

Helicobacter pylori Eradication Therapy Success Regarding Different Treatment Period Based on Clarithromycin or Metronidazole Triple-Therapy Regimens

Tajana Filipec Kanizaj,* Miroslava Katicic,* Bruno Skurla,* Mirjana Ticak,* Vanda Plecko† and Smilja Kalenic†

*Internal Medicine, University Hospital Merkur, Zagreb, Croatia, †Department of Microbiology and Parasitology, Medical School, University of Zagreb, Zagreb, Croatia

Keywords

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Reprint requests to: Tajana Filipec Kanizaj, Licka 33, 10000 Zagreb, Croatia.
E-mail: tajana_filipec@yahoo.com

Abstract

Background: The study compares the eradication success of standard first-line triple therapies of different durations (7, 10, and 14 days).

Materials and Methods: A total of 592 naive *Helicobacter pylori*-positive patients were randomized to receive pantoprazole, amoxicillin, and clarithromycin or metronidazole for 14 days (PAC14 or PAM14), 10 days (PAC10 or PAM10), or 7 days (PAC7 or PAM7). *H. pylori* eradication was assessed by histological, microbiological, and rapid urease examination.

Results: The intention-to-treat (ITT) and per-protocol (PP) analyses have shown no overall statistically significant differences between the eradication success of PACI and PAM treatment groups (ITT $p = .308$, PP $p = .167$). Longer treatment duration has yielded statistically significant increase in eradication success for clarithromycin (ITT $p = .004$; PP $p = .004$) and metronidazole (ITT $p = .010$; PP $p = .034$) based regimens. Namely, PAC10, PAC14, and PAM14 protocols resulted in eradication success exceeding 80% in ITT and 90% in PP analysis. Primary resistance to clarithromycin and metronidazole equals 8.2% and 32.9%, respectively. Prolonging the metronidazole-based treatment duration in patients with resistant strains resulted in statistically significant higher eradication success.

Conclusions: For all antimicrobial combinations, 14 days protocols have led to a significant increase of *H. pylori* eradication success when compared to 10 and 7 days, respectively. Prolonging the treatment duration can overcome the negative effect of metronidazole resistance. Only PAM14, PAC10 protocols achieved ITT success > 80% and should be recommended as the first line eradication treatment in Croatia.

Helicobacter pylori is a major gastroduodenal pathogen involved in the development of many gastroduodenal diseases including gastric cancer. Since its discovery in the 1980s, many different treatment regimens have been used in order to effectively eradicate *H. pylori* infection. In the Maastricht III Consensus Guidelines, authors agreed that effective eradication treatment should be successful in more than 80% of intention-to-treat (ITT) and 90% per-protocol (PP) treated patients [1]. As in many other countries, standard first-line treatment in Croatia is based on clarithromycin, amoxicillin, or metronidazole combined with proton-pump inhibitor (PPI). These can be applied to regions where primary resistances of clarithromycin or metronidazole are lower than 15–20% or 40%, respectively. Bacterial resistance to amoxicillin is low (i.e. < 1%)

in most countries. However, clarithromycin resistance varies significantly. It ranges from close to zero up to 25% and has significant impact on eradication success [2,3]. Resistance to metronidazole is much more common than to macrolides, but it exhibits lower impact on eradication success [2].

With varying antimicrobial resistance and declining eradication successes of the standard 7-day protocols, it is essential to constantly evaluate new treatment protocols with longer durations [4]. In previous studies conflicting results of treatment duration are reported and consensus about this issue is still lacking [5,6]. In the near future, longer treatments based solely on clarithromycin or metronidazole may become more popular as first-line therapies to compensate the growing antimicrobial resistance.

The primary objective of this study was to compare the efficacy of two first-line eradication protocols based on pantoprazole, amoxicillin plus clarithromycin, or metronidazole of different (7, 10, and 14 days) treatment durations. The secondary objective was to determine the impact of primary antimicrobial resistance and endoscopic findings related to eradication outcome.

Methods

Patients

From January 2002 to September 2005, 816 patients were screened. Due to dyspeptic complaints, all of the patients underwent an upper gastrointestinal endoscopy in the Croatian Referral Centre for *H. pylori* investigation (University Hospital Merkur, Zagreb). Before entering the study, all patients provided written informed consent. The research protocol was approved by the Clinical Research Ethical Committee of the University Hospital Merkur in Zagreb. All procedures were in accordance with the Declaration of Helsinki (1975; revision 1983).

On screening, upper gastrointestinal endoscopy was performed. Eight bioptic samples (four for histology, two for microbiology and two for rapid urease test) were obtained. *H. pylori*-positive status was proven by: histology (96% patients positive), microbiology (79% positive), and/or rapid urease (98% positive) examination. Patients were considered *H. pylori* positive if more than one of applied methods was positive.

Histology

Two biopsy samples were taken from antrum and two from the body of gastric mucosa. They were embedded in paraffin wax and stained with hematoxylin and eosin, modified 2% Giemsa stain and alcian blue–periodic acid-Schiff. Histologic sections of the antrum and body tissue were analyzed by single expert pathologist and graded for: *H. pylori* density, intensity of polymorphonuclear cells infiltrate (activity), intensity of mononuclear cells infiltrates (inflammation), atrophy, and intestinal metaplasia, as stipulated by the Updated Sydney System (Houston) [7]. Parameters were graded as none (0), mild (1), moderate (2), or marked (3). Patients were considered *H. pylori* positive if at least one biopsy sample was positive for bacterial presence.

Microbiology

Two biopsy samples were taken (from the antrum and body of gastric mucosa) and transferred to microbiology laboratory in tioglicol media. Bacteria isolation was

performed in microaerophilic atmosphere on Skirrow and Mueller-Hinton agar under 37 °C. All colonies were identified macroscopically (on 3rd, 5th, and 7th day), microscopically and by catalase, oxidase, and urease reaction. Metronidazole and clarithromycin resistances were proven by using the dilution agar method. The antimicrobial resistance to clarithromycin and metronidazole was considered positive if the minimal inhibitory concentration (MIC) is > 1 mg/L and > 16 mg/L, respectively.

Rapid Urease Test

Two biopsy samples were taken (from the antrum and body of gastric mucosa). A rapid urease test (CLO test®, Delta West, WA, Australia) was performed according to manufacturer's instructions and inspected for color change within 24 hours.

A total of 592 patients were eligible for the study. All were older than 18 years with positive *H. pylori*. The exclusion criteria were: previous eradication treatment, any antimicrobial treatment 2 months preceding the study, concomitant medication with: bismuth preparations, PPIs, H₂-receptor antagonists or non-steroidal anti-inflammatory drugs, other serious illnesses, sensitivity to any investigate medications, history of previous gastric surgery, and pregnancy. No concomitant use of antiseptics and antimicrobials was allowed during the study period.

According to the endoscopic findings, patients were divided into three groups: normal findings (non-ulcer dyspepsia; N), duodenal ulcers (including scars; D), and gastric ulcers (including scars; V).

Patients received triple eradication treatment consisting of pantoprazole (2 × 40 mg) + amoxicillin (2 × 1000 mg) + metronidazole (2 × 500 mg) or clarithromycin (2 × 500 mg) for 14, 10, or 7 days followed by 14 days of pantoprazole (40 mg once daily) maintenance treatment. Prior to the study, sealed envelopes containing different treatment protocols have been produced, numbered, and ordered using a random number generator. Personnel not involved in the trial assigned the subsequent envelopes to patient according to order of their referral to examination. The ratio for different treatment duration protocols was 2 : 2 : 1 (7, 10, and 14 days). The main reason for such decision was expectance of more adverse events as well as higher costs generated by the 14 days treatment. According to received eradication protocols, patients were additionally divided into six groups: pantoprazole + amoxicillin + metronidazole 14 days (PAM14), 10 days (PAM10), 7 days (PAM7) or pantoprazole + amoxicillin + clarithromycin 14 days (PAC14), 10 days (PAC10), and 7 days (PAC17).

The treatment success has been assessed 4–6 weeks after ending each treatment by personnel who did not know

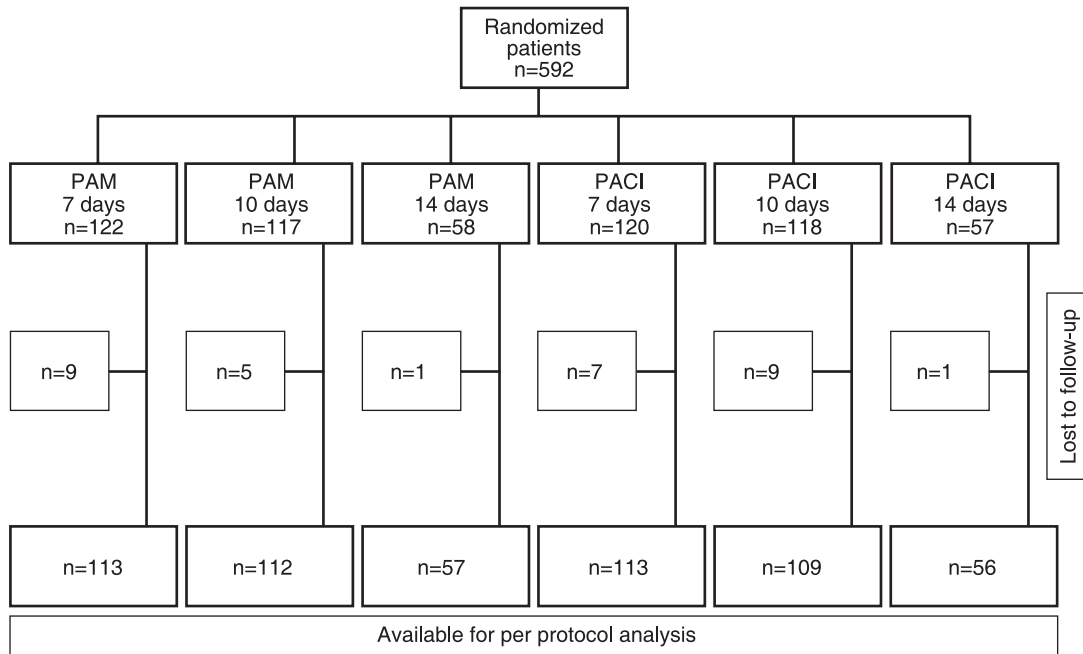


Figure 1 A flow diagram presenting entries and withdrawals from the study. PAM, pantoprazole + amoxicillin + metronidazole; PACI, pantoprazole + amoxicillin + clarithromycin.

which protocol was used. A second upper gastrointestinal endoscopy examination was performed in order to obtain biopsy samples for histologic, microbiologic, and rapid urease test. Patient compliance and adverse events have been evaluated through structured clinical interview.

Statistics

Analysis of baseline characteristics and eradication success between different treatment protocols was performed using the chi-squared test. The *t*-test was used to analyze the age distribution between the different patients groups. Logistic regression analysis was performed to determine if age, gender, antimicrobial resistance, endoscopic finding and treatment duration are independent predictors of eradication success. Data were analyzed according to ITT and PP criteria. The ITT analysis included all patients randomized to a treatment group, whereas in the PP analysis patients lost during follow-up or showing low compliance were excluded. SPSS 11.0 software was used in the statistical analysis.

Results

Study Population

Of 592 enrolled patients, 560 (94.6%) completed the study. Out of the remaining 32, 10 (1.6%) did not return for follow-up examination and 22 (3.7%) did not take

more than 90% of the prescribed medications. They were counted as failures in the ITT analysis (Fig. 1).

Two hundred ninety-seven patients received metronidazole (58 PAM14, 117 PAM10, 122 PAM7) and 295 clarithromycin (57 PACI14, 118 PACI10, 120 PACI7) based treatment protocol. All baseline characteristics were similar between the two (metronidazole and clarithromycin) treatment groups (Table 1).

Eradication treatment success for all six protocols according to ITT and PP analyses is presented in Table 2. Comparing the overall eradication rates, treatment protocols based on clarithromycin have demonstrated slightly better results (ITT 83.1%, PP 88.1%) than metronidazole (ITT 79.5%, PP 84.0%). However, this difference was not statistically significant (ITT *p* = .308; PP *p* = .167). Statistical significance was noticeable among protocols of different durations (ITT and PP *p* < .001). The same is valid for both clarithromycin (ITT *p* = .005; PP *p* = .004) and metronidazole (ITT *p* = .011; PP *p* = .034) based protocols. In the clarithromycin treatment group, the 14 days protocol has shown to be statistically significantly superior to the 10 days (ITT *p* = .052, PP *p* = .025) and 7 days (ITT *p* = .003, PP *p* = .005) protocols, respectively. The same is applicable for the metronidazole treatment group; the 14 days protocol was superior to the 10 days (ITT *p* = .029, PP *p* = .058) and 7 days (ITT *p* = .005, PP *p* = .019) protocols, respectively. There was no statistically significant difference in eradication success between 7 and 10 days based protocols.

Table 1 Patients baseline characteristics

	PAM7 (n = 122)	PAM10 (n = 117)	PAM14 (n = 58)	PACI7 (n = 120)	PACI10 (n = 118)	PACI14 (n = 57)	p
Gender (male/female)	73/49	68/49	39/19	56/64	70/48	29/28	.100
Age (year) mean ± standard deviation	54.1 ± 13.9	49.51 ± 15.7	53.74 ± 14.9	52.6 ± 12.8	51.3 ± 13.0	48.8 ± 13.3	.067
Diagnosis (V/D/N)	35/58/29	35/56/26	17/28/13	37/57/26	33/56/29	15/27/15	1
Antimicrobial resistance (R/NR)	32/65	30/63	16/31	8/88	7/83	4/40	M: .978 CI: .966

V, gastric ulcer; D, duodenal ulcer; N, normal finding; P, pantoprazole; A, amoxicillin; M, metronidazole; CI, clarithromycin; R, resistant strains; NR, non-resistant strains.

Treatment protocol	Eradication success ITT (%)	95% CI	Eradication success PP (%)	95% CI
PACI7	92/120 (76.7)	69.10–84.24	92/113 (81.4)	74.25–88.59
PACI10	98/118 (83.1)	76.28–89.82	98/109 (89.9)	84.26–95.56
PACI14	55/57 (96.5)	91.71–101.27	55/56 (98.2)	94.74–101.68
PAM7	90/122 (73.8)	65.96–81.58	90/113 (79.6)	72.23–87.07
PAM10	93/117 (79.5)	72.17–86.81	93/112 (83.0)	76.09–89.99
PAM14	54/58 (93.1)	86.58–99.62	54/57 (94.7)	88.94–100.54

Table 2 Eradication treatment success

P, pantoprazole; A, amoxicillin; M, metronidazole; CI, clarithromycin, ITT, intention-to-treat; PP, per-protocol.

Table 3 Multivariate analysis for clinical factors related to H. pylori eradication success (intention-to-treat analysis)

	Coefficient	Standard error	Odds ratio	95% CI	p
Antibiotic regimen	−0.335	0.265	0.205	0.42–1.20	.205
Therapy duration	0.396	0.170	0.019	1.06–2.07	.019
Antimicrobial resistance	−1.660	0.266	0.000	0.11–0.32	.000
Age	−0.001	0.008	0.866	0.98–1.01	.866
Gender	−0.006	0.227	0.977	0.63–1.55	.997
Endoscopic finding	−0.000	0.168	0.998	0.71–0.99	.998

According to the findings of the multiple logistic regression analysis (Table 3), independent predictors for eradication success were the difference in treatment duration (ITT $p = .019$, PP $p = .034$) and antimicrobial resistance (ITT and PP $p < .001$). Other baseline characteristics did not confirm any significant role in influencing eradication success. Overall, higher eradication success has been observed in patients with peptic ulcer disease (83%) than with non-ulcer dyspepsia (77%). However, the difference of 6% was not statistically significant (ITT $p = .109$).

Antimicrobial resistance to clarithromycin or metronidazole was evaluated depending on the treatment protocol applied. Due to difficulties with bacterial isolation, antimicrobial resistance results are missing for 125 (21.1%) of the enrolled patients (65 in clarithromycin and

60 in metronidazole group). The overall primary resistance was 8.2% to clarithromycin and 32.9% to metronidazole.

Eradication therapy success with different treatment protocols and antimicrobial resistance is presented in Table 4. Generally, patients infected with non-resistant strains had statistically significantly (ITT and PP $p < .001$) higher eradication rates than those infected with resistant strains. The same was observed in a separate analysis for clarithromycin and metronidazole (ITT and PP $p < 0.001$) treatment groups. The difference in eradication success between non-resistant and resistant strains was statistically significant in all (7, 10, and 14 days) protocols for clarithromycin and in 7 days protocol for metronidazole group, respectively (Fig. 2).

Prolongation of the treatment duration resulted in a constant increase of eradication therapy success for

Table 4 Eradication success in patients with non-resistant and resistant *H. pylori* strains (intention-to-treat analysis)

Therapy duration	Resistance	Eradication success					
		Metronidazole			Clarithromycin		
		Yes	No	<i>p</i>	Yes	No	<i>p</i>
7 days	R	14	18	.001	3	5	.008
	NR	58	7		70	18	
10 days	R	22	8	.303	4	3	.010
	NR	52	11		75	8	
14 days	R	14	2	.217	3	1	.039
	NR	30	1		39	1	

R, resistant strains; NR, non-resistant strains.

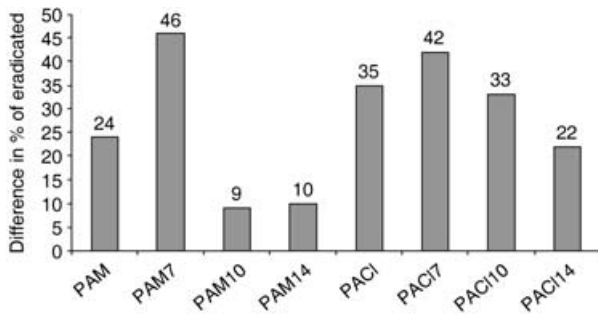


Figure 2 Difference in percentage of patients in whom *H. pylori* was eradicated with primary non-resistant and resistant strains in clarithromycin (PACI) and metronidazole (PAM) based treatment protocols of different durations (intention-to-treat analysis).

patients with non-resistant and resistant strains in both antibiotic groups (Fig. 3). Statistically significance was achieved in clarithromycin-based protocols for patients with non-resistant strains (ITT *p* = .010, PP *p* = .022), and in metronidazole for patients with resistant strains (ITT *p* = .005, PP *p* = .004).

There were no serious adverse events documented in both treatment groups. No statistically significant difference in

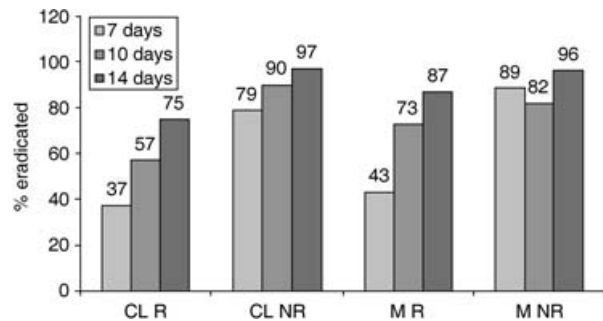


Figure 3 Percentage of patients in whom *H. pylori* was eradicated with primary non-resistant (NR) and resistant strains (R) in clarithromycin (CL) and metronidazole (M) based treatment protocols (intention-to-treat analysis).

adverse events was observed between all treatment groups (Table 5).

Compliance was acceptable in both treatment groups. Only 10 patients from the clarithromycin and eight from the metronidazole group dropped out from study due to non-compliance (less than 90% of drugs taken) which did not yield statistically significant difference in eradication rate.

Discussion

A combination of PPI with clarithromycin and amoxicillin or metronidazole is still recommended as the first-line *H. pylori* eradication treatment by Maastricht III [1] and most regional consensus statements. The exception is observed in the United States where 10 days treatment is recommended; however, even there a prospective randomized trial did not yield efficacy improvement for recommended 10 days based PACI protocol [8]. There is not a sufficient amount of representative studies available to make definitive statements about the optimal duration of treatment.

In this study, the eradication success higher than 80% in ITT and 90% in PP analysis was achieved by 14 days (ITT 96.5%, PP 98.2%) and 10 days (ITT 83.1%, PP 89.9%) PACI and 14 days (ITT 93.1%, PP 94.7%) PAM protocols.

Table 5 Percentage of adverse events in different treatment protocols

Adverse events (%)	PAM7 (n = 113)	PAM10 (n = 109)	PAM14 (n = 56)	PACI7 (n = 120)	PACI10 (n = 118)	PACI14 (n = 57)	<i>p</i>
Diarrhea	4.42	3.66	3.57	4.16	5.08	3.50	.994
Taste disturbance	7.07	7.33	10.71	4.16	5.08	7.01	.649
Nausea/Vomiting	8.84	10.91	7.14	3.33	4.23	5.26	.258
Headache	9.73	11.00	10.71	3.33	3.38	5.26	.067
Loss of appetite	2.65	2.75	3.57	2.50	2.54	1.75	.996
Abdominal pain	3.53	3.66	5.35	1.66	2.54	3.50	.837

P, pantoprazole; A, amoxicillin; M, metronidazole; Cl, clarithromycin.

For both treatment groups, the statistical significance was observed between protocols of different durations. In the clarithromycin group, according to ITT analysis, 14 days protocol showed 13.4% and 19.8% better eradication success than 7 and 10 days, respectively. In metronidazole group, observed difference is 13.4% and 19.8%, respectively. Our results are similar to some previously published where 14 days protocols showed 7–9% better eradication success than 7 days in all antimicrobial combinations [9,10]. Similarly, no difference in eradication success was observed between the 7 and 10 days protocols [8,11]. Our results are not in line with findings previously published about no possibility of improving eradication success in protocols with increased duration [5,12].

Some of the published data indicate that eradication success depends on the proportion of patients with non-ulcer dyspepsia included in the analysis [5,10]. Higher eradication therapy success is reported in patients with peptic ulcers than with non-ulcer dyspepsia [13]. In the study of Fuccio *et al.*, it was demonstrated that, opposite to ulcer patients, prolonged treatment has higher eradication success in patients with non-ulcer dyspepsia. This has not been confirmed by all authors [9], probably due to the smaller number of patients studied or the high overall eradication success, as pointed out by de Boer *et al.* [14]. Our results indicate that endoscopic finding is not an independent predictor of eradication success. Overall eradication success in patients with peptic ulcer disease was higher (83%) than with non-ulcer dyspepsia (77%), but this difference (of 6%) is not statistically significant.

The conflicting results from earlier studies may also be due to varying antimicrobial resistance as well as compliance rates within the populations studied. Based on the agar dilution method primary antimicrobial resistance is 8.2% to clarithromycin and 32.9% to metronidazole. Doore *et al.* previously published that the presence of metronidazole and clarithromycin resistance could reduce the efficacy of eradication treatment up to 33% and 55%, respectively [15]. Moreover, our results indicate considerable statistically significant reduction in the overall eradication success in patients with resistant strains in both therapeutic groups. Prolongation of treatment resulted in statistically significant improvements in eradication success for patients with resistant strains in metronidazole and non-resistant strains in clarithromycin group. It can be concluded that the major advantage of 14 days metronidazole protocol is related to the overcoming of influence of overall bacterial resistance on eradication success. In the clarithromycin group, prolonging the treatment duration did not yield statistically significant increase in eradication success in patients with resistant strains. A systematic review indicates eradication success of 0–48% for clarithromycin-resistant *H. pylori* infections in trials using standard triple

therapies [16]. No strategy supported overcoming the clarithromycin resistance. The current findings suggest that the prolonging the treatment duration to 14 days will result in the improvement of the overall eradication success. However, with constant antimicrobial resistance increase, it will not be possible to overcome antimicrobial resistance effect and each unsuccessful eradication treatment will inevitably lead to development of secondary resistant strains [17]. As a result, routine testing to primary antimicrobial resistance should become necessary in many countries.

In our study compliance was fairly good and not influencing eradication success. Prolongation in treatment duration did not result in statistically significant higher rates of adverse events for both regimens.

In agreement with Maastricht consensus recommendations (ITT > 80%), since there is no difference in adverse events and there is a relatively high clarithromycin and metronidazole resistance, it could be concluded that only 14 days metronidazole and 10 and 14 days based clarithromycin protocols are acceptable (for the studied population) as the first-line treatment protocols.

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