An Audit of Endoscopic RUT and Treatment for *Helicobacter pylori* in Clinical Practice

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Helicobacter pylori infection is ubiquitous. Endoscopic Rapid urease test [RUT] is sensitive and specific for diagnosing H. pylori organism during endoscopy. Retrospective analysis of the pattern of RUT performance by endoscopists in Southeast Bengal region in patients evaluated for upper gastrointestinal disorders was performed. The gastroscopy reports of consecutive patients from South-eastern Bengal attending a gastroenterology clinic were studied. The data along with relevant treatment history were entered into a questionnaire and the data was analyzed. Data of 151 patients were analyzed. 16 patients with reflux oesophagitis and growth in duodenum were excluded. Out of 135 patients, 47.4 % and 52.6% had peptic ulcers and non ulcer dyspepsia [NUD] respectively. Rapid urease test (RUT) was positive in 40.62% and 33.80% of peptic ulcer and NUD patients respectively (p = 0.477). However 32.45%patients on "premedication" and 62% without "premedication" were RUT positive, which was statistically significant (p= 0.014). There is also no difference (P > 0.05) in endoscopic diagnosis or result of RUT performed by gastroenterologists or nongastroenterologists. 81.25% of RUT positive NUD patients who received Triple therapy for H. pylori did not respond; but all [100%] responded to antidepressants. RUT was performed routinely in all patients undergoing gastroscopy irrespective of diagnosis. The RUT was routinely performed without cognizance of pre-endoscopy treatment. "Pre-treatment" results in erroneous underestimation of H. pylori infection. Antidepressants were superior to triple therapy for NUD even in H. pylori infected patients.

Keywords: Helicobacter pylori, Rapid urease test, Non-ulcer dyspepsia.

Helicobacter pylori infection is ubiquitous in both developing as well as developed countries. It is a gram negative, curved, microaerophilic and motile organism with multiple polar flagella having extraordinary ability to establish infections in human stomachs for years or decades. More than 50% of the world population is colonized with *H.pylori*^{1, 2}. Exposure occurs in childhood and approximately 80% of adults have been infected at some time. Sero-surveys indicate a seroprevalence of 22%-57% in children under the

age of five, increasing to 80%-90% by the age of 20, and remaining constant thereafter³⁻⁶ *H. pylori* commonly causes peptic ulcer, presenting as recurrent abdominal pain and is associated with 90% of duodenal ulcers and 80% of gastric ulcers⁷. *H. pylori* is also associated with gastric mucosa associated lymphoid tissue (MALT) lymphomas and gastric adenocarcinoma. There is an ambiguous between non-ulcer dyspepsia and infection with *H. pylori*. The pathophysiology of dyspepsia with *H. pylori* infection is unclear, but may include changes in acid secretion, abnormal motility, or altered visceral perception⁸ The prevalence of *H pylori* is higher in patients with non-ulcer dyspepsia than in healthy controls⁹

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Various methods to diagnose H. pylori infection are grouped as (a) Invasive methods and (b) Non invasive methods. The invasive methods are based on collection of endoscopic gastric biopsy specimens that are subjected to urease test, staining, culture, histology and molecular diagnostic techniques. The non invasive methods comprise urea breath test, serology and stool antigen test. Among invasive tests, Rapid urease test is a rapid, inexpensive, sensitive and specific diagnostic modality, which can identify H. pylori organism and can be also used for monitoring therapy. In the presence of *H. pylori* infection, urea is hydrolyzed to ammonia and carbon dioxide (CO₂) due to release of urease enzyme. The change in colour of the broth from pale yellow to deep pink is taken as a positive result. Bacteria other than H. pylori that produce urease in a small amount cannot survive in the gastric mucosa.

Our study is aimed to audit the pattern of RUT performance by endoscopists and audit of the response to treatment, in Southeast Bengal region in patients evaluated for upper gastrointestinal disorders.

MATERIALS AND METHODS

Retrospective analysis of records of consecutive patients attending a gastroenterology clinic for upper G.I. disorder with a past upper UGI endoscopy report was performed over a period of 7 Years from 05.11.03 to 24.06.10. During this period a total of 151 patients with dyspeptic symptoms were studied with their previous report. The records of these patients including endoscopic findings, RUT report and details of pre-procedure PPI/H₂RA therapy within 2 weeks, and post UGIE treatment were analyzed. As Rapid ureaseTest (RUT) has a high sensitivity, specificity, positive predictive value in the order of > 98%, >99 %,> 99% respectively10, positive RUT was considered as presence of H. pylori in the gastric mucosa in the above patients. The patients having "peptic ulcer disease" (gastric ulcer and duodenal ulcer) and normal or near-normal endoscopies (including findings of questionable clinical significance such as gastritis or duodenitis) categorized as "nonulcer dyspepsia" on endoscopy were included in the study. Presence of reflux oesophagitis, any growth in stomach or duodenum, and any disease outside

the stomach were excluded from this study. Peptic ulcer disease (PUD) group and nonulcer dyspepsia (NUD) group were again subdivided into two categories based on prior premedication or no premedication with PPI/H,RA before endoscopy.

Results of rapid urease test in all categories were analyzed. An audit of treatments used for H. pylori positive NUD patients and also the subjective [symptomatic] response to anti H. pylori treatment / anti- depressants was also analyzed during the current visit.

Definitions

Non ulcer dyspepsia (NUD) is defined as patients with central upper abdominal pain or discomfort for at least 12 weeks but a normal endoscopic appearance. Premedication means intake of proton pump inhibitors (PPIs) or histamine 2-receptor antagonists (H₂RAs) [within 2 weeks] prior to rapid urease testing.

Statistical Analysis

Data was entered and analyzed in Statistical Package for Social Sciences (SPSS) ver17.0. Chi square test/ Fisher's Exact Test was used for nominal values.

RESULTS

Out of 151 patients, 128 were males and 23 were females with M: F ratio 5.6: 1. Diagnosis by endoscopic findings is shown in Figure 1. Majority of patients had nonulcer dyspepsia (47%) followed by duodenal ulcer (31%) and gastric ulcer (11%). To prevent confounding in this study, sixteen were excluded due to presence of reflux oesophagitis in 15 patients and duodenal growth in one patient. Rest 135 patient i.e. 64 patients with peptic ulcer disease (47 duodenal ulcer, 17 gastric ulcer) and 71 patients of nonulcer dyspepsia (NUD) were included in the study (Fig 2).

Peptic ulcers were found to be more common in males (53.04%) than females (15%). On the contrary females suffered more from nonulcer dyspepsia than males (p= 0.002) as shown in Figure 3. Rapid urease test was negative in 62.6% of males and 65% of females respectively (p=1.000) shown in Table 2. There was positivity no gender difference in rapid urease test positivity. Rapid urease test was positive in 40.62% and 33.80% of peptic ulcer and NUD patients respectively (p=0.477). Further subgroup analysis was done

with premedication and without premedication to find out any differences. In peptic ulcer group, 36.5% with premedication and 58.3% without premedication were RUT positive (p=0.165). In NUD patients 29% with premedication and 66.6% without premedication were RUT positive (p=0.053). As premedication [PPIs or antibiotics prior to endoscopy] can influence the rapid urease test, further analysis was done in patients of both groups without premedication. In patients without premedication (Fig 2), positive rapid urease test was found only 58.3 % in peptic ulcer and 66.6% of NUD patients respectively (p=1.000). Overall out of 135 patients (Table-1), RUT positivity was seen in 32.45% and 61.9% patients on premedication and without premedication respectively (p = 0.014).

An Analysis of endoscopic pattern was done according to type of physicians (Table 2). Comparison of endoscopic diagnostic yield between untrained physicians [non-gastroenterologists] and trained physicians [gastroenterologists] showed that there was no difference in the proportion of patients having duodenal ulcer and nonulcer dyspepsia [NUD] (p=0.575). Similarly there was no difference in results of RUT (p=0.570) performed by different types of physicians (Table 2).

Since we considered positive RUT as evidence of *H. pylori* infection, percentage of positive RUT without prior therapy can be extrapolated as prevalence of *H. pylori* infection in peptic ulcers patients (58.3%), NUD (66.6%) and total patients (61.9%).

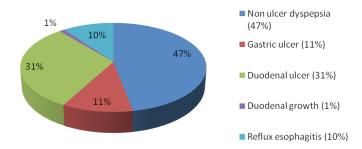


Fig. 1. Endoscopic findings

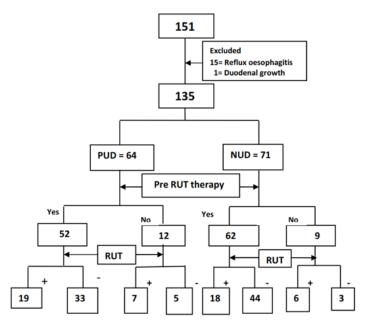


Fig. 2. Flow chart of study population

The results of analysis of response to triple therapy in RUT positive NUD patients has been shown in Figure 4. Out of 71 NUD patients, 24 patients had positive RUT. Of these positive RUT patients, 18 patients were given triple therapy and 6 patients were given PPI or other medications.

Two patients, who had taken triple therapy, did not come for follow up. The 16 patients of NUD, taking triple therapy, were assessed for symtomatical improvement after one month. Thirteen (81%) RUT positive NUD patients who received triple therapy for *H. pylori* did not respond, but all

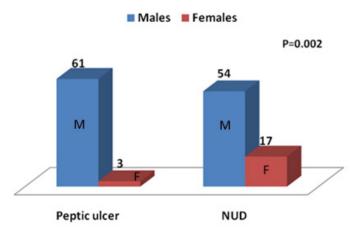


Fig. 3. Diagnosis according to gender

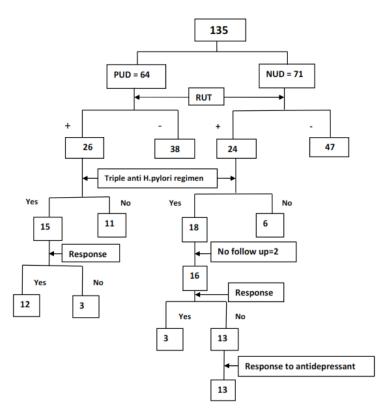


Fig. 4. Study flow chart of treatment J PURE APPL MICROBIO, **11**(2), JUNE 2017.

of the thirteen [100%] patients not responding to triple therapy responded to antidepressants (Figure -5). Using Fisher's exact test, antidepressants are extremely effective than triple therapy regimen for non ulcer dyspepsia (p value=<0.0001), even in Helicobacter pylori infected patients. However response to anti-*H. pylori* triple regimen was significant (p=0.0011) in RUT positive peptic ulcer (80%) patients compared to NUD (18.75%) patients.

DISCUSSION

Endoscopic findings of patients with upper gastrointestinal disorders from Southeast Bengal region revealed varied diagnosis. Non

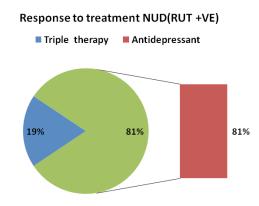


Fig. 5. Treatment response in rapid urease test positive NUD patients

ulcer dyspepsia (47%) was the commonest diagnosis followed by peptic ulcers (42%) and reflux oesophagitis (10%). However an endoscopic review of four series of dyspeptic patients in U.K. revealed NUD 34% followed by GERD 24% and peptic ulcers 20%^{11,12} High prevalence of peptic ulcers in our study may be due to increased prevalence of causative factor like H. pylori infection, low hygienic environment and overcrowding.

In our study, males suffered more from peptic ulcers than females, which may be due to more proneness for stress and strain as well as addiction for alcohol and smoking in males. Females seek medical attention for functional dyspepsia (85%) more often than for ulcers (47%). Endoscopy is done by both trained and untrained physicians throughout the country due to lack of sufficient number of trained doctors as well as proximity of patients to untrained physicians, however there was no difference in diagnosing peptic ulcers and performance of rapid urease test.

There are limited studies in literature comparing response of rapid urease test with premedication in peptic ulcers or non ulcer dyspepsia. In our study, there was no significant difference in result of rapid urease test in peptic ulcer and non ulcer dyspepsia patients with regards to premedication, which may be due to small samples size and noneradication of *H. pylori*

Table 1. Factors associated with r	rapid urease test result
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	RUT +VE(50)	RUT -VE(85)	p value
Males	43(37.4%)	72(62.6%)	1.000
Females	7(35%)	13(65%)	
Premedication	37(32.45%)	77(67.54%)	0.014
No premedication	13(61.9%)	8(38.1%)	
Peptic ulcer	26(40.62%)	38(59.38%)	0.477
NUD	24(33.80%)	47(66.2%)	

Table 2. Diagnosis according to type of physicians.

	Gastroenterologists	Nongastroenterologists	
Peptic ulcer	20(31.25%)	44(68.75%)	0.575
NUD	19(26.76%)	52(68.42%)	
RUT +VE	13(26%)	37(74%)	0.570
RUT –VE	26(30.59%)	59(69.41%)	

with respect to premedication. However, Overall analysis in 135 patients, demonstrated that prior PPI/H₂ RA therapy resulted in decrease in positivity of rapid urease Test (RUT) significantly, compared to the group who had not received prior PPI, as found in other studies^{13, 14}.

There are a number of studies¹⁵⁻¹⁸ on the effectiveness of triple therapy in peptic ulcer Patients, similar to our study. However, there are controversies regarding treatment of NUD patients. In our study, symptoms of 82% of NUD patients did not respond to anti H. pylori therapy, where as all NUD patients responded to anti-depressants, contrast to other studies16-18 Meta-analysis of twelve trials by Moayyedi¹⁹ showed H. pylori eradication treatment was significantly superior to placebo in treating non-ulcer dyspepsia (relative risk reduction 9% (95% confidence interval 4% to 14%)), one case of dyspepsia being cured for every 15 people treated. H. pylori eradication cost £56 per dyspepsia-free month during first year after treatment. Canadian Helicobacter pylori consensus conference also favours the H. pylori eradication to prevent development of ulcer or cancer as the lifetime risk of developing ulcers for people who are infected with H. pylori is 5-15%²⁰ A recent randomized clinical trial of 294 patients with uninvestigated dyspepsia in Canada found that treatment resulted in a sustained improvement in symptoms at 12 months in 50% of the patients treated to eradicate H. pylori compared with 36% in the placebo group²¹ This result was significant, and seven patients needed to be treated to cure one patient. The trial also showed that treatment was cost effective¹⁸ However another meta-analysis by Laine et al provided little support for the use of *H. pylori* eradication therapy in patients with nonulcer dyspepsia²². A study by Singh et al from Odisha also showed that antipsychotics rather than anti H. pylori treatment had a definite role in symptomatic amelioration of NUD patients²³. Another small randomized controlled trial by Mertz et al. demonstrated benefit for symptoms of nonulcer dyspepsia treated with amitryptiline 50 mg once daily at night24. Another prospective study on sixty patients (seropositive) found no benefit in-patients in dysmotility like NUD with anti H. *pylori* treatment with comparison to ulcer variety²⁵. Thus most studies favour the effectiveness of antidepressants over H. pylori treatment for NUD.

First, rampant use of antibiotics like amoxicillin, clarithromycin and metronidazole for other diseases sometimes with inadequate doses, may be responsible for resistance to these drugs used for *H. pylori* treatment. Further, our study population may have pre-dominant psychosomatic features, contributing to the pathophysiology of NUD. Besides, time to response measured after *H. pylori* treatment might be too short to get effective response from *H. pylori* treatment, compared to other studies¹⁵.

Our study on peptic ulcers showed 58% prevalence of H. pylori in contrast to an older study showing prevalence of *H. pylori* infection between 95% and 100%,³ which might be because of few small sample size. However, in a recent study from Kolkata, 70.04% patients were *H. pylori*—positive, which is similar to our study²⁶ In our study prevalence of *H. pylori* in NUD was found to be 67%, similar to other studies from different parts of India (South India 74%,²⁷ and New Delhi 54%²⁸).

Various studies have demonstrated the role of H. pylori in the pathophysiology of peptic ulcer, MALT, and gastric carcinoma. This raises the question whether eradication of H. pylori is a practically feasible or necessary in developing countries like India? According to Ramakrishna, eradication of *H. pylori* in NUD is not justifiable in India²⁹ Prevalence of *H. pylori* in normal population varies from 60 -80% in different studies in from various parts of India^{3, 27, 30 – 33} To eradicate the innocuous bacteria from our gastric flora, which is present since times immemorial³⁴ we have to treat nearly 70-80 crores of people, which is not possible as recurrence of infection occurs in around 60% of patients according to reports published in various Indian publications³⁵ In an Indian study of 45 patients followed up following eradication of H. pylori, recurrence of infection was detected in only one patient (2.4%) after one year³⁶. There are also other arguments against the eradication of H. pylori infection. All strains inhabitating the gastric mucosa are not virulent. Besides, Production of increased acidic environment in the stomach and other immune factors may be a barrier to other ingested pathogens^{37, 38.} In addition, the Possibility of protection from allergic and autoimmune diseases including asthma and Crohn's disease due to H. pylori infection compared to developed

countries may favour against treatment of this organism in developing countries like India³⁹ Various consensus statements regarding treatment of *H. pylori* in India have ruled out anti *H. pylori* therapy for NUD patients, as this may aggravate the symptoms instead of amelioration⁴⁰⁻⁴³

CONCLUSIONS

RUT was performed routinely in all patients undergoing gastroscopy irrespective of diagnosis and without cognizance of pre-endoscopy treatment. Functional dyspepsia patients seek advice of untrained gastroenterology physicians more than qualified gastroenterologists. "Prior treatment" results in erroneous underestimation of H. pylori infection by RUT alone. RUT performed in general practice (irrespective of recent drug therapy) can be fallacious for detecting H. pylori infection and deciding about institution of eradication therapy. Antidepressants were superior to triple therapy for NUD even in H. pylori infected patients. There is no rationale for performing RUT in NUD Patients or treating these patients with anti H. pylori therapy. There is a need for developing rational guidelines for performing RUT.

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