

High *Helicobacter pylori* numbers are associated with low eradication rate after triple therapy

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Abstract

This study tested the influence of pretreatment bacterial density on the eradication rate of *Helicobacter pylori* with triple therapy. One hundred and thirty two patients with endoscopically confirmed *H pylori* positive, duodenal ulcer or antral gastritis were treated with triple therapy (colloidal bismuth/metronidazole/amoxicillin) for two weeks. Pretreatment urease activity was assessed by the ¹⁴C-urea breath test (UBT) in all patients. The mean (SD) pretreatment UBT concentration was similar in patients with duodenal ulcers (318.4 (175.0)) and patients with antral gastritis (288.9 (165.5)). Overall eradication of *H pylori* was achieved in 85 of 132 patients (64.4%), but was significantly different between patients with high, intermediate, or low pretreatment urease activity (37.5%, 69.5%, and 87.8% respectively). The mean post-treatment UBT value of patients in whom eradication failed was in direct correlation with the pretreatment UBT values. In conclusion, bacterial density, as assessed by urease activity, is an important factor in predicting *H pylori* eradication. It is suggested that the pretreatment UBT has the potential to identify patients who require modification of the standard therapeutic regimen.

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Numerous studies have shown that eradication of *Helicobacter pylori* reduces the rate of peptic ulcer relapse, while persistence of the organism predicts relapse.¹⁻⁵ However, treatment of *H pylori* infection remains difficult. Most antibiotics show good activity against the organism in vitro, but when given as monotherapy to patients they offer limited benefit. Treatment currently accepted as the gold standard includes triple therapy with colloidal bismuth/metronidazole/amoxicillin or tetracycline, and is effective in 55-94% of patients.⁶ Two factors that have been shown to affect the efficacy of triple therapy are patient compliance and resistance of the organism to metronidazole.^{7,8} Other factors investigated are treatment duration and regimen.⁹ It has been found that the antral density of *H pylori* increases the rate of ulcer recurrence,¹⁰ however, there are no data on the effect of the pretreatment bacterial density on the eradication rate of *H pylori*.

Rauws *et al* have shown that one of the advantages of the urea breath test in the diagnosis of *H pylori* infection is that it also gives a quantitative assessment of the bacterial density in the stomach and correlates well with the histological findings.¹¹ This correlation has been validated recently by several independent studies.¹²⁻¹⁴

The purpose of this study was to evaluate the eradication rate of triple therapy in our patient population, and to examine the effect of the pretreatment bacterial density assessed by the ¹⁴C-urea breath test (UBT), on the eradication rate with this regimen.

Methods

The study included patients referred to our gastroenterology service for upper gastrointestinal symptoms, who were found to have endoscopically verified duodenal ulcers or chronic antral gastritis. During endoscopy prepyloric antral biopsy specimens were taken for histological examination and for rapid urease testing. In all patients ¹⁴C-UBT was performed before starting treatment for *H pylori* eradication. Patients were treated with the regimen: colloidal bismuth subcitrate (CBS, De-Nol) 120 mg four times daily, amoxicillin 500 mg thrice daily, and metronidazole 250 mg twice daily for 14 days. All the patients underwent a ¹⁴C-UBT four weeks after completion of the treatment for evaluation of *H pylori* eradication.

¹⁴C-UBT

The ¹⁴C-UBT was performed after an overnight fast. After a standard test meal to delay gastric emptying (Sustacal, Mead-Johnson), the patients ingested 2.5 µCi ¹⁴C-urea combined with 250 mg 'cold' urea. Breath samples were collected at 30 and 60 minutes. The result was expressed as a percentage of administered dose of ¹⁴C per mmol of expired CO₂ × 10⁴. A cumulative test value at 30 and 60 minutes in excess of 50 (% units) was defined as positive for *H pylori*. Using this method in our laboratory and comparing it with histological examination, culture, and rapid urease test we have found the test to be highly specific (100%) and sensitive (88%) for diagnosing *H pylori* infection.¹⁵ Pretreatment UBT results were compared using Student's *t* test, and χ² test was used to compare eradication rates among patient groups.

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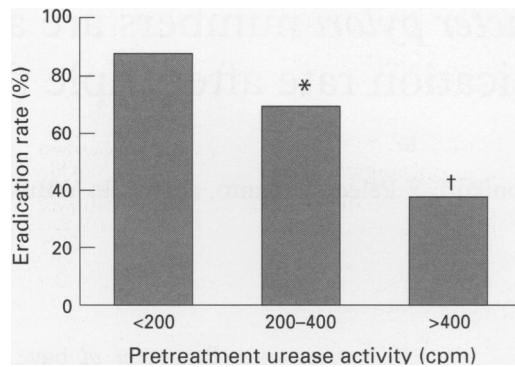


Figure 1: Eradication rates of *H pylori* in the various patient groups according to pretreatment urease activity. Difference from low density group: * $p < 0.001$, † $p < 0.0001$.

Results

PATIENTS

One hundred and thirty two patients (63 men and 69 women) entered the study. The endoscopic diagnosis was duodenal ulcer in 73 patients (55.3%) and non-ulcer dyspepsia with chronic antral gastritis in 59 patients (44.7%). All patients had *H pylori* infection by rapid urease testing, histological examination, and UBT.

The mean (SD) pretreatment UBT value in the group with duodenal ulcer was 318.4 (175.0), not significantly different from that of the patients with chronic antral gastritis, 288.9 (165.7). Based on the distribution of UBT values obtained in our laboratory during a one year period, patients were classified into three groups according to their urease activity before starting treatment. Low urease activity group was defined as a UBT value of <200, intermediate urease activity as 200–400, and high urease activity as >400. The number of patients in each group was 33, 59, and 40 respectively.

Eradication of *H pylori*

Eradication of *H pylori* was achieved in 85 of 132 patients (64.4%). Figure 1 shows the eradication rates in the three patient groups in relation to pretreatment urease activity. It can be seen that with identical treatment regimens, the eradication rate was significantly different between patients with low, intermediate, and high urease activity (87.8%, 69.5%, and 37.5% respectively, $p < 0.05$). Figure 2 shows

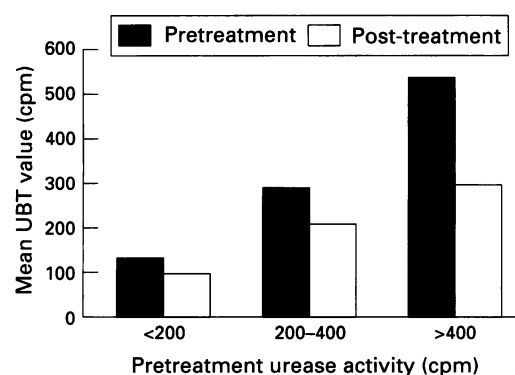


Figure 2: Mean pre and post-treatment UBT values of patients in whom eradication of *H pylori* was not achieved in the various patient groups.

the mean pre and post-treatment UBT values in patients who failed to eradicate *H pylori*. A clear correlation between the mean pre and post-treatment UBT values was seen. The mean post-treatment UBT value was significantly higher in the patient group with high pretreatment UBT value and lower in those with an initially low value.

Discussion

Eradication of *H pylori* infection is attracting increasing attention and acceptance as an important therapeutic consideration in the treatment of peptic ulcer disease. Currently, the most effective treatment includes triple therapy with colloidal bismuth/metronidazole/amoxicillin or tetracycline. With this combination a success rate of 55–94% can be achieved.⁶ Two main factors that are thought to affect the eradication rate are patient compliance and resistance to metronidazole. Graham *et al* have shown that in patients who take less than 60% of their treatment the eradication rate is reduced by about 25%.⁷ Resistance of *H pylori* to metronidazole is another significant problem and a difference in resistance between various geographical areas in the world have been shown.^{8–16} Although we did not examine specifically patient compliance and resistance of bacterial isolates to metronidazole, there is no reason to believe that a difference between the patient groups in our study in relation to these parameters could account for the results. Moreover, we have found in a previous study that the resistance to metronidazole in 18 different *H pylori* isolates from Israeli patient is as low as 6%.¹⁷ Published eradication rates for the regimen used in our study are between 55–90%.⁶ The overall eradication rate found in this study (64.4%), was not high, but well within this range extending from 38 to 88% in the three groups of patients depending on the initial UBT value. As previous reports have not related their data to UBT results, a comparison of results is not possible.

The findings of this study show a direct relation between the pretreatment UBT value and the eradication rate of *H pylori*. A high UBT value means high urease activity in the stomach. This can result either from high bacterial density or increased urease activity of an individual bacterial strain. Recent studies, however, have shown that urease activity as assessed by the UBT, correlates well with bacterial density as measured by microbiological methods.^{12–14} The UBT performed in our laboratory includes cold urea and a test meal, to further improve the correlation between the UBT value and total bacterial density.¹⁸ We also found that the mean post-treatment UBT value in patients whose treatment failed was higher in patients with high pretreatment urease activity than in those with low urease activity (Fig 2). As all patients received the same treatment for the same length of time, this correlation provides additional support for the importance of bacterial density as a factor in *H pylori* eradication.

Surprisingly, little attention has been given to the bacterial density or load as a possible factor in the eradication rate of *H pylori*. One reason is that pretreatment UBTs have not been routinely performed in most of the studies. The diagnosis of *H pylori* infection has usually been based on microbiological or histological examinations, or both, of minute tissue samples. These are subject to sampling problems, which make their use in global assessment of bacterial density unpractical.

Two recent studies, however, have included pretreatment urea breath testing in their protocol. Peterson *et al* examined the efficacy of monotherapy with clarithromycin in *H pylori* infection.¹⁹ They pointed out in their results that no correlation was found between the bacterial density and the eradication results. However, their small patient group (34 patients) and low eradication rate preclude reliable conclusions. In another study using triple therapy and pretreatment urea breath testing no reference to the effect of bacterial density on the eradication rate is provided.²⁰ Yet, the authors suggest in their conclusions that regardless of pathogenicity, the overall load of the organism may be important in determining the clinical outcome.

In conclusion, we found that a high UBT value, representing increased bacterial density of *H pylori* is associated with a significant reduction in the eradication rate after treatment with conventional triple therapy. These results show that pretreatment bacterial density should be taken into consideration when comparing the efficacy of various treatment regimens for *H pylori* eradication. Moreover, we suggest that a pretreatment UBT is useful when considering the choice of a therapeutic regimen. Prolongation of the treatment or giving higher dose of the same regimen may improve the eradication rate in cases with high bacterial density or load.

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