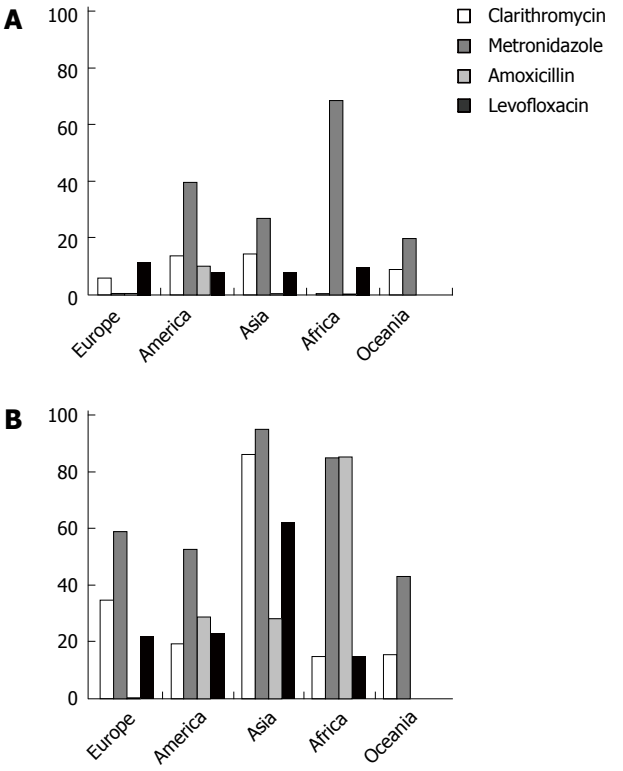

Figure 1 Comparison of the minimal (A) and maximal (B) resistance rates reported in five world continents (Europe, America, Asia, Africa, and Oceania) for the main antibiotics used for *Helicobacter pylori* eradication (clarithromycin, amoxicillin, metronidazole, and levofloxacin).

only in a limited number of patients to treat mycobacterial infections. For example, Heep *et al*[117] did not find a single resistant strain among 81 German patients tested in 1999, nor did Fujimura *et al*[118] among 52 strains in Japan. Even today in some regions such as Brazil, Ireland, and Senegal, no resistant strain has been detected[42,68,106], but data from Malaysia[37], Germany[48], and Iran[38] report a resistance rate of 2.2%, less than 5%, and 28.6%, respectively. Resistance is due to point mutations in the *rpoB* gene, as for other bacteria, and occurs in all rifamycin drugs, suggesting a potential risk of cross-resistances between antibiotics of the same family[119,120].

Furazolidone is a nitrofuran antibiotic. As a veterinary medicine, it is used to treat salmonids for *Myxobolus cerebralis* infections. In the past, it has been used in humans to treat diarrhea and enteritis caused by bacteria or protozoan infections, but since 1991 it has been recognized by the FDA as a carcinogenic agent and so is no longer used, except in a few developing countries that allow its use for human diseases[121]. It was previously used to treat traveler's diarrhea, cholera, and bacteremic salmonellosis. Its use to treat *H. pylori* infections was also proposed[122]. Primary furazolidone resistance is rare. In Spain[123], the rates were less than 2%, and in Bulgaria 1.8%[124]. Lower values have been described in China[34] (0.1%) and Brazil[42] (no resistant strains detected). A higher furazolidone resistance rate (9%) was found in Iranian children[125]. As the high cost of some drugs, such as clarithromycin and quinolones, prevents their use in developing countries, where a high prevalence of primary metronidazole resistance is also present, to overcome these limitations, furazolidone-based treatments have been suggested. On the other hand, the low rate of primary *H. pylori* resistance to furazolidone in developed countries may make the use of this drug attractive. In this case, however, it is imperative to consider that furazolidone-based first-line therapy achieves *H. pylori* eradication rates of 75.7% and 79.6%[126], and its use cannot ignore obvious ethical considerations in view of the carcinogenic evidence.

ANTIBIOTIC RESISTANCES: A COMMENT ON THE DATA IN THE LITERATURE

Figure 1 illustrates the simultaneous minimal and maximal resistance rates in five world continents (Europe, America, Asia, Africa, and Oceania). It is evident that clarithromycin shows a good prospect of success in Africa, Oceania, and few Northern European countries (*e.g.*, Norway), whilst in Southern Europe (*e.g.*, Italy, Spain, Portugal, and Greece) and even South Africa, the risk of failure is high. Metronidazole might be very effective in Lithuania, but its use should be strongly discouraged in Italy and Croatia as well as most American, Asian, and African countries. Amoxicillin appears to be a reliable option in many countries, but it is almost ineffective in Iran and Cameroon. Finally, levofloxacin, which has been proposed as an alternative to clarithromycin in the areas where this last key antibiotic shows a high resistance rate, has been shown to be moderately ineffective worldwide, aside from Oceania, thus confirming the rapid trend toward therapeutic failure. Therefore, proposals for wider use could induce a counterproductive effect.

Among the other antibiotics, tetracycline and rifabutin appear to have low resistance rates, even if the use of the latter drug is limited by the regulations of many countries, where it is not indicated in *H. pylori* infection care, even apart from its high cost. Finally, furazolidone, despite its effectiveness, has been forbidden in many countries.

An obvious point is that, in each country, an ideal specific therapy should be identified. Nevertheless, all the studies on resistances *in vitro* might lack positive feedback *in vivo*. In fact, therapy failure may depend on several factors, of both bacterial and host origin. Not infrequently, different factors act simultaneously in reducing antibiotic therapy efficacy in the same patient. Indeed, a poor compliance to the *H. pylori* eradication regimen is inversely associated with the probability of therapeutic success. Unfortunately, the approved eradication regimens require the combination of 3-4 different drugs in multiple daily doses. Therapy regimen complexity and the onset of side effects are associated with reduced patient compliance. The *in vitro* activity of various antibiotics is greatly reduced or eliminated *in vivo* by the very low pH values encountered in gastric juices. This explains

the need to include a proton pump inhibitor in *H. pylori* eradication regimens. However, a significant variability in gastric acid secretion among different subjects has been reported. A small proportion of subjects show a higher basal acid output in association with normal gastrin values. These hyper-secretor subjects probably have a large parietal cell mass and a low eradication rate[127].

These considerations may partially account for the wide discrepancies demonstrated between studies on resistances *in vitro* and the results of clinical trials *in vivo*. A final factor which might limit the reliability of *in vitro* resistance studies is the different methods used for detection. The methods are complex, expensive, and may often fail even in expert hands, and for this reason, their use is predominantly confined to research purposes.

MAIN THERAPEUTIC REGIMEN EFFECTIVENESS

Triple therapy is one of the oldest schemes for *H. pylori* eradication. In Europe, it was used successfully in the United Kingdom until 5 years ago[128], achieving an eradication rate of 92%. However, it is characterized by an enormous variability, if we consider the poor rate of 50% calculated in a German study in 2011[129]. The possibility of failure was very high in a Turkish study[130], where only 32.7% of eradication occurred. In Asia, a high percentage of eradication was seen in India (82.9%)[131], with a lower percentage in Korea (67.7)[132]. In the American continent, eradication rates range from 78% to 97%[133,134]. Data from Africa are more homogeneous, but the weight of resistances affects the possibility of the eradication achieved in 71%-78.2% of cases, in a multicentric and in a Moroccan study, respectively[135,136]. The only recent available data from Oceania derive from two trials in which rifampicin was used instead of clarithromycin as second-line regimen, which achieved eradication rates of 95% and 96.6%, respectively[137,138].

Quadruple therapy appears to be more effective than triple therapy, if we consider that in United States, Laine *et al*[139] reported a success rate of 87.7%, and a lower value was seen only in a Canadian study[140] (70.8%). However, in Europe, failures are more frequent: quadruple therapy was effective only in 64.8% of cases in a Greek study[141], despite a success rate of 91% in a British trial[128]. In Asian countries, the rates seem to be even more discouraging, ranging between 47.1% and 89.5% in Turkey[130] and China[142], respectively. No data are available from Africa to the best of our knowledge. Only one Australian study investigated the effectiveness of quadruple therapy, but using a novel combination of a proton pump inhibitor, bismuth subcitrate, rifabutin, and ciprofloxacin as a first-line regimen for patients allergic to penicillin, and achieving an eradication rate of 94.2%[143].

Concomitant therapy is a combination of antibiotics including amoxicillin, metronidazole, clarithromycin, and a proton pump inhibitor (PPI) for a period of five or seven days. It has proven very effective in Japan, where an eradication rate of 98.1%[144] was achieved, but in South Korea the percentage was much lower (63.2%)[145]. In two different European studies, the same author reported the minimal and the maximal eradication rates of concomitant therapy as 85.5% and 95.5%, respectively[146,147]. In a multicentric Southern American study, this therapy achieved only 78.7% eradication[148]. We did not find any results from Africa for this regimen. No further data are available from Oceania.

Sequential therapy is a ten-day therapy that consists of a PPI plus amoxicillin in the first 5 d and a PPI, clarithromycin, and metronidazole in the following 5 d. In Italy it has proven to be very useful compared to other combinations[149]; it achieved eradication rates that range between 97.3% in a pediatric population[150], 97% in an elderly population[151], and 89% in a multicentric study involving more than 1000 patients[83]. The data from other European countries, however, are very poor. A good performance of this therapy was demonstrated in Africa, with a positive outcome ranging between 89.9% and 94.2%[136,152]. However, in South America this scheme appears to be less effective, if we consider the Peruvian percentage of success of 73%[153] and overall rate of 81.1%[148]. In Asia, a good result was achieved in South Korea[154] (92.6% maximum), whilst in China[155] only 78.3% eradicated the bacterium. No data are available from Oceania.

Miscellaneous therapy has been recently introduced and includes sequences of different combinations of antibiotics. The main four studies are from the four continents that show promising results: Colombia 94%[156], Italy 85.7%[157], Iran 92.9%[158], and Taiwan 97.4%[159]. This regimen requires further confirmation of these excellent results, as well as an accurate evaluation of patient compliance owing to the risk of a large number of side effects and consequent drop-outs.

THERAPEUTIC REGIMEN EFFECTIVENESS: A COMMENT ON THE DATA IN THE LITERATURE

Although resistance reports describe alarming results, the outcomes of therapeutic schemes do not seem to parallel this scenario in most cases, since a success of more than 80% is often reached. Despite some of the factors that may explain this discrepancy between *in vitro* and *in vivo* results that have been mentioned previously, it is possible that other factors may elucidate this controversial point: (1) most studies are performed in single centers and include populations selected from geographic areas of irrelevant dimensions. This may be an important handicap for the reproducibility of the therapeutic regimen in other areas; (2) the selection of patients is limited to bacterial positivity, often based on non-invasive tests, and does not take into account some bacterial

factors such as the intra-gastric load[160], the possibility of primary resistances (which may even be different in the body and antrum of the same subject)[161], heteroresistance status, and CagA status[162,163]. Finally, the presence of coccoid forms[164] in the stomach may have clinical relevance, due to the potential reactivation of *H. pylori* in its spiral form following therapy; (3) the results of therapeutic studies may be affected by host factors such as PPI metabolism[165], parietal cell mass[166], and related gastric pH, which is strictly related to antibiotic MIC values, the mucus layer (which affects bacterium/antibiotic contact), the frequent patchy distribution of *H. pylori* in the stomach, and even its persistence in small areas (*e.g.*, cardiac) after apparently successful eradication; and (4) the already outlined technical problems related to resistance detections *in vitro*.

PROBIOTICS: HAVE THEY A ROLE IN *H. PYLORI* TREATMENT?

The possibility of probiotics interfering with *H. pylori* gastric colonization has been postulated by many authors and, therefore, many studies are available in the literature about the treatment of infected patients with beneficial bacteria supplementation. However, conflicting data have been obtained.

A review of available data showed that clinical trials can be divided into two groups: those using probiotics in association with antibiotic therapy and those using probiotics alone. In the first group, the efficacy of a single strain of probiotics associated with antibiotic triple or quadruple therapy generally resulted in a decrease of side effects such as diarrhea, bloating, nausea, and taste disturbances during treatment[167,168], as well as an improvement of the eradication rate. Some studies have tested the association of a multi-strain probiotic mixture associated with antibiotic therapy. Two of these[169,170] showed a reduction in the side effects of antibiotic therapy and a higher eradication rate than that obtained with a single strain, whilst the third study[171] did not obtain any significant result.

Among the second group of clinical trials (only probiotics) we found that most studies tested a single probiotic strain, especially *Lactobacillus* species, obtaining a *H. pylori* load reduction as expressed by the urea breath test delta value. Experience by our group confirmed this finding after oral administration of *Lactobacillus reuteri* ATC 55730, not only with a delta value reduction, but also with a semiquantitative fecal antigen decrease[172].

Recently, Szajewska *et al*[173] reported a very interesting meta-analysis of the effects of *Saccharomyces boulardii* supplementation in standard triple therapy, showing a significant effect in both increasing the eradication rate and reducing side effects, in a total of 1307 patients from five randomized controlled trials.

CONCLUSION

Therapeutic management of *H. pylori* remains an unsolved issue. Indeed, no therapy regimen is able to cure the infection in all treated patients, and a definite number remain infected despite several consecutive standard therapies. This therapeutic failure is often considered to be the consequence of incorrect treatment rather than treatment limitation, since this appears unacceptable in the antibiotic era. However, no clinical trial has reported an eradication rate of 100% to the best of our knowledge.

Therapeutic failures are attributed to increasing antibiotic resistance. However, this phenomenon has been widely studied and the results show controversial findings even in the same geographic area. For each world continent, minimal and maximal values of resistance to different antibiotics have been reported for different countries, although some regimens appear to be almost unknown in some areas.

Another enigma is the outcomes of several different therapeutic schemes, which often do not parallel *in vitro* findings even in the same areas. Moreover, some schemes are limited by their use in very small geographic districts. Finally, not all therapeutic trials have considered bacterial and host factors affecting the therapeutic outcome.

In conclusion, the "ideal therapy", paradoxically, appears to be a "utopia", despite the unprecedented volume of studies in the field and the real breakthrough in medical practice made by the discovery and the treatment of *H. pylori*. A key point could be the possibility, in the near future, to group *in vivo* and *in vitro* studies by geographic areas in order to identify the best therapy, which is certainly related to the local habitat. Indeed, the ample discrepancies observed in the different areas do not encourage the development of therapeutic guidelines that could be valid worldwide. The main challenge for the future might be identifying a successful solution for overcoming antibiotic resistances and, in this context, geography must be considered a relevant matter.

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P- Reviewers: Abenavoli L, Chuah SK, Day AS, Kim BW
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Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
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ISSN 1007-9327
9 771007 932045