

## Effect of *Helicobacter pylori* eradication on peptic ulcer healing

Humphrey J O'Connor, Chakravarthy Kanduru, Abdul S Bhutta, Judith M Meehan, Kenneth M Feeley, Kevin Cunnane

### Summary

**In a prospective study designed to assess the effect of *Helicobacter pylori* eradication on peptic ulcer healing, 85 consecutive patients with *H. pylori*-positive peptic ulcer disease were treated with a triple therapy regimen consisting of colloidal bismuth subcitrate 120 mg four times daily for 28 days, with metronidazole 400 mg three times daily and tetracycline 500 mg three times daily for the first seven days of treatment. *H. pylori* status was assessed by CLO test<sup>®</sup> and histology at least four weeks after completing therapy. Of 75 patients (88%) *H. pylori*-negative after therapy, 69 (92%) had healed ulcers compared with only five of 10 patients (50%) who remained *H. pylori*-positive ( $p = 0.003$ ). Cigarette smoking had no significant effect on ulcer healing. Our results suggest that *H. pylori* eradication may accelerate ulcer healing and provide further evidence that an effective helicobactericidal regimen is the treatment of choice in *H. pylori*-positive peptic ulcer.**

**Keywords:** *Helicobacter pylori*, peptic ulcer

### Introduction

The rediscovery of *Helicobacter pylori* has provoked a fundamental reevaluation of ideas on the aetiology and management of peptic ulcer. Perhaps the strongest evidence linking *H. pylori* and peptic ulcer is the fact that eradication of infection prevents ulcer relapse, effectively curing the disease. This seminal finding was first highlighted by Coghlan *et al.*<sup>1</sup> Subsequent studies continued to focus on the effect of *H. pylori* eradication on ulcer relapse<sup>2-4</sup> with less attention being paid to possible effects on ulcer healing. This prospective study was primarily designed to assess the effect of *H. pylori* eradication on peptic ulcer healing. A secondary aim of the study was to assess the impact of smoking and other factors on ulcer healing and *H. pylori* eradication.

### Patients and methods

#### PATIENTS

Patients were eligible for inclusion in the study if they were over 18 years of age, in good

general health, were found to have a gastric or duodenal ulcer at endoscopy, and had a gastric biopsy which gave a positive rapid urease test indicating the presence of *H. pylori* infection. An ulcer was defined as a circumscribed break in the mucosa measuring at least 5 mm in the longest diameter with apparent depth and covered with an exudate.

Patients were excluded if they had taken antibiotics or omeprazole in the preceding four weeks, bismuth-containing medication in the preceding three months, were on nonsteroidal anti-inflammatory drugs, had undergone peptic ulcer surgery, were pregnant, or had significant pathology at endoscopy other than gastric or duodenal ulcer. Prior to endoscopy, patients were questioned regarding current and past cigarette smoking. Ex-smokers were considered as nonsmokers for purposes of analysis in the study. All patients gave written informed consent for endoscopy and inclusion in the study.

#### ENDOSCOPY AND BIOPSIES

All the examinations were performed using an Olympus GIFIT 20 endoscope. If after inspection of the oesophagus, stomach, and duodenum, the patient was still considered eligible for inclusion in the study, three mucosal biopsy specimens were obtained using a standard biopsy forceps from the gastric antrum within 5 cm of the pylorus. One of the biopsy specimens was tested immediately for the presence of preformed urease activity using the CLO test<sup>®</sup> (Deltawest, Perth, Australia).<sup>5</sup> The remaining two specimens were fixed in 10% buffered formaldehyde, coded, and sent for histological evaluation.

Paraffin-processed histological sections were stained with haematoxylin and eosin and by a modified Giemsa stain method, and examined by an experienced pathologist blind to the clinical details and biopsy site. The modified Giemsa-stained sections were specifically examined for the presence of *H. pylori*, detected by the finding of characteristic curved bacilli on the mucosal surface.

#### THERAPY

Patients received a triple therapy regimen (see box). All medications were taken before meals.

Patients were counselled prior to starting therapy regarding the possibility of treatment-related gastrointestinal side-effects (nausea, taste disturbance, blackening of the stools),

**General Hospital,  
Tullamore,  
Co Offaly, Eire  
Department of  
Medicine**  
HJ O'Connor  
C Kanduru  
AS Bhutta  
JM Meehan  
KM Feeley  
**Department of  
Pathology**  
K Cunnane

Correspondence to  
Dr HJ O'Connor,  
Department of Medicine,  
General Hospital,  
Tullamore, Co Offaly, Eire

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**Triple therapy regime**

- colloidal bismuth subcitrate (120 mg qid for 28 days)
- metronidazole (400 mg tid for 7 days)
- tetracycline (500 mg tid for 7 days)

specifically advised to abstain from alcohol for the first week of therapy, and the importance of good compliance to the success of therapy was emphasised.

Repeat endoscopy to assess ulcer healing and *H. pylori* eradication was performed at least four weeks after completing therapy and at that time, patients were questioned regarding compliance and side-effects. Ulcer healing was defined as complete re-epithelialisation. *H. pylori* eradication was defined as the inability to detect evidence of infection on both the CLO test and histological evaluation.

**STATISTICS**

Differences in ulcer healing and *H. pylori* eradication between patient groups were tested for statistical significance using two-tailed Fisher's exact test. A *p*-value <0.05 was considered significant.

**Results**

Eighty-five patients were included in the study (see box).

**HEALING AND ERADICATION**

Ulcers healed in 74 patients (87%) but failed to heal in 11 (duodenal ulcer, 10; gastric ulcer, 1). Sixty duodenal ulcer patients had healed ulcers (82%) compared with nine gastric ulcer patients (90%). Seventy-five patients were *H. pylori*-negative after therapy (88%) and 10 remained *H. pylori*-positive. Of the 75 patients *H. pylori*-negative after therapy, 69 (92%) had healed ulcers compared with only five of the 10 patients (50%) who remained *H. pylori*-positive (*p* = 0.003) (figure).

There was no significant difference in age or gender between the *H. pylori*-positive and -negative groups (table 1). Three of the 10 gastric ulcer patients (30%) remained *H. pylori*-positive after therapy compared with only seven of the 73 duodenal ulcer patients (10%) (*p* = 1.0). Both patients with combined gastric and duodenal ulcer were *H. pylori*-negative after therapy.

**SMOKING, HEALING, AND ERADICATION**

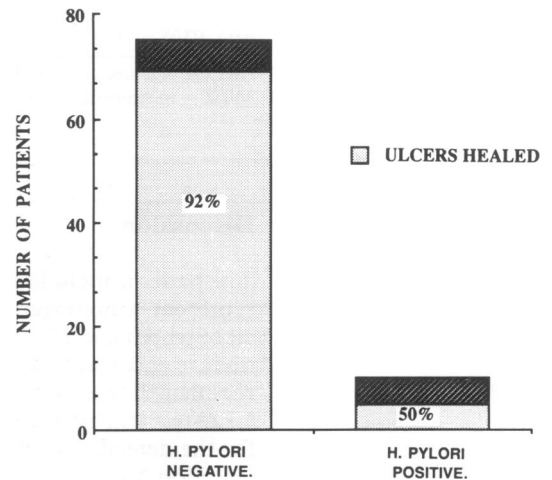
Of the 46 patients who smoked, 38 (83%) had healed ulcers compared with 33 (92%) of the 36 nonsmokers (*p* = 0.332). Thirty-eight of the smokers (83%) were *H. pylori*-negative after therapy compared with 34 (94%) of the nonsmokers (*p* = 0.173).

**SIDE-EFFECTS AND COMPLIANCE**

Three patients (duodenal ulcer, 2; gastric ulcer, 1) admitted to noncompliance with the treatment regimen. One patient misunderstood the treatment instructions and failed to take the

**Treatment group – 85 patients**

- 64 male
- mean age 47, range 22–74 years
- 46 smokers
- 73 duodenal ulcers
- 10 gastric ulcers
- 2 duodenal and gastric ulcers



**Figure** Effect of *H. pylori* eradication on peptic ulcer healing

**Table 1** Comparison of the patient groups *H. pylori*-negative and *H. pylori*-positive after therapy

	<i>H. pylori</i> -negative	<i>H. pylori</i> -positive
Number of patients	75	10
Mean age (range) (years)	45 (22–74)	37 (33–53)
Male:female	57:18	7:3
Duodenal ulcer	66 (90%)	7
Gastric ulcer	7 (70%)	3
Combined duodenal and gastric ulcer	2	–

**Table 2** Compliance and *H. pylori* eradication

	Compliant	Noncompliant
<i>H. pylori</i> -negative	75	0
<i>H. pylori</i> -positive	7	3

Fisher's exact test (two-tailed), *p* < 0.001.

antibiotics prescribed for the first week of therapy. Two patients prematurely discontinued antibiotic therapy because of nausea. Two of the three noncompliant patients were cigarette smokers. All three patients remained *H. pylori*-positive after therapy. All of the 75 patients who were *H. pylori*-negative after therapy said they complied with therapy whereas three of the 10 patients who were *H. pylori*-positive after therapy were noncompliant (*p* < 0.001) (table 2).

**Table 3** Effect of *H. pylori* eradication on peptic ulcer healing, previous studies

Study	Therapy	Patients (n)	Ulcer healing (%)	
			HP-positive	HP-negative
Marshall <i>et al</i> <sup>7</sup>	CBS <i>vs</i> CBS + TIN <i>vs</i> CIM <i>vs</i> CIM + TIN	100	61	92
Graham <i>et al</i> <sup>8</sup>	RAN <i>vs</i> RAN + AMOX + TET + MTZ	105	84	98
Hentschel <i>et al</i> <sup>9</sup>	RAN <i>vs</i> RAN + AMOX + MTZ	104	75	92
Hosking <i>et al</i> <sup>10</sup>	OM <i>vs</i> OM + CBS + TET + MTZ	155	78	95
McCarthy <i>et al</i> <sup>11</sup>	OM + MTZ + TET	43	34	66

AMOX = amoxicillin; CBS = colloidal bismuth subcitrate; CIM = cimetidine; HP = *H. pylori*; MTZ = metronidazole; OM = omeprazole; RAN = ranitidine; TET = tetracycline; TIN = tinidazole.

## Discussion

The patients included in this prospective study represent a homogeneous consecutive group, all of whom had *H. pylori*-positive peptic ulcer disease and received a standard triple therapy regimen. *H. pylori* status was assessed using the CLO test and histology, both accurate methods for the detection of the presence or absence of infection.<sup>6</sup>

The principal finding was that patients *H. pylori*-negative after therapy had significantly more healed ulcers than patients who remained *H. pylori*-positive (92% *vs* 50%). This finding is in accord with data already available on the effects of *H. pylori* eradication on peptic ulcer healing (table 3).<sup>7-11</sup> The beneficial effect of *H. pylori* eradication on ulcer healing was evident for both duodenal and gastric ulcer. The mucosal damage and inflammatory response which accompany *H. pylori* infection regress quickly after eradication of infection.<sup>12</sup> Rapid restoration of mucosal integrity may explain how eradication of *H. pylori* could facilitate the ulcer-healing process.

This study also afforded the opportunity to assess patient factors which might influence *H. pylori* eradication. Age and gender had no apparent effect on eradication but it is of interest that 30% of gastric ulcer patients remained *H. pylori*-positive after therapy compared with only 10% of duodenal ulcer patients. Cutler and Schubert,<sup>13</sup> using a triple therapy regimen, reported a 64% eradication rate in gastric ulcer compared with 91% in duodenal ulcer patients. About 70% of gastric ulcers are *H. pylori*-positive compared with over 90% of duodenal ulcers<sup>14</sup> but differences in virulence<sup>15</sup> or antibiotic sensitivity<sup>16</sup> have not been detected between *H. pylori* strains isolated from gastric and duodenal ulcer patients. It is possible that differences in the intragastric milieu between gastric and duodenal ulcer patients might influence the helicobactericidal efficacy of treatment regimens.<sup>17</sup>

Cigarette smoking is more common in patients with peptic ulcer disease than in non-ulcer controls.<sup>18</sup> Fifty-four per cent of our patients were regular cigarette smokers compared with a reported population prevalence of 27%.<sup>19</sup> We found that cigarette smoking had no significant effect on ulcer healing but cigarette

## Summary points

- more healed ulcers were found in patients rendered *H. pylori*-negative after triple therapy
- cigarette smokers have a lower *H. pylori* eradication rate than non-smokers

smokers had a lower *H. pylori* eradication rate than nonsmokers (83% *vs* 94%). Cutler and Schubert<sup>13</sup> reported a similar finding, while Unge *et al*<sup>20</sup> found that smoking also had a significant adverse effect on *H. pylori* eradication in patients treated with omeprazole and amoxicillin. Witteman *et al*<sup>21</sup> have reported that *H. pylori* in smokers acquire secondary metronidazole resistance more readily than *H. pylori* in nonsmokers. This novel finding might explain why *H. pylori* eradication therapy seems less effective in smokers than nonsmokers.

Although efficacious, triple therapy is a cumbersome multidrug regimen which does not encourage good compliance. That only three of our patients (4%) admitted to non-compliance may reflect the time and care spent counselling patients about the importance of compliance and the side-effects to expect with triple therapy. Our results, however, reiterate the critical relationship between non-compliance and treatment failure.<sup>22</sup> All three non-compliant patients remained *H. pylori*-positive after therapy whereas good compliance was associated with successful eradication and ulcer healing.

It is now firmly established that *H. pylori* eradication prevents peptic ulcer relapse, altering the natural history of the disease.<sup>23</sup> The fact that *H. pylori* eradication also accelerates ulcer healing adds further weight to the conclusion that an effective helicobactericidal regimen is the treatment of choice in *H. pylori*-positive peptic ulcer disease.

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