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BRIEF ARTICLE

Efficacy of a therapeutic strategy for eradication of *Helicobacter pylori* infection

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Abstract

AIM: To determine the efficacy of our therapeutic strategy for *Helicobacter pylori* (*H. pylori*) eradication and to identify predictive factors for successful eradication.

METHODS: From April 2006 to June 2010, we retrospectively assessed 2428 consecutive patients (1025 men, 1403 women; mean age 55 years, age range 18-92 years) with gastric histology positive for *H. pylori* infection referred to our unit for 13-C urea breath test (UBT), after first-line therapy with proton pump inhibitor (PPI) *b.i.d.* + amoxicillin 1 g *b.i.d.* + clarithromycin 500 mg *b.i.d.* for 7 d. Patients who were still positive to UBT were recommended a second-line therapy (PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + tinidazole 500 mg *b.i.d.* for 14 d). Third choice treatment was empirical with PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + levofloxacin 250 mg *b.i.d.* for 14 d.

RESULTS: Out of 614 patients, still *H. pylori*-positive after first-line therapy, only 326 and 19 patients respectively rechecked their *H. pylori* status by UBT after the suggested second and third-line regimens. "Per protocol" eradication rates for first, second and third-line therapy were 74.7% (95% CI: 72.7%-76.4%), 85.3% (95% CI: 81.1%-89.1%) and 89.5% (95% CI: 74.9%-103%) respectively. The overall percentage of patients with *H. pylori* eradicated after two treatments was 97.8% (95% CI: 97.1%-98.4%), *vs* 99.9% (95% CI: 99.8%-100%) after three treatments. The study found that eradication therapy was most effective in patients with ulcer disease ($P < 0.05$, $P = 0.028$), especially in those with duodenal ulcer. Smoking habits did not significantly affect the eradication rate.

CONCLUSION: First-line therapy with amoxicillin and clarithromycin produces an *H. pylori* eradication rate comparable or superior to other studies and second-line treatment can still be triple therapy with amoxicillin and tinidazole.

Key words: *Helicobacter pylori*; Eradication treatment; Rescue therapy; Eradication rate; Triple therapy; First-line therapy; Second-line therapy

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a bacterium that colonizes the stomach of about half the world's population and is considered the main cause of peptic ulcer[1,2] and mucosa-associated lymphoid tissue lymphoma[3,4]; furthermore it is an important risk factor for gastric adenocarcinoma[5,6] and also an associated factor for many gastric and non-gastric diseases[7]. *H. pylori* eradication is strongly recommended[8,9] in many clinical situations[10]. Different treatments have been proposed as effective[11,12] and meta-analyses are available comparing their results[13-15]. Prevalence of antibiotic resistance was found to be an important factor in the choice of the preferred regimen[16-19].

In particular, clarithromycin resistance is the strongest predictor of treatment failure[20,21]: in fact the eradication rate decreases below the recommended 80% threshold, when the prevalence of clarithromycin resistance reaches 15%-20%. On the other hand *in vitro* resistance to metronidazole may not accurately reflect resistance *in vivo*, and does not significantly affect the eradication rate[22]. In Northern Italy primary resistance to clarithromycin and metronidazole is reported to be 16.6% and 25.1% respectively[23].

The American College of Gastroenterology guidelines recommend first-line eradication with triple therapy consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin. The European (Maastricht Ⅲ Consensus) guidelines recommend first-line eradication with triple therapy on account of clarithromycin/metronidazole resistance. According to both guidelines, second-line therapy should be a bismuth-based quadruple treatment while third-line treatment should be based on antimicrobial susceptibility testing[24].

Our Trust policy is to suggest an antibiotic regimen to outpatients referred to our unit for 13-C urea breath test (UBT), or esophagogastroduodenoscopy (EGD) with assessment of the *H. pylori* status and found to be *H. pylori*-positive. We do not usually prescribe a bismuth-based second-line therapy and we do not base the choice of the third-line therapy on antimicrobial susceptibility testing. The aim of the present study is to determine the efficacy of this strategy for *H. pylori* eradication.

MATERIALS AND METHODS

Setting

Our UBT outpatient clinic is the only existing one in the Health District of Reggio Emilia, serving about 500 000 people in North Italy. EGD is performed in six different public hospitals and in several private practices.

Patients

Our policy was to suggest an eradication therapy to the general practitioners of outpatients found to be *H. pylori*-positive after EGD or 13-C UBT performed at our Unit. Before examination (EGD or UBT), a brief medical history was obtained, including reason for investigation, allergy, past and ongoing treatments, and smoking habits. In patients undergoing EGD, if *H. pylori* status assessment was indicated, it was obtained by histology, according to the Sydney classification.

UBT was performed using an isotope ratio mass spectrometer (Breathmat, Bremen). A delta value > 3.5 over baseline was considered a positive result. All patients *H. pylori*-positive after EGD or UBT received a letter for their general practitioner reporting the result of the test, the recommended antibiotic regimen and the suggestion to further submit the patient to our UBT outpatient clinic to confirm *H. pylori* eradication, at least 8 wk after the end of treatment. Standard first-, second- and third-line antibiotic regimens are shown in Table 1. Alternative antibiotic regimens were suggested to patients with known allergy to a particular antibiotic. Each patient also received a form, where she/he was instructed to mark consumption of the drugs and to record any suspected adverse effect. Compliance with the proposed treatment and adverse effects were checked, on the occasion of the resubmission of the patient. Nevertheless no attempt was made to contact patients, who did not return to our UBT outpatient clinic and no information about them was actively sought. Data about patients and treatments were prospectively collected in a purpose-built database.

In the present observational retrospective study, we included 2428 outpatients (Table 2 shows their characteristics), who underwent UBT from April 2006 to June 2010, after positive histological assessment of *H. pylori* status and after first-line eradication therapy with PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + clarithromycin 500 mg *b.i.d.* for 7 d.

Ethics and endpoints

The study was conducted according to the declaration of Helsinki. All patients consented to UBT. Although patients were informed about the purpose and potential side effects of the suggested treatments, a formal consensus about therapy was not obtained, because the therapy was always finally prescribed by the general practitioner after further evaluation and discussion with the patient. Furthermore none of the medications were prescribed as part of a clinical trial and therefore there was no need for study approval by the ethics committee at our hospital. The primary endpoints of the study were eradication rates of the suggested antibiotic regimens, as calculated per protocol in patients, who were referred to our UBT outpatient clinic after each line of treatment. Secondary endpoints were: (1) percentage of patients, still *H. pylori*-positive after first-line therapy, who achieved

Table 1 Antibiotic regimens suggested by our unit and eradication rates per protocol

	Patients	*H. pylori* eradicated and eradication rate per protocol (95% CI)	Patients treated and cumulative effect (95% CI)
First-line: PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + clarithromycin 500 mg *b.i.d.* for 7 d	2428	1814 74.7 (72.7-76.4)	
Second-line: PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + tinidazole 500 mg *b.i.d.* for 14 d	326	278 85.3 (81.1-89.1)	2140 97.8 (97.1-98.4)
Third-line: PPI *b.i.d.* + amoxicillin 1 g *b.i.d.* + levofloxacin 250 mg *b.i.d.* for 14 d	19	17 89.5 (74.9-103)	2111 99.9 (99.8-100)

PPI: Proton pump inhibitor; b.i.d.: Twice daily; *H. pylori*: *Helicobacter pylori*. Standard dosages for PPIs are as follows: lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg.

Table 2 Characteristics of patients who underwent urea breath test after treatment (%)

Patients characteristics	UBT after first-line therapy (2428 patients)	UBT after second-line therapy (326 patients)	UBT after third-line therapy (19 patients)
Women	1403 (58)	202 (62)	13 (68)
Men	1025 (42)	124 (38)	6 (32)
Mean age (range), yr	55 (18-92)	54 (21-86)	53 (27-80)
Peptic ulcer disease	202 (8.2)[1]	23 (7.1)	0
Previous gastric surgery and/or neoplasm	6 (0.2)[2]	3 (0.9)	0
Smokers	424/1082 (43.8)	59/287 (20.6)	3/17 (7.6)

[1]172 and 23 patients were found to be affected respectively by duodenal and gastric ulcer. 7 patients were affected by both gastric and duodenal ulcer; [2]1 patient was affected by low-grade mucosa-associated lymphoid tissue. Among the patients with a history of previous gastric surgery, 1 patient had undergone surgery for cancer, the others for peptic ulcer disease. UBT: Urea breath test.

H. pylori eradication, proved by UBT, at the end of study; and (2) factors predictive of successful eradication.

Statistical analysis

The data was analysed with SPSS v.18.0 (Chicago, Illinois United States). The significance level is 0.05. The data is summarized by the primary measures of central tendency and dispersion, as well as with frequencies and percentages with 95% CI. Pearson's Chi square and Fisher's exact test were used to compare frequencies, where appropriate.

RESULTS

The study flow chart is shown in Figure 1. Six hundred and fourteen patients (25.3%) were found to be *H. pylori*-positive to UBT, after the first-line antibiotic regimen.

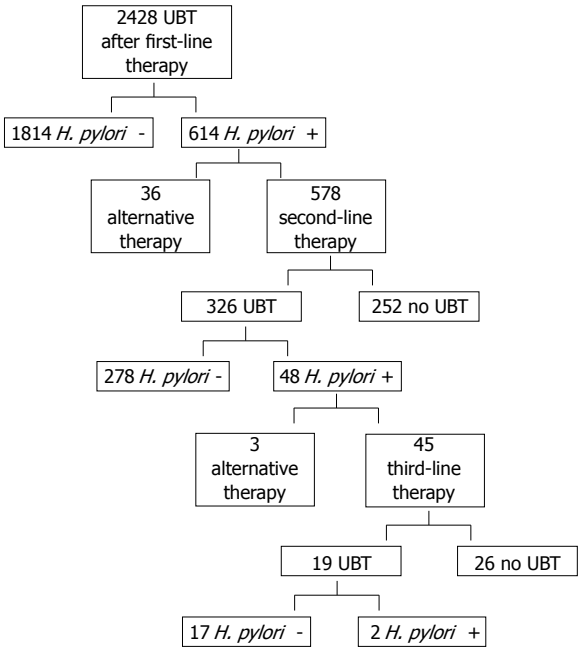

Figure 1 Flow chart of the study. UBT: Urea breath test; *H. pylori*: *Helicobacter pylori*.

Out of these patients, 326 (53.1%) were referred again to our unit to check eradication after second-line standard therapy. Out of the 48 still *H. pylori*-positive after second-line therapy, only 19 underwent UBT (39.6%).

An antibiotic regimen alternative to the second or third-line standard therapy was suggested by us, or by their general practitioner, to 40 patients (6.5%). Among the patients, who were referred to us for UBT, a small number reported a non-complete compliance with the received standard antibiotic regimen, because of side effects: this was the case in 13 patients (0.5%, 11 tested *H. pylori*-negative and 2 positive) during first-line therapy and in 9 patients (2.7%, all eradicated) during second-line therapy. Three out of 21 reported a previously unknown allergy to penicillin; all other side effects were minor (diarrhea, headache, metallic taste).

Eradication rates of the antibiotic regimen, as calculated in patients who subsequently checked *H. pylori* status by UBT, are reported in Table 1. The two patients who were still positive after the third treatment were advised to take bismuth-based quadruple therapy for 14 d and *H. pylori* was finally eradicated.

As shown in Table 3, peptic ulcer disease, but not smoking habits, was found to be predictive of successful eradication during first-line therapy. Stratifying patients according to the number of cigarettes smoked per day (data not shown), the eradication rate decreased proportionally to the increase in the number of cigarettes, though statistical significance was only borderline ($P = 0.056$).

Table 4 compares that characteristics of the patients who rechecked (297, 48.4%) or not (278) their *H. pylori* status, until the achievement of an UBT-proved *H. pylori*-negative status, or after the completion of third-line therapy, whichever came first.

Table 3 Factors investigated as potentially predictive of successful eradication (%)

Risk factor	Eradication rate	
	First-line antibiotic regimen	Second-line antibiotic regimen
Women	1029/1403 (73.3)	172/202 (85.1)
Men	785/1025 (76.6)	106/124 (85.5)
Peptic ulcer disease	167/206 (81.1)[1]	22/24 (91.7)
Non-ulcer disease	1647/2222 (74.1)[1]	54/71 (76.1)
Smokers	302/424 (71.2)	50/57 (94.7)
Non-smokers	1346/1 778 (75.7)	192/230 (83.5)

[1]Difference of frequencies: 6.9% (95% CI: 1%-12.8%, $P < 0.05$). If patients affected by duodenal ulcers is compared with patients with non-ulcer disease, the difference is 8.3% (95% CI: 2.3%-14.4%, $P < 0.05$).

Table 4 Characteristics of patients who rechecked or not their *Helicobacter pylori* status (%)

Patients characteristics	Rechecked their *H. pylori* status[1] (297 patients)	No recheck of their *H. pylori* status (278 patients)
Women/men	185 (62)/112 (38)	170 (61)/108 (39)
Mean age (range), yr	55 (21-86)	50 (20-92)
Peptic ulcer disease	21 (7)	17 (6)
Previous gastric surgery and/or neoplasm	2 (0.6)	1 (0.3)
Smokers	53 (20)	69 (27)

[1]Patient who rechecked their *Helicobacter pylori* (*H. pylori*) status, until the achievement of an urea breath test-proved *H. pylori*-status, or after the completion of the third-line therapy, whichever came first. Patients treated with alternative second and third-line antibiotic regimens are excluded.

DISCUSSION

In our study, patients were treated with first-line PPI-amoxicillin-clarithromycin therapy for 7 d only. A recent meta-analysis showed a minimal advantage of longer treatment[25].

All the different PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are shown to be equally effective in combination with antibiotic therapy[26] and higher H2 receptor antagonists (ranitidine)[27]: therefore we left the choice of PPI to the general practitioner. We also advised general practitioners to prescribe the double dose of PPI, because it has proved more effective in a recent meta-analysis[28].

The eradication rate after first therapy was 74.7%. This rate is comparable to the 76% achieved by the same regimen (for 10 d of treatment) in a recent study from Greece[29] and it is higher than the 56% found in a study with 14 d of PPI-clarithromycin-metronidazole[30,31].

The European and American guidelines recommend a bismuth-based quadruple treatment as second-line therapy; according to Maastricht guidelines, a PPI-amoxicillin-metronidazole therapy could be used if bismuth is not available.

In Italy bismuth salts are often available, but we preferred to recommend PPI-amoxicillin-tinidazole as second-line therapy, because the bismuth-based quadruple regimen is associated with a relatively high incidence of side effects and a worse compliance than the triple regimen; although a recent meta-analysis shows no statistically significant differences[32]. The PPI-amoxicillin-metronidazole regimen was reported to be effective as second-line therapy to achieve eradication rates of 89% and 64% for metronidazole susceptible and resistant strains, respectively[33]. In our study, this second-line regimen obtained an eradication rate of 85.3%. These results are superior to data reported by others after unsuccessful first-line treatment for the same regimen, for the bismuth-based quadruple combination[34] and also for a levofloxacin-based therapy[35].

The Consensus Conference recommended third-line rescue treatment based on antimicrobial susceptibility testing. We preferred not to perform susceptibility testing, choosing an empirical triple therapy with levofloxacin.

Two meta-analyses have suggested that levofloxacin-based rescue regimen is more effective and safer than quadruple therapy[35,36]. Levofloxacin resistance develops rapidly and it is one of the most effective antibiotics in the treatment of respiratory tract infections. For these reasons, we reserved its use for third-line therapy. In our study, levofloxacin-based third-line therapy achieved an eradication rate of 89.5%. Although we observed these excellent results in a small group of patients, our findings are consistent with other experiences[29,36] and support the use of a levofloxacin-based regimen as empirical third-line therapy of *H. pylori* infection.

The overall eradication rate after two and three treatments, respectively, is proved to be 97.8% and 99.9%. These results confirm the data already published in literature (Table 5).

During first-line treatment, the efficacy of therapy in patients with peptic ulcer disease was higher (81.1%) than in patients with non-ulcer disease (74.1%). This finding is in agreement with others experiences[37-39] and could be explained by a larger number of antibiotic-resistant *H. pylori* strains in non-ulcer disease patients.

The study also assessed the influence of smoking on treatment: the eradication rate was moderately higher in non-smokers (75.7% *vs* 71.2%). Recent studies demonstrated that smoking affects the eradication rate[40,41]; in our larger report the trend is negative but not yet statistically significant.

It should be noted that our study is not a clinical trial, but a retrospective revision of our practice. This may explain its major limitation; that is the high number of patients (45.3%), who did not have their *H. pylori* status rechecked after failure of first-line therapy. We do not know whether these patients did not undergo any further treatment, or they stopped therapy because of adverse effects, or decided not to repeat UBT after completion of the suggested regimen. Nevertheless the regimens suggested in our studies are usually relatively well tolerated and we do not believe that the high percentage of our patients lost at follow up was due to adverse effects. In the setting of an open-access UBT facility,

Table 5 Studies reporting eradication rates and cumulative effect of different therapeutic strategies

	% Eradication rate (number of patients)				
	First-line	Second-line	Third-line	Cumulative effect (Ⅱ to Ⅲ line)	Antimicrobial susceptibility testing before third-line
Gasbarrini *et al*[41] 2000	86 (2413)	82 (329)	77 (39)	99	Yes
Beales[42] 2001	73 (469)	70-73 (66)	65 (20)	94-98	Yes
Qasim *et al*[40] 2005	77 (3280)	56 (270)	38 (28)		
Gisbert *et al*[32] 2008	70 (500)	74 (343)	76 (136)	99.5	No
Rokkas *et al*[28] 2009	76 (540)	73 (120)	70 (30)	98	No
Present study	75 (2428)[1,2]	85 (326)	89 (19)	97.8-99.9	No

[1]172 and 23 patients were found to be affected respectively by duodenal and gastric ulcer. 7 patients were affected by both gastric and duodenal ulcer; [2]1 patient was affected by low-grade mucosa-associated lymphoid tissue. Among the patients with a history of previous gastric surgery, 1 patient had undergone surgery for cancer, the others for peptic ulcer disease. UBT: Urea breath test.

Qasim *et al*[40] reported that only 25% of their patients *H. pylori*-positive after first-line therapy, were proved to have eradication of *H. pylori* after second-line therapy or have rechecked their *H. pylori* status by UBT after third-line therapy. A high compliance with repeated courses of therapy is reported in prospective clinical trials[29,41], but it is conceivable that it may be difficult to replicate these good results in common clinical practice. Data are lacking about strategies useful to reinforce compliance with *H. pylori* eradication therapy in this setting. It should be noted that a high percentage of our patients did not achieve a proved *H. pylori*-negative status, despite the fact that our policy avoided invasive testing (EGD) to obtain antimicrobial susceptibility testing and regimens requiring assumption of a lot of pills, such as bismuth-based quadruple therapy.

We believe that efforts to introduce new effective antibiotic regimens, should parallel not only the emergence of new resistance, but also the efforts to target appropriate antibiotic regimens to the majority of patients requiring *H. pylori* eradication therapy. Our policy to suggest to the general practitioner an antibiotic regimen for each patient found to be *H. pylori*-positive may be criticized and it could be not generally applicable. Nevertheless different models of collaboration between gastroenterologists and general practitioners should be tested to improve effectiveness of *H. pylori* infection therapy in current practice.

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COMMENTS

Background

Helicobacter pylori (*H. pylori*) is considered an important risk factor for many gastric and non-gastric diseases. Different treatments have been proposed as effective for *H. pylori* eradication and meta-analyses are available comparing their results. Prevalence of antibiotic resistance was found to be an important factor in the choice of the preferred regimen.

Research frontiers

The European (Maastricht Ⅲ Consensus) and American (American College of Gastroenterology) guidelines recommend a therapeutic strategy for *H. pylori* eradication with clarithromycin and metronidazole for 7-14 d or amoxicillin and clarithromycin for 10-14 d as first-line therapy. They also suggest bismuth-based quadruple second-line therapy and third-line therapy based on antimicrobial susceptibility tests.

Innovations and breakthroughs

In the present study, about 75% of patients were cured with first-line therapy (proton pump inhibitor + amoxicillin + clarithromycin), 97.8% after the second-line therapy (proton pump inhibitor + amoxicillin + tinidazole) and 99.9% after the third-line therapy (proton pump inhibitor + amoxicillin + levofloxacin). No statistical differences in eradication rates in smokers and non-smokers were found, even if there is a negative trend. Patients with ulcer disease had an eradication rate superior to that of patients with non-ulcer disease. This study was conducted in an open access setting and showed only about half of the patients still *H. pylori*-positive after first-line therapy were finally proved to have successful eradication of *H. pylori*.

Applications

The high eradication rates of this study suggest that a regimen simpler than quadruple drug therapy may be preferred as second-line therapy at least in some patients and in some regions; furthermore the antimicrobial susceptibility test (and the esophagogastroduodenoscopy involved) would not be necessary after two failed treatments. The fact that nearly half of our patients still *H. pylori*-positive after first-line therapy did not reach a urea breath test (UBT)-proved *H. pylori*-negative status, despite the use of effective antibiotic regimens, suggests that strategies should be devised and implemented to improve the access of patients to appropriate therapies and to strengthen the compliance of patients to these treatments.

Terminology

H. pylori is a bacterium that colonizes the stomach of about half the world's population and is considered the main cause of peptic ulcer and mucosa-associated lymphoid tissue lymphoma; furthermore it is an important risk factor for gastric adenocarcinoma and also an associated factor for many gastric and non-gastric diseases. *H. pylori* infection can be detected by esophagogastroduodenoscopy (a biopsy is taken during endoscopy and it is sent to the hospital laboratory to be examined for histology) or UBT. In the 13-C UBT, person fast for about 6 h. A baseline breath sample is collected (person blow into a test tube), then person drink a solution of Carbon-13-urea in water. A second breath sample is taken after 30 min and analyzed by a mass spectrometer. If *H. pylori* is present in the stomach the Carbon-13-urea will be broken down and Carbon-13 will appear in the breath.

Peer review

These authors conducted a retrospective epidemiology study on over 2428 patients who were positive for *H. pylori* looking to determine the efficacy of a therapeutic strategy for *H. pylori* eradication based on first-line therapy with amoxicillin and clarithromycin and second-line treatment with amoxicillin and tinidazole. The authors found that the eradication therapy was most effective in patients with ulcer disease, especially with duodenal ulcer during first-line therapy.

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