

## ABSENCE OF BENEFIT OF ERADICATING *HELICOBACTER PYLORI* IN PATIENTS WITH NONULCER DYSPEPSIA

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### ABSTRACT

**Background** The relation between *Helicobacter pylori* infection and nonulcer dyspepsia is uncertain. We tested the hypothesis that curing the infection will relieve symptoms of dyspepsia.

**Methods** We randomly assigned 170 *H. pylori*-infected patients with nonulcer dyspepsia to receive twice-daily treatment with 20 mg of omeprazole, 1000 mg of amoxicillin, and 500 mg of clarithromycin for 14 days and 167 such patients to receive identical-appearing placebos; all patients were then followed through regular visits for 12 months. Symptoms were scored on diary cards for seven days before each visit. A carbon-13 urea breath test was performed at base line and repeated at 1 and 12 months, and endoscopic biopsy was performed at 12 months to determine *H. pylori* status. Treatment was considered successful if the patient had only mild pain or discomfort or none at all.

**Results** The rate of eradication of *H. pylori* infection was 90 percent in the active-treatment group and 2 percent in the placebo group at four to six weeks ( $P < 0.001$ ). At 12 months, there was no significant difference between groups in the rate of successful treatment (46 percent in the active-treatment group and 50 percent in the placebo group; relative likelihood of success with active treatment, 0.93; 95 percent confidence interval, 0.73 to 1.18;  $P = 0.56$ ). There was also no significant difference in the rate of successful treatment at 12 months between patients who were *H. pylori*-negative and those who were *H. pylori*-positive (48 percent vs. 49 percent). The rates of successful treatment were also similar when patients were analyzed according to the type of dyspepsia (ulcer-like, reflux-like, or dysmotility-like) and changes in the quality of life. There was no significant association between treatment success and histologic improvement in chronic gastritis at 12 months ( $P = 0.68$ ).

**Conclusions** We found no evidence that curing *H. pylori* infection in patients with nonulcer dyspepsia leads to relief of symptoms. (N Engl J Med 1999; 341:1106-11.)

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**D**YSPEPSIA refers to pain or discomfort centered in the upper abdomen.<sup>1</sup> Dyspepsia may indicate the presence of serious disease, such as peptic ulcer or gastric cancer.<sup>2,3</sup> However, the most frequent type is nonulcer dyspepsia, in which no definite structural or biochemical explanation for the symptoms can be identified.<sup>4,6</sup>

At least 50 percent of patients with dyspepsia who are seen in primary care settings have nonulcer dyspepsia.<sup>4,5</sup> The discovery of *Helicobacter pylori* has resulted in important advances in the management of dyspepsia. It is now accepted that peptic ulcer is causally linked to the infection and that all patients who have ulcers and *H. pylori* infection should receive therapy to eradicate the diathesis.<sup>7-11</sup> However, although approximately 30 percent of patients with nonulcer dyspepsia also have *H. pylori* infection,<sup>2-6</sup> it is controversial whether they should receive antibacterial treatment. In 1994, a National Institutes of Health consensus conference recommended against the use of therapy for *H. pylori* infection in patients with nonulcer dyspepsia because of a lack of evidence of benefit.<sup>7</sup> More recently, other expert groups in North America, Europe, and Australasia have cautiously, but not unanimously, endorsed treating such patients on a case-by-case basis.<sup>8-11</sup> The older clinical studies of the treatment of *H. pylori* in patients with nonulcer dyspepsia had contradictory results and were often methodologically flawed.<sup>12</sup> Two recent European trials were well designed but also reached conflicting conclusions.<sup>13,14</sup>

We conducted a study in the United States to determine the effect of eradicating *H. pylori* infection in patients with nonulcer dyspepsia. Since chronic gastritis may take a long while to resolve after the eradication of *H. pylori*,<sup>15</sup> we followed our patients for 12 months.

### METHODS

#### Patients

Between July 1996 and March 1998, consecutive patients in the United States who were 18 to 65 years of age were invited to participate if they had had at least moderate pain or discomfort (or both) centered in the upper abdomen as their predominant symptom<sup>1</sup> for a minimum of three days in the week before randomization; had had dyspepsia for at least three months; and had normal endoscopic findings in the esophagus, stomach, and duodenum. Patients with reflux esophagitis, Barrett's esophagus, chronic gastric or duodenal ulceration, duodenal or esophageal erosions, or cancer and those with more than five gastric erosions on

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upper endoscopy were excluded. Patients who predominantly had heartburn or symptoms of the irritable bowel syndrome were also excluded. Ongoing treatment with a histamine H<sub>2</sub>-receptor antagonist, a prostaglandin, or a prokinetic drug during the 7 days before enrollment was not permitted, nor was treatment with a proton-pump inhibitor, an antibiotic, or bismuth in the 30 days before enrollment. Similarly, patients with a history of peptic ulcer or gastroesophageal reflux (on the basis of endoscopy or 24-hour testing of esophageal pH) were excluded, as were those with potentially serious symptoms such as unintentional weight loss. Occasional use of nonsteroidal antiinflammatory drugs (fewer than five days per month) or low-dose aspirin was allowed. The study protocol was approved by the applicable institutional review boards at all study sites, and written informed consent was obtained from all patients.

### Study Design

At base line, patients were screened for *H. pylori* with use of a carbon-13 urea breath test according to a standard, validated protocol in a central laboratory (Meretek Diagnostics, Houston). The results were considered positive if the value at 30 minutes was more than 2.4 U above the base-line value.<sup>16</sup> The patients then filled out diary cards during a seven day run-in period. No study medication was dispensed during the run-in period.

Patients who had a positive urea breath test and symptoms of dyspepsia during the run-in period underwent endoscopy the day before randomization. Patients were randomly assigned according to a computer-generated randomization list (1:1) to receive either twice-daily treatment with 20 mg of omeprazole (Prilosec, Astra Merck, Wayne, Pa.), 1000 mg of amoxicillin, and 500 mg of clarithromycin (Biaxin, Abbott Laboratories, Abbott Park, Ill.) for 14 days or twice-daily treatment with identical-appearing placebos. Neither the investigators nor the patients were aware of the treatment assignments.

The patients returned 4 to 6 weeks and 3, 6, 9, and 12 months after the cessation of treatment. Diary cards were completed the week before each visit and then collected. Adverse events were recorded, and compliance was assessed by tablet count. Urea breath testing was performed at 4 to 6 weeks and at 12 months; upper endoscopy and biopsy were also performed at the 12-month visit. An antacid with a weak neutralizing capacity (aluminum hydroxide, magnesium hydroxide, and simethicone; Gelusil, Parke-Davis, Morris Plains, N.J.) was dispensed at each visit during the year of follow-up, and the use of this agent was recorded.

### Assessment of Dyspepsia

Symptoms of dyspepsia were assessed with diary cards and the Gastrointestinal Symptom Rating Scale.<sup>17</sup> Each day, patients recorded their worst symptoms of dyspepsia on diary cards according to a four-point scale in which a score of 0 indicated no pain or discomfort, a score of 1 mild pain or discomfort, a score of 2 moderate (annoying but not interfering with the daily routine) pain or discomfort, and a score of 3 severe (markedly interfering with the daily routine) pain or discomfort. This scale is reliable, valid, and responsive and provides global assessment of symptoms.<sup>18</sup>

The Gastrointestinal Symptom Rating Scale, a validated 15-item instrument that includes seven graded scales, was used retrospectively to assess symptoms that had occurred during the preceding week. The scores on this test can range from 0 (no symptoms) to 6 (very severe symptoms).<sup>17</sup> Using the Gastrointestinal Symptom Rating Scale, we classified the patients according to the type of symptoms: ulcer-like dyspepsia, defined as the presence of at least moderate stomach pain and hunger pain in the week before a visit; dysmotility-like dyspepsia, defined as the occurrence of two or more episodes of at least moderate bloating, nausea, stomach rumbling, or belching in the week before a visit; and reflux-like dyspepsia, defined as the presence of at least moderate heartburn or acid regurgitation in the week before a visit. None of the subgroups were mutually exclusive.

### Histologic Assessment

Two biopsy specimens were obtained from the antrum and body of the stomach and examined by an experienced histopathologist who was unaware of the patients' treatment assignments. The corpus specimens were obtained 6 to 7 cm from the cardia along the greater curvature. The antral specimens were obtained from the anterior and posterior walls, 2 cm proximal to the pylorus. All samples were stained with Genta stain.<sup>19</sup> The specimens were classified as indicating the presence of active or chronic gastritis. In specimens with active gastritis, the histologic findings were graded as follows: no polymorphonuclear cells, a score of 0; rare polymorphonuclear cells, only in lamina propria, a score of 1; less than 1 intraepithelial polymorphonuclear cell per high-power field, a score of 2; 1 to 10 intraepithelial polymorphonuclear cells per high-power field, a score of 3; more than 10 intraepithelial polymorphonuclear cells per high-power field, a score of 4; and pit abscesses, a score of 5. In specimens with chronic gastritis, the histologic findings were graded as follows: scattered mononuclear cells that were not adjacent to lymphocytes and plasma cells, a score of 0; a slight increase in the thickness of the lamina propria, a score of 1; a definite increase in subepithelial areas of the lamina propria, a score of 2; an increase in all areas of the lamina propria, a score of 3; an increase in the thickness of the lamina propria and in the number of intraepithelial lymphocytes, a score of 4; and obliteration of the lamina propria, a score of 5.

### Status at 12 Months

If the urea breath test, the histologic analysis, or both were positive at 12 months, the patient was considered to be *H. pylori*-positive. If both tests were negative, then *H. pylori* was not considered to be present. If a patient had only one negative test available or had taken antimicrobial agents before the assessment, thus confounding the interpretation of these tests, his or her *H. pylori* status was considered indeterminate.

### Assessment of the Quality of Life

The patients' quality of life was assessed at base line and at the 12-month follow-up visit with use of the validated 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36).<sup>20</sup> This instrument assesses eight aspects of the quality of life: physical function, pain, general health, vitality, social function, physical health, emotional health, and mental health. Scores on each of these aspects can range from 0 (worst) to 100 (best). A change of 5 points is considered clinically significant.<sup>21,22</sup>

### Statistical Analysis

The study was designed to enroll 335 patients and have 270 patients in the efficacy analyses (i.e., >80 percent). This number of patients would provide the study with the ability to detect a 20 percent difference in 12-month success rates with a power of 88 percent. The rate of symptom relief in the placebo group was assumed to be 40 percent.

Treatment was considered successful if a patient reported having no more than mild pain or discomfort centered in the upper abdomen (a score of 0 or 1) during the 7 days before the final (12-month) visit on the daily diary card. Treatment was considered to have failed if a patient had taken medication for dyspepsia (other than antacids) in the 30 days before the 12-month visit.

For patients whose symptoms were not assessed at 12 months but whose symptoms had been assessed at the 4-to-6-week visit or afterward, the most recent results were used for the 12-month values. Symptom relief was compared in the two groups with use of Fisher's exact test.<sup>23</sup> Each symptom included in the Gastrointestinal Symptom Rating Scale and each aspect of the SF-36 was analyzed with the use of descriptive statistics. The mean change in scores between the two groups was compared with use of analysis of variance.<sup>24</sup> Missing scores were imputed for the SF-36 if at least 50 percent of the questions in that portion had been

answered by the patient.<sup>22</sup> The number of antacid tablets taken between visits was analyzed with the use of descriptive statistics and Fisher's exact test.<sup>23</sup>

Chronic gastritis was considered to be healed if both antral and corpus specimens had an inflammation score of 0 or 1.<sup>19</sup> Active gastritis was considered to be healed if the score was 0.<sup>19</sup> Patients who did not undergo endoscopy after randomization were excluded. Fisher's exact test was used to compare healing of gastritis in the two treatment groups.<sup>23</sup> All P values were two-tailed.

## RESULTS

### Base-Line Characteristics of the Patients

We screened 640 patients and excluded 303: 54 had abnormal findings on endoscopy, 3 did not complete their diaries, 131 were negative for *H. pylori*, 34 had minimal symptoms, 12 declined to provide consent, and 69 had other underlying conditions. A total of 170 patients (74 of them men) were randomly assigned to receive omeprazole, amoxicillin, and clarithromycin, and 167 (77 of them men) were assigned to receive placebo. The mean number of patients recruited at each center was 6 (range, 1 to 42). A total of 150 patients in the active-treatment group and 143 in the placebo group were included in the intention-to-treat analysis. Excluded were patients who had a positive urea breath test but who were negative for *H. pylori* at base line according to histologic assessment and a urease slide test (CLO test, Delta West, Bentley, Australia) (4 in the active-treatment group and 3 in the placebo group), a disqualifying dyspepsia score at base line that was overlooked by the investigator (4 in the active-treatment group and 9 in the placebo group), or no data after randomization (12 in each group). The two groups were well balanced with respect to demographic and clinical features; only the prevalences of caffeine use and a family history of ulcer were higher in the active-treatment group (Table 1).

### Eradication of *H. pylori* Infection and Healing of Gastritis

Urea breath testing showed that 90 percent of the patients in the active-treatment group (121 of 135) were negative for *H. pylori* at four to six weeks (data were incomplete for 7 patients), as compared with 2 percent of the patients in the placebo group (3 of 139,  $P<0.001$ ). At 12 months, the rates were 80 percent (78 of 98; 19 indeterminate) and 5 percent (6 of 119), respectively, on the basis of histologic assessment and urea breath testing ( $P<0.001$ ). According to an intention-to-treat analysis (excluding those with missing or inadequate data), 86 percent of the patients in the active-treatment group (95 of 110) had complete resolution of active (polymorphonuclear cell) gastritis (grade 0) at 12 months, as compared with 8 percent of the patients in the placebo group (9 of 114,  $P<0.001$ ). Similarly, 67 percent of the patients in the active-treatment group (74 of 110) had an improvement in chronic (mononuclear cell) gastritis (grade 0 or 1), as compared

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE 293 PATIENTS INCLUDED IN THE INTENTION-TO-TREAT ANALYSIS.

CHARACTERISTIC	OMEPRAZOLE, AMOXICILLIN, AND CLARITHROMYCIN (N=150)	PLACEBO (N=143)
Mean age (yr)	46.3	46.5
Male sex (%)	43	48
Race (%)		
White	44	47
Black	16	20
Asian	2	2
Middle-class socioeconomic status (%)	48	52
Current smoker (%)	27	26
Alcohol use (%)	41	41
Caffeine use (%)	82	73
Mean weight (lb)*	168.3	170.0
Family history of ulcers (%)	34	23

\*To convert values for weight to kilograms, divide by 2.2.

with 18 percent of the patients in the placebo group (21 of 114,  $P<0.001$ ).

Compliance with treatment was excellent, with 94 percent of the patients in each group taking at least 90 percent of the 28 doses. Only 4 percent of patients in the active-treatment group and none of those in the placebo group discontinued treatment because of adverse events; 10 percent of the patients in the active-treatment group had a disturbance in taste, as compared with none of those in the placebo group; the respective rates of diarrhea were 11 percent and 5 percent.

### Relief of Symptoms

According to the intention-to-treat analysis, at 12 months, treatment was successful (defined as the presence of no more than mild pain or discomfort) in 46 percent of the patients in the active-treatment group (69 of 150) and 50 percent of those in the placebo group (71 of 142,  $P=0.56$ ) (Table 2). The rate of treatment success among patients who were *H. pylori*-negative at 12 months was 48 percent (59 of 124), as compared with 49 percent among those who were *H. pylori*-positive (73 of 150,  $P=0.90$ ). There was no significant difference in mean symptom scores between the two treatment groups (Fig. 1) at any point during follow-up.

The mean rate of antacid use at 12 months was 5.7 tablets per week in the active-treatment group and 5.2 tablets per week in the placebo group ( $P=0.74$ ). The use of other gastrointestinal drugs during the 12 months of follow-up was similar in the two groups:

TABLE 2. PRIMARY AND SECONDARY OUTCOMES AT 12 MONTHS.\*

OUTCOME	OMEPRAZOLE, AMOXICILLIN, AND CLARITHROMYCIN (N=150)	PLACEBO (N=143)	ABSOLUTE DIFFERENCE BETWEEN GROUPS (95% CI)	RELATIVE LIKELIHOOD OF OUTCOME (95% CI)	P VALUE
	percent				
Successful treatment†	46	50	-4 (-15 to 8)	0.93 (0.73 to 1.18)	0.56
No dyspepsia	28	23	5 (-5 to 15)	1.21 (0.82 to 1.80)	0.35
Severe dyspepsia	25	20	5 (-4 to 15)	1.26 (0.82 to 1.95)	0.33

\*CI denotes confidence interval.

†Successful treatment — the primary outcome — was defined as the presence of no more than mild pain or discomfort centered in the upper abdomen (a score of 0 or 1) in the 7 days before the 12-month visit.

H<sub>2</sub>-receptor antagonists were taken by 14 percent of the patients in the active-treatment group and 15 percent of those in the placebo group; proton-pump inhibitors were taken by 4 percent and 3 percent, respectively; bismuth by 1 percent and 1 percent; and prokinetic drugs by 1 percent and less than 1 percent.

In the group with ulcer-like dyspepsia, treatment was successful at 12 months in 41 percent of the patients who received active treatment (54 of 131) and 48 percent of the patients who received placebo (59 of 122). The corresponding rates were 42 percent and 49 percent in the group with dysmotility-like dyspepsia and 40 percent and 48 percent in the group with reflux-like dyspepsia.

The SF-36 scores are summarized in Table 3. At 12 months, the only significant differences between groups were in the scores for physical health, which were better in the placebo group, and for emotional health, which were better in the active-treatment group. However, most of the differences in the scores at 12 months were small and were not clinically significant.

**Outcome among Patients with Chronic Gastritis**

Patients with chronic gastritis were subdivided regardless of treatment into those with a score of 0 or 1 (no gastritis or mild gastritis) and those with a score of 2, 3, 4, or 5 (moderate or severe gastritis). At the 12-month follow-up visit, treatment was considered to have been successful in 54 percent of the patients with a score of 0 or 1 (14 of 26), as compared with 49 percent of the patients with a score of 2, 3, 4, or 5 (99 of 201, P=0.68).

**Development of Peptic Ulcer**

At the 12-month follow-up visit, a duodenal ulcer had developed in 2 percent of the patients in the active-treatment group (3 of 170), as compared with 4 percent of those in the placebo group (7 of 167,

P=0.22). The rate of development of gastric ulcers during follow-up was the same in the two groups (2 percent).

**DISCUSSION**

We tested the hypothesis that *H. pylori* is a cause of nonulcer dyspepsia but found no convincing evidence that eradication of this infection cures the disorder. Complete relief of symptoms at 12 months,

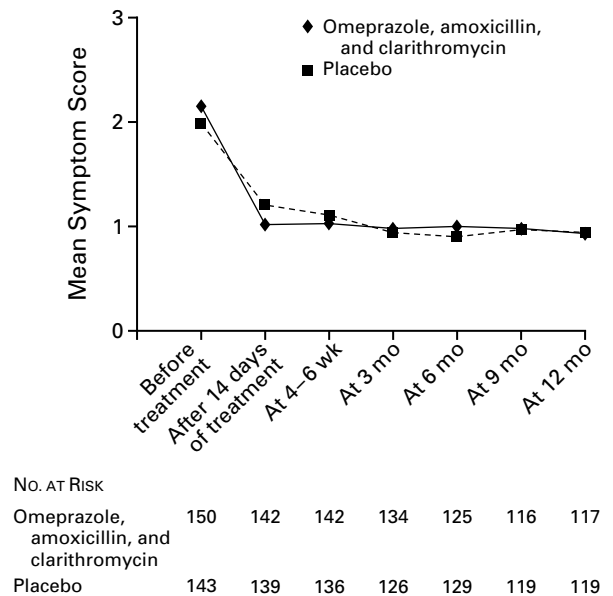


Figure 1. Mean Dyspepsia Symptom Scores Recorded on Diary Cards by the Patients during the Week before Each Visit, According to the Intention to Treat.

A score of 0 indicates no pain or discomfort, a score of 1 mild pain or discomfort, a score of 2 moderate pain or discomfort, and a score of 3 severe pain or discomfort.

**TABLE 3.** QUALITY OF LIFE ACCORDING TO THE MEAN SCORES ON THE 36-ITEM MEDICAL OUTCOMES STUDY SHORT-FORM GENERAL HEALTH SURVEY.\*

ASPECT	OMEPRAZOLE, AMOXICILLIN, AND CLARITHROMYCIN				PLACEBO			
	BEFORE TREATMENT	AT 4-6 WK	AT 6 MO	AT 12 MO	BEFORE TREATMENT	AT 4-6 WK	AT 6 MO	AT 12 MO
Physical function	76.0	77.8	77.4	80.5	81.6	84.3	79.1	82.3
Physical health	58.7	74.0	70.4	77.2	70.7	78.6	74.1	79.7†
Pain	53.3	67.6	68.7	70.7	56.4	65.8	67.6	70.5
General health	61.1	64.2	61.2	65.3	65.6	66.6	67.2	69.4
Vitality	51.7	57.2	56.8	59.8	53.9	58.1	60.3	61.6
Social function	69.8	79.1	76.7	80.0	73.7	79.9	81.2	83.8
Emotional health	70.4	76.5	73.4	84.8	74.5	81.6	78.9	81.0‡
Mental health	67.2	70.0	67.6	71.5	68.3	69.3	70.3	72.1

\*For each aspect of the instrument, scores can range from 0 (worst) to 100 (best).<sup>20</sup> A change of 5 points was considered clinically significant.

†P=0.05 for the comparison with the active-treatment group.

‡P=0.04 for the comparison with the active-treatment group.

for example, occurred in 28 percent of the patients who received omeprazole and antibiotics and 23 percent of those who received placebo. The results of assessments of other outcomes of dyspepsia were similar. Active treatment was not associated with a clinically significant improvement in the quality of life.

There have been a number of relatively small studies of the effect of the eradication of *H. pylori* infection on nonulcer dyspepsia, but most have had design limitations.<sup>7-12</sup> In particular, many studies with a negative outcome were very small.<sup>12,15,25</sup> Recently, well-designed, larger trials have reported conflicting results. McColl et al. conducted a single-center, randomized, placebo-controlled study of 318 patients in Scotland.<sup>14</sup> Triple therapy with omeprazole, amoxicillin, and metronidazole was compared with therapy with omeprazole alone for 1 week, with 12 months of follow-up. At one year, dyspepsia had resolved in 21 percent of the patients in the triple-therapy group, compared with 7 percent of the patients in the group given omeprazole alone — a significant difference. The results suggested that one in five patients with nonulcer dyspepsia will benefit from eradication therapy. Two factors — the high background rate of ulcer disease in the population from which the patients were recruited and the fact that endoscopic follow-up was not routinely performed — may in part explain the low rate of response to placebo, since patients in whom ulcer was misdiagnosed as nonulcer dyspepsia would be more likely to become symptomatic.

Other predominantly European multicenter trials have reached different conclusions. Blum et al. randomly assigned 348 patients to receive triple therapy with omeprazole, amoxicillin, and clarithromycin or therapy with omeprazole alone for one week; the

patients were then followed for a year.<sup>13</sup> Treatment was successful in 27 percent of the patients in the triple-therapy group and 21 percent of those in the placebo group — a difference that was not significant. Similarly, Talley et al. randomly assigned 275 patients to receive triple therapy with omeprazole, clarithromycin, and amoxicillin or placebo alone for one week.<sup>26</sup> At one year, 24 percent of the patients in the active-treatment group and 21 percent of those in the placebo group had relief of dyspepsia — also not a significant difference.<sup>26</sup>

In our study, the active-treatment group had a higher rate of response than did the triple-therapy groups in the European studies, presumably because of the primary outcome measure used, but the rate of response was similar in the placebo group. The rate of response to placebo did not decline during the 12 months of follow-up in our study despite the requirement that patients have symptoms of chronic disease before entry. One study with otherwise negative results reported that patients with resolution of gastritis were significantly more likely to have symptom relief than those who had persistent inflammation 12 months after triple therapy or placebo, although this finding was based on a secondary analysis.<sup>26</sup> We found, however, no association between histologic improvement in gastritis and relief of symptoms of dyspepsia, suggesting that the previous observations represent chance findings.

In conclusion, we assessed the clinical benefits of the eradication of *H. pylori* infection in patients with nonulcer dyspepsia in a randomized, double-blind, placebo-controlled study. We found no evidence that eradicating the infection leads to relief of symptoms 12 months after treatment.

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