The diagnostic accuracy of rapid urease biopsy test compared to histopathology in implementing "test and treat" policy for *Helicobacter pylori*

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Abstract

Background: *Helicobacter pylori* is one of the most important causes of the varied spectrum of gastroduodenal diseases. It is important to have a rapid diagnostic method to detect the organism so as to initiate the treatment early and check its progression to malignancy. **Aims:** To evaluate the diagnostic accuracy of rapid urease biopsy test in detecting *H. pylori* infection and implementation of "test and treat" policy. **Materials and Methods:** All patients of chronic dyspepsia not responding to conventional treatment were subjected to endoscopy, and mucosal biopsy samples were collected. A rapid urease test (RUT) and histopathology was performed on these samples and taking histopathology as gold standard for *H. pylori* demonstration, the diagnostic accuracy of RUT was evaluated. **Results:** The specificity, sensitivity, positive predictive value, negative predictive value, and diagnostic accuracy of RUT were 97.22%, 94.04%, 98.75%, 87.5%, and 95%, respectively. **Conclusion:** Use of a rapid diagnostic test viz., rapid urease biopsy test to confirm *H. pylori* infection is recommended for early diagnosis and treatment of *H. pylori* associated gastroduodenal diseases.

Key words: Diagnosis, *Helicobacter pylori*, histopathology, urease test

Introduction

The spectrum of gastroduodenal diseases is wide ranging from inflammatory lesions such as gastritis and peptic ulcer disease to frankly malignant ones such as gastric carcinoma and lymphoma. Of the diverse etiological associations of gastroduodenal disease, the most important is a bacterium named *Helicobacter pylori*.[1] Chronic infection of the gastric mucosa by this bacterium is the most common infection worldwide.[2]

Chronic gastritis, if left untreated, may progress to carcinoma.[1] Hence, whenever possible, it is necessary to identify the cause of gastritis to check the progression to carcinoma.[1] *H. pylori* being one such cause of chronic gastritis, rapid diagnosis with the help of chemical tests (rapid urease test [RUT]) is essential to formulate early and appropriate clinical strategies for better management of patients.

The "test and treat" policy is the recommended way to eradicate *H. pylori* in patients with uninvestigated dyspepsia if the prevalence of *H. pylori* is high.[3] India is considered to have a high prevalence of *H. pylori*.[3] This observational study was conducted to discover the prevalence of *H. pylori* disease in

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uninvestigated dyspeptic patients based on rapid urease biopsy test and to ascertain the role of this test in implementing the "test and treat" policy in this geographical area.

Materials and Methods

The study was conducted in the Department of Pathology and Gastroenterology over a period of 1-year. Patients more than 18 years of age, having clinical indications of upper gastrointestinal endoscopy, and patients not under treatment with proton pump inhibitors, bismuth compounds, antibiotics in the last 3 weeks, and H_2 blockers in the last 24 h were included in the study. Patients with esophageal disease, patients who have been previously treated with anti-*H. pylori* drug regime, patients who had ultrasonographic evidence of pancreatitis, biliary disease, or chronic liver disease, and patients with abnormal coagulation profile were excluded from the study. An informed consent and a thorough clinical history were taken from all the patients who were selected for the study. Routine blood and stool examinations were done. An ultrasonography (whole abdomen) was done to rule out pancreatic and biliary tract disease.

After an overnight fast (6 h), all the selected subjects underwent upper gastrointestinal endoscopy with flexible fiber-optic endoscope (Fujinon©) and the endoscopic findings were noted. In cases, which were endoscopically normal or only with erosions, mucosal biopsies were taken with sterile biopsy forceps (Olympus©) from four different sites: Cardia (greater curvature), antrum (greater curvature), incisura angularis (lesser curvature), and first part of duodenum. This was in accordance with the recommendations of Genta and Graham.[4] In cases with the presence of an ulcer (clinically benign) anywhere in the stomach or first part of duodenum, additional multiple bits of tissue were taken from the different edges of the lesion (over and above the four sites mentioned) for histopathological examination. In cases with the presence of a growth (clinically malignant) only, multiple bits of tissue from different edges of the growth were taken.

An additional mucosal biopsy was taken from the antrum for the RUT for *H. pylori* in all cases. In cases, where the antrum was involved with erosions/ulcer/growth, the biopsy was taken from surrounding normal mucosa for RUT. In this study, Pylotest™ kit manufactured and marketed by Halifax Research Laboratories, Kolkata was used for biopsy urease test [Figure 1]. Fresh mucosal biopsy samples from antrum were obtained with biopsy forceps and put in the urea gel media with the help of a needle and crushed. The results are usually obtained by 6–9 h but can be interpreted up to 24 h.[5] In this study, however, the positive results were obtained within 6–9 h, in majority of the cases. A known urease positive culture colony (*Klebsiella*) was taken as

a control for the test. All the mucosal biopsy samples obtained for histopathology were put in different bottles containing 10% formalin and properly labeled mentioning the site of biopsy. These tissue samples were routinely processed and stained with hematoxylin and eosin (H and E) for light microscopic examination. In some cases, a modified Giemsa stain was performed to demonstrate *H. pylori* in the tissue sections.[6]

Cases were considered to be *H. pylori* infected when both RUT and histology were positive. All the cases of chronic gastritis were reported following the guidelines put forward by the updated Sydney system of reporting,[7] with an additional note on the pathological involvement of the first part of duodenum. The malignant cases were diagnosed and classified according to the guidelines put forward by World Health Organization (WHO).[8]

Results

It was seen that maximum patients (31 out of 120, i.e., 25.83%) were in the age group of 38–47 years with a slight male preponderance (M: F = 1.2:1). The most common presenting symptom was upper abdominal pain (106 out of 120 cases, i.e., 88.3%) and the most common finding on endoscopy was ulcerative growth at the antrum (26 out of 120 i.e., 21.66%) followed by duodenal ulcer (25 out of 120 i.e., 20.83%) [Table 1].

It was observed that of all the 120 patients who underwent upper gastrointestinal endoscopy, 79 cases (65.83%) were positive for *H. pylori* infection. Results also showed that 24 out of 25 (96%) cases of duodenal ulcers, 13 out of 21 (61.9%) cases of gastric ulcers, and 13 out of 26 (50%) cases of ulcerative growth were positive for *H. pylori* [Table 2].

Taking histological demonstration of *H. pylori* as standard the definitions were derived and data were obtained as: True
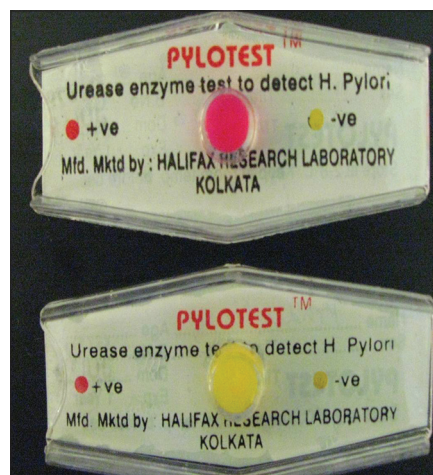

Figure 1: Rapid urease kit showing both positive (pink) and negative (yellow) result

positive = *H. pylori* detected by both histopathology and RUT = 79; true negative = *H. pylori* not detected by any of the two methods = 35; false positive = *H. pylori* detected by RUT but not by histopathology = 1; and false negative = *H. pylori* not detected by rapid urease but detected by histopathology = 5. The specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of RUT were 97.22%, 94.04%, 98.75%, 87.5%, and 95%, respectively.

On histopathological examination of all the 120 cases, 85 (70.83%) cases turned out to be inflammatory, 6 cases (5%) dysplastic, and 27 cases (22.49%) neoplastic (1 benign and rest 26 malignant). Two cases (1.66%) had no histopathological abnormality.

Of the 85 inflammatory lesions, most common diagnosis was chronic gastritis (in 29 cases i.e., 33.72%) followed by chronic gastritis with duodenitis (in 27 cases i.e., 31.39%) [Table 3].

Of the 6 dysplastic lesions, 4 (66.67%) were low-grade, and 2 (33.33%) were high-grade. Of the neoplastic cases, 1 was benign hyperplastic polyp, 25 were gastric adenocarcinoma, and 1 duodenal adenocarcinoma.

On classifying all the 25 cases of gastric adenocarcinoma on the basis of WHO guidelines (2000), 14 (56%) were tubular adenocarcinoma, 9 (36%) were diffuse, and 1 (4%) each of papillary and mucinous adenocarcinoma. The only case of duodenal adenocarcinoma was moderately differentiated. While evaluating for the presence of *H. pylori* infection on histopathology, it was found that 18 out of 29 (62.06%) cases of chronic gastritis were associated with *H. pylori* infection. An important observation in our study was that all cases of chronic atrophic gastritis were positive for *H. pylori* infection [Table 4].

Three out of 4 (75%) cases of low-grade and 1 out of 2 (50%) cases of high-grade dysplasia were positive for *H. pylori*. Thirteen out of 26 (50%) cases of adenocarcinoma were positive for *H. pylori* infection. Among the cases of gastric adenocarcinoma, 9 out of 14 (64.28%) cases of tubular adenocarcinoma, and 4 out of 9 (44.44%) cases of diffuse adenocarcinoma were positive for *H. pylori* [Table 5]. Figure 2 shows the distribution of the malignant cases based on WHO (2000) guidelines.

Discussion

H. pylori, as a cause of chronic gastritis, has always been a cause of concern for the treating physicians. Ghosal *et al*.[9]

Table 1: Distribution of cases based on endoscopic findings

Endoscopic findings	Number of patients (*n*=120)	Percentage
Ulcerative growth	26	21.66
Duodenal ulcer	25	20.83
Antral ulcer	21	17.50
Antral erosions	21	17.50
No abnormality	12	10
Duodenal erosions	9	7.50
Polyp	3	2.50
Fundal erosions	2	1.67
Fundal nodules	1	0.83

Table 2: Results of RUT confirmed by histology

Endoscopic findings	Number of cases	Number of cases showing RUT positive	Cases showing histological demonstration of *H. pylori*	Remarks
Ulcerative growth	26	13	13	
Duodenal ulcer	25	24	24	
Antral ulcer	21	13	14	1 case was FN on RUT
Antral erosions	21	17	20	3 cases were FN on RUT
No abnormality	12	5	6	1 case was FN on RUT
Duodenal erosions	9	7	7	
Polyp	3	1	0	1 case was FN on RUT
Fundal erosions	2	0	0	
Fundal nodules	1	0	0	

FN: False negative; RUT: Rapid urease test; *H. pylori*: Helicobacter pylori

Table 3: Inflammatory lesions on histopathology (*n*=85)

Diagnosis	Number of cases	Percentage
Chronic gastritis		
Antral	24	27.90
Pangastritis	4	4.65
Fundal	1	1.16
Chronic gastritis with duodenitis/duodenal ulcer	27	31.39
Chronic atrophic gastritis	24	27.90
Duodenitis/duodenal ulcer	4	4.65
Granulomatous lesion	1	1.16

Table 4: Inflammatory and benign histopathological lesions showing *H. pylori* positivity

Lesions	Number of cases	*H. pylori* positive	*H. pylori* negative	Percentage of *H. pylori* positive
Chronic gastritis				
Antral	24	14	10	58.33
Fundal	1	0	1	0
Pangastritis	4	4	0	100
Chronic antral gastritis with duodenitis/duodenal ulcer	27	27	0	100
Duodenal ulcer/duodenitis	4	1	3	25
Chronic atrophic gastritis	24	24	0	100
Granuloma	1	0	1	0
Hyperplastic polyp	1	0	1	0
Total	86	70	16	81.39

H. pylori: Helicobacter pylori

Table 5: Premalignant and malignant lesions showing *H. pylori* positivity

Lesions	Number of cases	*H. pylori* positive	*H. pylori* negative	Percentage of *H. pylori* positive
Dysplasia (6)	Low grade (4)	3	1	75
	High grade (2)	1	1	50
Gastric adenocarcinoma (25)	Tubular (14)	9	5	64.28
	Diffuse (9)	4	5	44.44
	Papillary (1)	0	1	0
	Mucinous (1)	0	1	0

H. pylori: Helicobacter pylori

Figure 2: Pie diagram showing histological typing of gastric adenocarcinoma based on World Health Organization guidelines (2000)

and Ahmed *et al.*[10] in their studies from India showed that the prevalence of *H. pylori* infection in adults approaches 90% in many developing countries, particularly those in the tropics. In 2007, Lynn *et al.*[11] and Sacco *et al.*[12] in their province based individual studies, have shown that in industrialized parts of the world (Western Europe, United States, Canada, and Australia), exposure tends to occur later in life, which results in a lower percentage of infected adults. In eastern Asia (e.g. Japan), where there has been a recent introduction of improved sanitation methods, there has been a clear trend toward a lower rate of *H. pylori* infection.[13]

Chen *et al.*[14] showed that the prevalence of *H. pylori* infection has been steadily declining in industrialized and emerging countries, which is probably a reflection of improved sanitary conditions, as well as widespread use of antibiotics. Despite declining rates of *H. pylori* infection, in general, the prevalence rate of *H. pylori* in patients who undergo endoscopy remains significant. Therefore, *H. pylori* should be considered in all gastric biopsy specimens examined, regardless of the patient's age or provenance.[2]

The diagnosis of *H. pylori* gastritis based solely on the endoscopic gross appearance of the gastric mucosa is not recommended. The accurate diagnosis of *H. pylori* gastritis rests either on the pathologic evaluation of gastric mucosal biopsies or by detection of urease in mucosal specimens by rapid urease biopsy test. *H. pylori* are curved or S-shaped bacilli and in this form are often easily recognized on routine H and E staining [Figure 3]. They are found within the surface mucus layer [Figure 4] and are easiest to identify within gastric pits, but in cases of heavy infection are also numerous overlying the surface epithelium. Special stains are necessary when screening biopsies for *H. pylori* as they facilitate recognition, especially when small numbers are present, and help distinguish the bacteria from fibrin or debris on the mucosal surface. A variety of stains has been used. A study by Rotimi *et al.* found that modified Giemsa is the method of choice because it is cheap, sensitive, and easy to perform and reproducible.[15] This is very satisfactory for routine use. Monteiro *et al.* found the sensitivity,
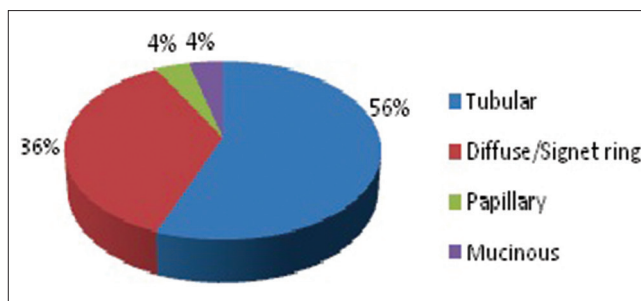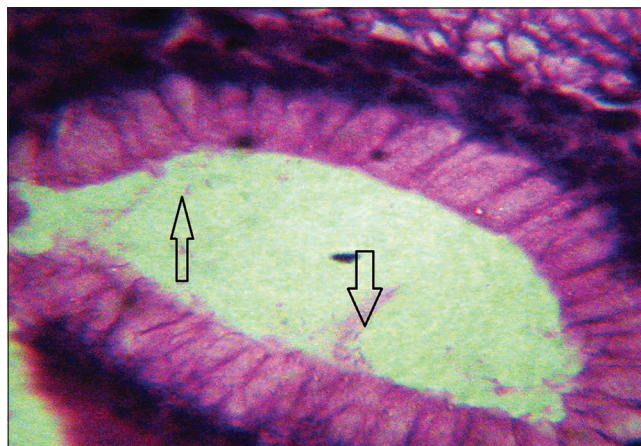

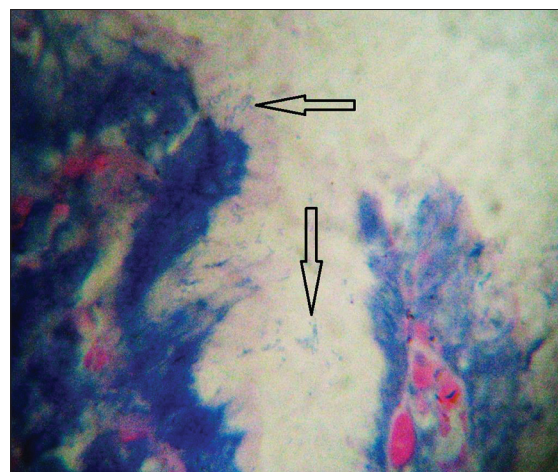**Figure 3:** Gastric gland lumen showing *Helicobacter pylori* (arrow) (H and E; ×1000)

Figure 4: Gastric surface mucosa showing numerous *Helicobacter pylori* bacilli (arrow) (Modified Giemsa; ×1000)

specificity, PPV, and NPV of histologic examinations by Giemsa stain is 93.8%, 98.2%, 97.9%, and 94.8%, respectively.[16]

First described by Mc Nulty and Wise in 1985, the rapid urease breath test has gained wide acceptance in the detection of *H. pylori* in mucosal biopsy samples.[17] Several studies[16,18-20] have found the sensitivity of this test between 80% and 99% and specificity between 92% and 100% taking histopathology as the gold standard for the detection of this bacillus. The

Table 6: Comparison of the statistical data of the present study with previous similar studies

Studies	Specificity	Sensitivity	PPV	NPV	Accuracy
Zaitoun *et al.* (1993)	100	94	100	-	-
Goh *et al.* (1994)	99.2	96.6	99.3	96.2	-
Cutler *et al.* (1995)	100	89.6	100	84.1	-
Monteiro *et al.* (2001)	96.4	83	95.1	87.1	-
Present study (2012)	97.22	94.04	98.7	87.5	95

PPV: Positive predictive value; NPV: Negative predictive value

overall sensitivities were 88–94% and specificities 99–100% in all the studies, including the present one [Table 6]. This shows that a positive RUT can well be considered to start the treatment regimen for *H. pylori* instead of waiting for the histopathological confirmation.

The present study also shows that, the presence of *H. pylori* infection in gastroduodenal diseases, is quite high, of which, a significant number of cases are associated with atrophy and intestinal metaplasia. Another important observation of this study is that, there is a high association of *H. pylori* infection in cases of gastric adenocarcinoma. Reviewed literature have revealed that there is a significant risk of progression to cancer in cases of *H. pylori* gastritis, more so, when they are associated with atrophy and metaplasia.[1] Therefore, it is suggested that detection of the organism at an early stage and eradication with appropriate treatment strategies might prevent disease progression and thus benefit the patients. However, a study of longer duration and with a larger population is required to obtain the actual prevalence of *H. pylori* in gastroduodenal diseases, in North Eastern region of India.

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Conflicts of interest
There are no conflicts of interest.

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