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Helicobacter pylori eradication: an up-to-date

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ABSTRACT

Helicobacter pylori (H pylori) is a gram negative, non-spore forming spiral the bacterium which colonizes the human stomach. This microorganism is not a commensally one, so the infection always causes gastric mucosal inflammation and damage. H. pylori has been detected in individuals of all ages throughout the world and its prevalence ranges between 20%-80%. H. pylori-related gastric diseases create a heavy burden on health care systems world-wide. In the current progress report, it has been described in a practical way, its several therapeutic treatment approaches. The eradication of H. pylori is not simple and the therapeutic schemes demand a combination of multiple pharmacological agents. Some schemes that have excellent eradication rates in developed countries do not show the same results in developing countries, and vice versa. These differences are secondary to primary antibiotic resistance of the bacterium. Despite the use of various treatment regimens, around 20%

of patients remain infected and need retreatment under different therapeutic schemes. These rescue antibiotic combinations also vary a lot among countries, since there are again, different resistance profiles, as well as, different antimicrobials availability.

KEYWORDS :

INTRODUCTION

Helicobacter pylori (*H pylori*) is a gram negative, non-spore forming spiral the bacterium which colonizes the human stomach[1]. This microorganism is not a commensally one, so the infection always causes gastric mucosal inflammation and damage[2]. *H. pylori* has been detected in individuals of all ages throughout the world and its prevalence ranges between 20%-80%[3]. In developing countries, the prevalence of infection can as high as 90%, whereas in developed countries, excluding Japan, the prevalence is below 40%[4]. In Brazil, 68% of the blood donors without gastrointestinal complaints had positive serology for *H. pylori* [5].

Several studies investigated risk factors for *H. pylori* infection, however only socioeconomic factors are truly related to it. Subjects with a low socioeconomic status had a higher likelihood of being *H. pylori* positive. Other risk factors are considered, like living in rural areas, in crowded homes and having contaminated sources of drinking water[6].

The way *H. pylori* is transmitted is still unclear. Interpersonal transmission appears to be the main route. Its infection is usually acquired early in childhood. In urban and rural Brazilian populations with a low socioeconomic status (SES) more than half the children are already colonized in the first 2-3 years of life[6,7].

The *H. pylori* infection has been associated with peptic ulcer disease, atrophic gastritis, type B low-grade mucosal-associated lymphoma and gastric adenocarcinoma[1]. The World Health Organization classified *H. pylori* as a group I carcinogen with an attributable risk of gastric cancer of 50%-60% [8]. Furthermore, the organism is also thought to be involved in other human illnesses such as hematologic and autoimmune disorders, insulin resistance and the metabolic syndrome[1]. There are evidence linking *H. pylori* and unexplained iron-deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B12 deficiency. In these disorders, *H. pylori* should be sought and eradicated[7,9]. Other indications for *H. pylori* eradication have been indicated in different consensus, such as Maastricht IV[9].

H. pylori-related gastric diseases create a heavy burden on health care systems world-wide. In its most recent analysis, the US. Department of Health and Human Services estimate that in 2004, the direct costs associated with peptic ulcer disease in the US alone were approximately $2.6 billion. Additional indirect costs associated with loss of work productivity were estimated to be over $518 million. The costs due to gastric cancer were estimated to be $487 million with indirect costs reaching $1.4 billion[10].

TREATMENT

Besides the indications for *H. pylori* treatment mentioned previously, none investigated dyspepsia represents a frequent disease where eradication is recommended, specifically in patients with no alarm features. In Brazil the "test and treat" strategy is the ideal method utilized to search for this bacterium. Invasive diagnostic methods are recommended in every patient with any alarm symptoms, older than 35 years of age, the ones who do not respond to an initial treatment strategy or whose symptoms are chronic[9,11].

A Brazilian study underwent esophagogastroduodenoscopy in patients with uninvestigated dyspepsia and demonstrated functional dyspepsia in 66% of the patients (20% with normal endoscopy results and 46% with gastritis), 18% had GERD and 13% had ulcers (duodenal in 9% and gastric in 4%). Four cases of gastric adenocarcinoma were identified (1.4%). The prevalence of *H. pylori* was 54%[12].

H. pylori treatment has many limitations. Until now there are no antibiotics specifically formulated against this microorganism. The *H. pylori* are usually located between mucus and gastric mucosa, a location that prevents antibiotics to reach the bacterium. Gastric pH interferes with biodisponibility of some antibiotics, such as amoxicillin, clarithromycin and metronidazole. The treatment is also limited by type of antibiotic formulation, since solutions could reach more easily the whole stomach surface. Many antibiotics are absorbed in the duodenum, after their absorption their efficacy is disturbed by low bacterium depth of invasion, liver metabolism and gastric juice volume[13]. Finally, the type of affection could also interfere.

Another key point in *H. pylori* eradication is the need to add an acid suppressor to the antibiotics. Especially proton pump inhibitors (PPI) are essential to achieving good eradication rates. PPI act directly against *H. pylori*. Urease activity is fundamental to bacterium survival in the gastric lumen, PPI block urease which facilitates antimicrobial function. Once intra gastric pH is elevated, *H. pylori* tends to invade more the gastric mucosa, leading to more vulnerability to antibiotics[14].

FIRST-LINE TREATMENTS IN AREAS WITH LOW CLARITHROMYCIN RESISTANCE (table 1 and 2)

The triple therapy is composed of a PPI (standard dose, *bid*), amoxicillin (1 g, *bid*), and clarithromycin (500 mg, *bid*), taken for 7 to 10 days. The most frequently reported side effects include gastrointestinal (GI) discomfort, diarrhea and altered taste. PPI-clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate is more than 15-20%[4,9,11,15].

In areas such as Brazil with low clarithromycin resistance, standard triple is still a very good option achieving almost 90% eradication rates. Areas with high clarithromycin resistance eradication rates drop to 57–73%. Increasing treatment length to 10 or 14 days augments efficacy by 5-6%, as well as treatment costs. This strategy should be considered in patients with more serious complications such as gastric cancer and lymphoma[7,16].

A systematic review of 31 studies showed the overall *H. pylori* antibiotic resistance rates were 17.2% for clarithromycin, 26.7% for metronidazole, 11.2% for amoxicillin, 16.2% for levofloxacin, 5.9% for tetracycline and 9.6% for two or more antibiotics. The rate of clarithromycin resistant strains in Europe ranged from 49% (Spain) to 0,8% (Netherlands). In Asian countries, the highest clarithromycin resistance rate was detected in Japan (40.7%) while the lowest value was found in Malaysia (2.1%)[17]. In the Middle East, data are available from Iran, where the prevalence of clarithromycin resistance was 17.1%[18], although no resistance was found in Kuwait[19]. In Africa, the rate of resistance to clarithromycin has distinct reports, 1% in Senegal[20] and 15,3% in South Africa[21].

In Oceania, resistance rates of clarithromycin range between 8.7% and 15.7%[22]. In Brazil, primary bacterial resistance to metronidazole and clarithromycin is around 56% and 9% respectively, and to levofloxacin 23% and bismuth 5%. There was no observed resistance to amoxicillin, tetracycline or furazolidone[23]. So, clarithromycin-based triple therapy is still a good option Brazil, with eradication rates approaching 90%[24].

In order to improve the efficacy of triple therapy we can augment the dose of PPIs. This increase in the eradication rates goes from 6% to 10% Other strategy is extending the duration of PPI-clarithromycin-containing triple treatment from 7 to 10-14 days, which improves cure rates from 4 to 5% respectively[4,9,25,26].

Clarithromycin can be replaced by azithromycin in triple therapy regimens for the eradication of *H. pylori* as shown in a clinical trial that compared two weeks regimen of clarithromycin (2×500mg) + amoxicillin (2×1 g) + omeprazole (2×20 mg) to a 10 day regimen of azithromycin (1×250 mg) + 14 days of amoxicillin (2×1 g) + omeprazole (2×20 mg), with 84,6% and 79,5% success rates, respectively[27]. However, a Brazilian study that used a combination of azithromycin 500 mg + omeprazole 20 mg, in a single daily dose, associated with amoxicillin 500 mg tid for 6 days reached eradication rates of only 41%. At least in Brazil, azithromycin is not a good option to treat *H. pylori* [28].

Triple therapy using PPI (standard dose, *bid*), metronidazole (250mg *qid*), and clarithromycin (500 mg, *bid*) is equivalent to the standard triple regimen, in regions with low resistance to metronidazole. Primary metronidazole resistance varies a lot, Africa (95%), America (44.1%), Asia (37.1%), Europe (17.0%) and Brazil (51%), which impacts in this regimen success. Besides that, this scheme when it fails, it prevents the posterior use of two classes of antibiotics, macrolides and imidazolic [9,17].

Another possible limitation of the standard triple therapy is allergy to penicillin, clinical situation common among our population. In this case, amoxicillin can be replaced by metronidazole, tetracycline and furazolidone[29].

SECOND-LINE TREATMENTS IN AREAS WITH LOW CLARITHROMYCIN RESISTANCE (table 1 and 2)

After standard PPI-based triple regimen failure, the use of quadruple therapy (proton pump inhibitor in standard dose + bismuth salt 120 mg *qid* + tetracycline 500 mg *qid* + metronidazole 250 mg *qid* for 10-14 days) can be used as second-line therapy[4,9,15,30].

A multicenter study conducted in Europe evaluated *H. pylori* eradication with quadruple therapy (bismuth subcitrate 140 mg, tetracycline 125 mg, and metronidazole 125 mg, three capsules *qid*, and omeprazole 20 mg *bid* for ten days) after previous failure of standard triple therapy. *H. pylori* eradication rates ranged from 94.7% to 95%[31].

In Brazil, an open cohort study included patients with peptic ulcer who had failed one or more *H. pylori* eradication regimens. The therapeutic regimen consisted of 20 mg omeprazole, 240 mg bismuth subcitrate, 1g amoxicillin, and 200 mg furazolidone, *bid* for 7 days. The eradication rate was 68.8%[32].

Other options available consist in an association of a PPI + levofloxacin 500mg *od* and amoxicillin 1g *bid*, with eradication rates around 70%[4,9,30,33,34].

Rakici *et al* compared levofloxacin (levofloxacin 500 mg daily, amoxicillin 1 g *bid.* and lansoprazole 30 mg *bid*. for ten days) and moxifloxacin (moxifloxacin 400 mg daily, amoxicillin 1 g *bid* and lansoprazole 30 mg *bid*.) triple therapies with similar eradication rates (92% X 91,8%, respectively)[35].

A Brazilian study reported a total eradication rate of 89% after a 7-day regimen of lansoprazole (30 mg), furazolidone (200 mg) and levofloxacin (250 mg) *bid* in patients who had failed to respond to at least one prior eradication treatment regimen. In those patients who had just one previous treatment the eradication rate was 100%[36].

Unfortunately, resistance to quinolones in general and to levofloxacin in particular, is easily acquired. In countries with a high consumption of these drugs, the resistance rate is increasing[9].

After two treatment failures, it is recommendable to look for bacterium sensibility, in order to choose the best antibiotic combination. Unfortunately, antimicrobial susceptibility testing is still not widely available. In this situation, it is important to know the overall *H. pylori* sensitivity in a specific region, in order to choose the best scheme. It is also important not to repeat previous treatments, as well as, quinolones, macrolides and imidazolics[9,13].

FIRST-LINE TREATMENTS IN AREAS WITH HIGH CLARITHROMYCIN RESISTANCE (table 3)

In areas with high clarithromycin resistance bismuth-containing quadruple therapies are recommended (PPI in standard dose + bismuth salts 120 mg *qid* + tetracycline 500 mg *qid* + metronidazole 250 mg *qid* for 10-14 days)[4,9].

Other option is the sequential scheme introduced by Zullo *et al* in 2000. It consists of administering a standard dose of PPI with amoxicillin (1g *bid*) for the 5 days, followed by a standard dose of a PPI, clarithromycin (500mg *bid*) and tinidazole (500mg *bid*) for another 5-day period. *H. pylori* eradication was achieved in all but one patient, with an eradication rate of 98% with intention-to-treat analysis[37]. In this strategy amoxicillin weakens bacterial cell walls in the first five days, preventing the development of drug efflux channels for clarithromycin and metronidazole used in the second phase[38]. In a meta-analysis with 10 randomized controlled trials, sequential therapy appears superior to standard therapy in naive treatment patients (93.4% X 76.9%)[39]. However, in regions such as Brazil, where the standard triple therapy still has high eradication profile, the sequential therapy does not bring any advantage. The eradication rates of the sequential and standard therapies are the same, 86%[24].

Concomitant therapy is used instead of sequential therapy in areas where the resistance to clarithromycin is greater than 20% and bismuth-based quadruple therapy is not available. Concomitant therapy involves the simultaneous administration of 3 antibiotics (metronidazole, clarithromycin, and amoxicillin) and a PPI for 10 days. The efficacy of this therapeutic option is still discussed. Recent meta-analysis compared sequential and concomitant therapies and concluded that there were no differences between them[40].

Hybrid therapy is a recently reported scheme that consists of 2 steps: (1) treatment with a PPI and amoxicillin (1 g/12 hours) for 7 days, followed by (2) a PPI and three antibiotics, amoxicillin (1 g/12 hours), metronidazole (500 mg/12 hours), and clarithromycin (500 mg/12 hours), for other 7 days[4]. A systematic review evaluated the efficacy this scheme compared to concomitant and sequential therapies. The eradication rates were 88.6%, 86.3%, and 84.7%, respectively (ITT)[41].

SECOND-LINE TREATMENTS IN AREAS WITH HIGH CLARITHROMYCIN RESISTANCE (table 2)

For the case in which bismuth-based quadruple therapy fails, a triple therapy containing a PPI, levofloxacin, and amoxicillin is recommended. Rising rates of levofloxacin resistance should be taken into account[9].

THIRD LINE TREATMENT OPTIONS

The Maastricht IV consensus recommends antibiotic susceptibility testing to be done in the event of two treatment failures[9]. There are some disadvantages to this strategy. *H. pylori* culture requires endoscopically obtained gastric biopsy specimens, is time-consuming, costly and the successful culture rate ranges from 75% to 90%. Rapid molecular methods, such as polymerase chain reaction tests, may be an option to speed up the detection of resistance to macrolides and fluoroquinolones, but are not widely available[42]. It is important to know antibiotic susceptibility in different areas and stratify antibiotic treatments based on this[43].

RIFABUTIN BASED REGIMENS

Rifabutin is a spiropiperidyl derivative of rifampin-S, an antitubercular compound and has been shown to exhibit high in vitro activity against *H. pylori*. Low resistant strains have been isolated[44]. Gisbert et al. support the use of rifabutin-based triple therapies as a strategy after multiple eradication failures[45].

Rifabutin can cause rare but serious myelotoxicity which appears to be dose- dependent, widespread usage may contribute to another global problem: the rising trend of multidrug resistant tuberculosis. Therefore, rifabutin should be used only as "rescue" therapy after amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin have failed to eradicate *H. pylori* [42].

RIFAXIMIN BASED THIRD-LINE REGIMEN

Rifaximin is an oral antibiotic that belongs to the rifabutin family. It is not absorbed by the gastric and intestinal mucosa and is highly concentrated in the gastrointestinal tract. It has a broad-spectrum of in vitro activity against Gram-positive or Gram-negative enteric bacteria. Because it is not absorbed, rifaximin has a low risk of causing bacterial resistance[46].

Yun *et al* proposed that rifaximin can have a role in third line eradication therapy. In this study, patients who had failed both triple and quadruple standard regimens. In total, 482 patients were enrolled in this study. Forty-seven out of 58 patients who failed with the second-line regimen received rifaximin(200mg three times a day), levofloxacin (500mg once a day) and lansoprazole (15mg twice a day) for 1 week. The eradication rate for the third regimen was 65%, the cumulative eradication rate by the time patients had reached the third-line treatment was 96%. However, in this study, treatment success was determined by one negative ^{13}C-UBT result after only 1 week of stopping antibiotics or PPI, and this may lead to false negative results[47].

FOLLOW-UP AFTER *H.PYLORI* TREATMENT

After *H. pylori* treatment, the success of eradication can be determine with a non-invasive test as urea breath test, at least 4 weeks after the end of the treatment. Although if the treatment was indicated to gastric ulcer or MALT lymphoma, is necessary to perform an upper digestive endoscopy for confirmation of eradication[9].

Recurrence of *H. pylori* infection after eradication is rare in developed countries and more frequent in developing countries. Most recurrent cases are attributed to recrudescence (recolonization of the same strain within 12 months) rather than to reinfection (colonization with a new strain after more than 12 months). Meta-analysis of cases with a longer follow-up after eradication revealed an annual recurrence rate of 1.45% (RR 0.54) in developed countries and 12.00% (RR 0.92) in developing countries[48].

A study conducted in Brazil with peptic ulcer patients in a 5-year follow-up demonstrated a annual reinfection rate of 1,8%, similar of developed countries[49].

USE OF PROBIOTICS

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (WHO 2001). It has been recognized that probiotics can exhibit an inhibitory effect against *H. pylori* due immunologic and non immunologic mechanisms: competition at the site of the stomach mucosal epithelium; production of substances against *H. pylori*, such as acetic, propionic or butyric acid; regulation of immune function and secretion of immunoglobulin A to improve mucosal defensive ability; strengthening tight junctions between epithelial cell, inhibition of urease activity and production of bacteriocins[50].

The use of probiotics in conjunction with antibiotics can be used in order to increase eradication rates and decrease adverse effects due to antibiotic therapy, specially antibiotic associated diarrhea and pseudomembranous colitis. A meta-analysis using *Lactobacilli* and *Bifidobacteria* containing probiotics demonstrated higher eradication rates in probiotic groups (82.63% and 87.42% vs 67.85%). Side effects were observed in 15.37% (probiotics), *vs* 31.01% for control group[51].

A Brazilian double-blind placebo controlled trial evaluated the eradication rate and adverse effects of a probiotic compound (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus, Bifidobacterium bifidum* and *Streptococcus faecium*) plus an eradication scheme (furazolidone, tetracycline and lansoprazole for 7 days), compared to antibiotics

plus placebo. The per-protocol eradication rate with active probiotic was 89.8% and with placebo, 85.1% (p = 0.49); per intention to treat, 81.8% and 79.6%, respectively (p = 0.53). The rate of side effects at 7 days with active probiotics was 59.3% and 71.2% with placebo (p = 0.20). At 30 days post treatment, it was 44.9% and 60.4%, respectively (p = 0.08). The study showed no significant difference in efficacy or adverse effects[52].

Many trials have been published studying the importance of probiotics in *H. pylori* eradication regimens with different results. It is important to note that probiotic effects are strain dependant. More evidence is needed, although probiotics seem to show promising results[9,50,51,53].

ECABET SODIUM

Recent studies evaluate the addiction of ecabet sodium in the *H. pylori* eradication regimens. Ecabet sodium is a dehydroabietic acid derivative that was originally purified from pine resin and has local cytoprotective activity for the gastric mucosa, but is not absorbed into the systemic circulation. Recent studies have demonstrated that ecabet sodium has anti-*H pylori* activity. *In vitro* studies have shown that ecabet sodium inhibits the urease activity of *H pylori* and its adhesion to the gastric epithelial cells. In addition, ecabet sodium is reported to have a strong concentration- dependent bactericidal effect on *H. pylori* under acidic conditions. A meta-analysis included 13 randomized controlled trials and showed that eradication rate in the ecabet sodium-containing quadruple therapy group was higher than that in the standard triple therapy group (84.5% vs 74.55%), p<.001. The analysis also showed that the eradication rate in the ecabet sodium-containing triple therapy group was significantly higher than that in the PPI plus amoxicillin or clarithromycin therapy group (74.6% vs

43.9%), p<.001)(ITT), 74.6% vs 43.9%,p<.001) (PP).Supplementation with ecabet sodium during *H. pylori* eradication therapy improves the eradication rate[54].

H. PYLORI VACCINE

In order to minimize the costs in *H. pylori* treatment and associated diseases studies have been done in mice to demonstrate the feasibility of developing a vaccine for *H. pylori* infection, and for testing antigens, routes of immunization, dose, and adjuvant. These successes however, have not translated well in clinical trials[10].

CONCLUSIONS

H. pylori infection is the world´s most predominant infection within the gastrointestinal tract. In the current progress report, it has been described in a practical way, its several therapeutic treatment approaches. The eradication of *H. pylori* is not simple and the therapeutic schemes demand a combination of multiple pharmacological agents. Some schemes that have excellent eradication rates in developed countries do not show the same results in developing countries, and vice versa. These differences are secondary to primary antibiotic resistance of the bacterium. One good example of that is what we see in Europe and the United States, where the use of metronidazole is indicated as initial regimen, along with PPI and amoxicillin, while in Brazil is little used, due to high bacterial resistance. Table 4 shows different *H. pylori* eradication schemes. Despite the use of various treatment regimens, around 20% of patients remain infected and need retreatment under different therapeutic schemes. These rescue antibiotic combinations also vary a lot among countries, since there are again, different resistance profiles, as well as, different antimicrobials availability.

Table 1: Maastricht treatment recommendations for *H. pylori* in low clarithromycin resistance areas.

	Treatment	Option
First line	PPI, Amoxicillin/ metronidazole, clarithromycin	Bismuth quadruple
Second line	PPI, levofloxacin, amoxicillin	Bismuth quadruple
Rescue	Based on antimicrobial susceptibility	

PPI: proton pump inhibitor
Adapted from Maastricht IV report[9]

Table 2: Brazilian Consensus recommendations for *H. pylori* treatment

First line

A) PPI, amoxicillin, clarithromycin (7 days)
B) PPI, furazolidone, clarithromycin (7 days)

Second line

PPI, amoxicillin, levofloxacin (10 days)
PPI, amoxicillin/doxyciclin, furazolidone, bismuth salt (10-14 days)
PPI: proton pump inhibitor
Adapten from III Brazilian Consensus[7]

Table 3: Maastricht treatment recommendations for *H. pylori* in high clarithromycin resistance areas

	Treatment	Option
First line	Bismuth quadruple	Non-bismuth quadruple (sequential or concomitant)
Second line	PPI, levofloxacin, amoxicillin	
Rescue	Based on antimicrobial susceptibility	

PPI: proton pump inhibitor
Adapted from Maastricht IV report[9']

Table 4: *H. pylori* eradication schemes

Treatment schemes	Contents
Standard triple	PPI, clarithromycin, amoxicillin (7-14 days)
Quadruple	PPI, bismuth salt, metronidazole/tinidazole and tetracycline/amoxicillin (7-14)
Levofloxacin based	PPI, amoxicillin, levofloxacin
Furazolidone based	PPI, levofloxacin, furazolidone (7-10 days) PPI, claritromycin, furazolidone (7-10 days) PPI, amoxicillin, furazolidone (7-10 days) PPI, tetracycline, furazolidone (7 days) PPI, bismuth salt, metronidazole, furazolidone (7-14 days) PPI, bismuth salt, amoxicillin, furazolidone (7-14 days)
Sequential	PPI, amoxicillin (5 days) followed by PPI, clarithromycin and metronidazole (5 days)
Concomitant	PPI, amoxicillin, clarithromycin and metronidazole (10-14 days)
Rifabutin	PPI, amoxicillin and rifabutin (7-14 days)

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