Original Article

Antral Atrophy, *Helicobacter pylori* Colonization, and Gastric pH

BERNARDO RUIZ, MD, PELAYO CORREA, MD, ELIZABETH T.H. FONTHAM, DrPH, AND THIRUVENGADAM RAMAKRISHNAN, MD

The association between the topographic distribution of *Helicobacter pylori* colonization, inflammation and atrophy of the gastric mucosa, and fasting gastric pH was studied in a population with high prevalence of multifocal atrophic gastritis. Increasing atrophy of the antrum was associated with decreasing *H pylori* colonization of the antrum itself, but increasing colonization of the corpus. Advanced atrophy was associated with high fasting gastric pH. However, after therapeutic eradication of *H pylori*, inflammation subsided and gastric pH decreased indicating improved acid secretion despite persistent atrophy. The authors propose that antral atrophy fosters the colonization of oxyntic mucosa by *H pylori*, thus impairing acid secretion and causing hypochlorhydria that may further promote colonization of the oxyntic mucosa. Eradication of *H pylori* significantly improves hypochlorhydria. It may restore acid secretion in most patients, regardless of the presence of atrophy, which is an effect that may be of great benefit in halting the process of gastric carcinogenesis. (Key words: *Helicobacter pylori*; Chronic gastritis; Atrophy; Gastric pH; Hypochlorhydria) Am J Clin Pathol 1996;105:96–101.

Inconsistent findings have been published regarding the effects of *Helicobacter pylori* on gastric acidity and acid secretion.[1-14] Most studies are based on a very small number of observations, deal only with duodenal ulcer patients or asymptomatic volunteers, and do not consider the type of gastritis, the presence of atrophy, or the effect of *H pylori* colonization in the different specialized areas of the gastric mucosa.

Helicobacter pylori infection causes hypergastrinemia and hyperacidity, which is a mechanism that has been related to the etiology of duodenal ulcers, in at least in some individuals.[4,7,15] However, at Charity Hospital in New Orleans, *H pylori* infection is often associated with hypochlorhydria. Hypochlorhydria is thought to be a consequence of atrophic gastritis and has been related to the etiology of gastric cancer.[16] We examined the associations among the presence, abundance, and topographic distribution of *H pylori* infection in the gastric mucosa, mucosal atrophy, and fasting gastric pH in patients referred for endoscopy.

MATERIALS AND METHODS

Subjects of this study were referred for endoscopy at Charity Hospital in New Orleans, had not taken antibiotics, bismuth, or drugs that inhibit acid secretion during the previous 2 weeks and gave a written informed consent. This study was approved by the Louisiana State University Medical School Institutional Review Board.

Patients were examined after overnight fast. Immediately after passing the endoscope into the stomach, up to 50 mL of gastric juice were aspirated into a sterile container. Gastric juice pH was measured with a calibrated digital pH meter soon thereafter. Two antral biopsies (distal greater curvature and lesser curvature adjacent to the incisura angularis) and one biopsy from the gastric corpus (mid anterior wall) were fixed in buffered formalin and embedded in paraffin. Reported history of peptic ulcers and endoscopic observation of peptic ulcers were registered.

Patients infected with *H pylori* were prescribed bismuth subsalicylate 640 mg/day for 28 days, combined with amoxicillin 2 g/day and metronidazole 2 g/day on days 8 to 21. These patients were scheduled for a second endoscopy immediately after completion of treatment.

Modified Steiner preparations[17] were used to evaluate *H pylori* infection in the oxyntic and antral mucosae. The density of colonization was graded in each location as absent, scarce, moderate, or abundant (0–3+). Hematoxylin-and-eosin preparations were used to evaluate atrophy, intestinal metaplasia, neutrophilic and lymphocytic infiltrates, and the damage to the surface epithelium. These variables were graded in the oxyntic and antral mucosae as absent, mild, moderate, or severe (0–3+) by an observer blinded for the *H pylori* readings. Atrophy, defined as loss of glands, was estimated in well-

From the Departments of Pathology and Medicine, Louisiana State University Medical Center, New Orleans, Louisiana.

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Address reprint requests to Dr. Correa: Department of Pathology, Louisiana State University Medical Center, New Orleans, LA 70112.

oriented biopsies showing the whole thickness of the mucosa. The damage to the superficial epithelium was defined as the depletion of the apical mucus, evaluated with periodic acid–Schiff preparations, together with the observation of reduced cytoplasmic mass, epithelial pits, and microerosions in hematoxylin-and-eosin preparations. A global histologic diagnosis was assigned to each patient following previously published criteria.[18]

Fasting gastric pH readings were not normally distributed and this fact could not be corrected by transformation approaches; therefore, nonparametric methods of analysis were used. The median was used as central tendency measure. Median absolute deviation, defined as the median of the differences between each data point and the median, was used as a measure of spread or variability. Box plots, showing percentiles 10th, 25th, 50th, 75th, and 90th and outlier observations, were used for the graphic display of the distributions. The overlapping of distributions as shown does not necessarily imply lack of statistical significance. Two-tailed Wilcoxon signed rank test was used for paired comparisons before and after treatment. Two-tailed Mann-Whitney U test was used for unpaired comparisons between groups. The chi square statistic and a two-tailed chi square *P* value were used to relate the abundance of *H pylori* in the oxyntic and antral mucosae to the extent of atrophy in the antral mucosa.

RESULTS

Two hundred twenty-eight patients were examined. They ranged in age between 20 and 69 years (mean 45.6); 161 (70.6%) were black; 153 (67.1%) were female; and 158 (69.3%) were *H pylori*-positive. Infected patients had

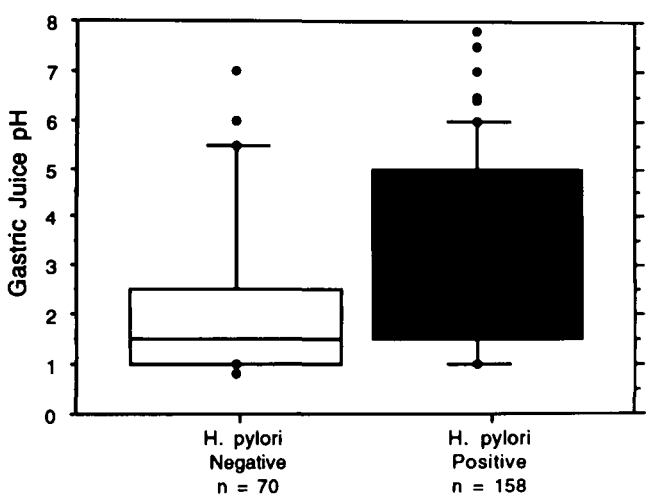

FIG. 1. Fasting gastric juice pH versus *Helicobacter pylori* status.

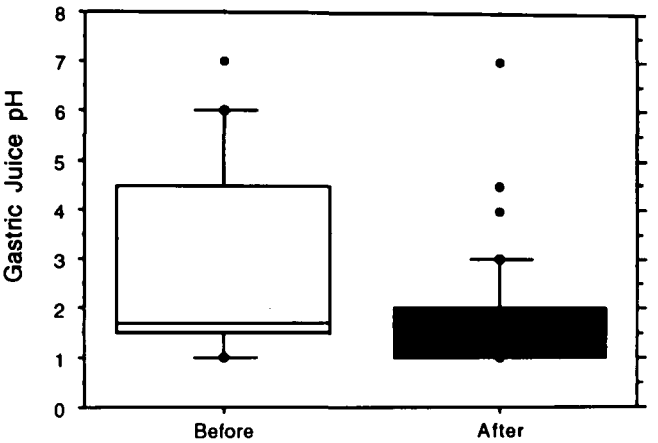

FIG. 2. Fasting gastric juice pH before and after clearance of *Helicobacter pylori* infection (n = 74).

significantly higher fasting gastric pH than those not infected ($P = .0015$, Fig. 1). Ninety-eight patients received the combined triple therapy and came back for a second endoscopy, and 74 (75.5%) cleared the infection. This clearance rate is fairly typical at Charity Hospital in New Orleans. Lack of compliance has been estimated as the principal cause for treatment failure in about 40% of the cases. Patients who cleared *H pylori* infection had a significant decrease in fasting gastric pH ($P < .001$ Fig. 2).

Table 1 shows the association between gastric pH and the abundance of *H pylori* organisms visualized in the oxyntic and antral mucosae. Only *H pylori*-positive patients are included in this Table. Two patients did not have colonization in the antrum, but *H pylori* was visualized in the oxyntic mucosa. Compared with patients who had small or moderate numbers of *H pylori* organisms in the oxyntic mucosa, those showing large numbers (3+) at that location had higher gastric pH ($P < .001$). The opposite association was observed in the antrum (ie, patients with few organisms had higher gastric pH than those with more abundant colonization [$P < .001$]). Patients with more abundant *H pylori* in the

TABLE 1. MEDIAN GASTRIC JUICE pH (MEDIAN ABSOLUTE DEVIATION) *VERSUS* NUMBER OF *HELICOBACTER PYLORI* ORGANISMS IN THE OXYNTIC AND ANTRAL MUCOSAE

	No. of H. pylori *Organisms*			
	None 0	*Small* 1+	*Moderate* 2+	*Large* 3+
Oxyntic mucosa	—	(n = 13)	(n = 103)	(n = 42)
	—	1.6 (0.6)	1.5 (0.5)	4.5 (1.5)
Antral mucosa	(n = 2)	(n = 25)	(n = 61)	(n = 70)
	6.0 (0.0)	4.5 (1.5)	1.6 (0.6)	1.5 (0.5)

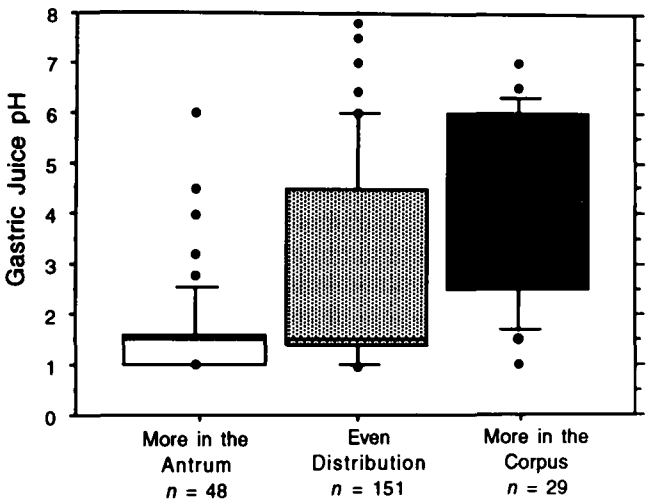

FIG. 3. Fasting gastric juice pH versus distribution of *Helicobacter pylori* in the antral and ocyntic mucosae.

oxyntic mucosa than in the antral mucosa had a significantly higher pH than patients with an even distribution (Fig. 3, $P < .001$) or those with more abundant organisms in the antrum ($P < .001$).

One hundred forty-three patients (62.7%) had multifocal atrophic gastritis, and 114 of them (79.7%) were *H pylori*-positive. *H pylori*- positive patients with moderate or severe atrophy (n = 56, median pH 2.5) had a significantly higher gastric pH than those with mild atrophy or no atrophy (n = 90, 1.5, $P = .01$). Among *H pylori*-negative patients, there was no significant difference in pH between those with moderate or severe atrophy (n = 56, median pH 1.5) and those with mild atrophy or no atrophy (n = 9, median pH 1.5). Twelve *H pylori*-positive patients and five *H pylori*-negative patients could not be evaluated for the extension of atrophy because of inappropriate orientation of the specimens. No difference in gastric pH was observed after clearance of the infection between patients with moderate or severe atrophy (n = 38, median pH 1.5) and those with mild atrophy or no atrophy (n = 35, median pH 1.5).

As shown in Table 2, the observed frequency of abundant *H pylori* (3+) in the oxyntic mucosa was directly related to the extent of atrophy in the antral mucosa (chi square = 11.78, $P < .01$). The abundance of *H pylori* organisms in the antral mucosa was not significantly related to the degree of antral atrophy. However, there was a tendency for patients with moderate and severe antral atrophy to have less abundant *H pylori* colonization at the same location. No significant association was found between the presence or severity of atrophy in the oxyntic mucosa and the distribution of *H pylori* organisms or fasting gastric pH. Only 14 patients showed atrophy in the oxyntic mucosa, and in 7 of them it was only mild.

Thirty-six patients had intestinal metaplasia, and 33 (91.7%) of them were *H pylori*-positive. There was no significant difference in gastric pH between patients with and without metaplasia. However, only two patients had intestinal metaplasia that comprised more than 30% of the tissue examined. Both of these patients had gastric pH ≥6.0.

The neutrophilic and lymphocytic inflammatory infiltrates and the damage to the superficial epithelium were positively associated both in the oxyntic and the antral mucosae with the degree of colonization by *H pylori*. Among *H pylori*-positive patients, the greater the damage to the surface epithelium the higher the gastric pH. However, this association was stronger in the oxyntic mucosa (median pH 3.6 for patients with moderate or severe damage versus 1.5 for those with mild damage or no damage, $P < .001$) than in the antral mucosa (median pH 2.5 versus 1.6, respectively, $P = .06$). Patients with moderate or severe neutrophilic (acute) infiltrate in the oxyntic mucosa (median pH 4.5) had higher gastric pH than those with mild or no infiltrate (median pH 1.5, $P < .001$). This association was not observed in the antral mucosa. Similarly, patients with moderate or severe lymphocytic (chronic) infiltrate in the oxyntic mucosa (median pH 2.5) had higher gastric pH than those with a mild or absent infiltrate (median pH 1.6, $P = .03$). Again, this association was not observed in the antral mucosa.

Twenty-seven patients had gastric ulcers not located in the pyloric or prepyloric regions (21 were *H pylori*-positive), 11 had pyloric or prepyloric ulcers (9 were *H pylori*-positive), 9 had duodenal ulcers (8 were *H pylori*-positive) and 4 had ulcers in more than one location (all *H pylori*-positive). Patients with duodenal ulcers had lower fasting gastric pH than patients with ulcers in other locations or without ulcers, but the differences were not statistically significant.

DISCUSSION

It has been proposed that the effect of *H pylori* on gastric acid secretion varies with the duration of the infec-

TABLE 2. OBSERVED FREQUENCY OF ABUNDANT (3+) *HELICOBACTER PYLORI* ORGANISMS IN THE OXYNTIC AND ANTRAL MUCOSAE *VERSUS* ANTRAL ATROPHY

	Antral Atrophy			
	Absent 0	*Mild* 1+	*Moderate* 2+	*Severe* 3+
Oxyntic mucosa	7/33	11/57	15/41	9/15
	21.2%	19.3%	36.6%	60.0%
Antral mucosa	16/33	28/57	17/41	5/15
	48.5%	49.1%	41.5%	33.3%

tion.[19] In this respect, it has been well documented that hypochlorhydria occurs during the acute phase of the primary infection.[20-23] However, no consistent effects of the infection on acid secretion have been demonstrated once chronic active gastritis develops. Chronic gastritis progresses in some individuals to multifocal atrophic gastritis that is supposed to cause a gradual loss of secretory function and hypochlorhydria.[16]

The results of this study show that chronic *H pylori* infection *per se* can cause hypochlorhydria; that the probability of hypochlorhydria is directly associated with the abundance of *H pylori* organisms in the oxyntic mucosa and with the extent of damage and inflammation at this location; and that the abundance of *H pylori* organisms in the oxyntic mucosa is positively associated with the degree of antral atrophy.

These findings verify observations reported by Karttunen and colleagues[24] in a Finnish population. In a smaller study in a population with a lower prevalence of *H pylori* infection and atrophic gastritis, they also found that patients with more abundant *H pylori* in the corpus than in the antrum have much higher gastric pH than those with an even distribution or more abundant organisms in the antrum, and that the abundance of *H pylori* organisms in the corpus was positively correlated with the grade of atrophy in the antrum. Additionally, Maaroos and colleagues[25] observed in a Estonian population that an abundant *H pylori* colonization in the corpus was associated with the presence of antral atrophy, but they did not study the effect of this distribution on gastric pH. The joint consideration of these observations and our findings makes it very likely that the degree of antral atrophy determines the abundance of *H pylori* colonization of the oxyntic mucosa and the effect of the infection on gastric pH.

Ammonia generated by *H pylori*'s urease can neutralize the acidity locally, generating the so-called "ammonia cloud." This local pH change may be sufficient to interfere the feedback inhibition of gastrin release,[7] although stoichiometrically, it can have minimal or no direct effect on global gastric acidity as measured in gastric juice. *Helicobacter pylori* infection increases blood levels of gastrin.[15] Multiple mechanisms have been proposed for this effect,[7,15,26-31] but most imply a local effect of *H pylori* in the antral mucosa, directly or indirectly affecting the G cells and/or the D cells. However, in the oxyntic mucosa, there is good evidence that *H pylori* impairs the secretory function of parietal cells. This effect can be caused either directly by *H pylori* inhibitory products[32-36] or indirectly by the inflammatory response to the infection.[19] These disparate effects of *H pylori* in antral and oxyntic mucosae, together with the variable distribution of *H pylori* in those two areas here reported, may explain the seemingly inconsistent effects of the infection on acid secretion. We propose that in the absence of antral atrophy, a relatively abundant colonization of the antrum occurs with only little compromise of the corpus. Under these circumstances, the infection causes hypergastrinemia that, unopposed by any significant inhibition of parietal cells, increases acid secretion favoring the development of duodenal ulcers. When antral atrophy is established, colonization of the oxyntic mucosa is favored, and this significantly impairs acid production by parietal cells despite persistence of high levels of gastrin. This mechanism may explain why hypochlorhydria is seldom associated with *H pylori* infection in populations with low prevalence of atrophic gastritis, such as those with high frequency of duodenal ulcers.

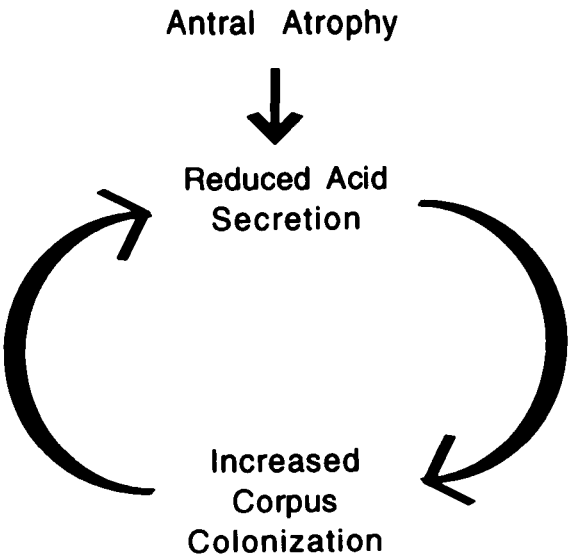

FIG. 4. Proposed scheme relating colonization of gastric corpus by *Helicobacter pylori* to antral atrophy and reduced acid secretion.

It is not clear what causes the increased colonization of the gastric corpus when antral atrophy occurs. In a recent report, Kuipers and coworkers[37] suggest that acid secretion *per se* is an important determinant for the observed distribution pattern of *H pylori* between antral and oxyntic mucosae. They observed a substantial reduction in the number of *H pylori* organisms in the antrum with a concomitant increase in *H pylori*-associated inflammation of the oxyntic mucosa after 8 weeks of omeprazole therapy. Based on these observations and our findings, we propose a mechanism that may explain the widespread colonization of the gastric corpus in patients with multifocal atrophic gastritis (Fig. 4). In those patients, evolving antral atrophy may lead to a gradual loss of acid secretion, which may favor a gradual colonization of the oxyntic mucosa, setting up a vicious cycle

of increasing colonization of the oxyntic mucosa and decreasing acid secretion.

Different strains of *H pylori* may differ in their capacity of inducing atrophy and this outcome may be linked to the production of specific cytotoxins.[38,39] The importance of bacterial toxins and toxic by-products of the inflammatory response should be explored in relation to their potential to alter the acid secretion. Such toxic products may either cause antral atrophy or may have direct local effects in the antral and/or oxyntic mucosae.

An additional issue that may have important implications should be noted. According to our findings, multifocal atrophic gastritis does not cause hypochlorhydria, except perhaps in the most advanced cases, unless *H pylori* infection is also present. Clearance of the infection in patients with atrophy substantially decreases fasting gastric pH such that pH differences between those with and without atrophy are eliminated. Hypochlorhydria may promote the endogenous formation of *N*-nitroso compounds and may alter oxidation-reduction balance in the gastric microenvironment favoring the oxidative damage of the gastric epithelium and occupies a central place in a proposed model of gastric carcinogenesis.[16] It follows that eradication of *H pylori*, by eliminating or improving hypochlorhydria, may prove prophylactic against carcinogenesis, even in patients who have already developed atrophy.

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