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TOPIC HIGHLIGHT

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Helicobacter pylori therapy: Present and future

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Abstract

Helicobacter pylori (*H. pylori*) plays a crucial role in the pathogenesis of chronic active gastritis, peptic ulcer and gastric mucosa-associated lymphoid tissue-lymphoma, and is also involved in carcinogenesis of the stomach. *H. pylori* treatment still remains a challenge for physicians, since no current first-line therapy is able to cure the infection in all treated patients. Several factors may help in the eradication of therapy failure. We reviewed both bacterial and host factors involved in therapeutic management of the *H. pylori* infection. In addition, we evaluated data on the most successful therapy regimens - sequential and concomitant therapies - currently available for *H. pylori* eradication.

Key words: *Helicobacter pylori*; Antibiotic resistance; Virulence factors; Therapy; Eradication

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is a worldwide disease with a significant morbidity and mortality. Indeed, *H.pylori* infection is the leading cause of non-ulcer dyspepsia, peptic ulcers and gastric tumors, including low-grade mucosa-associated lymphoid tissue-lymphoma and adenocarcinoma[1-4]. In addition, it has also been recognized that the interaction between *H. pylori* and non-steroidal, anti-inflammatory drugs is damaging to the gastroduodenal mucosa[5]. Moreover, among extra-digestive diseases, reliable data exist documenting the relationship between *H.pylori* infection and both idiopathic thrombocytopaenic purpura and idiopathic iron deficiency anaemia[6,7].

Although *H. pylori* prevalence is decreasing in developed countries, it remains very high in developing countries, where infection occurs early in childhood. Indeed, low socio-economic and educational levels, living in a family with a high number of siblings, and use of external water have been identified as risk factor for infection onset[8]. Moreover, in some countries such as Chile and Peru, *H. pylori* has been isolated from municipal water, whilst it is absent in developed countries[8]. The infection persists virtually long-life if not opportunely treated.

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 num-

ber of patients remain infected despite several consecutive standard therapies[9]. This therapeutic failure would appear to be unacceptable in the "antibiotic era".

WHY *H. PYLORI* THERAPY FAILS?

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.

Bacterial factors

The "ecological niche": Due to its urease production and presence of flagella, *H. pylori* is able to survive in the gastric environment over a wide pH spectrum, to penetrate the gastric mucous layer, and to reach the gastric epithelium where it can be found attached to cells and even within cells[10]. In this "gastric niche", *H. pylori* could be protected against both antibiotic action and immune response. Indeed, the high efficacy of several antibiotics *in vitro* appears to be strongly reduced *in vivo* because of both difficult diffusion into mucous layer and inactivation at low pH values. It is been also suggested that *H. pylori* may persist in a limited region of the stomach, the gastric cardia, even following successful eradication from the antrum and gastric body. Such a phenomenon has been attributed to an insufficient antibiotic concentration in this gastric area[11]. Similarly, immunoglobulins produced in all infected patients exert a reduced activity or are inactivated at low pH values. Moreover, *H. pylori* is able to camouflage its surface, reducing the exposure of antigens by masking flagella with lipopolysaccarides which mimic the host carbohydrates. Finally, due its motility, *H. pylori* the bacterium is skilled at escaping direct contact with the immune cells, slowly migrating across gastric mucosa[12].

Coccoid form: As for other bacterial species, the existence of viable but not culturable bacterial forms has been reported for *H. pylori*. These coccoid forms have being identified as a natural evolutionary stage of spiral *H. pylori*. Although are unable to grow in culture, these bacterial forms have been shown to be able to infect mice and pigs. Of note, these dormant forms of *H. pylori* are not susceptible to antibiotic action, which requires active bacterial proliferation[13]. The presence of coccoid forms in the stomach may have a clinical relevance, due to the potential reactivation of *H. pylori* in its spiral form following therapy.

Bacterial load: Several studies have reported that the high bacterial load is a significant risk factor in therapeutic failure when using current triple therapies[14-16]. It was suggested that delta values greater than 35% over baseline (DOB) values could be considered to point to high risk of the therapeutic failure. Nevertheless, our recent data failed to confirm this observation[17].

Virulence factors: There is evidence that some *H. pylori* virulence factors significantly affect bacterial susceptibility towards different antibiotics. Some studies reported that CagA-positive *H. pylori* strains seem to be more susceptible to antibiotics when compared to CagA-negative. Similarly, presence of the VacA s1m1 allele increases bacterial susceptibility, compared to the VacAs2m2 allele[18]. From a biological point of view, the relationship between the outcome of eradication therapy and CagA status has been attributed to the severity of gastritis due to the cytotoxin. In this event, the increased mucosal blood flow may favour antibiotic diffusion through the gastric mucosa. Another possible mechanism is the increased antibiotic activity on actively replicating bacterial cells. Indeed, the presence of CagA and VacA s1m1 confer rapid growth to *H. pylori* strains a[19].

Primary antibiotic resistance: Undeniably, primary antibiotic resistance is recognized as the main factor affecting the efficacy of current *H. pylori* eradicating regimens[20]. Bacterial resistance appears to be increasing worldwide, most likely due the large use of antibiotics such as macrolides, quinolones, amoxicillin, and nitroimidazoles in clinical practice. A recent, systematic review updated knowledge of the level of primary *H. pylori* resistance towards different antibiotics worldwide[21].

Clarithromycin remains the most powerful antibiotic against *H. pylori* currently available, and primary resistance towards this drug has been found to be the main factor hampering the efficacy of standard therapies[22]. Various polymerase chain reaction-based studies have demonstrated that point mutations in the peptidyltransferase region, encoded in domain V of 23S rRNA, are responsible of *H. pylori* resistance towards clarithromycin. The more frequent mutations associated with clarithromycin resistance are the adenine to transitions at positions 2142 and 2143 of rRNA (A2143G and A2143C), whilst the substitution of adenine by cytosine at position 2142 (A2142C) is less frequent. These mutations are able to prevent the binding between clarithromycin and the ribosomal subunit and are responsible of more than 90% of clarithromycin resistance in developed countries[22]. Of note, we found that presence of the A2143G point mutation, rather than the A2142G or A2142C mutation, markedly reduces *H. pylori* eradication rate[23].

Very high resistance rates towards metronidazole have been reported, particularly in developing countries and in female patients[22]. Complex and multiple mechanisms are implicated in the development of imidazole resistance, including point mutations, deletion in rdxA gene, and pump efflux system. Primary metronidazole resistance seems to exert only a minor impact on therapeutic outcome[24].

Primary *H. pylori* resistance towards levofloxacin is significantly increasing worldwide. Point mutations in the Quinolones Resistance-Determining Region of *gyrA* prevent binding between the antibiotic and the enzyme, conferring antibiotic bacterial resistance to quinolones.

This observation is clinically relevant as levofloxacin-based therapy is generally used as second-line regimen. Finally, primary resistance towards either tetracycline or amoxicillin remain particularly low, most likely due to the requirement to develop simultaneous mutations in the respective genes[25].

Host factors

Patient compliance: It would appear counterintuitive that an antibiotic therapy cannot exert its whole action when it is not taken for the well-established period and dose. Poor compliance to *H. pylori* eradication regimen is inversely associated with the probability of therapeutic success. It has been reported that 12% of patients prematurely stopped the eradication therapy, as a result of side-effects[20]. Unfortunately, the approved eradication regimens require the combination of 3-4 different drugs in multiple daily doses. Therapy regimen complexity and side-effects incidence are associated with a reduced patient compliance. In this context, the persuasive ability of the physician, together with elucidation of the possible, generally mild, side-effects, is of fundamental importance for therapeutic success.

Gastric acid secretion: The *in vitro* activity of various antibiotics is greatly reduced or eliminated *in vivo* by the very low pH values encountered in the gastric juice. This explains the need to include a proton pump inhibitor (PPI) 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 values of the gastrin. In these hypersecretor subjects, who probably have a larger parietal cell mass, lower eradication rates have been reported[26]. Besides this phenomenon, eradication therapy success depends on metabolism and bio-availability of PPIs, which is genetically determined. Indeed, PPIs are to a large extent metabolized in the liver by the cytocrome P450, isozyme CYP2C19. Based on gene polymorphism, subjects are sub-grouped in poor, intermediate and extensive metabolizers[27]. Although some controversial data do exist, standard PPI doses seem to be insufficient in extensive metabolizer patients to achieve sufficient pH inhibition to allow antibiotic activity in gastric mucosa, with consequent lower eradication rates[28].

Gastroduodenal diseases: Several studies have reported lower *H. pylori* cure rates in patients with non-ulcer dyspepsia, compared to those with peptic ulcer disease[29]. Such a difference has been attributed, at least in part, to infection with different *H. pylori* strains. Indeed, dyspeptic patients are more frequently infected with less virulent (cagA negative; vacA s2 or m2 genotype) and slow proliferating strains than are peptic ulcer patients. These bacterial strains would appear less susceptible towards antibiotics, and cause a less marked inflammation, as discussed above[18,19]. In addition, some studies have found a higher prevalence of primary clarithromycin resistance in non-ulcer dyspepsia than in peptic ulcer patients, although conflicting data have been reported[21,30,31].

Smoking habit: Consistent data have indicated that ongoing smoking negatively affects the therapeutic success rate following standard therapies[32,33]. It has been hypothesized that smoking may induce a decrease in gastric blood flow and mucus secretion, and therefore reduce the efficacy of treatment by reducing the delivery of antibiotics into gastric mucosa. A further possible explanation may be that the smoking habit can induce gastric acid hypersecretion which, in turn, reduces antibiotic activity[34].

CURRENT THERAPIES

Standard triple therapies

Although 7-d triple therapies (PPI, clarithromycin plus amoxicillin or metronidazole) have been the most used treatment in the management of *H. pylori* infection, their efficacy has decreased gradually worldwide during the last decade. This has been largely related to a worldwide increase of bacterial resistance, particularly against clarithromycin, the key antibiotic in the *H. pylori* treatment. Based on these observations, current European guidelines confirmed the use of a standard 7-d triple therapy only in those areas where primary clarithromycin resistance is lower than 15%(20%, whilst a prolonged 14-d regimen or a quadruple therapy should be used when the bacterial resistance rate is higher[35]. However, following the prolonged 14-d triple therapy the eradication rate was only 70% eradication in non-ulcer dyspepsia patients and 81.7% in peptic ulcer patients[36,37]. On the other hand, a meta-analysis failed to find a significant difference in the success rate between 7-d quadruple and standard triple therapies as a first-line treatment[38]. In addition, bismuth salts are no longer available in several western countries, so that the quadruple therapy is not feasible worldwide. Based on these evidences, different various attempts have been performed aiming made to increase efficacy of first-line therapies, such as to these include the use of new antibiotics (i.e., such as quinolones-based therapy[39] (or and switching to different antibiotic combinations regimens, such a the "sequential" therapy and the "concomitant" therapy.

Sequential therapy

The sequential regimen is a simple dual therapy combining a PPI with amoxicillin 1 g (both twice daily) given for the first five days followed by a triple therapy including a PPI, clarithromycin 500 mg, and tinidazole (all twice daily) for the remaining five days[39]. The first 5-d phase includes the administration amoxicillin which acts in reducing bacterial load and favouring the efficacy of the subsequent 5-d phase with clarithromycin-tinidazole. Moreover, amoxicillin pre-treatment prevents the incidence of secondary clarithromycin resistance, by destroying bacterial membrane and increasing its intra-

cellular concentration[23].

Several trials have documented a high (> 90%) eradication rate following sequential therapy, in patients with either peptic ulcer disease or non-ulcer dyspepsia, in elderly patients, and in children[40]. In addition, traditional factors affecting efficacy of triple therapies, do not influence the performance of sequential therapy[19]. A comprehensive, pooled-data analysis enrolling more than 1800 patients found an eradication rate as high as 93.5%[41], and 2 meta-analysis studies confirmed these data[42,43]. The higher efficacy of sequential therapy as compared to triple therapy, observed first in Italian studies, has been confirmed in other countries, such as Taiwan, Korea, Panama, Spain, and Romania[44]. Sequential therapy achieved higher eradication rate than triple therapy in patients infected with clarithromycin resistant strains[45]. It should be noted that by substituting tinidazole with metronidazole the eradication rate tended to be lower[44]. Moreover, by modifying the original drug combination in sequential therapy, using tetracycline instead of clarithromycin, failed to increase the eradication rate[46]. Two studies found that a levofloxacin-based instead of clarithromycin-based sequential therapy appears to be highly effective[47,48]. However, such a modified sequential therapy prevents the use of a levofloxacin-based second-line therapy, rendering difficult the subsequent therapeutic approach in the eradication failure patients[49]. The use of first-line sequential therapy is advised in current Italian guidelines[1], and largely supported by different opinion leaders[50,51].

Concomitant therapy

Concomitant therapy comprises PPI plus amoxicillin, clarithromycin, and metronidazole given altogether. This therapy was first introduced as an alternative to standard triple therapies more than 10 years ago, and the treatment duration of the originally proposed regimen was only 5 d[23,38]. A recent meta-analysis of 15 studies found a high efficacy for this regimen, with an eradication rate of 90%. However, it was noted that the eradication rate increased with therapy duration, being 85% at 3 d, 88% at 4 d, 89% at 5 d, 93% at 7 d and 92% at 10 d[52]. Another meta-analysis of 9 studies including only 7-d concomitant therapy calculated an eradication rate of 90% using intention to treat analysis and 93% using per-protocol analysis[53]. Pooled estimates of the five randomised controlled trials showed the superiority of concomitant therapy over triple therapy (odds ratio: 2.86; 95% CI: 1.73-4.73)[54], and this finding was confirmed in a more recent study, showing a 91.1% eradication rate in 3428 patients following a concomitant therapy as compared to 80.6% in 418 patients receiving a triple therapy regimen[55].

Sequential vs concomitant therapy

Randomised trials, comparing the efficacy of the sequential and concomitant administration of the same drugs are very scant. In one multicenter study, a head to head comparison between a 10-d sequential and 10-d concomitant therapy was performed. Bacterial eradication was achieved in 92% and 93% at ITT, respectively, and 93% for both treatments at PP analysis, with comparable prevalence of side effects (31% *vs* 27%), and comparable compliance to the therapy (96% *vs* 98%)[56]. Another randomised study comparing a 5-d concomitant therapy with the 10-d sequential regimen (with metronidazole) in a Latin American population, reported comparable and disappointingly low eradication rates (74% *vs* 76%)[54].

To date, sequential therapy has been proved effective also in clinical practice, where eradication rates are generally almost 10% lower than that observed in clinical trials[57,58]. In addition, a 10-d levofloxacin-based triple therapy has been shown to be effective following the failure of sequential therapy[59]. Data on the efficacy in clinical practice as well as in rescue therapy that should be used following concomitant regimen failure are still lacking.

Future molecules

Currently available antibiotics active against *H. pylori* in vivo are very scant. Therefore, new molecules are urgently needed. Several patents have been registered for molecules showing high bactericidal effects *in vitro*, some of them active even towards clarithromycin and metronidazole resistant strains[60-62]. Unfortunately, for *H. pylori* infection the activity *in vitro* does not strictly correlate with *in vivo* efficacy. Moreover, it takes several years before to test these potentially interesting molecules in humans. On the other hand, potential vaccines are still in the experimental phase[63].

CONCLUSION

Efficacy of standard triple therapies is decreasing worldwide, mainly due to an increasing prevalence of primary antibiotic resistance. Therefore, to cure *H. pylori* in clinical practice is becoming progressively more difficult, and some patients require more than two consecutive therapeutic regimens. To date, better results have been achieved by using either sequential or concomitant therapy. While waiting for novel molecules and vaccines, both of these treatments could be considered as first-line treatment for *H. pylori* infection.

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