TO ASSESS THE PREVALENCE OF HELICOBACTER PYLORI IN PATIENTS WITH CHRONIC RENAL FAILURE AND TO STUDY THE GASTRIC MUCOSA IN THESE PATIENTS

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

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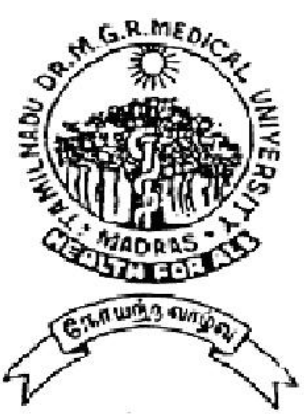

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CHENNAI

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INTRODUCTION

Upper gastrointestinal endoscopy is routinely performed everyday for a number of patients in the department of Medical Gastroenterology, Government Rajaji Hospital. It is generally considered the diagnostic method of choice in uninvestigated dyspepsia because it allows identification of structural causes of dyspepsia and most importantly excludes carcinoma, but examination of all patients is hard to perform. The reason is the high annual incidence of dyspepsia. The issue is even more important in developing countries like ours with limited access to diagnostic services. There is no generally accepted consensus about the age cut off for upper GI endoscopy, because it mainly depends on the regional age-specific incidence of gastric cancer.

The association of Helicobacter pylori with various gastrointestinal disorders has been studied in the past few years. The relation between peptic ulcer and H.pylori is well established throughout world literature. The ultra rapid urease test has been

used in the past few years to study the presence of organism in the endoscopic specimen. Though there are several methods used to detect the organism, most of them are expensive and cumbersome to perform. This test provides a quicker and cheaper means to study the organism with a high degree of sensitivity and specificity.

The association of H.pylori with peptic ulcer and gastric adenocarcinoma was suggested by its discoverer Barry Marshall. In 1984, it was again described shortly after subsequent studies assessed its role in GERD and non ulcer dyspepsia. It was found to be one of the etiological factors for gastric adenocarcinoma and gastric MALTomas in 1991. It was identified as a grade I carcinogen in 1994 and the importance of its eradication in patients with a positive family history of carcinoma was stressed. Its association with non ulcer dyspepsia is less well understood despite several studies in the past. The histology of non ulcer dyspepsia has also not been studied in detail in the past. The few studies which are available indicate that there could be a role for H.pylori but has not been determined with accuracy.

REVIEW OF LITERATURE

Upper gastrointestinal tract symptoms are common in patients with chronic kidney disease (CKD) who require peritoneal dialysis (PD) or hemodialysis (HD). Anorexia, singultus (hiccups), nausea, vomiting, epigastric pain, and heartburn are common manifestations of azotemia. Delayed gastric emptying is common in CKD. Although the prevalence of peptic ulcer is only 2%, which is not significantly different from that in the general population, gastritis, duodenitis, and mucosal erosions are commonly seen.368 Various data suggest that neither hyperacidity, hypergastrinemia, or H. *pylori* play major roles in the pathogenesis of uremic gastropathy, although these data have recently been called into question.

Impaired mucosal cytoprotection has been postulated but not proved. Also seen on esophagogastroduodenoscopy are esophagitis, Brunner's gland hyperplasia, gastric fold thickening, and nodular duodenitis (which resolves after renal transplantation) and

angiodysplasia. GERD may be related to the absence of *H. pylori* infection, amyloidosi, and PD, which increases intra-abdominal pressure. In controlled studies, the incidence of gallstones in CKD is similar to healthy controls.

It is possible that angiodysplastic lesions in the upper and lower gastrointestinal tract are no more common in patients with CKD than in the general population but are discovered more frequently because of their greater tendency to bleed. Angiodysplasia in kidney disease represent acquired lesions formed by repeated episodes of submucosal venous outflow obstruction resulting in incompetent precapillary sphincters with subsequent arteriovenous communication.

Angiodysplastic lesions are much more likely to bleed in patients with CKD than in patients with normal renal function, perhaps because of uremic platelet dysfunction. In a series of, CKD patients with upper gastrointestinal hemorrhage, gastric ulcer (37%) and duodenal ulcer (23%) were the two most common bleeding

lesions, but angiodysplasia of the upper gastrointestinal tract was the cause of bleeding in 13%. In contrast, angiodysplasia was only responsible for 1.3% of upper intestinal tract bleeding in control patients. In CKD patients with recurrent hemorrhage, angiodysplasia was the most frequent cause of bleeding. Angiodysplasia as a cause of bleeding was most closely associated with the duration of renal failure and the need for hemodialysis. In CKD, peptic lesions may be managed successfully with standard medical treatments in appropriate "renal" doses and angiodysplasia may be treated with laser, electrocoagulation, or surgery.

Small intestinal complications of CKD include ileus, ulceration, and nonocclusive ischemic bowel disease. Diarrhea may occur secondary to bacterial overgrowth related to abnormal small intestinal motility. In addition, exocrine pancreatic insufficiency has been documented in a number of hemodialysis patients. The cause of the condition is not known, but Patients may improve clinically with pancreatic enzyme replacement.

Patients with CKD appear more likely to develop colonic perforation from ruptured diverticula, fecalomas (secondary to the use of aluminum-containing antacids or barium), or cecal ulcers that may bleed profusely. Life-threatening hemorrhage from rectal ulcers has also been reported. Colonic intussusception and ileus are also encountered in CKD. The diarrhea experienced by some patients with CKD appears to be related to abnormal bile acid metabolism. Ischemic colitis in patients receiving HD tends to be more right sided in anatomic distribution, which is associated with poor outcome.

HELICOBACTER PYLORI

After its discovery by Warren and Marshall in the year 1982 and its association with gastritis, it has been extensively studied in the pathogenesis of various gastric lesions. It is a spiral gram negative bacterium which is motile and mainly colonizes the zone beneath the gastric mucus which overlies the gastric epithelial cells. The organism may be found in any part of the stomach but prefers the antrum where the parietal cells are scanty in number or absent. H.pylori can be demonstrated in saliva, gastric juice and dental plaques by the sensitive PCR technique. Oro oral and feco-oral are likely pathways of transmission.

The infection is more prevalent in the developing countries (up to 90%) and is facilitated by conditions of overcrowding, poor living facilities. Low socioeconomic status and low education level are also known to increase infection rates. Rate of acquisition of infection increase with age and there is no specific gender predilection. There are high infection rates among smokers.

PATHOGENESIS OF GASTRIC LESIONS

Cag A gene possessing strains are common in people with peptic ulcer or adenocarcinoma. All HP strains possess Vac A gene but only 40% are toxigenic. The characteristic motility of the organism allows it to move rapidly through viscous mucus. Once the organism is safely encased in the mucus, it is able to fight the gastric acidity with the help of urease and converts urea into ammonia, which is a strong base, thus creating a cloud of acid neutralizing chemicals around the organism and protecting it from gastric acidity.

Another defense that the organism has is that, the body's natural defenses cannot reach the bacterium in the mucus lining of the stomach. The immune system responds strongly to the infection with a host of immune cells which unfortunately cannot get through the gastric lining.

But they are localized just outside the stomach lining and thus a vicious cytotoxic immune response ensues, producing gastritis and peptic ulceration. It may not be the organism itself which causes peptic ulcer but in fact the host response to H.pylori.

Although the organism is non invasive, the bacterium stimulates chronic gastritis by provoking a local imflammatory response in the underlying epithelium due to a variety of cytotoxins. Once infection in the antrum is established, there is depletion of antral somatostatin and stimulation of gastrin release from G cells. Subsequent hypergastrinemia stimulates acid production by the parietal cells, leading to duodenal ulceration. The role of HP in gastric ulcer is less clear but HP probably reduces gastric mucosal resistance to attack from acid and pepsin. Host response to infection is characterized by an acute neutrophilic infiltrate in the acute stage followed by a chronic inflammatory cell infiltrate in the later stages, the Th I response predominating.

The following types of chronic gastritis have been found to be associated with HP infection

Type A : atrophic in nature and have parietal cell antibodies

Type B : no parietal cell antibodies

Type AB : atrophic and patchy

Chronic gastritis in HP has been found to be associated with intestinal metaplasia and increases risk of gastric adenocarcinoma. HP infection has been very strongly linked to duodenal ulcer, the prevalence rates reaching close to 100%. Eradication of HP in DU gives awarding results. The most serious lesion caused by HP is gastric cancer. The pathogenesis is represented as follows by Correa's multi step hypothesis.

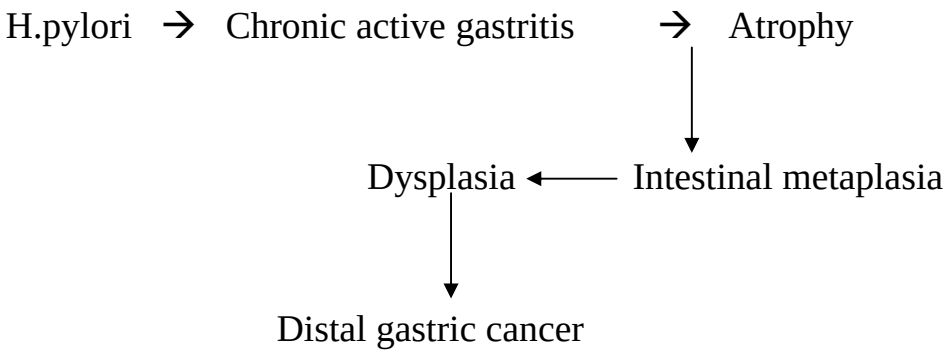

TABLE – 1

Association of HP with various gastric disorders

Chronic gastritis	50-65%
Duodenal ulcer	95-98%
Gastric ulcer	60-75%
Non ulcer dyspepsia	50-60%
Gastric adenocarcinoma	six fold increase
Gastric MAL Toma	93-98%

DIAGNOSIS OF INFECTION

The presence of H.pylori in the stomach can be detected by several invasive and non invasive methods.

Table - 2

Invasive	Non invasive
Culture	Serology
Histology of biopsied specimen	Urea breath test
Rapid urease test	Stool antigen test, PCR, urine antigen

The choice of the test used depends upon the accuracy, cost, availability and whether the patient will be undergoing endoscopy. Stool antigen tests are increasingly being used as simple non invasive methods for H.pylori diagnosis. Serology is useful as a screening test but cannot differentiate between current and past infection.

TABLE - 3

COMPARISONS OF VARIOUS METHODS OF DETECTION OF HP

Feature	Histo	Culture	RUT	ELISA	UBT	SAT	PCR
Sensitivity (%)	90	86	88-92	90-100	95-100	91	93-96
Specificity (%)	88	100	92-100	91-100	95-100	93	100
Invasive	+	+	+	-	-	-	-
Expensive	+	+		-	-	-	+
Results within 24 hrs	-	-	+	-	+	+	+
Can Confirm eradication	-	-	-	-	+	-	+
Accuracy affected by recent treatment with PPI / antibiotics	+	+	+	-	+	-	-

Histo - Histology,

+= Yes, - = No, PCR = polymerase chain reaction,

RUT = rapid urease test, URT = urea breath test,

SAT = stool antigen test, ELISA=enzyme linked immunosorbent assay

MANAGEMENT OF DYSPEPSIA AND H.PYLORI INFECTION

The clinician evaluating a patient with dyspeptic symptoms should recognize the limitations of history taking and physical examination in this setting. The principal utility of the clinical history and physical examination is to

(1) Identify patients with GERD and NSAID- induced dyspepsia

(2) Identify patients with alarm symptoms who may require early investigation.

Patients who have typical symptoms of reflux disease should be managed as having GERD. Patients whose symptoms are predominantly related to bowel function may have IBS and should be treated appropriately.

Alarm features are used to try and identify patients who need early investigation with endoscopy. The negative predictive value was always >97% in various trials, reflecting the fact that upper gastrointestinal malignancy was a rare diagnosis.

There are 5 initial approaches to the management of dyspepsia:

(1) Empirical acid suppression;

(2) A non-invasive test for H pylori, with a urea breath test, stool antigen test, or serology, and reserving endoscopy for positive cases;

(3) A noninvasive test for H pylori and eradication therapy for positive cases;

4) Empirical H pylori eradication therapy without testing;

5) Early endoscopy.

PATIENTS WITH DYSPEPSIA AND ALARM SYMPTOMS

Due to the small but clear-cut increase in the risk of upper gastrointestinal malignancy, new-onset alarm symptoms or new onset of symptoms after the age of 55 years should prompt early endoscopy. This cutoff was chosen because the risk of malignancy in most populations is < 10 per 100,000 below the age of 55 years. The probability of detecting an early gastric cancer is therefore very low below this age.

PATIENTS WITH DYSPEPSIA AND NO ALARM SYMPTOMS

The optimal management strategy for the patient who presents with new onset dyspepsia and no alarm features has been dominated by testing for H pylori and treating all positive cases empirically with antibacterial therapy. However, there are other choices, including no testing but empirical medical therapy (e.g., an anti secretory agent) with any subsequent investigation reserved for failures or immediate evaluation by upper endoscopy in all cases and targeting therapy based on the results.

In primary care, empirical anti secretory therapy remains popular. Only a minority of patients with dyspepsia has peptic ulcers, and even fewer have cancer. Therefore, in 1985, the American College of Physicians recommended, based on a literature review of outcomes and cost, that antisecretory medical therapy is preferable for patients without obvious organic disease who are younger than 45 years of age. The American College of Physicians further suggested that endoscopy (rather than a barium series) should be reserved for patients who have little or no response to therapy after 7-10 days or for patients whose symptoms

have not resolved after 6-8 weeks. However, whether this age threshold is still applicable and the utility of empirical therapy now continue to be debated, especially in terms of continuing such treatment on a long-term basis in those with undiagnosed H pylori infection.

The 3 strategies that have undergone intense evaluation are empirical acid suppression, H pylori test and treat, and early endoscopy. Preliminary data suggest that H pylori test and treat is more cost-effective than empirical PPI therapy in patients with dyspepsia. As a strategy, the efficacy of H pylori test and treat will vary according to whether the test is performed in primary or secondary care and the prevalence of infection in the population.

“Cure" is to be offered to the patients who are infected and an alternate approach for those who test negative.

THE MANAGEMENT OF DOCUMENTED NON ULCER / FUNCTIONAL DYSPEPSIA

1. Initial PPI therapy
2. Acid suppression,
3. Prokinetic therapy,
4. H pylori eradication therapy, and
5. Psychological therapies.

Overall, the only therapies that have established efficacy in functional dyspepsia are H pylori eradication and PPI therapy. H.pylori eradication is the most cost-effective approach in patients who are positive because this treatment is only given once for a long-term effect. In H pylori-negative patients with functional dyspepsia and those who fail to respond to eradication therapy, a one month course of PPI therapy may be warranted.

The association between H.pylori and the non ulcer dyspepsia has been analysed for many years and various studies have tried to prove the association so that these patients can be subjected to eradication therapy. But definite evidence is lacking. A study

performed in Germany by Bajorsky et al concluded that HP-infection per se contributes to dyspepsia. 85% HP positive dyspeptic patients improved after HP-eradication, when other potential. organic causes for dyspepsia had been ruled out. However, many patients did not completely recover but the symptoms only partly decreased which parallels the persistence of part of the inflammatory infiltration in the gastric mucosa. This emphasizes the importance of HP-gastritis as an organic disease causing dyspeptic symptoms.

The first national workshop on H.pylori was held in Mumbai in the year 1997 and the significant conclusions were as follows

1. The prevalence of H.pylori infection in healthy or asymptomatic persons in India varied from 31-84 %.
2. Prevalence mainly depends on the age, socioeconomic status, housing, sanitation and methods used for diagnosis.
3. Age related prevalence studies show that in India, infection occurs at an earlier age than in the west.
4. The frequency of H.pylori in non ulcer dyspepsia varies from 60-85% and no correlation was found between the degree of

gastric inflammation and symptoms of non ulcer dyspepsia.

5. There is no large study on the histological picture of the gastric mucosa and its correlation to symptom response.

6. Invasive techniques have been the preferred mode of diagnosis of H.pylori in India; of these tests rapid urease test has been most popular, both the commercially available kits and the in house developed ones.

Anitha Kamath et al compared the sensitivity and specificity of a commercially available urease test and an in house prepared urease test using histology as the gold standard. The inhouse urease test was cheap and more sensitive than the commercially available helicocheck kit.

Thayumanavan L et al, Madurai studied the prevalence of H.pylori in gastroduodenal diseases during routine upper gastrointestinal endoscopies at Madurai and concluded that the organism is widely prevalent in southern parts of Tamil Nadu, the rapid urease test is cheap, simple and useful for detecting the organism, and the prevalence of infection was nearly as high in non ulcer dyspeptics (66%) as those with DU (86%).

In the research setting, culture should be included in the protocol for confirming eradication, till the urea breath test is widely available. Serology is ideal for epidemiological studies.

Warren Marshall observation proved that greater than 90% of DU patients were infected compared to 40% of controls.

Four endoscopic surveys showed H.pylori infection in 43-79% of NUD patients. These numbers were well above control in three of these surveys. At least 50% of infected persons had no symptoms. Some have found that infected patients are likely to have reflux like or ulcer like symptoms.

The EUROGAST study group showed a positive correlation between the prevalence of gastric cancer and H.pylori in different parts of the world. The correlation was convincing and statistically significant. PC Jain et al studied the presence of H.pylori in patients with upper gastrointestinal symptoms using the rapid urease test and found significant prevalence of the organism in both ulcer and non ulcer dyspepsia.

There have been very few studies on the histopathological aspects of non ulcer dyspepsia and its relation to H.pylori. One study done in Nigeria found that significant mucosal lesions were found in patients who were infected with H.pylori despite normal endoscopy. Studies from India are lacking.

ERADICATION OF HELICOBACTER PYLORI

All patients suffering from gastric or duodenal ulcers who are infected with H.pylori should be treated with antimicrobials regardless of whether they are suffering from the initial presentation of the disease or from recurrence. Drugs known to cause dyspepsia should be discontinued wherever possible. However, the issue of eradicating H.pylori in non ulcer dyspepsia remains controversial. Recent studies suggest that H.pylori should be eradicated even in non ulcer dyspepsia. H. pylori eradication is defined as negative test for H.pylori atleast 28 days after therapy.

FACTORS WHICH MODIFY TREATMENT

1. Bismuth and PPIs specifically inhibit the bacterial enzyme urease so that urease based tests might fail to detect residual infection or recurrence.
2. H.pylori tends to move to the proximal stomach during suppression of acid secretion. So biopsy based tests become inaccurate

3. C^{13} and C^{14} urea breath tests are most accurate because they sample the whole stomach and so regarded as gold standard to confirm eradication.
4. Serology is not useful to confirm eradication as it takes at least 6 months for the antibody titer to fall significantly
5. Dual therapy with a two week combination of omeprazole or ranitidine or bismuth citrate and either amoxicillin or clarithromycin eradicated H.pylori in 50-80%. In triple therapy, eradication may be around *50-70%*. One week, twice daily PPI based triple therapy eradicates in about 90%. Second line regimens include seven days treatment with omeprazole and thrice daily amoxicillin and metronidazole or a PPI based regimen.

TABLE 4

TRIPLE REGIMENS WITH AMOXICILLIN AND METRONIDAZOLE

	REGIMEN 1	REGIMEN 2	REGIMEN 3
Drug	Omeprazole+	Ranitidine+	Bismuth+tetracycline/
	amoxicillin+	amoxicillin+	amoxicillin+
	metronidazole	metronidazole	metronidazole
Dose (daily)	40mg once+	300mg once+	120mg 4 times+
	500mg thrice+	750mg thrice+	500mg 4 times+
	400mg thrice	500mg thrice	200-400mg 4 times
Duration	7 days	12 days	2 weeks
Efficacy	95%	90%	60-90%
Side effects	Diarrhea, nausea		

These standard triple regimens have been replaced by shorter regimens which contain amoxicillin or clarithromycin along with a proton pump inhibitor. These regimens are equally effective in eradicating the organism.

TABLE 5 LOW DOSE TRIPLE THERAPY

	REGIMEN 1	REGIMEN 2
Drugs	PPI+ Clarithromycin+	PPI + Amoxicillin+
I		
	Metronidazole	Clarithromycin
Dose(daily)	I Once/twice daily+	Twice +
	250mg twice+	1 gm twice+
	400mg twice	250-500 mg twice
Duration	7 days	
Efficacy	90%	90.%
Side effects	Uncommon: diarrhea, nausea with metronidazole	

QUADRUPLE THERAPY

PPI (once/twice daily), colloid bismuth sub citrate (120mg four times daily), tetracyc1ine (500 mg four times daily), metronidazole (400-500mg 3-4 times daily)

Duration of therapy : seven days

Efficacy : 85-95%

Side effects : diarrhea, nausea

SEQUENTIAL THERAPY

Day 1-5

Proton pump inhibitors twice a day

Amoxicillin one gram twice a day

Day 6-10

Proton pump inhibitors twice a day

Clarithromycin 500 mg twice a day

Tinidazole 500 mg twice a day.

Sequential therapy gives an eradication rate of around 98%. The sequential therapy gave a higher eradication rate than the conventional triple therapy and it has been suggested that it should be made the standard eradication therapy for H.pylori.

AIMS AND OBJECTIVES

1. To study the prevalence of H. Pylori in CRF patients.
2. To study the endoscopic findings of CRF patients and correlate with their dyspeptic symptoms.
3. To study the histopathology of Antral mucosa and their relation to dyspepsia and H. Pylori.

MATERIALS AND METHODS

Study Group :

The study was conducted on outpatients, inpatients visiting medicine department and Nephrology department. Approval from the ethical committee was obtained. The study was a cross sectional study conducted for a period of one year between November 2009 to October 2010.

Inclusion Criteria :

1. Patients aged > 18 years
2. Elevated renal parameters > 3 months
3. USG abdomen showing B/L contracted kidneys
4. Anemia
5. Dyspeptic symptoms for > 3 months duration including
    1. Loss of appetite
    2. Nausea / vomiting
    3. Epigastric discomfort / pain
    4. Abdominal fullness / bloating
    5. Early sateity
    6. Loss of taste

7. Abnormal taste in mouth
8. Ammoniacal mouth smell
9. Oral ulcers
10. Weight loss

Exclusion Criteria :

1. Intake of NSAIDS for past 15 days
2. Acute gastro intestinal bleed
3. Severe systemic illness
4. Coronary artery disease / CCF
5. Patients refusing endoscopy

METHODS :

A total number of 50 CRF patients were studied as per inclusion and exclusion criteria.

A detailed history was elicited from the patient about the dyspeptic symptoms and duration of symptoms. The symptoms are classified under 10 sub headings and scoring was done.

Each symptom was given minimum score of 0 and maximum score of 3. Total symptoms scoring can be upto 30. History about other systemic illness and drug intake in the past was elicited.

Personal history, regarding Smoking, alcohol intake and Betalnut chewing was taken.

Each patient is examined for any epigastric tenderness or mass abdomen.

Their, Recent investigations were noted. Eg. Hb%, Urea, Creatinine, Electrolytes, Urine analysis, USG Abdomen.

A detailed informed consent was obtained from the patients undergoing UGI endoscopy.

All patients were advised overnight fasting and OGD was performed on empty stomach in the next morning.

OGD was performed with flexible fibreoptic endoscope and the mucosa of stomach and pylorus was analysed for any lesion.

Scope was passed upto II part of duodenum to findout any pathology. Then biopsy was taken from antral mucosa for histopathology. An additional sample was taken from antral mucosa for the tissue ultra rapid urease reaction.

After sterilization the scope and biopsy forceps were washed with sterile distilled water. So that no error occurred in the test due to changes in pH.

THE ULTRA RAPID UREASE TEST

This test is a modification of the standard ureas_ test so that a positive result is available almost immediately. The basic principle behind the test is that H.pylori produces large quantities of urease which rapidly hydrolyses urea to ammonia. The urea in the test solution is hydrolysed to ammonia by the preformed urease present in the H.pylori positive antral biopsy specimen.

The color of the solution changes from yellow to pink due to the change in pH of the solution. The test solution consists of O.5ml of freshly prepared 1 % urea in sterile distilled water to which is added two drops of 1 % phenol red as a pH indicator in clean capped bottles.

PROCEDURE AND RESULTS

A single antral mucosal biopsy was taken within five centimeters of the pylorus and the specimen was placed immediately within the test solution and remained undisturbed.

H.pylori positive specimens changed the color of the solution from yellow to pink and the results were read within one minute. Negative test specimens were observed for 12 hours stored in a refrigerator. Though the intensity and velocity of colour change varied with patients, those who tested positive developed a faint pink color change around the biopsy specimen immediately. The whole solution changed to pink color immediately in some, whereas in others a faint pink color developed over a period of time. Bacterial load is said to be the factor affecting velocity and intensity of color change. Solutions without H.pylori remained yellow throughout.

MERITS AND DEMERITS

Various studies have compared the diagnostic accuracy of the RUT with all other diagnostic modalities. The test has been shown to have a sensitivity and specificity of 90% and 100% respectively. The test does not give false positive results unlike the conventional urease test in which contaminants like Proteus

and Pseudomonas may give a positive result with prolonged incubation. The rapidity of the test is said to be due to the urea in water solution which is unbuffered like the Christenson's urea broth. The test solution is very inexpensive and easy to prepare. The endoscopist detects the infection even before the instrument is withdrawn. Treatment can be instituted at once and the outpatient reviews can be reduced.

The main disadvantage is that the procedure is invasive requiring endoscopy and biopsy. Though mostly colonization of bacteria in the gastric mucosa is concentrated at the antrum, the distribution may be patchy and biopsy from multiple sites is said to further increase the sensitivity of the test. This procedure cannot be used for screening a general population where a serum based test like ELISA is more practical.

Biopsy specimens from the body, fundus and antrum were analysed for histopathological changes after staining, with routine hematoxylin and eosin.

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using SPSS Statistics Software version 17.0. Using this software, frequencies, percentages, means, standard deviations, Pearson chi square and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULT ANALYSIS OF OBSERVED DATA

Majority of patients were from in and around Madurai. The age of the patients ranged from 26 to 70 years.

Among the 50 patients, 38 were males and 12 were females. Mean age of the study population 51.08 $\pm$ 10.02

Table 1 : Age Distribution

			RUT		
			Negative	Positive	Total
Age (Binned)	26 - 40	Count	7	0	7
		% within Age (Binned)	100.0%	.0%	100.0%
	41 - 55	Count	17	12	29
		% within Age (Binned)	58.6%	41.4%	100.0%
	56 - 70	Count	11	3	14
		% within Age (Binned)	78.6%	21.4%	100.0%
	Total	Count	35	15	50
		% within Age (Binned)	70.0%	30.0%	100.0%

Mean age = 51.08 + 10.02

P = 0.071 Not significant

Symptomatology :

Gastro intestinal symptoms were analysed under 10 headings such as

1. Loss of appetite
2. Nausea / vomiting
3. Epigastric Discomfort / Pain
4. Abdomen – Fullness / Bloating
5. Early sateity
6. Loss of taste
7. Abnormal taste in mouth
8. Ammoniacal mouth smell
9. Oral ulcers
10. Weight loss

Each symptom was given a score of 0 to 3.

0 - No symptoms

1 - Symptoms recalled on direct questioning

2 - Symptoms present but not impairing activities

3 - Symptoms interfering with daily work and life.

Symptoms scores were added for each patient giving a possible score ranging from 0 -30. If patient had less than 10 scores he was graded as mild, 11-20 – moderate and > 20 severe dyspepsia.

Table – 2 Symptoms Score

			RUT		
			Negative	Positive	Total
Symptom Score (Binned)	0 - 10	Count	19	11	30
		% within SymScore (Binned)	63.3%	36.7%	100.0%
	11 - 20	Count	16	4	20
		% within SymScore (Binned)	80.0%	20.0%	100.0%
	Total	Count	35	15	50
		% within SymScore (Binned)	70.0%	30.0%	100.0%

P = 0.208 - Not significant

30 patients had mild dyspeptic symptoms. 20 patients had moderate dyspeptic symptoms. 36.7% of mild dyspeptic category and 20% of moderate dyspeptic category had H.pylori positivity.

Table –3 Symptoms Analysis

Symptoms	No.of cases
Loss of appetite	48
Nausea / vomiting	43
Epigastric discomfort	47
Abdominal fullness	42
Early satiety	40
Loss of taste	31
Abnormal taste	18
Ammoniacal mouth smell	18
Oral ulcer	16
Weight loss	39

Most frequent symptoms among CRF patients were loss of appetite, nausea/vomiting, epigastric discomfort.

Table : 4 Sex Distribution

			RUT		
			Negative	Positive	Total
Sex	Female	Count	10	2	12
		% within Sex	83.3%	16.7%	100.0%
	Male	Count	25	13	38
		% within Sex	65.8%	34.2%	100.0%
	Total	Count	35	15	50
		% within Sex	70.0%	30.0%	100.0%

Out of 50 CRF patients 38 were males, and 12 were females. 34.3% in males and 16.7% in females are H.pylori positive.

Table : 5

Alcohol

			RUT		
			Negative	Positive	Total
Alcohol	No	Count	24	9	33
		% within Alcohol	72.7%	27.3%	100.0%
	Yes	Count	11	6	17
		% within Alcohol	64.7%	35.3%	100.0%
	Total	Count	35	15	50
		% within Alcohol	70.0%	30.0%	100.0%

P 0.558 - Not significant

Out of 50 patients, 33 do not consume alcohol, 17 consume alcohol. H.pylori positivity in alcoholic is 35.3%. Non alcoholic is 27.3%.

Table – 6 : SMOKING

			RUT		
			Negative	Positive	Total
Smoking	No	Count	20	7	27
		% within Smoking	74.1%	25.9%	100.0%
	Yes	Count	15	8	23
		% within Smoking	65.2%	34.8%	100.0%
	Total	Count	35	15	50
		% within Smoking	70.0%	30.0%	100.0%

P = 0.496 - Not significant

Among the 50 CRF patients, 23 are smokers, 27 are non smokers. H.pylori positivity in smokers is 34.8% and non smokers is 25.9%.

Table -7 UGI scopy

			RUT		
			Negative	Positive	Total
UGI_Scopy	Normal	Count	34	14	48
		% within UGI_Scopy	70.8%	29.2%	100.0%
	Abnormal	Count	1	1	2
		% within UGI_Scopy	50.0%	50.0%	100.0%
	Total	Count	35	15	50
		% within UGI_Scopy	70.0%	30.0%	100.0%

P = 0.529 - Not significant

Among the 50 CRF patients, 48 had normal endoscopy, 2 had abnormal endoscopy with findings of duodenal ulcer in one patient and Gastritis in one patient.

29.2% of normal endoscopy is positive for H.pylori. 50% of abnormal endoscopy is positive for H.pylori.

Table – 8 Biopsy

			RUT		
			Negative	Positive	Total
Biopsy	Normal	Count	32	12	44
		% within Biopsy	72.7%	27.3%	100.0%
	Abnormal	Count	3	3	6
		% within Biopsy	50.0%	50.0%	100.0%
	Total	Count	35	15	50
		% within Biopsy	70.0%	30.0%	100.0%

P = 0.254 Not significant

Out of 50 specimens, 44 showed normal gastric mucosa. 6 had abnormal findings.

Lymphocytic infiltration in laminapropria = 5

Inflammatory cells in submucosa = 1

Table –9 GFR

			RUT		
			Negative	Positive	Total
GFR (Binned)	<= 15.00	Count	8	4	12
		% within GFR (Binned)	66.7%	33.3%	100.0%
	15.00 – 29.00	Count	23	11	34
		% within GFR (Binned)	67.6%	32.4%	100.0%
	30.00 - 59.00	Count	4	0	4
		% within GFR (Binned)	100.0%	.0%	100.0%
	Total	Count	35	15	50
		% within GFR (Binned)	70.0%	30.0%	100.0%

P = 0.393 - Not significant

DISCUSSION

Majority of the patients were from in and around Madurai.

Age of patients ranged from 26-70 years. Out of 50 patients with CRF → 38 were males and 12 were females. Out of them 30% were positive for H.pylori which goes well with the world statistics of H.pylori prevalence in general asymptomatic population.

	V. Misra et al study, Allahabad	Saudi Arabian study	Croatia study	Our study
H.pylori prevalence in CRF	35.2%	42%	45%	30%

In a study conducted by Kerari EM et al at Nairobi, Kenya they have analysed the endoscopic findings and H.pylori prevalence in CRF patients with dyspepsia. They found that there is no statistical difference between the prevalence of H.pylori in CRF patients and controls.

Symptomatology :

In our patients mild to moderate dyspepsia is encountered. 60% had mild dyspeptic symptoms with symptom score 0-10 and 40% had moderate dyspeptic symptoms with symptom score 10-20

63.3% of the mild dyspeptic category are negative for H.pylori and 36.7% of the mild dyspeptic category are positive for H.pylori.

80% of the moderate dyspeptic category are negative for H.pylori and 20% of the same category are positive for H.pylori.

Again we find that severity of dyspeptic symptoms have no correlation with the H.pylori positivity.

In a study conducted by V. Misra et al in Allahabad – the conclusion was that the patients with CRF have significant UGI symptoms which mainly occur due to metabolic changes in response to high urea concentrations in gastric juice and are not related to H.pylori infection.

Another study in Italy done by Nardone G et al showed clearly that Uremic patients with H.pylori positivity show low symptoms score and high frequency of peptic lesions.

Ammonia generated by the action of urease producing organism(s) or urea is generally held responsible for gastro intestinal symptoms in Uremia. However little information is available on the exact organism(s) available.

It is concluded that H.pylori present in the gastroduodenal mucosa of patients with renal failure does not appear to play significant role in severity of dyspeptic symptoms in uremic patients.

UGI scopy and H.pylori :

UGI scopy was normal in 96% of patients and only in 4% it was abnormal 2% antral gastritis and 2% duodenal ulcer in 2nd part of duodenum.

Among those with normal endoscopy 29.2% have H.pylori positive and 70.8% have H.pylori negative.

Among those with abnormal endoscopy 50% positive for H.pylori and 50% negative for H.pylori.

Similar study was conducted in Kuwait in 77 patients with CRF a prospective study. In this the result was that there is no direct correlation between UGI scopy, H.pylori positivity and dyspeptic symptoms.

	Normal Scopy		Abnormal Scopy	
	Kuwait study	Our study	Kuwait study	Our study
H.Pylori Positive	46 %	29.2%	54%	50%
H.pylori negative	54%	70.8%	46%	50%

Biopsy & Histopathology :

Lymphocytic infiltration in the Lamina propria and inflammatory cells in the submucosa was found in 6 patients.

3 of them were H.pylori positive and 3 were negative. However no lymphoid follicles are found in any of the specimens which is pathognomonic of H.pylori infections.

GFR and H.pylori positivity

Patients with GFR < 15 ml / min are 12 in no out of them 33.33% are positive for HP.

Patients with GFR 15 to 29 ml → 34 in no. and out of them → 4% are positive.

Patients with GFR 30 - 59 ml → 4 in no. out of them 0% positive.

CONCLUSION

1. Prevalence of H.pylori in CRF patients is very much similar to non CRF patients.
2. Severity of dyspeptic symptoms do not correlate with H.pylori postivity in CRF patients.
3. Endoscopic findings do not have any relation to H.pylori positivity in CRF patients.

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ABBREVIATIONS

UGI	Upper Gastro intestinal
HP	Helicobacter pylori
H. Pylori	Helicobacter pylori
OGD	Oesophago gastro duodenoscopy
PPI	Proton pump inhibitor
PCR	Polymerase chain reaction
RUT	Rapid urease test
Th	T. Helper
CRF	Chronic renal failure
USG	Ultrasonogram
CKD	Chronic kidney disease
GFR	Glomerular filteration rate

BIBLIOGRAPHY

1. Sleisenger and Fordtran's Gastrointestinal and Liver diseases : 8th edition 2007.
2. Harrison's Principles of Internal Medicine, 17th edition, 2008.
3. Kerari E.M. et al – Endoscopic findings and Prevalence of H.Pylori in CRF patients, University of Nairobi.
4. Simunic Miroslav et al, Are dyspeptic symptoms in CRF aggrevated by H.pylori infections Goatic
5. Abdul Rahman et al – University of Al khobar, Saudi Arabia Does H pylori Infection in CRF increase the risk of Gastroduod lesions – a prospective study.
6. Aydemir S. et al, Turkey about Effects of H.pylori infection in air gastric epithelial cell kinetics in patients with CRF.
7. Nardone G et al from Italy – Gastro duodenal lesions and H. pylori infections in dyspeptic patients with and without CRF.

8. Watanabe H et al from Japan - Pathophyusiology of Gastric acid secretions in patients CRF : Influence of H. Pylori infections.

9. Misra V et al from Allahabad about Endoscopic and histological changes in UG1 tract of patients with CRF.

10. Mak SK et al from Hongkong about Efficacy of a 1 week course of PPI based triple therapy for eradicating H. pylori in patients with and without CRF.

11. Yo Shida N, Granger DN et al, about Mechanisms involved in H. Pylori Induced inflammation, gastroenterology 1993.

12. Peek RM, J. et al, Pathophysiology of H. pylori induced gastritis and PUD, J Med, 1997.

13. Peterson W, Fendrick AM, Cave DR, Peura DA, Hep related : Guidelines for testing and treatment : Arch Intern Med 2000.

14. Mohammed AR. Marhoon. H. Pylori. Basics and Clinical overview. Saudi Med J. 2009 ; 26(4)

15. Anitha Kamath, Preethi. R. Mehtha Satish. G. Kulkarni, Sandeep S. Shah, Sensitivity and specificity of two rapid urease tests with regard to histology for detection of H. pylori infection. Indian Journal of Gastroenterology, 1997; 16 (1) 34.

16. Thayumanavan L et al, Prevalence of H.pylori in gastro duodenal diseases during routine UGI endoscopies at Madurai – Indian Journal of gastroenterology 1997.

17. Marshal BJ, Warren JR : Unidentified curved Bacilli in stomach of patients with gastritis and peptic ulceration Lancet 1984 ; 1311 – 1315.

18. Jain PC et al. Efficacy of RUT in diagnosis of H. pylori in patients with Acid peptic disease dept of medicine, GR, Medical college, Gwalior, JAPI 2001.

19. Vaira D et al. Sequential therapy versus Standard triple drug therapy for H.pylori eradication. A randomized trial, Ann Intern Med 2007, April 17.

FIGURE 1: DISCOVERERS OF H.PYLORI: BARRY MARSHALL AND WARREN

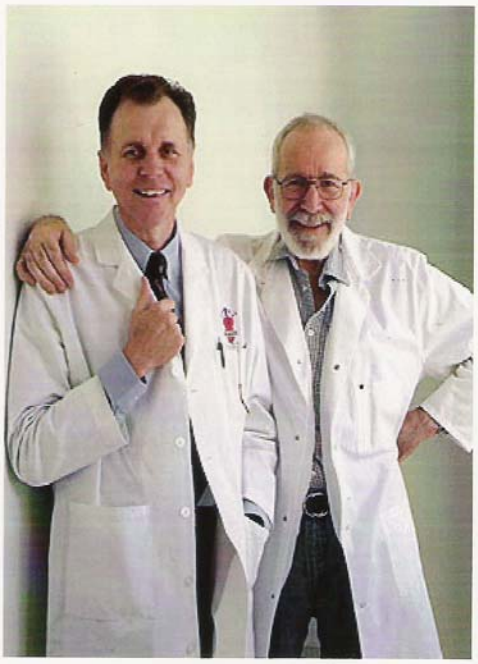


FIGURE 3: GASTRIC MUCOSA: HISTOPATHOLOGY AND H.PYLORI

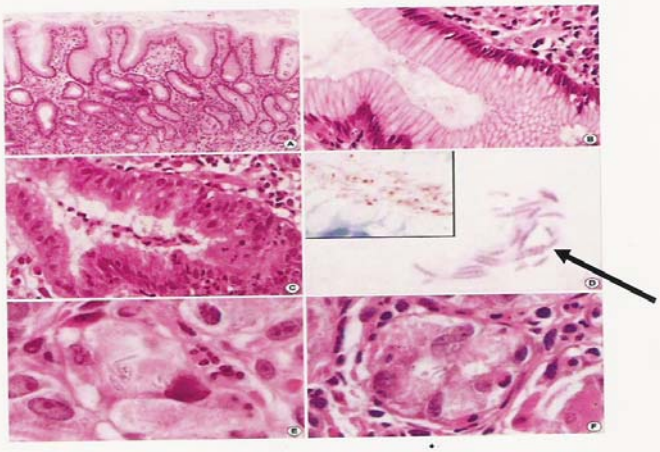
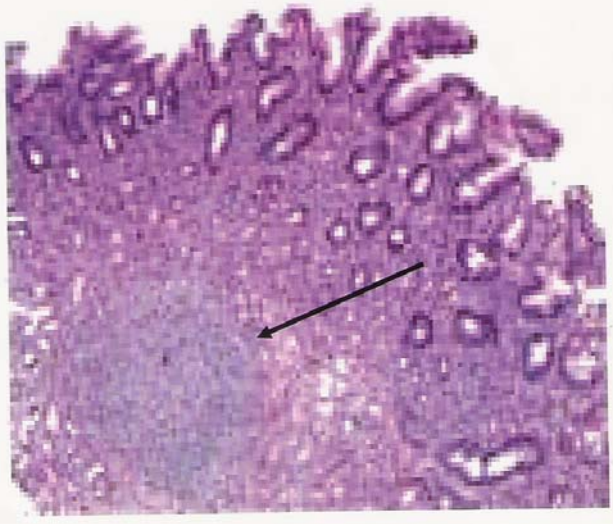


FIGURE 4: GASTRIC INTRAMUCOSAL LYMPHOID AGGREGATES



MASTER CHART

S. No.	IP No.	Sex	Age	Alcohol ±	Smoking ±	Symptom Score	HB%	DM ±	Urea mg %	Creatinine mg%	GFR ml/min	Urine Alb.	UGI Scopy	RUT	Histopathology
1.	97925	F	50	-	-	14	8	-	169	4.6	12.93	+++	N	-	Normal
2.	103050	F	63	-	-	8	9	+	168	9.9	6.48	loaded	N	-	Normal
3.	104725	F	45	-	-	13	6.2	+	279	8.9	8	+++	N	-	Normal
4.	063241	F	60	-	-	13	7.8	-	53	1.5	31.11	++	N	-	Normal
5.	062128	F	55	-	-	12	8	-	56	2.1	25.29	++	Antral Gastritis	+	Focal Collection of Lymphocytes
6.	43291	F	55	-	-	12	8.8	-	60	2.2	26.83	++	N	-	Normal
7.	21454	F	42	-	-	9	9	-	88	4.2	17.82	++	N	+	Lamina propria inflammatory cells
8.	21440	M	50	+	+	8	7.5	-	84	4.8	14.84	-	N	-	Normal
9.	21438	M	41	-	-	13	8.8	-	68	3.9	22.91	-	N	+	Normal
10.	21443	M	53	+	+	9	9	-	68	4.2	17.83	-	N	+	Normal
11.	023501	M	43	-	-	7	8	-	120	6	11.22	-	N	+	Normal
12.	045624	M	26	-	-	10	9.6	-	147	4.5	16.53	-	N	-	Normal
13.	043216	M	45	+	+	7	7.8	-	111	4.5	14.66	++	Duodenal ulcer	-	Normal
14.	39109	M	33	+	+	8	8.6	-	48	1.9	46.92	+	N	-	Normal

15.	59745	M	50	+	+	9	9	-	131	3.4	20.22	++	N	-	Normal
16.	82421	M	43	-	-	9	8	-	143	3.9	21.41	++	N	+	Normal
17.	62814	M	50	-	-	6	9.8	-	100	3.8	21.71	+	N	-	Normal
18.	102920	M	52	-	+	7	8.6	+	144	3.4	22.28	++	N	+	Normal
19.	100721	M	60	+	+	8	7.6	-	53	2.4	32.4	+	N	-	Normal
20.	009200	M	50	-	-	10	6.8	-	106	3.9	21.79	-	N	+	Normal
21.	80003	M	55	-	-	10	5	-	80	3.2	21.39	-	N	-	Normal
22.	7314	M	55	+	+	3	12.4	-	115	4.3	18.47	-	N	-	Normal
23.	32891	M	54	+	+	7	8.6	-	78	3.2	22.39	-	N	+	Normal
24.	23521	M	61	-	-	3	9.2	+	88	2.8	21.55	-	N	-	Normal
25.	63214	M	55	-	+	8	8.2	-	62	2.4	33.44	-	N	-	Normal
26.	23891	M	55	+	+	8	6.8	-	82	4.1	17.27	-	N	+	Normal
27.	36381	M	62	+	+	6	9	-	111	4.8	13.09	-	N	+	Normal
28.	63241	M	60	+	+	6	10.2	+	66	2.4	26.85	-	N	-	Normal
29.	96388	M	28	-	-	4	6	-	72	3.4	22.87	-	N	-	Normal
30.	238601	M	48	+	+	6	6	-	108	6.5	12.18	-	N	+	Normal
31.	263821	M	52	-	-	5	9	-	98	2.4	29.53	-	N	-	Normal
32.	238060	M	46	-	+	8	9	-	80	4.2	18.65	-	N	-	Limphocytic Infiltration
33.	64290	M	68	-	+	6	8.6	-	56	4.8	12.5	++	N	+	Chronic Inflammatory cells
34.	23841	M	60	-	-	7	9	+	94	3.8	4	++	N	-	Normal

35.	285392	M	58	+	+	10	8.5	-	82	2.8	23.59	++	N	-	Normal
36.	7281	F	55	-	-	12	6.8	-	86	3.8	21.72	-	N	-	Limphocytic Infiltration
37.	73120	M	55	+	+	12	9.5	+	64	4.2	16.3	-	N	+	Normal
38.	61230	M	60	-	-	10	8	-	80	4.1	16.26	-	N	-	Limphocytic Infiltration
39.	84291	M	65	-	-	14	9	-	78	2.8	20.46	-	N	+	Normal
40.	299856	F	35	-	-	12	8.9	-	80	3.2	22.78	-	N	-	Normal
41.	67321	M	42	-	+	11	9.2	-	68	2.8	28.19	-	N	-	Normal
42.	42525	M	38	-	+	14	8	+	88	3	28.83	++	N	-	Normal
43.	24261	M	70	-	-	14	8.2	-	40	1.8	28.08	-	N	-	Normal
44.	55165	M	60	-	+	15	8	-	68	4	16.11	-	N	-	Normal
45.	054209	M	35	+	-	16	6.8	-	82	2.8	22.19	-	N	-	Normal
46.	056150	M	60	+	+	14	7	-	56	3.8	17.51	-	N	-	Normal
47.	059822	F	51	-	-	19	8	-	82	6.2	10.36	-	N	-	Normal
48.	069487	M	55	+	+	13	8	+	80	4.2	16	-	N	-	Normal
49.	82639	F	35	-	-	16	6.8	-	98	5.2	13.46	-	N	-	Normal
50.	760097	F	55	-	-	14	7	-	86	4.6	15.09	-	N	-	Normal