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) [9]. 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 [9].

*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 [3-9]. *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 [9].

Several tests are available to detect *H pylori* in patients with ulcer or dyspepsia. The more commonly used tests are the evaluation of biopptic specimens during upper G1 endoscopy, the detection of serum anti-*H pylori* antibodies and breath tests with 13C-labeled urea [8].

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 therapeutically 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]. Chromosomal 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 heterogenous 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 [17].

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 [29-32]. 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, 28].

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 [32, 33, 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 concur 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, 33]. 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 [13].

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 [41]. 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 [42]. 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 [43].

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 [44-47]. 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% [44].

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 [46-51]. Many other combinations have been used [52] 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 [53, 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 [57]. 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 [60]. 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 [58]. Therefore, these two drugs are not recommended for third-line therapy [52, 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. In addition, in vitro susceptibility cannot predict eradication success. 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. Levofloxacin inhibits the DNA synthesis, has a good oral absorption and is well tolerated. Fluoroquinolones are active against *H pylori* in vitro and have a synergistic effect with PPIs. Primary resistance to levofloxacin ranges between 8%-31% in different countries or regions.

Recently, Gatta et al. 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 eradication 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, is well tolerated and has no major side-effects.

A more recent prospective multicentric study 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. Therefore, Coelho et al. 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. 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. Therefore, it seems advisable to reserve levofloxacin to third-line rescue treatment to avoid the increase of the resistance phenomenon.

**Rifabutin-based therapy**

Rifabutin is a spiropiperidyl derivative of rifamycin-S, an antitubercular compound. Rifabutin inhibits the beta-subunit of *H pylori* DNA-dependent RNA polymerase encoded by the rpoB gene. Rifabutin is expensive and unavailable in various countries and has side effects (leukopenia and thrombocytopenia, with myelotoxicity). It has been suggested to reserve the use of rifabutin for the treatment of multiresistant *Mycobacterium tuberculosis* strains. *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. Furthermore, rifabutin is chemically stable at a wide pH range.

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%. On the other hand, Qasim et al. have achieved only a 38% eradication rate

A more recently single centre prospective study 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 significant drop in eradication rate from 86.6% to 66.6%. Borody et al. 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. It is widely used in low income populations because it is inexpensive. It kills *H pylori* strains resistant to furazolidone are rare and its potential to develop resistance is as low as bismuth compounds or amoxicillin. Furthermore, it has no cross-resistance to metronidazole and is effective in populations with a high prevalence of metronidazole resistance. It has poor oral absorption and presents some side effects, especially gastrointestinal ones. 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 furazolidone (200 mg, b.i.d) 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. 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.
troleandomycin 200 mg (b.i.d.) has shown an eradication rate of 90% as third-line therapy in 10 patients with metronidazole resistance by culture \[86\]. Furthermore, 7 d triple-regimen comprising of furazolidone (200 mg, b.i.d.), amoxicillin 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 \[58, 59\] 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 \[19, 26\]. 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) \[59\]. 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 \[88, 90\] 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 (1000 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.

**REFERENCES**

1. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002; 347: 1175-1186
2. Gasbarrini A, Franceschi F, Aruzzi A, Ojetti V, Candelli M, Torre ES, De Lorenzo A, Anti M, Pretolani S, Gasbarrini G. Extraintestinal manifestations of *Helicobacter pylori* gastric infection. Gut 1999; 45 Suppl 1: I9-I12
3. Perez-Perez GI, Rothenbacher D, Brenner H. Epidemiology of *Helicobacter pylori* infection. Helicobacter 2004; 9 Suppl 1: 1-6
4. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut 1994; 35: 742-745
5. Kikuchi S, Dore MP. Epidemiology of *Helicobacter pylori* Infection. Helicobacter 2005; 10 Suppl 1: 1-4
6. Technical annex: tests used to assess *Helicobacter pylori* infection. Working Party of the European *Helicobacter pylori* Study Group. Gut 1997; 41 Suppl 2: S10-S18
7. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; 1: 1311-1315
8. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. European *Helicobacter pylori* Study Group. Gut 1997; 41: 8-13
9 Proceedings of the American Digestive Health Foundation International Update Conference on Helicobacter pylori. McLean, Virginia, USA, February 13-16, 1997. Gastroenterology 1997; 113: 553-569
10 Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection. J Gastroenterol Hepatol 1998; 13: 1-12

11 Coelho LG, León-Barúa R, Quigley EM. Latin-American Consensus Conference on Helicobacter pylori infection. Latin-American National Gastroenterological Societies affiliated with the Inter-American Association of Gastroenterology (AIGE). Am J Gastroenterol 2008; 95: 2688-2691

12 Malfertheiner P, O’Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of Helicobacter pylori infection—the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther 2002; 16: 167-180

13 Parente F, Cucino C, Bianchi Porro G. Treatment options for patients with Helicobacter pylori infection resistant to one or more eradication attempts. Dig Liver Dis 2003; 35: 523-528

14 Hua JS, Zheng PY, Fong TK, Khin MM, Bow H. Helicobacter pylori acquisition of metronidazole resistance by natural transformation in vitro. World J Gastroenterol 1998; 4: 385-387

15 Lederger J, LEDERBERG EM. Replica plating and indirect selection of bacterial mutants. J Bacteriol 1952; 63: 399-406

16 Tomb JE, White O, Kerlavare AG, Clayton RA, Sutton G, Fleischmann RD, Ketchum KA, Lennard H, Gill S, Dougherty BA, Nelson K, Quinckeck JH, Zhou L, Kirkness EF, Peterson S, Lopez B, Richardson D, Dodson R, Khalig HG, Glodek A, McKenney K, Felzgerald JM, Lee N, Adams MD, Hickey KE, BG, Gocayne JD, Utterback T, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fuji C, Bowman C, Wathay L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. The complete genome sequence of the gastric pathogen Helicobacter pylori. Nature 1997; 388: 539-547

17 Huang QJ, Hunt RH. Treatment after failure: the problem of “non-responders”. Gut 1999; 45 Suppl 1: 140-144

18 McAlonan BJ, Hennessy TW, Bensler JM, Brunen DL, Parkison AJ, Morris JM, Reasonover AL, Hurthart DA, Bruce MG, Sacco F, Butler JC. The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for Helicobacter pylori infections. Ann Intern Med 2003; 139: 463-469

19 Heep M, Kist M, Strobel S, Beck D, Lenn N. Secondary resistance among 554 isolates of Helicobacter pylori after failure of therapy. Eur J Clin Microbiol Infect Dis 2000; 19: 538-541

20 Filotto A, Franceschi M, Rassou M, Mautino M, Leandro MD, Bazzola L, Furlan F, Di Mario F. Incidence of secondary Helicobacter pylori resistance to antibiotics in treatment failures after 1-week proton pump inhibitor-based triple therapies: a prospective study. Dig Liver Dis 2002; 34: 667-672

21 Peitz U, Sulliga M, Wolle K, Leodolter A, von Arnim C, Kahl S, Stolte M, Börsch G, Labenz J, Malfertheiner P. High rate of post-therapeutic resistance after failure of macrolide-nitroimidazole triple therapy to cure Helicobacter pylori infections: impact of two second-line therapies in a randomized study. Aliment Pharmacol Ther 2002; 16: 315-324

22 Qasim A, O’Morain CA. Review article: treatment of Helicobacter pylori infection and factors influencing eradication. Aliment Pharmacol Ther 2002; 16 Suppl 1: 24-30

23 Broutet N, Tchamgoué S, Pereira E, Lamouliatte H, Salamon R, Megraud F. Risk factors for failure of Helicobacter pylori therapy—results of an individual data analysis of 2751 patients. Aliment Pharmacol Ther 2003; 17: 99-109

24 Crone J, Granditsch G, Huber WD, Binder C, Innerhofer A, Aman D, Hirsch EM. Helicobacter pylori in children and adolescents: increase of primary clarithromycin resistance, 1997-2000. J Pediatr Gastroenterol Nutr 2003; 36: 368-371

25 Perri F, Qasim A, Marras L, O’Morain C. Treatment of Helicobacter pylori infection. Helicobacter 2003; 8: 53-60

26 Borody T, Ren Z, Pang G, Clancy R. Impaired host immunity contributes to Helicobacter pylori eradication failure. Am J Gastroenterol 2002; 97: 3032-3037

27 Miki I, Aoyama N, Sakai T, Shirasaka D, Wambura CM, Maekawa S, Kuroda K, Tamura T, Kitai T, Sakaeda T, Okumura K, Kasuga M. Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of Helicobacter pylori infection with lansoprazole- or rabeprazole-based triple therapy in Japan. Eur J Gastroenterol Hepatol 2003; 15: 27-33

28 Furuta T, Shirai N, Xiao F, El-Omar EM, Rabkin CS, Sugimura H, Ishizaki T, Ohashi K. Polymorphism of interleukin-1 beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004; 2: 22-30

29 Russo F, Berloco P, Cuomino R, Caruso ML, Di Matteo G, Giorgio P, De Francesco V, Di Leo A, Ierardi E. Helicobacter pylori strains and histologically-related lesions affect the outcome of triple eradication therapy: a study from southern Italy. Aliment Pharmacol Ther 2003; 17: 421-428

30 Megraud F, Lamouliatte H. Review article: the treatment of refractory Helicobacter pylori infection. Aliment Pharmacol Ther 2003; 17: 1333-1343

31 Megraud F. Basis for the management of drug-resistant Helicobacter pylori infection. Drugs 2004; 64: 1893-1904

32 McLaughlin RM, O’Morain CA, O’Connor HJ. Eradication of Helicobacter pylori: recent advances in treatment. Fundam Clin Pharmacol 2005; 19: 421-427

33 Gisbert JP, Pajares JM. Review article: Helicobacter pylori ‘rescue’ regimen when proton pump inhibitor-based triple therapies fail. Aliment Pharmacol Ther 2002; 16:1047-1057

34 Howden CW, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998; 93: 2330-2338

35 de Boer WA, Tytgat GN. Regular review: treatment of Helicobacter pylori infection. BMJ 2000; 320: 31-34

36 Rinaldi V, Zullo A, De Francesco V, Hassan C, Winn S, Stoppino V, Faleo D, Attili AF. Helicobacter pylori eradication with proton pump inhibitor-based triple therapies and re-treatment with ranitidine bismuth citrate-based triple therapy. Aliment Pharmacol Ther 1999; 13: 163-168

37 Zullo A, Hassan C, Campo SM, Lorenzetti R, Febbraro I, De Matthais M, Porto D, Morini S. A triple therapy regimen after failed Helicobacter pylori treatments. Aliment Pharmacol Ther 2001; 15: 1193-1197

38 Gisbert JP, Gisbert JL, Marcos S, Grávalos RG, Carpio D, Pajares JM. Seven-day ‘rescue’ therapy after Helicobacter pylori treatment failure: omeprazole, bismuth, tetracycline and metronidazole vs. ranitidine bismuth citrate, tetracycline and amoxicillin. Aliment Pharmacol Ther 1999; 13: 1311-1316

39 Michopoulos S, Tsibouris P, Bouzakis H, Balta A, Vougadiotis J, Broutet N, Kralios N. Randomized study comparing omeprazole with ranitidine as anti-secretory agents combined in quadruple second-line Helicobacter pylori eradication regimens. Aliment Pharmacol Ther 2000; 14: 737-744

40 Gomollón F, Ducón JA, Ferrero M, García Cabezudo J, Guirao R, Simón MA, Montoro M. Quadruple therapy is effective for eradicating Helicobacter pylori after failure of triple proton-pump inhibitor-based therapy: a detailed, prospective analysis of 21 consecutive cases. Helicobacter 1999; 4: 222-225

41 Watanabe Y, Aoyama N, Shirasaka D, Maekawa S, Kuroda K, Miki I, Kachi M, Fukuda M, Wambura C, Tamura T, Kasuga M. Levofloxacin based triple therapy as a second-line treatment after failure of Helicobacter pylori eradication with standard triple therapy. Dig Liver Dis 2003; 35: 711-715

42 Nista EC, Candelli M, Cremonini F, Cazzato IA, Di Caro S, Gabrielli M, Santarelli L, Zocco MA, Ojeti V, Carloni E, Cammarata G, Gassarrini G, Gassarrini A. Levofloxacin-based triple therapy vs. quadruple therapy in second-line Helicobacter pylori treatment: a randomized trial. Aliment Pharmacol Ther 2003; 18: 627-633

43 Wong WM, Gu Q, Lam SK, Fung FM, Lai KC, Hu WH, Yee YK, Chan CK, Xia HY, Yuen MF, Wong BC. Randomized controlled study of rabeprazole, levofloxacin and rifabutin triple therapy vs. quadruple therapy as second-line treatment for Helicobacter pylori infection. Aliment Pharmacol Ther 2003; 17: 553-560
antibiotic resistance: prevalence, import

infection in Iran.

Aliment Pharmacol Ther 2003; 16: 1457-1460

Peri F, Festa V, Clemente R, Villani MR, Quitadamo M, Caruso N, Bergoli ML, Andriulli A. Randomized study of two "rescue" therapies for Helicobacter pylori-infected patients after failure of standard triple therapies. Am J Gastroenterol 2001; 96: 58-62

Canducci F, Ogetti V, Pela P, Gasbarrini G, Gasbarrini A. Rifabutin-based Helicobacter pylori eradication "rescue therapy". Aliment Pharmacol Ther 2001; 15: 143

Peri F, Festa V, Clemente R, Quitadamo M, Andriulli A. Rifabutin-based "rescue therapy" for Helicobacter pylori-infected patients after failure of standard regimens. Aliment Pharmacol Ther 2000; 14: 311-316

Treiber G, Ammon S, Malfertheiner P, Klotz U. Impact of furazolidone-based quadruple therapy for eradication of Helicobacter pylori after previous treatment failures. Helicobacter 2002; 7: 225-231

Ebrahimi-Dariani N, Mirmomen S, Mansour-Ghanafi E, Noormohammadpour P, Sotoodehmanesh R, Haghpanah B, Bahrami H. The efficacy of furazolidone-based triple therapy for eradication of Helicobacter pylori infection in Iranian patients resistant to metronidazole-based triple therapy. Med Sci Monit 2003; 9: P105-P1108

Pakhere H, Malekzadeh R, Merat S, Khabliyan M, Fazel A, Alizadeh BZ, Massarrat S. Clarithromycin vs. furazolidone in quadruple therapy regimens for the treatment of Helicobacter pylori in a population with a high metronidazole resistance rate. Aliment Pharmacol Ther 2001; 15: 411-416

Isakov V, Domareva I, Koudryavtseva L, Maev I, Ganskaia Z. Furazolidone-based triple "rescue therapy" vs. quadruple "rescue therapy" for the eradication of Helicobacter pylori resistant to metronidazole. Aliment Pharmacol Ther 2002; 16: 1277-1282

Zullo A, Vaira D, Yakil N, Hassan C, Gatta L, Ricci C, De Francesco V, Menegatti M, Tampieri A, Perna F, Rinaldi V, Peri F, Papadía C, Fornari F, Filati S, Mete LS, Merla A, Poti R, Marinone G, Savioli V, Clemente R, Quitadamo M, Andriulli A, Milicua JM. "Rescue" therapy with rifabutin after multiple treatment failures of standard regimens. Aliment Pharmacol Ther 2003; 18: 90-94

Beales IL. Efficacy of Helicobacter pylori eradication therapies: a single centre observational study. BMC Gastroenterol 2001; 1: 7

Cammarota G, Martino A, Pirozzi G, Cianci R, Branca G, Nista F, Perna F, Ricci C, De Francesco V, Tenni A, Maccarone M, Mancia G, Angiletta M, Soria A, Ferrara L, D'Amico A, Cianci R, Branca G, Nista F.Failure of two eradication treatments: a meta-analytical approach. Dig Dis Sci 2000; 45: 68-76

Gisbert JP, Pajares JM. Helicobacter pylori "rescue" therapy after failure of two eradication treatments. Helicobacter 2005; 10: 363-372

Zullo A, Hassan C, Lorenzetti R, Winn S, Morini S. A clinical practice viewpoint: to culture or not to culture Helicobacter pylori? Dig Liver Dis 2003; 35: 357-361

Megraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut 2004; 53: 1374-1384

Gomollon F, Sicilia B, Ducos JA, Sierra E, Revillo MJ, Ferrero M. Third line treatment for Helicobacter pylori: a prospective, culture-guided study in peptic ulcer patients. Aliment Pharmacol Ther 2000; 14: 1335-1338

Vicente R, Sicilia B, Gallego S, Revillo MJ, Ducos J, Gomollon F. [Helicobacter pylori eradication in patients with peptic ulcer after two treatment failures: a prospective culture-guided study]. Gastroenterol Hepatol 2002; 25: 438-442

Kim JJ, Kim JG, Kwon DH. Mixed-infection of antibiotic susceptible and resistant Helicobacter pylori isolates in a single patient and underestimation of antimicrobial susceptibility testing. Helicobacter 2003; 8: 202-206

Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. Drugs 2003; 63: 2769-2802

Matsuzaki K, Koyama H, Chiba A, Omika K, Harada S, Sato Y, Hasegawa M, Kobayashi I, Kaneko A, Sasaki J. [In vitro activities of levofloxacin and other antibiotics against fresh clinical isolates]. Jpn J Antibioll 1999; 52: 571-584

Sánchez JE, Saenz NG, Rincón MR, Martín IT, Sánchez EG, Martinez M. Susceptibility of Helicobacter pylori to mupirocin, oxazolidinones, quinupristin/dalfopristin and new quinolones. J Antimicrob Chemother 2000; 46: 283-285

Tanaka M, Isogai E, Isogai H, Hayashi S, Hirose K, Kimura K, Sugiyama T, Sato K. Synergic effect of quinolone antibacterial agents and proton pump inhibitors on Helicobacter pylori. J Antimicrob Chemother 2002; 49: 1039-1040

Best LM, Haldane DJ, Bezanson GS, Veldhuyzen van Zanten SJ. Helicobacter pylori: primary susceptibility to clarithromycin in vitro in Nova Scotia. Can J Gastroenterol 1997; 11: 298-300

Cabrita J, Oloastro M, Matos R, Manhente A, Cabral J, Barros R, Lopes Al, Ramalho P, Neves BC, Guerreiro AS. Features and trends in Helicobacter pylori antibiotic resistance in Lisbon area, Portugal (1998-1999). J Antimicrob Chemother 2000; 46: 1029-1031

Gatta L, Zullo A, Perna F, Ricci C, De Francesco V, Tampieri A, Bernabucci V, Cavina M, Hassan C, Ierardi E, Morini S, Vaira D. A 10-day levofloxacin-based triple therapy in patients who have failed two eradication courses. Aliment Pharmacol Ther 2005; 22: 45-49

Zullo A, Hassan C, De Francesco V, Lorenzetti R, Marignani M, Angeloletti S, Ierardi E, Morini S. A third-line levofloxacin-based rescue therapy for Helicobacter pylori eradication. Dig Liver Dis 2003; 35: 232-236

Zullo A, Hassan C, Lorenzetti R, Morini S. Helicobacter pylori eradication: do we have another ace up our sleeve? Dig Liver Dis 2001; 33: 805-806

Gisbert JP, Castro-Fernández M, Bermejo F, Pérez-Aisa A, Ducons J, Fernández-Bermejo M, Bory F, Cosme A, Benito LM, López-Rivas L, Lamas E, Fabón M, Olivares D. Third-line rescue therapy with levofloxacin after two H. pylori treatment failures. J Antimicrob Chemother 2006; 101: 243-247

Coelho LG, Moretsohn LD, Vieira WL, Gallo MA, Passos MC, Cindr JM, Cerqueira MC, Vitelli L, Ribeiro ML, Mendonça S, Pedrazzoli-Júnior J, Castro LP. New once-daily, highly effective rescue therapy triple after multiple Helicobacter pylori treatment failures: a pilot study. Aliment Pharmacol Ther 2005; 21: 783-787

Heep M, Beck D, Bayerdörffer E, Lehnh R, Rifampin and rifabutin resistance mechanism in Helicobacter pylori. Antimicrob Agents Chemother 1999; 43: 1497-1499

Brogden RN, Fitzon A. Rifabutin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1994; 47: 983-1009

Rossi G. [An update on the antibiotic therapy of tuberculosis]. Recenti Prog Med 1999; 90: 241-243

Qasim A, Sebastian S, Thornton O, Dobson M, McLaughlin R, Buckley M, O’Connor H, O’Morain C. Rifabutin- and furazolidone-based Helicobacter pylori eradication therapies after failure of standard first- and second-line eradication attempts in dyspepsia patients. Aliment Pharmacol Ther 2005; 21: 91-96

Borody TJ, Pang G, Wettstein AR, Clancy R, Herdman K, Surace R, Llorente R, Ng C. Efficacy and safety of rifabutin-containing ‘rescue therapy’ for resistant Helicobacter pylori infection. Aliment Pharmacol Ther 2006; 23: 481-488

Allamirano A, Bondani A. Adverse reactions to furazolidone and other drugs. A comparative review. Scand J Gastroenterol Suppl 1989; 169: 70-80
Howden A, Boswell P, Tovey F. *In vitro* sensitivity of *Campylobacter pyloridis* to furazolidone. *Lancet* 1986; 2: 1035

Segura AM, Gutiérrez O, Otero W, Angel A, Genta RM, Graham DY. Furazolidone, amoxicillin, bismuth triple therapy for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1997; 11: 529-532

Haas CE, Nix DE, Schentag JJ. *In vitro* selection of resistant *Helicobacter pylori*. *Antimicrob Agents Chemother* 1990; 34: 1637-1641

Kwon DH, Lee M, Kim JJ, Kim JG, El-Zaatari FA, Osato MS, Graham DY. Furazolidone- and nitrofurantoin-resistant *Helicobacter pylori*: prevalence and role of genes involved in metronidazole resistance. *Antimicrob Agents Chemother* 2001; 45: 306-308

Treiber G, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for *Helicobacter pylori* eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med* 2002; 162: 153-160

Xiao SD, Liu WZ, Hu PJ, Ouyang Q, Wang JL, Zhou LY, Cheng NN. A multicentre study on eradication of *Helicobacter pylori* using four 1-week triple therapies in China. *Aliment Pharmacol Ther* 2001; 15: 81-86

Ahuja V, Bhatia V, Dattagupta S, Raizada A, Sharma MP. Efficacy and tolerability of rifampicin-based rescue therapy for *Helicobacter pylori* eradication failure in peptic ulcer disease. *Dig Dis Sci* 2005; 50: 630-633

Sanaka M, Kuyama Y, Yamanaka M, Iwasaki M. Decrease in serum concentrations of *Helicobacter pylori* IgG antibodies during antituberculosis therapy: the possible eradication by rifampicin and streptomycin. *Am J Gastroenterol* 1999; 94: 1983-1984

Pilotta A, Franceschi M, Rassu M, Furlan F, Scagnelli M. *In vitro* activity of rifabutin against strains of *Helicobacter pylori* resistant to metronidazole and clarithromycin. *Am J Gastroenterol* 2000; 95: 833-854

Fujimura S, Kato S, Kawamura T, Watanabe A. *In vitro* activity of rifampicin against *Helicobacter pylori* isolated from children and adults. *J Antimicrob Chemother* 2002; 49: 541-543

Dore MP, Marras L, Maragkoudakis E, Nieddu S, Manca A, Graham DY, Realdi G. Salvage therapy after two or more prior *Helicobacter pylori* treatment failures: the super salvage regimen. *Helicobacter* 2003; 8: 307-309

Tucci A, Polli L, Caletti G. Treatment of the “ineradicable” *Helicobacter pylori* infection. *Am J Gastroenterol* 1999; 94: 1713-1715

S- Editor Wang J  L- Editor Wang XL  E- Editor Zhang Y

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