

# Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole

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## Abstract

To test the hypothesis that *Helicobacter pylori* infection is associated with a decreased intragastric acidity during omeprazole therapy, ambulatory 24 hour dual point gastric pH recordings were performed in 18 *H pylori* positive and 14 *H pylori* negative subjects. There was a four to six week washout period between the two pH recordings made in each subject after one week courses of placebo or omeprazole, 20 mg daily. During placebo, median 24 hour pH values were not different in the corpus (*H pylori* positive=1.5, negative=1.4;  $p=0.9$ ) or antrum (*H pylori* positive=1.3, negative=1.2;  $p=0.1$ ). However, during omeprazole treatment, median 24 hour pH values were higher in *H pylori* positive subjects, both in the corpus (*H pylori* positive=5.5, negative=4.0;  $p=0.001$ ) and antrum (*H pylori* positive=5.5, negative=3.5;  $p=0.0004$ ). During placebo treatment, the only difference between the two groups was a higher later nocturnal pH in the antrum in the *H pylori* positive group. During omeprazole treatment, gastric pH was higher both in the corpus and in the antrum in the *H pylori* positive group for all periods, except for mealtime in the corpus. These data indicate that omeprazole produces a greater decrease in gastric acidity in subjects with *H pylori* infection than in those who are *H pylori* negative. It is not, however, known whether there is a causal relationship between *H pylori* infection and increased omeprazole efficacy.

(Gut 1995; 36: 539–543)

Keywords: Acid inhibition, *Helicobacter pylori*, omeprazole, intragastric pH-metry.

Omeprazole has been shown to have both direct<sup>1</sup> and indirect<sup>2,3</sup> effects on *Helicobacter pylori*, but it is not known whether infection with the organism may itself influence gastric acidity during omeprazole therapy. It has been reported that during treatment with omeprazole, the intragastric pH is higher in patients with duodenal ulceration than in healthy controls.<sup>4,5</sup> It is unclear whether this reduction in gastric acidity is observable in all subjects with *H pylori* infection, or whether it is confined to a subset of patients who develop peptic ulceration. If the increased susceptibility to omeprazole is related solely to *H pylori* infection then *H pylori* negative subjects and *H pylori* positive subjects without ulceration should show different degrees of acid

suppression in response to an equal dose of omeprazole.

To test the hypothesis that *H pylori* infection is associated with decreased intragastric acidity during treatment with omeprazole, we have conducted gastric pH-metry in *H pylori* positive individuals and compared the pH data with those obtained previously in 14 *H pylori* negative individuals.

## Methods

### SUBJECTS

Fourteen *H pylori* negative healthy subjects (seven men and seven women, age range: 22–46 years) and 18 *H pylori* positive subjects (11 men and seven women, age range: 22–45 years) were studied. Students and employees of a university hospital who had volunteered for an *H pylori* screening programme were also invited to participate in the present study. *H pylori* status was determined using the <sup>13</sup>C urea breath test performed before enrolment and confirmed serologically by a specific ELISA technique (Roche), in the *H pylori* positive group.

None of the subjects had a history of gastrointestinal disease or other illnesses. At the time of enrolment, all were asymptomatic and were taking no medication except the oral contraceptive pill or paracetamol. Subjects were excluded if they had a history of alcohol or drug abuse. Smokers were not excluded from the study, but they were asked not to smoke during pH-metry.

All subjects gave written, informed consent, and the study was conducted according to the Declaration of Helsinki. The protocol was approved by the local ethical committee.

### PROTOCOL

#### Treatment plan

Subjects received a one week course of omeprazole (20 mg once daily) and a one week course of placebo. The *H pylori* negative subjects received placebo and omeprazole treatment sequentially, following a single blind design. The *H pylori* positive subjects were treated in a randomised, cross over, double blind fashion. Washout periods lasted four to six weeks between treatments.

#### 24 hour pH-metry

At the end of each one week treatment period, 24 hour intragastric pH-metry was performed using a standard protocol. Subjects arrived at

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Accepted for publication  
15 July 1994

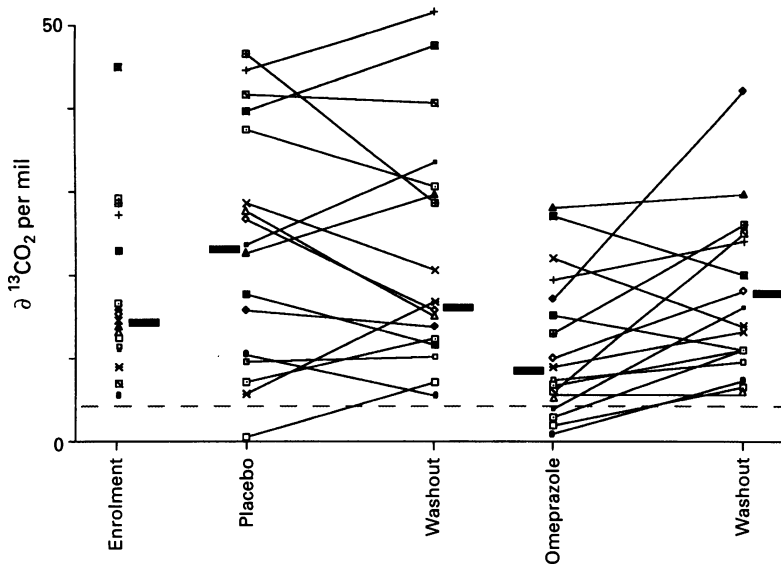


Figure 1:  $^{13}\text{C}$  urea breath test results in the *H. pylori* positive group at enrolment, after omeprazole treatment, after placebo and after washout periods of four to six weeks. The broken line shows normal cut off value for excess  $\delta^{13}\text{CO}_2$  per mil, horizontal bars show median values. Four transiently negative breath tests were observed during omeprazole treatment and one was observed during placebo administration. All subjects had a positive result after washout periods.

the laboratory at 08:00 hours after an overnight fast. The pH measuring assembly was passed through an anaesthetised nostril and positioned fluoroscopically, so that the proximal pH electrode was located in the corpus, 5 cm from the cardia, and the second electrode was located in the antrum, 7.5 cm distally. Recordings started at 08:30 and standard meals, prepared in the hospital, were provided for all subjects.<sup>6</sup> After the supervised ingestion of the study medication at 08:45, subjects returned home with instructions to eat breakfast at 09:15, lunch at 13:00, and supper at 19:00. At the start of the recording, subjects were provided with two litres of water to be consumed during the study, but other beverages were not allowed. Subjects retired to bed at 22:00 and arose at 06:00 to return to the laboratory by 08:15. The position of the assembly was checked before removal at 08:30. Subjects were instructed to use the event marker on the data logger to mark the start and end of each meal, the times at which they retired to bed and got up, and the occurrence of any other important event.

#### Equipment

Intragastric pH measurements were performed using two combined glass pH electrodes (GK2801C, Radiometer, Copenhagen, Denmark). The electrodes were covered by a silicon rubber tube (OD/ID 3.0 mm/2.5 mm) with one electrode at the tip and the other situated at 7.5 cm proximally. The electrodes were connected to a 512 kbyte memory data logger (LZ-105, Kaufhold, Berlin, Germany), in which electrode potentials were stored without prior processing. The pH electrodes were calibrated before and after each recording, using standard buffer solutions of pH 1.09 and 7.38 at room temperature (S1368 and S1356,

Radiometer, Copenhagen, Denmark). At the end of each recording, data were transferred to a computer (Atari-Mega-ST4, Atari Sunnyvale, Ca, USA) running under the OS-9 operating system (Microware, Des Moines, IA, USA), and were transformed to pH values after correction for buffer temperature and 24 hour pH electrode drift. Data were transferred to a computer disk for later analysis and storage.

#### $^{13}\text{C}$ urea breath test

In all subjects, breath tests were performed before enrolment. In subjects found to be *H. pylori* positive, additional breath tests were conducted before and after each treatment week. Two breath samples were obtained before and 30 minutes after administration of 100 mg of  $^{13}\text{C}$  urea mixed in 100 ml orange juice.<sup>7</sup> The ratio  $^{13}\text{CO}_2/^{12}\text{CO}_2$  was measured by mass spectrometry; the ratio in the 30 minute sample was subtracted from that in the baseline breath sample and compared with a reference value.<sup>8</sup> Results were expressed as excess  $\delta^{13}\text{CO}_2$  per thousand ( $\delta^{13}\text{CO}_2$  per mil), and a value of  $>5$  was considered as a positive result.

#### DATA ANALYSIS AND STATISTICAL EVALUATION

As in previous studies<sup>9</sup> we predefined the following time intervals; entire recording (0830–0830), mealtime periods (0915–1115, 1300–1500, 1900–2100), night-time (2200–0600), and the remaining combined non-meal daytime period. The overall night-time period was divided into early (22:00–02:00) and late (02:00–06:00) night-time; individual median pH values for each period of interest were obtained for statistical analysis. Summary 24 hour pH curves for each individual were obtained by calculating consecutive 1 minute median pH values resulting in 1440 data points; group curves are presented as means for *H. pylori* positive and *H. pylori* negative groups.

The Mann-Whitney U test was used to compare median pH values between groups and the Wilcoxon rank test for paired data was used to compare pH values within each group.

Multiple comparisons between breath test values at enrolment, after treatments, and after washout periods were performed using the Friedman test, followed by Wilcoxon-Wilcox.

#### Results

Fourteen *H. pylori* negative subjects completed the study and no adverse events attributable to omeprazole were detected. Seventeen *H. pylori* positive subjects completed the study. Data from one *H. pylori* positive subject were excluded when the subject was found to be achlorhydric (median 24 hour pH of 6.2 during administration of placebo). A second subject was withdrawn during omeprazole treatment and replaced, because of the development of high transaminase activities which returned to normal after stopping treatment.

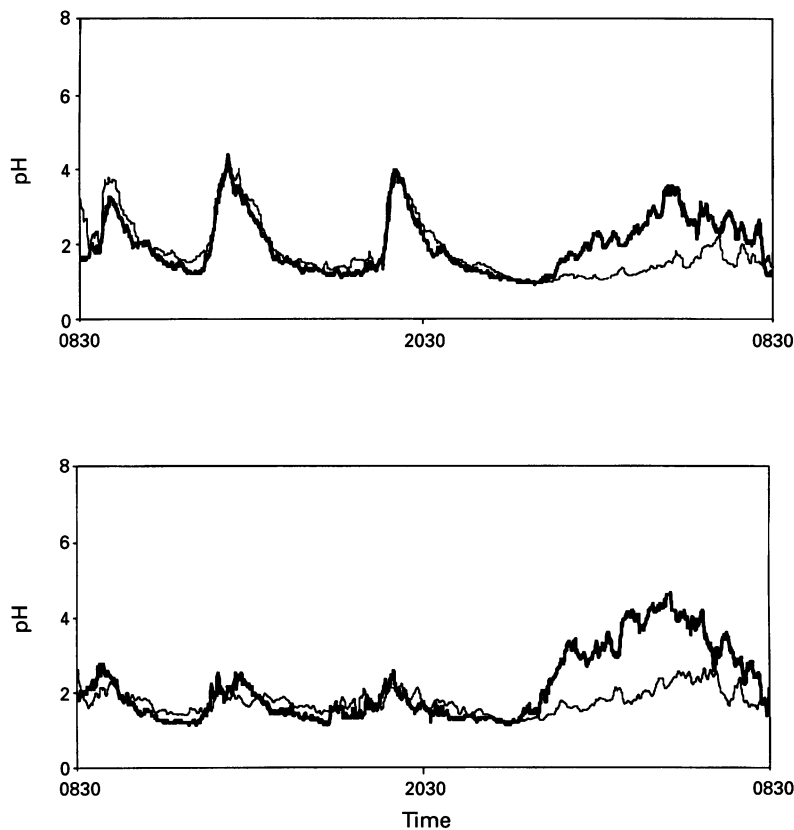


Figure 2: Placebo mean pH curves for the corpus (upper), and antrum (lower) 24 hour recordings in *H pylori* positive subjects (heavy line) and *H pylori* negative subjects (thin line). Similar median 24 hour gastric pH values were observed in both groups, in the corpus ( $p=0.9$ ) and in the antrum ( $p=0.1$ ).

#### <sup>13</sup>C UREA BREATH TEST AND SEROLOGY

The median  $\delta^{13}\text{CO}_2$  per mil did not change after the placebo treatment period compared with the values obtained at enrolment; one subject had a negative breath test after placebo but it became positive after the washout period. The median  $\delta^{13}\text{CO}_2$  per mil was lower after omeprazole treatment period than at enrolment ( $p<0.01$ ) or after placebo ( $p<0.01$ ), but the effect was transient and after the washout period the breath tests were again positive in the four subjects whose breath tests had become negative after omeprazole (Fig 1).

All subjects who had a positive breath test also had a positive serology. Transiently negative breath tests were also associated with positive serology, although serological titres in these four cases were lower than those obtained during enrolment (data not shown).

TABLE I Median pH values (95% CI) in the corpus for the entire 24 hour recording and for other time periods during the placebo and omeprazole treatment phases in *Helicobacter pylori* positive (HP+ve) and negative (HP-ve) subjects

Time	Placebo		Omeprazole	
	HP+ve	HP-ve	HP+ve	HP-ve
24 Hours	1.5 (1.3-1.7)	1.4 (1.2-2.0)	5.5 (4.5-5.6)	4.0 (2.6-4.6)
		$p=0.9$		$p=0.001$
Mealtime	2.3 (2.1-3.0)	2.0 (1.6-2.9)	5.6 (5.1-5.6)	5.2 (4.1-5.8)
		$p=0.1$		$p=0.2$
Daytime	1.3 (1.2-1.7)	1.4 (1.2-2.1)	5.4 (4.1-5.6)	2.9 (2.1-4.3)
		$p=0.5$		$p=0.001$
Night-time	1.1 (0.9-1.8)	1.1 (1.0-1.8)	4.7 (3.2-5.2)	1.9 (1.3-2.5)
		$p=0.3$		$p=0.007$
Early night-time	1.0 (0.9-1.2)	0.9 (0.7-1.3)	2.7 (2.1-4.4)	1.4 (1.0-1.9)
		$p=0.4$		$p=0.008$
Late night-time	1.4 (1.2-3.1)	1.2 (1.0-1.3)	6.5 (4.2-7.0)	2.1 (1.3-5.4)
		$p=0.07$		$p=0.0007$

#### INTRAGASTRIC pH-METRY

During placebo administration, the mean 24 hour pH curves were similar in the two groups in both the antrum and corpus, apart from a somewhat higher later nocturnal pH in *H pylori* positive subjects (Fig 2). Similarly, the median 24 hour pH values in the two groups were not different and nor were the mealtime, non-meal daytime, and nocturnal median pH values. However, the late nocturnal median pH values were higher in the *H pylori* positive subjects in the antrum ( $p=0.03$ ) but not in the corpus ( $p=0.07$ ) (Tables I and II).

During omeprazole administration, the mean 24 hour pH curves in both the antrum and corpus were clearly higher in the *H pylori* positive than in the negative subjects, throughout the entire recording period (Fig 3). The median 24 hour pH values were higher in the *H pylori* positive group as were the median non-meal daytime and nocturnal pH values; the mealtime pH values were higher in *H pylori* positive subjects in the antrum but not in the corpus (Tables I and II).

#### Discussion

During omeprazole treatment, the median 24 hour pH values in the *H pylori* positive subjects were appreciably higher than in the *H pylori* negative subjects. The difference was evident during the entire recording, except for mealtime periods, but was most noticeable during the nocturnal part of the recording. In contrast, during placebo treatment, the median 24 hour pH values did not differ between the two groups and the 24 hour pH profiles were similar.

Previous studies have suggested that omeprazole might produce a greater fall in gastric acidity in duodenal ulcer patients than in healthy subjects,<sup>4,5</sup> but it was not possible to say whether this was a result of the presumed *H pylori* infection or whether it was associated rather with an ulcer diathesis in these patients. The results of the present study suggest that it may be the *H pylori* infection, and not the ulcer diathesis, which is associated with the greater susceptibility to omeprazole.

It seems likely that the *H pylori* related accentuation of omeprazole induced gastric hypoacidity is prolonged since this interaction would be consistent with the efficacy of omeprazole noted in duodenal ulcer patients.<sup>4,5</sup> However, it is not clear whether this interaction will persist after eradication of *H pylori*, and, if it does persist, how long it will be evident. At present, the mechanisms underlying the interaction between *H pylori* and omeprazole are unknown and it is, therefore, difficult to predict the possible consequences. It is possible that the presence of *H pylori* and its subsequent suppression or eradication in patients with reflux oesophagitis (a disease unrelated to *H pylori*) may change the therapeutic efficacy of a given dose of omeprazole. If the *H pylori* related effect is dependent on the presence and concentration of *H pylori* in the gastric mucosa, it is also possible that the suppression of *H pylori* in patients with peptic



TABLE II Median pH values (95% CI) in the antrum for the entire 24 hour recording and for other time periods during the placebo and omeprazole treatment phases in *Helicobacter pylori* positive (HP+ve) and negative (HP-ve) subjects

Time	Placebo		Omeprazole	
	HP+ve	HP-ve	HP+ve	HP-ve
24 Hours	1.3 (1.1-2.3)	1.2 (1.1-1.4)	5.5 (4.5-5.7)	3.5 (2.0-4.2)
Mealtime	1.5 (1.3-2.2)	1.4 (1.1-1.5)	5.5 (4.6-5.5)	4.4 (2.0-4.8)
Daytime	1.2 (0.9-1.9)	1.2 (1.0-1.4)	5.6 (4.4-5.7)	2.8 (1.6-4.0)
Night-time	1.5 (1.4-3.3)	1.2 (1.0-1.4)	5.8 (3.9-5.9)	2.5 (1.4-3.6)
Early night-time	1.1 (1.0-1.6)	1.0 (0.9-1.1)	2.8 (1.6-4.3)	1.6 (1.1-2.1)
Late night-time	4.1 (2.7-4.8)	1.4 (1.1-1.6)	6.8 (6.0-7.0)	4.3 (1.8-6.1)

ulcer disease who are pretreated with omeprazole may alter the efficacy of eradication regimens which require the concomitant administration of an antisecretory agent.

The mechanisms responsible for the enhanced effect of omeprazole on intragastric pH in the *H pylori* positive subjects are unclear. It may be that *H pylori* has only an indirect effect on the efficacy of omeprazole, related to the development of an immune cell infiltrate and gastritis. Mononuclear cells produce factors which liberate gastrin<sup>10</sup> and stimulate acid secretion by histamine release from enterochromaffin-like cells.<sup>11 12</sup> It is, therefore, possible that gastritis is responsible for the decreased antral somatostatin<sup>13-16</sup> and increased plasma gastrin<sup>17-22</sup> seen in *H pylori* infection. The resulting parietal cell stimulation would decrease the intracanalicular pH<sup>23</sup> leading either to increased transformation of omeprazole into the active sulphenamide form, or to increased availability of proton

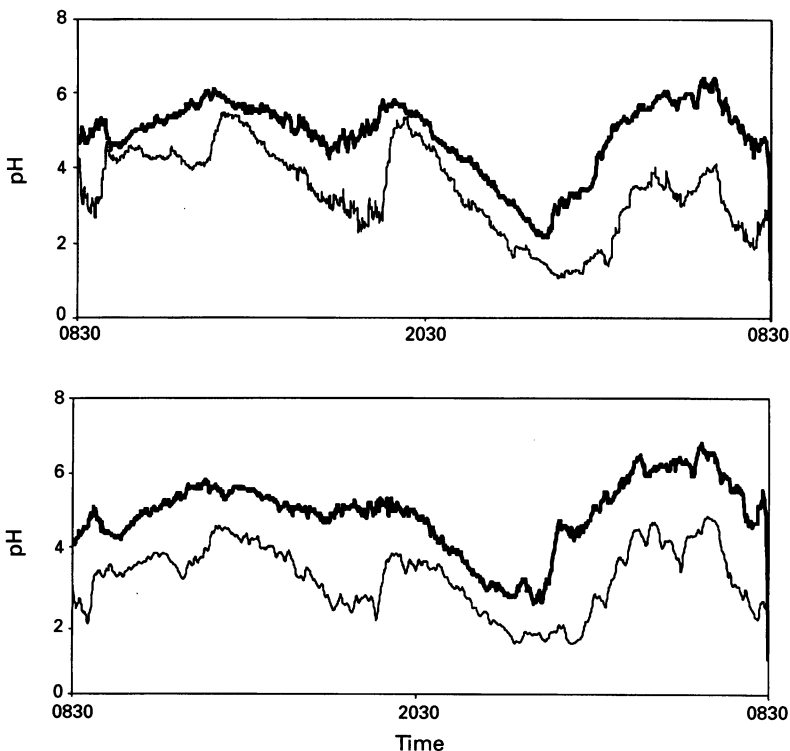


Figure 3: Mean pH curves for the corpus (upper) and antrum (lower) 24 hour recordings in *H pylori* positive subjects (heavy line) and *H pylori* negative subjects (thin line) during omeprazole therapy. Gastric acidity was decreased to a much greater extent by omeprazole in *H pylori* positive subjects (corpus:  $p=0.001$ ; antrum:  $p=0.0004$ ) than in *H pylori* negative subjects.

pumps susceptible to the activated omeprazole.

It has been reported that *H pylori* density decreases in the antrum and increases in the corpus after four weeks of omeprazole therapy.<sup>24 25</sup> Theoretically, this could increase the exposure of parietal cells to a variety of substances released by *H pylori* which can inhibit acid secretion in vitro.<sup>26 27</sup> However, the subjects in the present study received omeprazole at a lower dose for only one week and it is unknown whether this would, in fact, be adequate to produce the reported redistribution of *H pylori* within the stomach and a consequent improvement of the gastritis sufficient to affect gastric acidity. The fact that the <sup>13</sup>C urea breath test became transiently negative in only a minority of subjects (Fig 1), suggests that the decreased acidity was not due to an effect of omeprazole on *H pylori* density. Confirmation of this supposition would, however, require gastric pH studies earlier and later during the course of omeprazole therapy with endoscopic biopsies from the antrum and corpus to monitor changes in *H pylori* density and mucosal inflammation.

The daytime intragastric pH profiles found during placebo administration in both groups are similar and consistent with the pH curves recorded in healthy subjects in previous studies.<sup>28</sup> The nocturnal pH increases in *H pylori* positive subjects appear an exaggeration of the pattern observed in *H pylori* negative subjects. We have previously shown that although nocturnal alkalisation may be partly caused by duodenogastric reflux, other possibilities, such as mucosal wedging of the antral electrode, must also be considered.<sup>9</sup> The more noticeable peaks in pH found in the *H pylori* positive group could be explained by an effect of the organism on gastric motility, leading to more rapid gastric emptying of acid or to increased reflux. However, no clear relationship has been established between *H pylori* infection and altered gastrointestinal motility.<sup>29-32</sup> Acid hyposecretion, as a result of either mucosal atrophy<sup>33</sup> or direct inhibition of acid production induced by *H pylori* infection, is another possible explanation for the higher nocturnal pH found in *H pylori* positive subjects during omeprazole treatment. It is unlikely that any of the *H pylori* positive subjects in this study had gastric mucosal atrophy, since they were, in general, young, and the pH curves during placebo administration showed no evidence of hypoacidity. On the other hand, acid secretory inhibitors produced by *H pylori* have been investigated only in vitro<sup>26 27 34</sup> and their clinical relevance is not known.

Ammonia and carbamate produced by *H pylori* and the consequent neutralisation of secreted gastric acid<sup>35 36</sup> may also be responsible for the increased gastric pH observed during omeprazole administration in *H pylori* positive subjects. Studies investigating this possible mechanism will probably require prolonged monitoring of intragastric ammonia.

Although indirect, the current study suggests an important interaction between

omeprazole and *H pylori* status. Direct evidence will require the investigation of *H pylori* positive subjects tested before and after eradication. As the effects of *H pylori* infection on gastric feedback mechanisms, such as gastrin, may be long lasting,<sup>22 37</sup> such studies should allow sufficient time after *H pylori* eradication for healing of associated gastritis, which may itself modify gastric acidity.

In conclusion, *H pylori* infected subjects have a higher intragastric pH during treatment with omeprazole than *H pylori* negative subjects, although there is no difference between the two groups with regard to gastric acidity in the absence of omeprazole. Further studies are required to determine whether the increased susceptibility to omeprazole is a consequence, directly or indirectly, of *H pylori* infection or whether the increased omeprazole efficacy and *H pylori* infection are co-phenomena associated with another underlying abnormality.

Supported by Swiss National Fund 32-36349.92.

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