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The importance of corpus biopsies for the determination of *Helicobacter pylori* infection

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ABSTRACT

Background: The aim of this study was to determine whether an antral biopsy alone represents an adequate tissue sample to diagnose the presence of *Helicobacter pylori* on the mucosa. Furthermore, we explored the conditions associated with the presence of *H. pylori* in the corpus.
Methods: Consecutive patients who underwent an upper gastrointestinal endoscopy at a single centre between January 1995 and May 1997 were studied. Biopsies were taken at each endoscopy to assess the presence of *H. pylori*: two antral and two corpus biopsies for histological examination and one antral and one corpus biopsy for the CLO test.
Results: A total of 620 patients underwent an upper gastrointestinal endoscopy, 307 (50%) were *H. pylori* infected. In 80% of the endoscopies there was total agreement between the performed biopsy tests. The addition of corpus biopsies increases the diagnostic yield by 10% in *H. pylori*-positive patients. Patients with only corpus infection more often showed atrophy and intestinal metaplasia compared with patients with both antral and corpus infection, 37 *vs* 20%, respectively (OR 2.2, 95% CI 1.1-4.4).
Conclusion: One biopsy from the antrum or corpus seems to be inadequate to diagnose the presence of *H. pylori* on the mucosa. Patients with an infection exclusively in the corpus more often had worse mucosa pathology.

INTRODUCTION

Helicobacter pylori is a gram-negative bacterium involved in the pathogenesis of peptic ulcer disease, nonulcer dyspepsia, gastric carcinoma and lymphoma.[1-4] The prevalence of *H. pylori* colonisation ranges from around 25% in developed countries to over 80% in developing countries. Therefore, diagnosis and subsequent eradication of *H. pylori* may be responsible for a reduction in morbidity and mortality. Several invasive and noninvasive diagnostic tests can be used to determine *H. pylori* status. Of all the available tests, invasive tests (histology, culture, and rapid urease tests) are considered the most accurate. However, there is no established gold standard for diagnosing *H. pylori* status. Invasive tests are mainly limited by their proneness to sampling error, because of the patchy distribution of the bacteria throughout the stomach.[5,6] Furthermore, the relative distribution of the bacteria may be altered due to the development of gastric atrophy or metaplasia and after acid suppression or antibiotic therapy.[7-9] These circumstances yield the possibility of false-negative results if only the antrum or only the corpus is used as biopsy site.
The guidelines of the European *Helicobacter pylori* Study Group recommend that prior to treatment two antral biopsies should be taken for histological examination, for rapid urease testing, and for culture.[10] The biopsy site mentioned in these guidelines is only partly evidence based. This is reflected by the results of several studies which investigated the most suitable biopsy sites for histology to detect *H. pylori* status. Hazell *et al.* found it necessary to take antral and corpus biopsies,[11] while Genta *et al.* reported that it was sufficient to take only antral biopsies.[12] Satoh *et al.* found that in their Japanese study population it was best to take at least one corpus biopsy.[13] However, these studies were limited by relatively small patient populations or by patient selection. As a consequence, it is unclear how often the presence of *H. pylori* on the

mucosa may not be identified if only antral or corpus biopsies are collected. Most endoscopists use only antral biopsies. Therefore, the aim of this study was to examine how many patients with *H. pylori* present on their mucosa would be misdiagnosed by only taking antral biopsies for *H. pylori* testing. Furthermore, we investigated in which patients *H. pylori* was only present in the corpus.

METHODS

Study population

The study population consisted of consecutive patients undergoing routine upper gastrointestinal endoscopy at the Bernhoven Hospital in Oss between January 1995 and May 1997. All patients were symptomatic and had been referred either to the outpatient clinic for evaluation by a gastroenterologist, or to the open-access endoscopy by general practitioners for diagnostic upper gastrointestinal endoscopy. Patients were investigated by one of three experienced endoscopists. A standard biopsy protocol, which consisted of taking three biopsies from the antrum and three biopsies from the corpus, was used for *H. pylori* diagnosis at all times. Patients were asked not to take any acid secretion inhibitory therapy in the week before the upper gastrointestinal endoscopy. Patients with a history of *H. pylori* eradication therapy and patients in whom not all six test results for the presence of *H. pylori* were available were excluded from the study.

Investigations

At baseline, gender and age of the patient were noted. For each endoscopy gastrointestinal conditions and histopathological findings were recorded by the endoscopist and by the pathologist, respectively. Antral and corpus biopsies were assessed for *H. pylori* by histological examination and by rapid urease testing. Test outcome for each method was assessed independently from the other test results. For histological examination, two antral and two corpus specimens were fixed in neutral buffered 4% formaldehyde. *H. pylori* identification was performed on Giemsa-stained sections of paraffin-embedded tissue. To measure urease activity, we performed the CLO-duo test (Delta West, Bentley, WA, Australia), which contains two wells. Two mucosal biopsies, one from the antrum and one from the corpus, were placed in the two separate wells containing the test reagent, which enabled us to document the presence of urease activity separately for the two biopsy sites. The reaction was analysed after 24 hours.

Data analysis

The positive or negative occurrence of *H. pylori* for each of the tests was noted. Antrum and corpus were defined as being *H. pylori* positive if both histology and the CLO test were positive for antrum and corpus, respectively. Combining *H. pylori* status for antrum and corpus provides four possible outcomes. All scores were entered into a database. Statistical analysis was carried out using χ^2 tests. Unadjusted analysis for age, gender, and gastroduodenal pathology, assessed endoscopically as well as histologically, were calculated in order to identify factors related to the distribution of *H. pylori* infection. In addition, an adjusted regression analysis was constructed by selecting patient characteristics found to be significantly associated with *H. pylori* present only in the corpus. All analyses were performed using SAS statistical software (SAS Institute, Inc., Cary, NC, USA). Statistical significance was determined by $p<0.05$.

RESULTS

A total of 620 patients underwent an upper gastrointestinal endoscopy in which the standard biopsy protocol was followed. The mean age of the patients (±SD) was 53 ± 15 years; 258 (42%) were women. None of the patients were diagnosed with gastric carcinoma, 57% had functional dyspepsia, 20% gastroduodenal ulcers, 19% reflux oesophagitis and in 4% other diagnosis were found. *H. pylori* infection was identified in 307 (50%) of the patients. In 80% of the endoscopies there was total agreement between the performed diagnostic tests for *H. pylori* status (*table 1*). Histology of the corpus was the

Table 1

Frequency of the different combinations of H. pylori status for each of the biopsy tests examined in antrum and corpus

HISTOLOGY ANTRUM	CLO TEST ANTRUM	HISTOLOGY CORPUS	CLO TEST CORPUS	FREQUENCY N=620	%
+	+	+	+	230	37.1
-	-	-	-	268	43.2
-	+	+	+	13	2.1
+	-	+	+	8	1.3
+	+	-	+	37	6.0
+	+	+	-	5	0.8
-	-	+	+	10	1.6
-	+	-	+	18	2.9
-	+	+	-	0	0
+	-	-	+	0	0
+	-	+	-	2	0.3
+	+	-	-	4	0.6
+	-	-	-	1	0.2
-	+	-	-	3	0.5
-	-	+	-	0	0
-	-	-	+	21	3.4

only negative test in 6%. Both histology tests were negative and both CLO tests were positive in 3%. CLO test of the corpus was the only positive test in 3%.
With the chosen definition for *H. pylori* status in antrum and corpus, combined antral and corpus biopsies increased the yield compared with antral biopsies alone by 31(5%) and compared with corpus biopsies alone by 46 (7%) (*table 2*). In patients with positive test results for antrum and/or corpus *H. pylori* was identified from only antral biopsies in 46 out of 307 (15%) patients, and from only corpus biopsies in another 37 patients (10%).
Defining *H. pylori* status in the antrum and corpus as positive if only one of the two tests instead of both tests were positive resulted in more positive results.
Furthermore, changing the definition showed a considerable decrease in the number of patients who were considered positive for antrum and negative for corpus (from 46 to 8 patients), whereas there was no difference in the number of patients who were considered negative for antrum and positive for corpus (31 patients).
Atrophy and/or intestinal metaplasia, revealed by histological examination, were found significantly more often in the antrum than in the corpus (18 *vs* 2% of all patients, respectively, p<0.05). Patients with *H. pylori* present in only corpus biopsies more often showed atrophy and metaplasia compared with the other possible outcomes, 39 *vs* 17%, respectively (adjusted odds ratio 3.0, 95% CI 1.4-6.1).

DISCUSSION

In current practice *H. pylori* detection is often based on antral biopsies alone, as recommended by the European *Helicobacter pylori* Study Group.[10] Our results demonstrate that if *H. pylori* status was based on only antrum biopsies, 10% of all *H. pylori*-positive patients would be misdiagnosed. The addition of corpus biopsies increases the diagnostic yield of invasive tests in a group of patients that seems to be of great importance because of the underlying mucosa pathology.
A number of studies have investigated whether it is necessary to take both antral and corpus biopsies for the diagnosis of *H. pylori*. Laine *et al.* reported that prior to treatment a single antral biopsy for detection of *H. pylori* provided excellent sensitivity.[14] Genta *et al.* assessed 12 biopsy sites of the stomach for the presence of *H. pylori* by histological examination and found that performing two antral biopsies provides the detection of *H. pylori* in virtually all infected patients.[12] Patients having extensive gastric atrophy with intestinal metaplasia were not enrolled in this study.
Our results indicate that patients with *H. pylori* present only in corpus biopsies showed atrophy and intestinal metaplasia significantly more often. This is explained by the fact that in our study the antrum was the predominant site for atrophy and intestinal metaplasia and the prevalence

Table 2
Biopsy test outcomes for antrum and corpus by patient characteristics

	N	ANTRUM + CORPUS + N=230 (37%)	ANTRUM - CORPUS - N=313 (51%)	ANTRUM + CORPUS - N=46 (7%)	ANTRUM - CORPUS + N=31 (5%)
Gender					
Male	362	59%	59%	61%	48%
Female	258	41%	41%	39%	52%
Age					
0< years ≤45	192	31%	32%	30%	22%
45< years <60	213	33%	36%	37%	26%
≥60	215	36%	32%	33%	52%
Macroscopic diagnosis					
Peptic ulcer disease	125	33%	9%	37%	19%
Gastritis/duodenitis	215	37%	32%	43%	32%
Oesophagitis	118	14%	24%	20%	3%
Normal	137	14%	30%	7%	26%
Microscopic diagnosis					
Atrophy/metaplasia in antrum	113	16%	20%	7%	35%
Atrophy/metaplasia in corpus	12	2%	2%	0%	10%
Atrophy/metaplasia	115	16%	20%	7%	39%

Biopsy site (antrum or corpus) + : both histology and CLO test give positive test results for H. pylori status at that biopsy site.

of *H. pylori* decreases from gastric mucosa with atrophy and intestinal metaplasia.[7] There is considerable variation in the prevalence of atrophy, intestinal metaplasia and gastric cancer. Our study was performed in the Dutch population and the results are probably applicable for the Western population. The study by Satoh *et al.* was performed in Japan, where the prevalence of gastric atrophy, intestinal metaplasia and gastric cancer is much higher compared with the Western world.[13] They reported that a corpus biopsy would be the most important site to determine *H. pylori* status. Therefore, the preferential biopsy site probably depends on local prevalence of atrophy or metaplasia.

H. pylori infection is known to play an important role in the development of gastric atrophy, intestinal metaplasia,[15] and gastric carcinoma.[3,16,17] Uemura *et al.* found in their study that among patients with *H. pylori* infection, those with corpus predominant gastritis, severe gastric atrophy, and intestinal metaplasia are at particularly high risk for gastric cancer.[3] Therefore, our findings that patients with *H. pylori* only present in corpus biopsies showed gastric atrophy and intestinal metaplasia significantly more often, suggest that patients at high risk for gastric cancer might be misdiagnosed for *H. pylori* infection if only antrum biopsies are taken. Since the antrum is the predominant site for gastric carcinoma, our finding that the antrum showed more atrophy and intestinal metaplasia further supports the role of *H. pylori* in the development of gastric carcinoma as suggested by others.[18] Although some studies reported improvement of preneoplastic gastric lesions after the cure of *H. pylori* infection,[19,20] there is still debate whether eradication of *H. pylori* results in regression of atrophy and intestinal metaplasia.

A limitation of our study was that, although we asked patients not to take acid secretion inhibitory therapy, we did not assess whether they really did so. Especially proton pump inhibitors are known to shift the distribution of *H. pylori* proximally, and could at least in part account for the ones with *H. pylori* present only in corpus biopsies. However, when this study was performed proton pump inhibitory therapy was a rarity before an endoscopy was performed, quite the reverse from current practice.

Furthermore, the definition of *H. pylori* infection used in this study might be disputable. For a patient to be considered *H. pylori* positive at a biopsy site both tests needed to be positive as compared with only one of the two tests, potentially resulting in a higher occurrence of false-negatives. However, the diagnostic yield for corpus biopsies remained unchanged while the yield for antral biopsies decreased considerably if only one of the tests instead of both tests needed to be positive. This further supports the importance of obtaining corpus biopsies.

Finally, we distinguished two categories: metaplasia present or absent and ignored the intensity of inflammation. A biopsy specimen may have one goblet cell or consist entirely of intestinal metaplasia. The extent and the grade of metaplasia, and in particular of atrophy, are quite important in determining the type of gastritis.

In conclusion, the combination of antral and corpus biopsies instead of antrum biopsies alone significantly increases the diagnostic yield of invasive *H. pylori* testing. Adequate tissue sampling results in patients being discovered with an infection exclusively in the corpus, the corpus-predominant gastritis with more ominous prognostic implications.

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