The Effect of Culture Results for *Helicobacter pylori* on the Choice of Treatment Following Failure of Initial Eradication

Benjamin Avidan MD[1], Ehud Melzer MD[1], Nathan Keller MD[2] and Simon Bar-Meir MD[1]

Departments of [1]Gastroenterology and [2]Bacteriology, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

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Abstract

Background: Current treatment for the eradication of *Helicobacter pylori* in patients with peptic disease is based on the combination of antibiotic and anti-acid regimens. Multiple combinations have been investigated, however no consensus has been reached regarding the optimal duration and medications.

Objectives: To assess the efficacy of two treatment regimens in patients with peptic ulcer disease and non-ulcer dyspepsia, and to determine the need for gastric mucosal culture in patients failing previous treatment.

Methods: Ninety patients with established peptic ulcer and NUD (with previously proven ulcer) were randomly assigned to receive either bismuth-subcitrate, amoxycillin and metrnidazole (BAM) or lansoprasole, clarithromycine and metronidazole (LCM) for 7 days. Patients with active peptic disease were treated with ranitidine 300 mg/day for an additional month.

Results: Eradication failed in 8 of the 42 patients in the BAM group and in 2 of the 43 patients in the LCM group, as determined by the ^{13}C urea breath test or rapid urease test (19% vs. 5%, respectively, $P = 0.05$). Five of these 10 patients were randomly assigned to treatment with lansoprazole, amoxycillin and clarithromycin (LAC) regardless of the culture obtained, and the other 5 patients were assigned to treatment with lansoprazole and two antibacterial agents chosen according to a susceptibility test. Eradication of *H. pylori* was confirmed by the ^{13}C urea breath test. The same protocol (LAC) was used in all patients in the first group and in four of the five patients in the second group. The culture results did not influence the treatment protocol employed.

Conclusions: Combination therapy based on proton pump inhibitor and two antibiotics is superior to bismuth-based therapy for one week. Gastric-mucosal culture testing for sensitivity of *H. pylori* to antibiotics is probably unnecessary before the initiation of therapy for patients with eradication failure.

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NUD = non-ulcer dyspepsia

Helicobacter pylori is currently considered a major etiological factor in peptic ulcer disease [1,2], and eradication of this organism significantly lowers recurrence and complication rates [3–6]. The goals of treatment are ulcer healing and eradication of *H. pylori* infection from the foregut. Eradication is currently defined as negative tests for *H. pylori* for at least 28 days following the end of treatment [7]. The failure rate of eradication of *H. pylori* in peptic ulcer patients is 10–20% [8]. Resistance to antibiotics is considered the principal reason for eradication failure [9,10]. The role of culture and susceptibility tests as a guide indicating a second therapeutic trial has not been thoroughly investigated.

The aims of the present study were to compare bismuth-based with lansoprazole-based triple therapies for 7 days for the eradication of *H. pylori* and to assess the role of susceptibility-guided treatment in patients failing a first attempt of *H. pylori* eradication.

Methods

Patients and experimental protocols

The study, approved by the regional ethics committee, was divided into two sequential phases:

- ***Phase 1***

In the first phase, 90 patients with active peptic ulcer disease on endoscopy (duodenal or gastric ulcer) or non-ulcer dyspepsia were included. All patients underwent esophago-gastro-duodenoscopy and gastric-antral biopsy for fast urease test (CLO test, TelmerPharm GmbH, Germany) to detect the presence of *H. pylori* [9]. Exclusion criteria included consumption of antibacterial agents within a month prior to randomization, previous therapy for eradication of *H. pylori*, sensitivity to penicillin, previous history of severe liver or kidney disease, pregnancy, or the consumption of non-steroidal anti-inflammatory drugs.

Patients were randomly assigned to two open-labeled treatment groups. Group A consisted of 45 patients treated with bismuth-subcitrate (480 mg/day), amoxycillin (2 g/day) and metronidazole (1 g/day) in four divided doses for 7 days.

Group B comprised 45 patients treated with lansoprazole (60 mg/day), clarithromycine (1 g/day) and metronidazole (1 g/day) in two divided doses for 7 days. Patients were assessed before, and 1 and 6 weeks after the study. The assessment included the presence of symptoms, adverse effects and compliance. Questionnaires were used to evaluate four symptoms: abdominal pain, heartburn, nausea, and vomiting. Pill count at the end of therapy was used to assess compliance.

Eradication was determined 6 weeks following cessation of treatment by ^{13}C urea breath test using a mass spectrometer (Micromass, UK) [7]. Patients with gastric ulcer underwent EGD to confirm healing of the ulcer, and the presence of *H. pylori* was assessed by urease test and histology.

Patients from both groups in whom *H. pylori* eradication failed were eligible for the second phase of the study. Each patient underwent EGD and six biopsy specimens were obtained from each, three from the antrum and three from the body of the stomach. Biopsies were cultured and tested for susceptibility to antibiotics. Histology, looking for *H. pylori,* and urease test were also performed.

• *Phase 2*

Patients in whom *H. pylori* eradication failed were randomly assigned to two treatment protocols. Half the patients received lansoprazole (60 mg/day), amoxycillin (2 g/day) and clarithromycine (1 g/day) (LAC) in two divided doses for 10 days, regardless of the culture results. The other half received lansoprozole (60 mg/day) and two antibacterial agents, according to culture results, for 10 days. Patients in whom *H. pylori* failed to grow in culture were assigned to treatment that had not been given in phase 1. Eradication was assessed by ^{13}C urease breath test 6 weeks following the end of phase 2.

Susceptibility testing

Two biopsy specimens from the gastric antrum and corpus, placed in 0.9% normal saline, were used for culture and susceptibility tests. The plates were incubated in a micro aerophilic condition at 37°C in a chocolate agar for up to 10 days. *H. pylori* strains were tested for metronidazole, clarithromycine and amoxycillin susceptibility by means of the E-test [10,11]. Resistance was defined with the following minimal inhibitory concentration breakpoints: metronidazole >16 mg/L, clarithromycin >8 mg/L and amoxycillin >8 mg/L [12].

Statistics

H. pylori cure rates were compared using the chi-square test with Fisher's exact test. Different demographic parameters were compared by Fisher's exact test and Student's *t*-test.

Results

Ninety patients enrolled in the study. Five patients, three from group A and two from group B, dropped out – 3 because of loss to follow-up and 2 due to adverse effects of medications. The suspected adverse effects were weakness for 3 days in a group B patient and one week of dysgeusia and burning sensation on the tongue in a group A patient. No other side effects were reported. Patients' characteristics are presented in Table 1.The two groups were very similar in their demographic pattern, disease distribution, and compliance.

Table 1. Patients' characteristics

	BAM	LCM
Age (yr, mean ± SD)	47.6±12.1	45.3±11.9
Smokers	14	15
Male sex, No. (%)	26 (51)	25 (49)
Duodenal ulcer	35	30
Gastric ulcer	0	4
NUD	8	9
Compliance (% ± SD)	97.5±7.8	99.6±2.1

BAM = bismuth subcitrate, amoxycillin, metronidazole,
LCM = lansoprazole, clarithromycine, metronidazole

Symptoms improved in both groups at a similar rate, in 35 of 42 patients (83%) in group A and 39 of 43 (91%) in group B ($P=0.4$). An additional two patients in group A demonstrated an improvement 6 weeks after the end of the treatment. Eradication of *H. pylori* was achieved in 75 patients (88%) with the first therapy. Failure of eradication was observed in 10 patients, 8 from group A (19%) and 2 from group B (5%) ($P=0.05$). These patients entered the second phase of the study. Five patients received LAC and the other five patients were treated with lansoprazole and two antibacterial agents chosen according to sensitivity testing. All the patients in both groups completed the course of 10 days treatment with no side effects. *H. pylori* was eradicated in all the patients receiving LAC. As it turned out, based on sensitivity testing in four of five patients, amoxycillin and clarithromycin were chosen for treatment. All were resistant to metronidazole. In the fifth patient, no *H. pylori* grew in the culture despite its detection by direct microscopy, positive urease test and urease breath test. The combination of lansoprazole, clarithromycin and metronidazole was then given for 10 days and resulted in successful eradication of *H. pylori.*

Discussion

In the present study we compared two treatment regimens for the eradication of *H. pylori.* We wish to mention that this study was not supported by the pharmaceutical industry.

The combination of lansoprazole, clarithromycin and metronidazole was superior to bismuth-subcitrate, amoxycillin and metronidazole given for a week. The eradication rate achieved with antibiotics and proton pump inhibitor-based therapy in our study is similar to that in previous reports [13,14]. Retreatment following *H. pylori* eradication failure is associated with a lower success rate [12,15]. Borody et al. [16] achieved a 78% cure rate using therapy based on four medications: bismuth-subcitrate, amoxycillin and tetracycline or metronidazole together with omeprazole. In another study, Borody and colleagues [17] administered the 12 day combined

EGD = esophago-gastro-duodenoscopy

treatment of omeprazole, bismuth-subcitrate, amoxycillin and clarithromycin and successfully eradicated *H. pylori* in 39 of 46 patients (85%) who had failed previous treatment. However, the occurrence of pseudomembranous colitis in four patients led the authors to question the safety of this regimen [17]. Seppala et al. [18] achieved eradication with bismuth-subcitrate based quadruple therapy in 42 of 48 patients (87%) in whom metronidazole-based triple therapy had previously failed. Megraud [19] suggested the use of susceptibility testing to select the appropriate therapy since resistance of *H. pylori* to antibacterial agents is considered to be a major cause of failure. However, culturing the organism is cumbersome because it requires special handling and is time consuming and expensive. Furthermore, there is a lack of precise correlation between susceptibility testing *in vitro* and actual *H. pylori* eradication success rates [12,19].

With regard to the role of testing for *H. pylori* sensitivity to antibacterial agents as an indication for a second therapy in patients who failed the first one, we found that it does not affect the choice of combination therapy. In all biopsy specimens, *H. pylori* strains were sensitive to amoxycillin and clarithromycin, and eventually all but one patient received LAC with good response. In the patient in whom *H. pylori* could not be cultured, this therapy was also effective. This patient would have responded to LAC as well because none of the *H. pylori* strains in our study were resistant to amoxycillin. The high success rate of therapy in the 10 non-responders is consistent with the report by Lerang et al. [20], who demonstrated a 100% cure rate in patients who failed metronidazole-based triple therapy and were successfully treated with omeprazole, amoxycillin and clarithromycin. All the patients in that study had culture-positive biopsy specimens, but sensitivity test results were not used as a guide for second-line treatment as they were in our study. Reilly et al. [21] achieved *H. pylori* eradication using the same combination in 18 of 21 patients (86%) in whom metronidazole-based triple therapy had previously failed, but data on antibiotic susceptibility were lacking.

In conclusion, we demonstrated that 7 days of treatment with the lansoprazole, clarithromycin and metronidazole combination is superior to 7 days treatment with the bismuth, amoxycillin and metronidazole combination to eradicate *H. pylori*. Ten days of triple therapy with lansoprazole, clarithromycin and amoxycillin is a highly effective second-line treatment for patients who failed the first eradication attempt. Moreover, culture and sensitivity testing is probably not needed for the selection of antibiotics for the second therapeutic attempt and should be reserved only for patients in whom two or more eradication attempts had failed.

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Correspondence: Dr. S. Bar-Meir, Director, Dept. of Gastroenterology, Sheba Medical Center, Tel-Hashomer 52621, Israel. Phone: (972-3) 530-2679, Fax: (972-3) 530-3070, email: barmeir@netvision.net.il