^{13}C-Urea Breath Test to Validate Eradication of *Helicobacter pylori* in an Israeli Population

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Abstract

Background: The ^{13}C-urea breath test is the best non-invasive test to validate *Helicobacter pylori* eradication. Serology is unreliable for this purpose due to the slow and unpredictable decline in the antibody titer.

Objectives: To characterize a specific group of patients who were treated for *H. pylori* and tested for successful eradication by ^{13}C-UBT in our central laboratory, to correlate the eradication success rate with specific drug combinations, and to evaluate other factors that may influence eradication success.

Methods: ^{13}C-UBT for *H. pylori* was performed in the central laboratory of Clalit Health Services. The breath test was performed by dedicated nurses in 25 regional laboratories and the samples were analyzed by a mass spectrometer (Analytical Precision 2003, UK). The physician who ordered the test completed a questionnaire computing demographic data (age, gender, origin), indication, use of non-steroidal anti-inflammatory drugs or proton pump inhibitor, and combination of eradication therapy.

Results: Of the 1,986 patients tested to validate successful *H. pylori* eradication, 539 (27%) had a positive test (treatment failure group) and 1,447 (73%) had a negative test (successful treatment group). Male gender, older age and European-American origin predicted better eradication rates. Dyspeptic symptoms and chronic PPI therapy predicted treatment failure. Combination therapy that included clarithromycin had a higher eradication rate than a combination containing metronidazole. The combination of omeprazole, amoxicillin and clarithromycin achieved an eradication rate of 81.3%, which was better than the combination of omeprazole, metronidazole and clarithromycin (77.2%) (not significant), or of omeprazole, amoxicillin and metronidazole (66.1%) ($P < 0.01$).

Conclusion: Gender, age, origin, dyspepsia and PPI therapy may predict *H. pylori* eradication results. Our findings also support an increase in metronidazole resistance of *H. pylori* strains in Israel, as reported in other countries. We recommend combination therapy with omeprazole, amoxicillin and clarithromycin and avoidance of metronidazole as one of the first-line eradication drugs.

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Helicobacter pylori infection is highly prevalent in many countries, and almost half of the world population is infected [1]. Since peptic ulcer disease, cancer and lymphoma may be a consequence of *H. pylori* infection, it is therefore essential that health providers be able to establish the diagnosis using a highly sensitive method [2]. ^{13}C-urea breath test is such a test and has the highest sensitivity among the non-invasive tests [3–7]. Among the non-invasive tests, ^{13}C-UBT is the best for the validation of *H. pylori* eradication [6]. Serology is unreliable for this purpose due to the slow and unpredictable decline in the antibody titer [9].

In Israel *H. pylori* is usually eradicated by a combination of a proton pump inhibitor and two antibiotics for 1 week, according to the MACH 1 study [10]. The accepted eradication rates in intention-to-treat analysis [10] are: 90.6% for omeprazole, amoxicillin and clarithromycin (OAC), 85.5% for omeprazole, metronidazole and clarithromycin (OMC), and 75.8% for omeprazole, amoxicillin and metronidazole (OAM). It has been suggested that for many patients with uncomplicated ulcer disease, non-ulcer dyspepsia or uninvestigated dyspepsia, it is reasonable to simply monitor for recurrent symptoms. This protocol was changed at the recent Maastricht meeting of the European Helicobacter Pylori Research Group (EHPRG), which recommended evaluation by ^{3}C-UBT of every case [11].

The primary aim of the present study was to characterize a specific group of patients treated for *H. pylori* and tested for successful eradication by ^{13}C-UBT in our central laboratory, and to correlate eradication success rate with specific drug combinations. The secondary aim was to evaluate other factors that may influence eradication. Our study represents the eradication rate in symptomatic patients in daily practice and not during a controlled study.

Methods

^{13}C-UBT for *H. pylori* was performed in the central laboratory of Clalit Health Services. The breath test was performed by dedicated nurses in 25 regional laboratories and the samples were analyzed by a mass spectrometer (Analytical Precision 2003, UK). A consecutive series of 1,986 patients were examined for validation of a successful eradication; there were 1,080 women (54%) and 906 men (46%) with a mean age of 51.4 years (range 16–98). *H. pylori* infection was diagnosed before eradication attempt by rapid urease test and histology [11].

Patients were given 75 mg urea labeled with ^{13}C in 200 ml of orange juice, and breath samples were collected at times 0 (before ^{13}C intake) and 30 minutes after ^{13}C intake. The results are expressed as the difference between the two scores (delta over baseline). The cut-off ^{13}C/^{12}C at T30'-T0' was 3.5, according to referral laboratories and the manufacturer's instructions. The

^{13}C-UBT = ^{13}C-urea breath test
PPI = proton pump inhibitor

patients were asked to stop treatment with H2 antagonists, proton pump inhibitors, or any antibiotics, a week before the test. If the indication validated *H. pylori* eradication, the test had to be taken at least 1 month after the end of the eradication treatment. The physician who ordered the test completed a questionnaire computing demographic data (age, gender, origin), indication, use of non-steroidal anti-inflammatory drugs, or PPI, and the combination of drugs used for eradication therapy.

Statistical analysis was performed by *t*-test and Chi-square test as needed. A *P* value of less than 0.05 was considered significant.

Results

Since a positive test indicated treatment failure (treatment failure group) and a negative test treatment success (successful treatment group), these two groups were separated and compared. A positive test was obtained in 539 patients (27%) and a negative test in 1,447 (73%). There were 219 men (40.7%) in the treatment failure group and 687 men (47.5%) in the successful treatment group ($P = 0.008$). There were more patients of European-American origin and older than 50 years in the successful treatment group than in the treatment failure group ($P = 0.03$ and $P = 0.0001$, respectively) [Table 1].

There were significantly more dyspeptic patients and more chronic PPI users in the treatment failure group than in the successful treatment group ($P = 0.001$ and $P = 0.008$, respectively) [Table 2]. There was no statistically significant difference between the groups when other indications for the test, in addition to validation of successful *H. pylori* eradication, were studied.

The most common treatment combinations used for *H. pylori* eradication are presented in Table 3. The omeprazole, amoxicillin and clarithromycin (OAC) combination was used in 19.7% of the treatment failure group and in 31.9% of the successful treatment group ($P < 0.0001$). By contrast, the omeprazole, amoxicillin and metronidazole (OAM) combination was used in 26.8% of the treatment failure group and in 19.4% of the successful treatment group ($P < 0.0001$) [Table 3]. As shown in Table 4, the combination of omeprazole, amoxicillin and clarithromycin achieved an eradication rate of 81.3%, which was better than omeprazole, metronidazole and clarithromycin (77.2%) (not significant), or omeprazole, amoxicillin and metronidazole (66.1%) ($P < 0.01$).

Regimens that contained clarithromycin were used in 47.4% of the treatment failure group and in 62.6% of the successful treatment group ($P = 0.0001$). Metronidazole was part of the combination used in 65.3% of the treatment failure group and in 50.5% of the successful treatment group ($P = 0.0001$).

Table 1. Demographic data

	Treatment failure group	Successful treatment group	Relative ratio	*P*
No. of patients	539 (27.1%)	1,447 (72.9%)		
Gender				
Men	219 (40.7%)	687 (47.5%)	1.17	0.008
Women	320 (59.3%)	760 (52.5%)	0.89	
Age				
Mean ± SD	48.2 ± 12.3	52.5 ± 14.8		0.001
Median	50	55		
Age (yrs)				
< 18	49 (9.0%)	100 (6.9%)	0.77	
19–50	232 (42.9%)	490 (33.9%)	0.79	0.0001
> 50	258 (47.8%)	857 (59.2%)	1.24	
Origin				
Europe-America	193 (35.9%)	627 (43.3%)	1.21	
Asia-Africa	236 (43.7%)	547(37.8%)	0.86	0.03
Israel	110 (20.4%)	273(18.9%)	0.93	

Statistical analysis was performed by *t*-test and Chi-square test as needed.

Table 2. Other indications for ^{13}C-UBT

Subgroups	Treatment failure group (n = 539)	Successful treatment group (n = 1,447)	Relative ratio	*P*
Dyspepsia	363 (67.3%)	854 (59.0%)	0.88	0.001
Symptoms other than dyspepsia	278 (51.6%)	667 (46.1%)	0.89	NS
Duodenal ulcer	132 (24.5%)	326 (22.5%)	0.92	NS
Gastric ulcer	14 (2.6%)	59 (4.1%)	1.58	NS
PPI therapy	278 (51.6%)	667 (46.1%)	0.89	0.008
NSAID therapy	31 (5.8%)	81 (5.6%)	0.97	NS
Family history of gastric cancer	10 (1.9%)	42 (2.9%)	1.53	NS

Statistical analysis was performed by *t*-test and Chi-square test as needed.
NSAIDs = non-steroidal anti-inflammatory drugs

Table 3. Treatment combinations

Combination	Treatment failure group (n = 539)	Successful treatment group (n = 1,447)	RR	Difference	SE	95%CI of difference	*P*
OAC	106 (19.7%)	462 (31.9%)	1.62	-0.122	0.023	-0.167 to -0.077	0.000
OAM	144 (26.8%)	281 (19.4%)	0.72	0.074	0.021	0.033 to 0.115	0.000
OMC	46 (8.6%)	156 (10.8%)	1.26	-0.022	0.015	-0.052 to 0.008	0.175
Other	155 (28.7%)	392 (27.1%)	0.94	0.016	0.023	-0.028 to 0.060	0.514

O = omeprazole, A = amoxicillin, C = clarithromycin, M = metronidazole, RR = relative ratio, difference = difference between proportions, SE = standard error of difference, CI = confidence interval.

Table 4. Eradication rate in the different drug combinations

Combination	No. of patients	No. of negative tests	Eradication rate (%)
OAC	568	462	81.3
OMC	202	156	77.2
OAM	425	281	66.1

O = omeprazole, A = amoxicillin, C = clarithromycin, M = metronidazole.

Discussion

We found that prediction criteria for treatment success were male gender, older age and European-American origin. A possible explanation for our findings may be that compliance varies among these groups. Older men of European-American descent may have more chronic diseases, such as ischemic heart disease, arterial hypertension or diabetes mellitus, and may be accustomed to regular medications. Moayyedi et al. [12] similarly found that *H. pylori* eradication with omeprazole, clarithromycin and tinidazole was less successful in women. This result needs further evaluation. Our results suggest a possible increase in metronidazole resistance of *H. pylori* strains as described in both Israel and the United States [13,14]. Thus, we recommend a combination therapy of OAC and avoidance of metronidazole as a first-line eradication therapy. It was not surprising to find a higher rate of dyspeptic patients and PPI users among the treatment failure group patients. Moayyedi et al. [12] demonstrated that eradication was less successful in patients who had received pretreatment with H2 receptor antagonists, suggesting that these agents should be avoided, if possible, before the patient commences therapy. *H. pylori* may cause dyspepsia, and eradication therapy may be beneficial at a rate of 10% over placebo [15]. PPI use is frequent in dyspeptic patients, and may be an indirect marker for failed *H. pylori* eradication in this setting. A similar idea was suggested by Annibale and co-workers [16], who found a non-significant decrease in eradication rate with omeprazole pretreatment in peptic ulcer patients.

In a prospective study of 248 infected patients, Perri et al. [17] tried eradication therapy with pantoprazole, clarithromycin and amoxicillin. They found that age older than 45, smoking and high pretreatment ^{13}C-UBT results were independent predictors of eradication failure. Eradication rate was low, 63%, by intention-to-treat analysis [17]. Our findings suggest an increased eradication rate with age, perhaps due to a decrease in smoking in Israel in this age group. Georgopoulos and colleagues [18] studied 80 consecutive infected patients with duodenal ulcer or non-ulcer dyspepsia. *H. pylori* was eradicated in 88.8% of the patients with omeprazole, clarithromycin and amoxicillin taken for 10 days [18]. This regimen failed to eradicate a strain that was clarithromycin-resistant. Age, gender, smoking, ulcer disease and compliance with therapy were not found to be predictive factors of *H. pylori* eradication with this regimen. It was speculated that a higher degree of inflammation accompanies more aggressive strain infections, which are more vulnerable to antibiotic therapy [19]. Inflammation may be important for mucus degradation and allows better antibiotic penetration and altered vascular and epithelial permeability [18,19].

Our patients were tested to validate *H. pylori* eradication, and 73% (the successful treatment group) had a negative test (successful eradication). This, of course, is not an indicator of the general success rate of eradication therapy in Israel, since the patients were referred for ^{13}C-UBT after therapy if they were symptomatic or had demonstrated endoscopic pathology. Thus, the rate of 73% is an underestimate of the success of eradication therapy in Israel. More patients in the treatment failure group received drug combinations with metronidazole than in the successful treatment group, and fewer combinations contained clarithromycin. Combination therapy with clarithromycin was better than combinations that contained metronidazole.

References

1. Everhart JE. Recent development in the epidemiology of Helicobacter pylori. *Gastroenterol Clin North Am* 2000;29:559–78.
2. Williams MP, Pounder RE. Helicobacter pylori: from the benign to the malignant. *Am J Gastroenterol* 1999;94 (Suppl):s11–6.
3. Logan RP. Urea breath tests in the management of Helicobacter pylori infection. *Gut* 1998;43 (Suppl 1):s47–50.
4. Sheu BS, Lee SC, Yang HB, Lin XZ. Quantitative results of 13C urea breath test at 15 minutes may correlate with the bacterial density of H. pylori in the stomach. *Hepatogastroenterology* 1999;46:2057–62.
5. Hawtin PR. Serology and urea breath test in the diagnosis of H. pylori infection. *Mol Biotechnol* 1999;11:85–92.
6. Perri F, Clemente R, Pastore M, et al. The 13C urea breath test as a predictor of intragastric bacterial load and severity of Helicobacter pylori gastritis. *Scand J Clin Lab Invest* 1998;58:19–27.
7. Savarino V, Vigneri S, Celle G. The 13C urea breath test in the diagnosis of Helicobacter pylori infection. *Gut* 1999;45(Suppl 1):18–22.
8. Cutler AF, Prasad VM. Long term follow-up of Helicobacter pylori serology after successful eradication. *Am J Gastroenterol* 1996;91:85–8.
9. Perez-Perez GI, Culter AF, Blaser MJ. Value of serology as a noninvasive method for evaluation the efficacy of treatment of Helicobacter pylori infection. *Clin Infect Dis* 1997;25:1038–43.
10. Lind T, Veldhuyzen van Zanten SJO, Unge P. Eradication of Helicobacter pylori using one week triple therapies combining omeprazole with two antimicrobials – the MACH 1 study. *Helicobacter* 1996;1:138–44.
11. Malfertheiner P, Megraud F, O'Morain C, et al. Current European concepts in the management of Helicobacter pylori infection – the Maastricht Consensus Report. The European Helicobacter Pylori Study Group (EHPSG). *Eur J Gastroenterol Hepatol* 1997;9:1–2.
12. Moayyedi P, Chalmers DM, Axon AT. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate Helicobacter pylori. *J Gastroenterol* 1997;32:24–7.
13. Avidan B, Weiss B, Chowers Y, Younash A, Bar-Meir S, Keler N. Sensitivity and resistance of Helicobacter pylori to antibiotic treatment. *Harefuah* 1999;137:272–4 (Hebrew).
14. Weisfeld AS, Simmons DE, Vance PH. In vitro susceptibility of pretreatment isolates of Helicobacter pylori from the multicenter United States clinical trials [Abstract]. *Gastroenterology* 1996;110:A295.
15. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating Helicobacter pylori infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;339:1869–74.
16. Annibale B, D'Ambra G, Luzzi I, et al. Does pretreatment with omeprazole decrease the chance of eradication of Helicobacter pylori in peptic ulcer patients? *Am J Gastroenterol* 1997;92:790–4.
17. Perri F, Villani MR, Festa V, Quitadamo M, Andriulli A. Prediction of failure of helicobacter pylori eradication with the standard "Maastricht triple therapy." *Aliment Pharmacol Ther* 2001;15:1023–9.
18. Georgopoulos SD, Ladas SD, Karatapanis S, et al. Factors that may affect treatment outcome of triple helicobacter pylori eradication therapy with omeprazole, amoxicillin and clarithromycin. *Dig Dis Sci* 2000;45:63–7.
19. Spiller RC. Is there any difference in helicobacter pylori eradication rates in patients with active peptic ulcer, inactive peptic ulcer and functional dyspepsia? *Eur J Gastroenterol Hepatol* 1999;11(Suppl 2):S25–8, S43–5.

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