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EDITORIAL

Third-line rescue therapy for *Helicobacter pylori* infection

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Abstract

H pylori gastric infection is one of the most prevalent infectious diseases worldwide. The discovery that most upper gastrointestinal diseases are related to *H pylori* infection and therefore can be treated with antibiotics is an important medical advance. Currently, a first-line triple therapy based on proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) plus two antibiotics (clarithromycin and amoxicillin or nitroimidazole) is recommended by all consensus conferences and guidelines. Even with the correct use of this drug combination, infection can not be eradicated in up to 23% of patients. Therefore, several second line therapies have been recommended. A 7 d quadruple therapy based on PPI, bismuth, tetracycline and metronidazole is the more frequently accepted. However, with second-line therapy, bacterial eradication may fail in up to 40% of cases. When *H pylori* eradication is strictly indicated the choice of further treatment is controversial. Currently, a standard third-line therapy is lacking and various protocols have been proposed. Even after two consecutive failures, the most recent literature data have demonstrated that *H pylori* eradication can be achieved in almost all patients, even when antibiotic susceptibility is not tested. Different possibilities of empirical treatment exist and the available third-line strategies are herein reviewed.

Key words: *Helicobacter pylori*; Third-line rescue therapy; Antimicrobial resistance; Levofloxacin; Rifabutin; Furazolidone; Doxycycline

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INTRODUCTION

Helicobacter pylori (*H pylori*) is a spiral-shaped bacterium that is attached to or just above the gastric mucosa. The organism can persist in the stomach indefinitely and may not cause clinical illness for many years after infection. Indeed, a large number of infected patients never develop any symptoms. However, a large body of literature has associated *H pylori* infection with gastritis and gastric malignancies (gastric adenocarcinoma and MALT-lymphoma)[1]. Chronic *H pylori* infection has also been associated with several extra intestinal diseases, such as autoimmune thrombocytopenia, sideropenic anemia and chronic urticaria but the pathogenesis is still not known [2].

H pylori gastric infection is one of the most prevalent infectious diseases worldwide with an estimation of 40%-50% of the world population. Remarkable differences are due to geographical, socio-economical and demographic factors [3, 4]. *H pylori* transmission is still not completely understood. In addition, among infected patients, the reasons why only some develop symptoms is still a matter of speculations. The more generally accepted point of view is that bacteria are likely spread from person to person by fecal or oral transmission. Humans are the primary reservoir of *H pylori* infection [5].

Several tests are available to detect *H pylori* in patients with ulcer or dyspepsia. The more commonly used tests are the evaluation of bioptic specimens during upper GI endoscopy, the detection of serum anti *H pylori* antibodies and breath tests with ^{13}C-labeled urea [6].

The discovery that most upper gastrointestinal diseases are the consequence of *H pylori* infection and can be treated with antibacterials is an important medical advance [7]. In the last few decades, *H pylori* eradication has been standardized. The occurrence of resistance to therapeutic regimens is a growing problem.

Selection of papers was based on those papers thought to be more relevant to the authors based on two criteria: larger studies and novel studies even if based on limited series of patients, in which case this limit was stated.

FIRST-LINE THERAPY

The first-line therapy protocol is now generally accepted [8-12], which consists of proton pump inhibitor (PPI) (b.i.d.) or ranitidine bismuth citrate (RBC) plus two antibiotics: clarithromycin (500 mg, b.i.d.) and amoxicillin (1 g, b.i.d.) administered for 7 d. Metronidazole (500 mg, b.i.d.) can be used as an alternative to amoxicillin. However, even with

the correct use of these drug combinations, infection is not eradicated in 10%-23% of patients [13].

FACTORS DETERMINING PRIMARY ERADICATION FAILURE

H pylori may develop resistance to the prescribed antibacterials and may acquire resistance by acquisition and recombination of genes from other bacteria [14]. Chromosomic mutations can also induce resistance [15]. Gene acquisition is unlikely because *H pylori* lives alone in a unique ecological niche and is equipped with multiple restriction systems to avoid the introduction of hexogenous DNA [16]. Therefore, resistance is generally thought to be the consequence of point mutations. Indeed metronidazole targets DNA and a high mutation rate is observed [15].

After the development of eradication therapies, *H pylori* resistant strains have rapidly disseminated [17-21]. Several mechanisms are involved in the development of resistance. First, the lack of patient compliance is assumed to be a key factor in eradication failure, which occurs because adverse events are relatively frequent and lead to treatment discontinuation [22, 23]. Second, insufficient antibiotic concentration at the site of infection contributes to the spreading of resistant strains [22, 23].

An emerging problem is that general practitioners prescribe treatments without adequate diagnosis and do not adhere to eradication guidelines [24, 25]. Given the importance of host immune response in *H pylori* infection, the role of immunity in eradication failure can be hardly argued. However, data are anecdotal. Borody *et al* [26] suggested that IL-4 is important in *H pylori* eradication and hypothesized that IL-4 defect contributes to eradication failure.

Cytochrome P450, isoenzyme 2C19 [27] and interleukin-1-beta polymorphisms can interfere with acid secretion and have the activity of antimicrobial agents [28].

Finally, socio-economic factors (smoking habit), geographical factors, gender, histological changes also affect the eradication success [23-25]. Disease phenotypes also contribute to eradication failure. In fact, the failure rate in duodenal ulcer is 21.9%, lesser than in nonulcer dyspepsia (33.7%). In addition, the presence of histological fibrosis and lympho-epithelial lesions leads to poor eradication rates [23, 29].

Large studies on all these possible mechanisms of failure are lacking, but clarithromycin resistance appears to be the most important mechanism [30, 31].

SECOND-LINE THERAPY

Second-line therapy has been extensively reviewed by several authors[30, 32-34]. Therefore, we herein only discuss the Maastricht guidelines and some of more recently proposed protocols using new antimicrobial drugs, such as levofloxacin, rifabutin and furazolidone.

Most authors concord that culture after a first eradication failure is not thought to be necessary to start the second-line therapy. The assessment of *H pylori* sensitivity to antibiotics may be useful only after failure of the second-line therapy [8, 9, 35]. As second-line therapy, the Maastricht 2-2000 Consensus Report suggests a quadruple therapy based on bismuth (120 mg, q.i.d.), tetracycline (500 mg, q.i.d.), metronidazole (500 mg, t.i.d.) and antisecretive agent (PPI, b.i.d.) for a minimum of 7 d [12].

Further trials have shown that replacing the proton pump inhibitor and the bismuth compound of the quadruple therapy by RBC also achieves good results, with an eradication rate ranging between 57%-95% [36-39]. The failure of second line quadruple therapy is associated with its discontinuation because of the high incidence of side effects (6%-68%) [40]. Low compliance for the high number of pills to be taken each day also affects the clinical results [24]. However, in second-line regimens, new combination of drugs has been used. A triple therapy with the combination of levofloxacin, rabeprazole and tinidazole or amoxicillin has been proposed as an alternative to Maastricht [41]. This protocol shows an eradication rate higher than 90% compared to quadruple therapies given for 7 d (63%) with a lower incidence of side effects [42].

Rifabutin has been shown to have a good eradication rate (87%), if administered at a high dose (300 mg) in combination with amoxicillin and PPI, as compared to quadruple therapy [43-47]. Rifabutin shows an important side effect (mielotoxicity) [46]. Wong *et al* [43] showed that a combination of levofloxacin, rifabutin and rabeprazole has a high efficacy with an eradication rate >90% [43].

Furazolidone is also used to replace metronidazole in quadruple therapy [48-51]. Different *in vivo* studies have confirmed the efficacy of regimens containing a high-dose furazolidone [200 mg, b.i.d.] as the second-line therapy in patients with metronidazole-resistance [48-51]. Many other combinations have been used [31] with various rates of success. Bacterial eradication may fail in up to 40% of cases after the suggested second-line regimens. As a consequence, to treat patients who have already undergone the first- and second-line therapies is a common challenge.

THIRD-LINE RESCUE THERAPY

Currently, a standard third-line therapy is lacking. Different groups have tested various therapeutic protocols [33, 52, 53]. When available, endoscopy with culture and consequent antibiotic susceptibility testing remains the most appropriate option for patients with two eradication failures [54-56] to avoid a widespread use of expensive antibiotics such as rifabutin. The use of these drugs may also induce severe side-effects and development of *H pylori* resistant strains [30]. However, systematic use of culture is questionable [57]. Culture implies general endoscopic risks and is expensive as well as time-consuming due to *H pylori* difficult growth and not always available on a routine basis [58].

The sensitivity of bacterial culture is not 100% even in expert hands [6]. Moreover, amoxicillin and tetracycline rarely induce resistance [58, 59]. On the other hand, most of *H pylori* isolates after two eradication failures are resistant to metronidazole and clarithromycin, respectively [55]. Therefore, these two drugs are not recommended for third-line therapy [22, 56]. Our own previous data also show high resistance rates to metronidazole and clarithromycin even if the previously used regimens did not include either

of these two drugs [55]. In addition, *in vitro* susceptibility cannot predict eradication success [60-62]. Taken together, these data suggest that cultures are not strictly necessary to decide upon a third-line protocol.

The third-line therapy should avoid metronidazole and clarithromycin and antibiotics that are likely to have contributed to development of resistance. A consensus for third-line therapies has not been presently reached. Herein we discuss those based on levofloxacin, rifabutin, furazolidone and doxycycline.

Levofloxacin-based therapy

Levofloxacin is a broad-spectrum fluoroquinolone, active against Gram-positive and negative bacteria and atypical respiratory pathogens [63]. Levofloxacin inhibits the DNA synthesis, has a good oral absorption and is well tolerated [64]. Fluoroquinolones are active against *H pylori in vitro* [65] and have a synergistic effect with PPIs [66]. Primary resistance to levofloxacin ranges between 8%-31% in different countries or regions [55, 67, 68].

Recently, Gatta *et al* [69] have proposed a third-line treatment after two eradication failed courses without fluoroquinolones, with standard dose of PPIs (b.i.d.), levofloxacin (250 mg, b.i.d.) and amoxicillin (1 g, b.i.d.) for 10 d. The eradications rates of 76.2% and 84.6% according to ITT and PP analysis, respectively, have been achieved in 151 enrolled patients in a prospective open study. The levofloxacin-based treatment could eradicate most of the strains (92.3%) which are resistant *in vitro* to both clarithromycin and metronidazole, but susceptible to levofloxacin. The primary resistance to levofloxacin found in this study was 14%. Furthermore, this drug combination, successfully employed as rescue therapy [70], is well tolerated and has no major side-effects [71].

A more recent prospective multicentric study [72] reports data of 100 patients who have failed two eradication courses without fluoroquinolones. This study demonstrated that a regimen of levofloxacin (500 mg, b.i.d.), amoxicillin (1 g, b.i.d.) and omeprazole (20 mg, b.i.d.) for 10 d can achieve an eradication rate of 60% or 66% according to ITT and PP analysis. The treatment was given without previous sensitivity test.

Low compliance with the current regimens is one of the main causes of failures [24]. Therefore, Coelho *et al* [73] have proposed a combination of rabeprazole (20 mg), levofloxacin (500 mg) and furazolidone (200 mg) (two tablets) administered at a single dose for 10 d. Twelve patients who failed at least two eradication courses are successfully treated. Per-protocol and intention-to-treat eradication rates were 100% and 83.3%, respectively. However, because of the paucity of patients in third-line therapy, these data have to be confirmed in larger series. Furthermore, cultures obtained before treatment from some patients show no resistance to furazolidone, while 87% of the samples analyzed are sensitive to levofloxacin. No severe adverse effects are observed [73]. Therefore, the results after the levofloxacin-based triple therapy for ten days in patients with two eradication failed courses with amoxicillin, clarithromycin, metronidazole, tetracycline and bismuth, are encouraging. However, the resistance to quinolones is easily acquired, and the resistance rate is relatively high in countries with a high consumption of these drugs [55, 68]. Therefore, it seems advisable to reserve levofloxacin to third-line rescue treatment to avoid the increase of the resistance phenomenon [72].

Rifabutin-based therapy

Rifabutin is a spiropiperidyl derivative of rifamycin-S, an antitubercolar compound. Rifabutin inhibits the beta-subunit of *H pylori* DNA-dependent RNA polymerase encoded by the rpoB gene [74]. Rifabutin is expensive and unavailable in various countries and has side effects (leukopenia and thrombocytopenia, with myelotoxicity) [46]. It has been suggested to reserve the use of rifabutin for the treatment of multiresistant *Mycobacterium tuberculosis* strains [53, 75]. *H pylori* is highly susceptible *in vitro* to rifabutin and no resistant strains have been isolated from patients treated or untreated for *H pylori* infection [74, 75]. Furthermore, rifabutin is chemically stable at a wide pH range [76].

Three different trials have shown that rifabutin (300 mg o.d. or 150 mg b.i.d)-based therapies in combination with amoxicillin (1 g, b.i.d.) and standard dose of PPIs (b.i.d.) are a good third-line strategy, achieving the eradication rate of at least 70% [46, 47, 53]. On the other hand, Qasim *et al* [77] have achieved only a 38% eradication rate [77].

A more recently single centre prospective study [78] studied 67 patients who failed to respond to two or more courses. The result showed that when the rifabutin dose is reduced from 300 mg to 150 mg, it results in a signficant drop in eradication rate from 86.6% to 66.6% [45]. Borody *et al* [78] have shown that a 12 d regimen with low-dose rifabutin (150 mg a day) in combination with increased frequency of amoxicillin (1 g, t.d.s.) and pantoprazole (80 mg, t.d.s.) could achieve an overall eradication rate of 92.1% in patients harbouring double resistance strains to metronidazole and clarithromycin, with an eradication rate of 95.7%. Mild side effects are found in 40% of patients. Unlike regimens which use higher doses of rifabutin, no patients develop drug-related neutropenia or thrombocytopenia after treatment. Nevertheless, the main problem with a widespread use of rifabutin is the concern that antibiotic resistance may develop against *Mycobacterium avium* in HIV-infected patients. Therefore, the use of this drug for *H pylori* is questionable.

Furazolidone-based therapy

Furazolidone is a broad-spectrum nitrofuran, active against Gram-negative and positive bacteria and protozoa by inhibiting bacterial enzymes [79]. It is widely used in low income populations because it is inexpensive. It kills *H pylori* [80,81]. Strains resistant to furazolidone are rare [82, 83] and its potential to develop resistance is as low as bismuth compounds or amoxicillin [84]. Furthermore, it has no cross-resistance to metronidazole [83] and is effective in populations with a high prevalence of metronidazole resistance [85]. It has poor oral absorption and presents some side effects, especially gastrointestinal ones [79]. Concomitant intake of alcohol and MAO-inhibitors should be avoided as other interacting drugs. Furazolidone may induce a disulfiram-like reaction to alcohol and is an MAO-inhibitor. One week quadruple regimen with lansoprazole (30 mg, b.i.d), bismuth (240 mg, b.i.d.), tetracycline (1g, b.i.d.) and fura-

zolidone 200 mg (b.i.d.) has shown an eradication rate of 90% as third-line therapy in 10 patients with metronidazole resistance by culture [48]. Furthermore, 7 d triple-regimen comprising of furazolidone (200 mg, b.i.d), amoxicilin 1 g (b.i.d.) and standard dose of PPI (b.i.d.), achieves an eradication rate of 60% in 10 patients who failed first-line, second-line and rifabutin-based triple therapy [77].

In conclusion, in developing countries where resistance to metronidazole is usually very high [12], furazolidone in combination with tetracycline, bismuth and PPI for one week is very effective, safe and cost effective against *H pylori* as the third-line therapy.

Doxycycline-based therapy

Doxycycline is a widely used tetracycline antibiotic for several infections. With respect to tetracycline, doxycycline requires the administration of only two tablets per day, leading to a better compliance in patients undergoing eradication therapies. Furthermore, Heep *et al* [19] have found no secondary resistance to doxycycline in *H pylori* isolates from patients who failed one or more eradication therapies.

Quadruple regimens represent the most widely used rescue therapy. Yet, it is limited by lack of patient compliance due to the large number of tablets and by several side-effects. The classic quadruple therapy includes bismuth salts which have a synergistic effect on antibiotics possibly by decreasing the bacterial load, PPI which facilitates antibiotic activity by increasing the gastric pH, tetracycline with a low rate of resistance in *H pylori* isolates, and metronidazole [58, 59]. Induction of metronidazole resistance has suggested a new protocol, namely replacing tetracycline with doxycycline (because it requires the administration of only two tablets per day) and metronidazole with amoxicillin (because its resistance is less 1%), 1-week-quadruple therapy with doxycycline (100 mg, b.i.d.), amoxicillin (1 g, b.i.d.), omeprazole (20 mg, b.i.d.) and bismuth salts (120 mg, two tablets b.i.d). This treatment has proved to be a highly effective third-line 'rescue' therapy, achieving 91% eradication rate in patients harbouring metronidazole and clarithromycin resistant *H pylori* strains (by ITT analysis) [55]. This regimen, showing excellent compliance (99%) and mild side-effects, may well constitute the test available option for the third-line rescue treatment.

Rifampicin-based therapy

Rifampicin is a semisynthetic derivative of rifamycin B. The target is the DNA-dependent DNA polymerase, mainly the beta subunit [86]. Rifampicin inhibits the growth of most Gram-positive and negative microorganisms. The clinical efficacy of rifampicin against *H pylori* has been discovered by the observation of the decrease of anti-*H pylori* antibodies in patients on rifampicin-containing antitubercular therapy [87]. Rifampicin has an excellent *in vitro* efficacy against *H pylori* [88, 89] and a favorable pharmacokinetics. Less-expensive rifabutin is available in many countries. A single-center study has shown that 10 d rifampicin (450 mg o.d.)-triple therapy in combination with esomeprazole (40 mg b.i.d.) and tetracycline (1 000 mg b.i.d.) can achieve an eradication rate of 32.1% and 31.6% (by ITT analysis), if given as second-line or third-line therapy, respectively. Side effects are common but minor.

In conclusion, rifampicin-based rescue therapy is not as effective as a salvage-based therapy for *H pylori* eradication [86].

CONCLUSION

An undisputed third line strategy to cure *Helicobacter pylori* is still lacking. Eradication rates >90% can be achieved following the Maastricht guidelines for first- and second-line therapies. New first-line alternative strategies are needed, considering the development of primary and secondary resistances. Second-line therapy depends on which regimen is used initially, the re-administration of any antibiotics against which *H pylori* has probably become resistant, as metronidazole and clarithromycin or drugs with cross-resistance to these or previously used antimicrobial are not recommended. To face treatment failures, several third-line 'rescue' therapies have been tested, achieving good eradication rates. In our opinion, levofloxacin-triple (eradication rate of 92%) [69] and doxycycline-quadruple (eradication rate of 91%) [55] are more active on resistant strains. They are safe, better tolerated and less expensive than rifabutin-based regimen. Moreover, the widespread use of rifabutin may be a major concern due to the possible development of antibiotic resistance. We believe that the worldwide aid tubercular emergency and the risk to develop *Mycobacterium*-resistant strains strongly suggest a conservative approach reserving rifabutin to antitubercular therapy. This is especially recommended in countries where alternative drugs are available. In developing countries where resistance to metronidazole is usually very high, the 7 d furazolidone-quadruple third-line therapy is effective against *H pylori* (with eradication rates of 90%), safe and cost-effective.

In conclusion, our review shows that *Helicobacter pylori* eradication can be eventually obtained even in the few patients who experience up to 8 consecutive failures [78, 90, 91]. This can be done by different drugs as reported in the different protocols discussed above.

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