World Journal of Gastroenterology

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World J Gastroenterol 2017 September 21; 23(35): 6379-6384

DOI: 10.3748/wjg.v23.i35.6379

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Resistance to clarithromycin and gastroenterologist's persistence roles in nomination for *Helicobacter pylori* as high priority pathogen by World Health Organization

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Author contributions: Amin TBA collected the primary data and designed the first draft and finally wrote the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Manuscript source: Invited manuscript

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Received: July 3, 2017
Peer-review started: July 4, 2017
First decision: July 28, 2017
Revised: August 6, 2017
Accepted: August 25, 2017
Article in press: August 25, 2017
Published online: September 21, 2017

Abstract

Due to the increasing prevalence of clarithromycin resistance, future of management of *Helicobacter pylori* (*H. pylori*) infections need to be recognized. To now, clarithromycin was the best effective, well-tolerated and safe antibiotic used in treatment of the bacterium, but, increasing trend of resistance reduced efficacy of recommended regimens. Indeed, gastroenterologists are mostly unable to start appropriate therapy-according to the sensitivity profile-due to the certain difficulties in routine *H. pylori* culture procedure and being time consuming method. This announcement by World Health Organization (WHO) was an onset to reconsider current challenging dilemma about *H. pylori* clarithromycin resistant isolates. Therefore, investigating of various factors affecting this nomination by WHO is highly welcomed. In fact, WHO enumerated more than 16 pathogens which seriously threats human life and public health, thus better management or effective guidelines are necessary. Here for the first time, we nominated this phenomenon as "gastroenterologist's persistence" which should be equally investigated as antibiotic resistance. The ability of gastroenterologists to win the game against *H. pylori* infections is highly influenced by their collaboration with diagnostic laboratories to apply susceptibility patterns before any prescription. In conclusion, closer collaboration between two important partners (gastroenterologists and microbiologists) in management of *H. pylori* infection may hopefully trigger an era to remedy current crisis in clarithromycin resistance, a later gastric cancer can be practically preventable.

Key words: Resistance; Clarithromycin; *Helicobacter pylori*; World Health Organization

Core tip: Due to the increasing prevalence of clarithromycin resistance, future of management of *Helicobacter pylori* (*H. pylori*) infections need to be rewritten. To now, clarithromycin was the best tolerated and safe antibiotic used in treatment of the bacterium, but, increasing trend of resistance reduced efficacy of therapeutic regimens recommended. In this paper, we discussed that why persistence of gastroenterologists is a critical item need to be considered if we really aim to increase efficacy of prescribed antibiotics against *H. pylori*.

Abadi ATB. Resistance to clarithromycin and gastroenterologist's persistence roles in nomination for *Helicobacter pylori* as high priority pathogen by World Health Organization. *World J Gastroenterol* 2017; 23(35): 6379-6384 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i35/6379.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i35.6379

INTRODUCTION

Helicobacter pylori (*H. pylori*) is an infectious agent colonizes half of the world population and must be eradicated with suitable antibiotics[1,2]. Of twenty years ago, *H. pylori* was recognized as a major cause of peptic ulcers, thus many of these clinicians attempted to treat those colonized individuals with antibiotic[3]. Later, the World Health Organization (WHO) recommended that bacterial elimination can be a useful strategy to decrease mortality of gastric cancer in the world. Subsequently, in the first half of 2017, WHO listed the clarithromycin resistant-*H. pylori* in the category of high priority which requires intense attention on the treatment. This announcement by WHO is an onset to reconsider current challenging dilemma about *H. pylori* clarithromycin resistant isolates. Therefore, investigating of various factors affecting this nomination by WHO is highly welcomed. In fact, WHO enumerated more than 16 pathogens which seriously threats human life and public health, thus better management or effective guidelines are necessary. New visions of *H. pylori* treatment as well as the better insight of uncertain prescription of antibiotics in the fight against this bacterium is guaranteeing the solution to address the dilemma. Until 2004, *H. pylori* standard triple therapy include proton pump inhibitor (PPI), amoxicillin and clarithromycin providing the acceptable eradication rate, however, increased prevalence of antibiotic resistance hampered continuing the triple therapy for next years. As such, newer formulations were in the focus of researches among the gastroenterologists and microbiologists. As first line treatment for *H. pylori*-positive subjects, bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole are now highly recommended by many international guidelines[4-11]. Therefore, it seems that clarithromycin has an inevitable role in *H. pylori* treatment and even bacterial resistance seems not be able to remove its existence from therapeutic lines. In next section, we review the importance of clarithromycin and how the bacterium became resistant to this commonly used drug in treating the *H. pylori*.

H. PYLORI THERAPY-CLARITHROMYCIN AS KEY ANTIBIOTIC

Due to the traditional microbiologic rule, an infectious agent should be treated with appropriate antibiotics following the susceptibility tests. Despite many problematic infectious bacteria, the story is different for *H. pylori*. Notably, the success chance of regimen include clarithromycin, if a resistant bacterium exists, is less than 40%. This disappointing rate can apparently reflect the irrefutable role of clarithromycin as a core antibiotic in *H. pylori* therapy. The problem with this critical role is that antimicrobial resistance to this drug is sharply increasing and our hopes to have successful eradication regimens (*i.e.,* consistent treatment success > 90%) including the clarithromycin is unfortunately falling.

CLARITHROMYCIN MECHANISM OF ACTION AND RESISTANCE

Clarithromycin is a bacteriostatic antibiotic mostly used in childhood to treat upper respiratory infections, but, its application to treat *H. pylori* is the most used indication[12,13]. The main action mode of clarithromycin as one of the wide-spectrum antibiotics used in *H. pylori* therapy is to prevent protein translation. Current knowledge about mechanisms of resistance to clarithromycin has shown the importance of several point mutations in the peptidyltransferase region encoded in domain V of 23s rRNA[14-16]. In 1996, versalovic *et al*[14] has shown that responsible mutations in the peptidyltransferase region cause an inhibition in binding space between the ribosomal subunit dedicated to specific antibiotic-related protein synthesis and clarithromycin.

Following the first exposure to the clarithromycin, spontaneously mutations (in both 23S rRNA operons) confer *H. pylori* resistance phenotype and genotype. The direct impact of these mutations is emergence of *H. pylori* strains resistant to clarithromycin. To now, two major mutations A2142G and A2143G were listed as main cause of antibiotic resistance in clinical isolates[17]. Indeed, the problem is started since the first exposure is not occurred against *H. pylori*. Clarithromycin is usually used to treat upper respiratory infections, therefore, colonized *H. pylori* is exposed in childhood

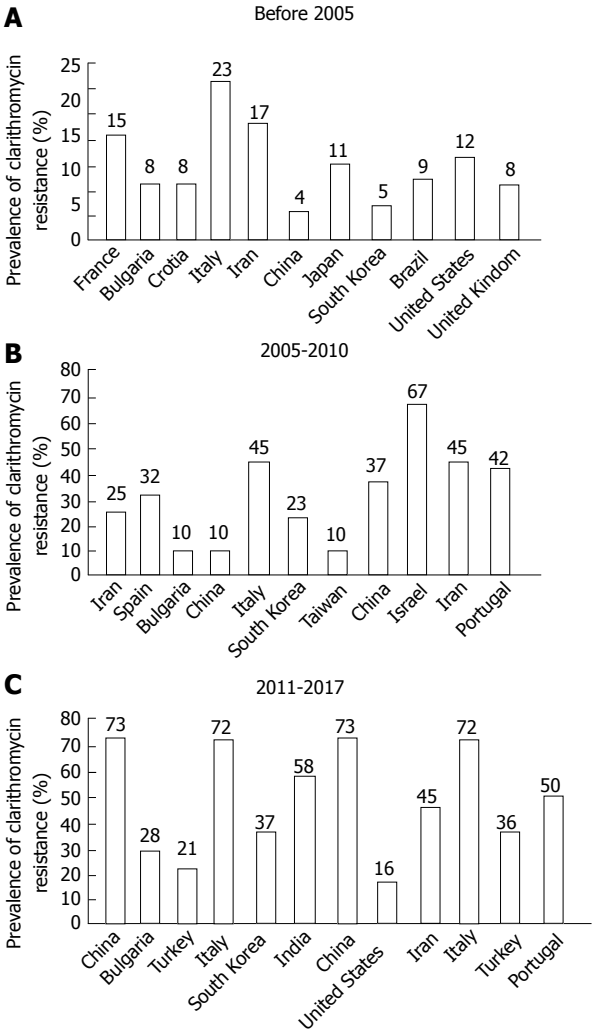

Figure 1 Resistance to clarithromycin among the *Helicobacter pylori* isolates in various countries. A: Before 2005; B: 2005-2010; C: 2011-2017.

already, while no gastroduodenal disorders happened! Another problematic side of this scenario is that antibiotic stress can easily increase the frequency of inducing mutations in cells. This fact in light of relevant usage of clarithromycin for upper respiratory infections in childhood can excuse why we need to be worried about wide-spread prescription of clarithromycin in clinical practice. In brief, our bacteria are almost resistant before we start to use clarithromycin against them in anti-*H. pylori* therapy. In other hands, efflux pump system is also a potential mechanism that confers clarithromycin resistance[18]. Current findings are insisting on at least four families of gene clusters of efflux pumps in *H. pylori* isolates[18,19]. Of them, the family that is found only in Gram-negative bacteria, is the resistance-nodulation-cell division (RND). Bina *et al*[20] was first reported this family of efflux pumps, but additional data are missing to prove exact role of these structures to induce antibiotic resistance in *H. pylori*. The present data show that existence of efflux pumps in *H. pylori* strains can have synergic effect to induce antibiotic resistance in parallel with 23S rRNA mutations. The different angle of the problem is that while we still publishing the papers indicating on increased the emergence of clarithromycin resistance, our holistic view on the rationale for skyrocketing increase in resistance to clarithromycin is missing. Because of antibiotic resistance is a dynamic phenomenon, it may be found with outstandingly different rates even in a state of a country. In reality, the spread of clarithromycin resistant-*H. pylori* has another dimension which remains often undiscussed. Given a sharp increase in clarithromycin resistance during the last decade worldwide (P value < 0.011), *H. pylori* become difficult to eradicate even using various treatment guidelines (Figure 1). Within these three 5 years duration, we can understand the clarithromycin is getting more and more useless antibiotic against *H. pylori* in many countries.

CLARITHROMYCIN RESISTANCE: MOLECULAR DETECTION METHODS

Indeed, in absence of reliable culture-based method to produce data on susceptibility tests, molecular methods were developed rapidly in last decade[17]. Based on available molecular methods tracking 23S rRNA gene, a long list of methods have been developed to quickly identify resistance in colonized *H. pylori* strains to the clarithromycin (Table 1).

Apart from progress have been made, still we are lacking in a quick method with accurate findings. Taking together, real-time PCR can be proposed as best option to be used in hospitals and even smaller centers. During the last years, many companies started to produce this machine and now it is way cheaper than 10 years ago (almost 10 folds). Therefore, we are suggesting to apply this machine to see what kind of mutations are existed 23S rRNA gene and forthcoming susceptibility profile will be easier to present.

NEW DIMENSION OF PROBLEM: GASTROENTEROLOGIST'S PERSISTENCE

Face to face with the problem, we definitely need gastroenterologists more actively involved. So far, due to the clinical and official settings, many of microbiologists do not have any access to the patients. The data for antibiotic susceptibility tests mainly come from laboratories which are dominated by microbiologists. Thus, as a historic conflict between clinicians and basic medical scientists, lack of connection can result in blind antibiotic prescription by the gastroenterologists. Another evidence for this conflict is that almost none of famous microbiologists are co-authored in recently published guidelines on treatment or diagnosis of the *H. pylori.* Moreover, the story is exacerbated when the microbiology journals have no scope for publishing such guidelines. This existed, but, unwanted gap deserves an intense attention to improve management of patients carrying *H.*

Table 1 Molecular methods to identify mutations induce clarithromycin resistance in clinical *Helicobacter pylori* isolates

Methods	Advantages	Disadvantages	PCR-based method	Ref.
Real-time PCR	Quick and reliable High specificity, high sensitivity	Relatively expensive	Yes	[21]
PCR-LiPA	Fast and cheap	Moderate specificity and sensitivity	Yes	[22]
DNA sequencing	Produce many information,	Expensive, Time-consuming protocol	Yes	[23]
3′-mismatch PCR	Fast and high specificity	Produce limited data on the gene, not practically useful	Yes	[24]
RFLP	High specificity, high sensitivity	Risk of contamination Low reproducibility	Yes	[15,25]
FISH	High specificity, high sensitivity	Need invasive approach so not good for children	No	[26,27]

FISH: Fluorescence in situ hybridisation; RFLP: Restriction fragment length polymorphism; PCR-LiPA: PCR line probe assay.

pylori with resistance to clarithromycin. As we described above, in infectious diseases, treatment is highly recommended based on susceptibility pattern, a fact does not follow in the case of *H. pylori*. In other words, treatment of *H. pylori* in many of clinics are based on personal experiences by the gastroenterologists than antibiotic susceptibility tests determined in a microbiology laboratory. With this regard, an incoherent connection between those two populations is a major cause of inappropriate drug prescription ending in increased antibiotic resistance worldwide. Therefore, WHO announced that we are facing with the new generation of resistant *H. pylori* isolates to clarithromycin which endangers effectiveness of current chemotherapy against the bacterium. By continuing the current situation, the replacement of *H. pylori* by WHO in a critical level of priority in a ranking of threatening pathogen is not far from the mind. The next uninvestigated part of the problem is a natural persistence of clinicians on the application of susceptibility patterns reported by microbiologists! For example, metronidazole resistance is not under 60% in many of regions worldwide[28-31], but any trials can show intrinsic tendency among the clinicians who aim to use this ineffective drug for eradicating the *H. pylori*. Taking together, our knowledge about antibiotic resistance has evolved nicely during the relatively short time we treating the *H. pylori*, however, we need new insight on how to increase the reliability among the clinicians to use susceptibility pattern to efficiently eliminate the bacterium especially in patients at least with severe gastroduodenal disorders. Here for the first time, we called this phenomenon as "gastroenterologist's persistence" which should be equally investigated as antibiotic resistance. The ability of gastroenterologists to win the game against *H. pylori* infections is highly being influenced by their collaboration with diagnostic laboratories to apply susceptibility patterns before any prescription. Therefore, two major targets should be considered, (1) antibiotic resistance; and (2) clinician's persistence. Invasive nature of gastroscopy is a considerable factor that influence on rare access to culture-based information on susceptibility tests. Defeating most of the recommended guidelines to eliminate the *H. pylori* can be a major output of neglecting the clinician's persistence.

CONCLUSION

Nowadays, therapeutic failures in anti-*H. pylori* regimens has emerged as major concern for both gastroenterologists and microbiologists. The recent announcement by WHO should be considered as an alarming sound that indicates on emergence of clarithromycin-resistant strains causing global *H. pylori* treatment failure. Since clarithromycin has a critical role in the success of therapeutic regimens against the *H. pylori*, the spread of its resistant strains can easily hamper our attempts to eradicate this microbe. Conclusively, it is not the exaggeration to consider this antibiotic as the main drug in the treatment of *H. pylori*. We need to repeat that all records insisting on using the clarithromycin before recommending as anti-*H. pylori* agent should be considered as serious alarming item. Although the ideal and effective therapy to eliminate the *H. pylori* is not available, but optimizing the current formulations especially, cautious application of clarithromycin in regions with resistance rate > 20% is a likely successful approach. New research direction to produce and suggest novel antibiotics are welcomed to compensate the lacking in antimicrobial agents listed as therapeutic options. In future, application of MALDI-TOF as a novel method can be used directly to detect mutations from biopsy sample; a suggestion which is not far away. To my knowledge, this is one the first paper that pinpoints the gap between gastroenterologists and microbiologists following nomination for *H. pylori* as high priority pathogen by WHO. To be honest, although the persistence of gastroenterologists is a critical factor to increase antibiotic resistance among *H. pylori* strains, but, difficulties in bacterial culture, time consuming procedure of culture and high cost for rapid detection

of resistance are the list which belongs to another side of involving individuals. Finally, closer collaboration between two important partners (gastroenterologists and microbiologists) in management of *H. pylori* infection may hopefully trigger an era to remedy current crisis in clarithromycin resistance, a later gastric cancer can be practically preventable.

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P- Reviewer: Adachi Y, Emara MH, Kocazeybek B, Kreisel W, Lei YC, Yamaoka Y **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Ma YJ