PREVALENCE OF HELICOBACTER PYLORI INFECTION AND ENDOSCOPIC FINDINGS IN PATIENTS WITH DYSPEPSIA AT MOI TEACHING AND REFERRAL HOSPITAL

BY:

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DECLARATION

DECLARATION BY THE STUDENT

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ABSTRACT

Background: *H. pylori* is known to be a highly prevalent infection among persons in developing countries. It is firmly established as the etiologic agent for acute and chronic gastritis and a predisposing factor in peptic ulcer disease, gastric carcinoma and B-cell mucosa-associated lymphoid tissue (MALT) lymphoma. Despite this significant morbidity and mortality associated with it, data in developing countries is lacking on several aspects of this infection. Data on prevalence among patients with dyspepsia is especially lacking at MTRH.

Objectives: To determine the prevalence of *H. pylori* infection among patients with dyspepsia referred for upper gastrointestinal endoscopy at MTRH, to describe endoscopic findings among patients with dyspepsia and to define the socio-demographic status of the patients with *H. pylori* infection.

Study Design: A descriptive cross sectional study.

Setting: Moi Teaching and Referral Hospital endoscopy unit, Eldoret, Kenya.

Patients and Methods: Those enrolled were adult patients referred for upper endoscopy and who had dyspepsia and had given informed consent. Those who had taken proton pump inhibitors, H2 receptor blockers, bismuth salts or antibiotics or those in whom endoscopy was unsuccessful were excluded. Patients meeting the inclusion criteria had their demographic data taken. They then underwent upper gastrointestinal endoscopy and endoscopic findings were noted. Mucosal biopsies were taken from the body and antrum of the stomach and then used for rapid urease test for *H. pylori*. The rapid urease test used was Esokit® Hp test. Data was analyzed with SPSS and p-value of 0.05 was considered significant in all analyzes. Frequency tables were generated for categorical variables. Chi-square test with goodness of fit was used to assess any association between variables among *H.pylori* positive and negative arms.

Results: A total of 126 patients were studied, 65 (51.6%) were male and 61 (48.4%) were female. 78 (61.9%) were between 25 and 54 years of age. Among all patients, 66 (52.3%) of them were *H. pylori* positive. 53.8% (35) of males were *H. pylori* positive compared to 50.8% (31) of females. Most common abnormal finding were noted to be gastritis in 69.8% (88) of patients followed by duodenitis in 33.3% (42) and peptic ulcer disease in 30.1% (38) of patients. Only 4% (5) of patients had normal findings. Among the 38 patients with peptic ulcer disease 73.7% (28) were *H. pylori* positive.

Conclusion: This study showed that more than half of patients with dyspepsia are *H. pylori* positive and prevalence is lower than in previous studies. Gastritis remains the most common endoscopic finding among patients with dyspepsia and also among those with *H. pylori*. Peptic ulcer disease had the strongest association with *H. pylori* infection.

Recommendation: Given high number of *H. pylori* negative patients in this study, a study on other causes of dyspepsia is recommended. Dyspepsia should be used as a sole reason to treat for *H. pylori*. Given the high association between *H. pylori* and peptic ulcer, it is recommended that all patients with peptic ulcer disease be treated for *H. pylori.*

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LIST OF ABBREVIATIONS

ACG	-	American College of Gastroenterology
EHSG	-	European Helicobacter Study Group
IREC	-	Institutional Research and Ethics Committee
MIC	-	Minimum Inhibitory Concentration
MTRH	-	Moi Teaching and Referral Hospital
MALT	-	Mucosa-associated lymphoid tissue
PUD	-	Peptic ulcer disease
PMF	-	Proton Motive Force
PPI	-	Proton Pump Inhibitor
WHO	-	World Health Organization

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DEFINITION OF TERMS

The following terms are defined using Rome III criteria.[1]

Dyspepsia

Dyspepsia is defined as one or more of the following symptoms: Postprandial fullness (termed postprandial distress syndrome), early satiation (meaning inability to finish a normal sized meal or postprandial fullness) and epigastric pain or burning epigastric pain (termed epigastric pain syndrome).

Non Ulcer Dyspepsia

Non ulcer dyspepsia is defined as dyspepsia in which no identifiable cause can be found. There are no lesions seen on endoscopy.

Case Definition

H. pylori infection is defined as present based on a positive rapid urease test at endoscopy.

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CHAPTER ONE

INTRODUCTION

1.1 Background

Helicobacter pylori, is a Gram-negative, microaerophilic bacterium. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer.[2]

In 1982 when two Australian scientists, Barry Marshall and Robin Warren first isolated *H. pylori*, initially known as *Campylobacter pylori*, few if any gastroenterologists would have predicted that almost 30 years later, this bacterium would have been shown to be one of the most common bacterial infections in humans and the etiologic agent of the majority of upper gastrointestinal disease. At that time the conventional thinking was that no bacterium can live in the human stomach as the stomach produced extensive amounts of acid which was similar in strength to the acid found in a car-battery. Barry Marshall and Robin Warren "re-wrote" the text-books with reference to what causes gastritis and gastric ulcers. In recognition of their very important discovery, they were awarded the 2005 Nobel Prize for Medicine and Physiology.

H. pylori infection is a common infection with an estimated half of the world's adult population having been exposed to this organism.[3] Recent studies show that genetic diversity in *H. pylori* decreases with geographic distance from East Africa, the birthplace of modern humans.[4] Using the genetic diversity data, simulations indicate that the bacteria seem to have spread from East Africa around 58,000 years ago. Their

results indicate modern humans were already infected by *H. pylori* before their migrations out of Africa, remaining associated with human hosts since that time.[4]

Today, *H. pylori*, as it is now known, is firmly established as the etiologic agent of acute and chronic gastritis and a predisposing factor in peptic ulcer disease, gastric carcinoma, and B-cell mucosa-associated lymphoid tissue (MALT) lymphoma.[5] *H. pylori* is an important etiological factor in the development of peptic ulcer disease, gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphomas.[6] As a result, the World Health Organization (WHO) has classified *H. pylori* as a Class 1 carcinogen.

Previous studies in Kenya have shown high prevalence of *H. pylori* in various populations.[7, 8] Patients infected often manifest with several signs and symptoms including epigastric pain, nausea, bloating and anorexia. All this contribute significantly to a poor quality of life of patients.

Despite its importance, there are no studies in the local setting to address the gap in knowledge of the level of *H. pylori* infection. Patterns of infection vary among different regions, among different races and even among different socioeconomic groups.[9] The pattern of infection in one group of people cannot be used to extrapolate on the pattern of infection in a different group. Furthermore there are no guidelines on the treatment of *H. pylori* in the local setup. Treatment is usually started based on symptoms and not on diagnosis. Lack of studies in the local setup to address who and when to treat is partly the reason for treatment being started on the basis of symptoms. This study will form a foundation upon which more studies on *H. pylori* can be done.

1.2 Problem Statement

There is overwhelming evidence showing that infection with *H. pylori* is higher in the developing countries as compared with the developed countries.[10] Despite this, studies on specific aspects of *H. pylori* in developing countries are still few. Local studies show high prevalence of *H. pylori* among Kenyans.[7] Due to widespread use of antibiotics, resistance is developing, and in a local study, virtually all *H. pylori* isolated were resistant to metronidazole.[11] Evidence of clarithromycin resistance has been established in other studies.[12] To forestall development of such a scenario, it is necessary that we develop protocols on when treatment for *H. pylori* can be started in our setup.

H. pylori infection is significantly associated with development of gastric cancer. Gastric cancer mortality is high and hence early detection of the causative agent will have a significant impact on prevention or delay progression to development of gastric malignancies.

Knowledge on the magnitude of *H. pylori* infection in our setup is missing. Since this would form a foundation on other studies on treatment and diagnostic protocols for *H. pylori* the missing data on the prevalence of H. pylori among patients with dyspepsia is a big problem.

1.3 Justification

Given the magnitude of the problem as stated above, the study was seeking to address the lack of knowledge on the level of infection of *H. pylori* among patients referred for endoscopy. Patients with dyspepsia referred for endoscopy are usually a special

group of patients that have borne the burden of poor response to treatment for different ailments.

Given the invasiveness of endoscopy, patients who undergo this procedure should obtain maximum benefit from it. Rapid urease test at endoscopy is highly beneficial to patients in that it shortens the time a patients can know about *H. pylori* status after endoscopy.

In the local setup, most patients are on treatment for *H. pylori* based on symptoms of dyspepsia alone based on older studies that had shown very high prevalence in this group of patients. It is therefore justified to do a follow up study to determine whether prevalence of *H. pylori* has changed or not and whether we need to change the current treatment strategy.

Treatment for *H. pylori* is expensive regardless of the protocol. Treatment should be based on definite diagnosis, and where this is not possible, treatment based on symptoms of dyspepsia should be based on the likelihood of infection with the organism. Such likelihood can only be established based on studies using patients from our population since we cannot extrapolate based on studies elsewhere. Furthermore, given the classification by WHO of *H. pylori* as a class I carcinogen, it is justified to develop protocols for detection of this organism early enough to prevent progression to gastric malignancies. The results from this study will help in the development of diagnostic and treatment protocols in our setup.

1.4 Research Questions

1. What is the prevalence of *H. pylori* infection among patients with dyspepsia undergoing upper gastrointestinal endoscopy at MTRH?
2. What are the upper gastrointestinal endoscopic findings of patients with dyspepsia?
3. What are the demographic features of patients with *H. pylori*?

1.5 Broad Objective

To establish the prevalence of *H. pylori* and upper gastrointestinal endoscopic findings among patients with dyspepsia.

1.6 Specific Objectives

1.6.1 Primary Objective:

To determine the prevalence of *H. pylori* infection among patients with dyspepsia referred for upper gastrointestinal endoscopy at MTRH.

1.6.2 Secondary Objective

1. To describe the endoscopic findings among patients with dyspepsia;
2. To describe the socio-demographic status of patients with *H. pylori* infection.

CHAPTER TWO

LITERATURE REVIEW

2.1 Prevalence

An accruing body of literature suggests that not all humans are equally at risk of infection by this gut pathogen. Khalifa et al found that the overall prevalence of *H. pylori* infection in developed countries is lower than that in developing countries.[13] The average prevalence in a sample of developing countries was 60% compared with 41.9% in developed countries.[13]

Globally, prevalence varies from country to country and even within countries, prevalence varies in different regions. Khalifa et al review of different prevalence studies found prevalence rates ranging 20% to 30% in the united states among whites but one study found prevalence of 70% among Texan blacks.[13] A study in Switzerland showed prevalence rates of 7.3% among natives but 30% among immigrants. Among the Japanese, the prevalence was 30%. Rural and urban Brazil had prevalence of 84.7% and 63.7% respectively.[13]

Regionally, studies in Egypt established a prevalence of 88% in Alexandria but only 60% in Cairo.[13] Abiodun et al in 2010 found a prevalence rate of 64% among Nigerians.[14]

Locally, based on a study done in 1993, the prevalence of *H. pylori* among Kenyans with dyspeptic symptoms is very high, ranging from 80.5% among patients without lesions on endoscopy to 100% in patients with confirmed peptic ulcer disease on

endoscopy.[7] No follow up studies have been done to show the progression in prevalence since then and no studies have been done on *H. pylori* in Eldoret.

2.2 Microbiology of *H. pylori*

Helicobacter pylori is a spiral shaped, microaerophilic, gram negative bacterium measuring approximately 3.5 microns in length and 0.5 microns in width. The organism can be biochemically characterized as catalase, oxidase, and urease positive. Urease appears to be vital for its survival and colonization. Bacterial urease activity is clinically important because it forms the basis for several invasive and noninvasive tests to diagnose infection.

The organism's urease, motility, and ability to adhere to gastric epithelium are factors that allow it to survive and proliferate in the gastric milieu.[15]

2.3 Pathophysiology of *H. pylori*

H. pylori exclusively colonizes gastric type epithelium, which suggests specific recognition of cell type by the bacterium.[16] Bacterial attachment is partially mediated by a number of adhesins and outer membrane proteins. Bab A, the best characterized of the adhesin proteins, mediates binding to fucosylated Lewis blood group antigens on host cells. *H. pylori* can also bind to class II MHC molecules on the surface of gastric epithelial cells and induce apoptosis and binding of the organism's urease to surface class II MHC is itself sufficient to induce apoptosis.[17]

H. pylori elaborate several enzymes that can cause cellular damage by direct or indirect mechanisms. Urea, when hydrolyzed by bacterial urease, can form

compounds such as ammonium chloride and monochloramine that can directly damage epithelial cells. In addition, the urease enzyme itself is antigenic producing injury by stimulating inflammatory cells.[18] Bacterial phospholipases can alter the phospholipid content of the gastric mucosal barrier, changing its surface tension, hydrophobicity, and permeability.[19] *H. pylori* produces more catalase enzyme than most other bacteria. This enzyme protects the organism from toxic oxygen metabolites liberated by activated neutrophils and allow it to survive and proliferate in an inflamed and damaged gastric mucosa. Bacterial proteolytic enzyme activity can further degrade mucus.[19]

2.4 Natural History of *H. pylori* Infection

Natural acquisition of *H. pylori* infection occurs, for the most part, in childhood. Once established within the gastric mucosa, the bacterium persists for life. Studies in children suggest, however, that in the early years of life prior to the establishment of infection, transient infection with *H. pylori* may be common.[20]

Interestingly, in a recent study by Malaty et al.[21], acquisition and loss of infection were shown to differ in children who, although matched for socio-economic class, were from different racial backgrounds. The rate of acquisition of infection among African American children was found to be four times higher than that among Caucasian children. Loss of infection over the 12-year period was shown to be significantly higher (50%) among Caucasian children as compared with African American (4%), with the latter group either remaining infected or becoming re-infected.[21] This may suggest hereditary and genetic susceptibility but this has not been

proven by studies. Racial differences alone could not explain the differences in this study.

Thus, based on current evidence, it appears that in the early years of life spontaneous clearance of infection might occur. Further studies are required to determine factors that may lead to natural clearance of infection in children.

2.5 Factors Influencing the Transmission of *H. pylori*

2.5.1 Socioeconomic Status

Numerous studies conducted throughout the world have shown low socioeconomic status to be associated with an increased prevalence of *H. pylori* infection. In particular, the socioeconomic status of a subject during childhood is considered to be an important determinant of the development of *H. pylori* infection.[22]

The influence of living conditions on the prevalence of *H. pylori* infection is clearly illustrated in countries where socioeconomic conditions have significantly improved over the last few decades. For example, in Japan the fall in prevalence of *H. pylori* infection in subjects less than 40 years of age has been related to the significant improvement of the Japanese economy, and hence living conditions, following the Second World War.[23]

2.5.2 Genetic Predisposition

To date, there have been few studies that have examined the role of genetic predisposition in relation to *H. pylori* infection. In an attempt to examine the importance of genetic factors on the acquisition of *H. pylori* infection, Malaty et al.

compared the sero-prevalence of *H. pylori* infection in 100 monozygotic and 169 dizygotic twins reared together and reared apart. As a result of this study, Malaty et al. concluded that genetic effects influenced the acquisition of *H. pylori* infection due to greater similarities within monozygotic twin pairs and that sharing of the same rearing environment also contributed to the familial tendency for acquiring *H. pylori* infection.[24]

2.6 Mode of Transmission

Evidence of gastro-oral transmission was suggested by Varoli, et al in 2001.[25]The presence of *H. pylori* in the gastric juice of up to 58% of patients infected with *H. pylori* raises the possibility that refluxed gastric juice may represent a vehicle of transmission for this organism.[25] Premastication of food by African mothers prior to feeding their children has been shown to be a risk factor for *H. pylori* infection.[26]

There is evidence for and against fecal-oral transmission of *H. pylori*. Attempts to culture *H. pylori* from feces have by and large been unsuccessful. In 1994, however, the first report of the isolation of *H. pylori* from human feces appeared in the literature. In this study Thomas et al. isolated *H. pylori* from the feces of 1 infected adult and 9 of 23 randomly selected children living in a Gambian village.[27]

2.7 Clinical Aspects of *H. pylori*

Dyspepsia is the main presenting symptom in patients with *H. pylori* infection. A clear association between *H. pylori* and functional dyspepsia has not been established. *H. pylori* is a well-known cause of chronic active gastritis.[28]

Health care providers have defined dyspepsia in different ways. As a result, a multitude of esophageal, gastro-duodenal, pancreatic, and hepatobiliary disorders could underlie the symptoms. In addition, disagreement about what constitutes dyspepsia has complicated the interpretation of clinical research studies and confused practitioners.

An international committee of clinical investigators (Rome III Committee) defined dyspepsia as one or more of the following symptoms: Postprandial fullness (termed postprandial distress syndrome), early satiation (meaning inability to finish a normal sized meal or postprandial fullness) and epigastric pain or burning epigastric pain (termed epigastric pain syndrome).[1]

These criteria were preferred to the previous criteria (Rome II), which included pain or discomfort centered in the upper abdomen. It may be associated with distention, belching, nausea or anorexia. Most dyspeptic patients either have no identifiable cause of dyspepsia (non-ulcer dyspepsia, NUD), or have peptic ulcer disease (PUD), namely, gastric or more commonly, duodenal ulcers. Less common causes of dyspepsia include gastric cancer and pancreatic disease. Upper gastrointestinal endoscopy is currently the main diagnostic modality in the work-up of dyspeptic patients.

2.8 Diagnosis of *H. pylori*

The current standard for diagnosing *H. pylori* gastritis requires antral biopsy for urease test with or without histology.[29]

There are a number of clinical circumstances in which testing for *H. pylori* is considered. More recent guidelines were published in 2006 by the European Helicobacter Study Group (EHSG)[30]and in 2007 by the American College of Gastroenterology (ACG)[12].

The ACG guidelines made the following conclusions. First, testing for *H. pylori* should be performed only if the clinician plans to offer treatment for positive results. Secondly, testing is indicated in patients with active peptic ulcer disease, a past history of documented peptic ulcer or gastric MALT lymphoma. The test-and-treat strategy for *H. pylori* (i.e., test and treat if positive) is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 years and have no "alarm features" (bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer, previous esophago-gastric malignancy). Deciding which test to use in which situation relies heavily upon whether a patient requires evaluation with upper endoscopy and an understanding of the strengths, weaknesses, and costs of the individual test[12].

The diagnosis of *H. pylori* can usually be established during endoscopy by one of three methods: biopsy urease test, histology, and less commonly bacterial culture. Histology is advantageous in detection of intestinal metaplasia and mucosa-associated lymphoid tissue (MALT).[12] However, it is prone to sampling error and inter-observer variability. Culture of *H. pylori* has been traditionally difficult but while techniques are improving, it still has high rates of false negatives. Serology is non-specific in identifying patients with active disease and would be inappropriate in the proposed study. This forms the basis of choosing to use the rapid urease test in this study.[12]

General recommendations have been proposed by the American College of Gastroenterology[12] stating that when endoscopy is indicated, the test of first choice is a urease test on an antral biopsy. Routine gastric histology is generally not necessary and is expensive. Serology can also be used but does not distinguish reliably between active and past infection. Furthermore, the positive predictive value of serology is poor in areas where the prevalence of *H. pylori* infection is low. Thus, stool or breath testing are better alternatives to serology. Biopsy urease tests have reduced sensitivity in patients taking PPIs, recent antibiotics and in patients with recent active gastrointestinal bleeding.

2.9 Treatment, resistance and clinical benefits

With the emerging resistance of *H. pylori* to the medications in use, Lwai-Lume, et al (2005) studied drug susceptibility pattern of *H. pylori* in patients with dyspepsia. All isolated *H. pylori* organisms were resistant to metronidazole. There was a rising MIC for tetracycline and metronidazole compared to that found in a previous study in 1991 clearly demonstrating increasing resistance to the drugs in use.[11]

Given this, strict guidelines need to be developed on treatment of *H. pylori* in the local population. General guidelines in use are based on American college of gastroenterology and the Maastricht guidelines.[12] The first line is usually a triple therapy of proton pump inhibitor, clarithromycin and amoxicillin or metronidazole. Bismuth containing quadruple treatments remain the best second choice treatment, if available.

2.10 *H. pylori* in Kenya

A limited number of studies have been done on *H. pylori* in Kenya. Initial studies were limited to description on the lesions found on upper gastrointestinal endoscopy. One such study by Lule, et al(1987)[31] described the endoscopic experience among patients with peptic ulcer disease at the Kenyatta National Hospital. The clinical patterns among patients with duodeno-gastic reflux on endoscopy was described by Ogutu, et al(1989)[32] As the understanding of the pathophysiology of *H. pylori* grew, especially its association with the morbidity of peptic ulcer disease, studies started focusing on *H. pylori* at endoscopy.

The first study of such kind was done by Lule, et al(1991)[8] where sixty six patients with dyspeptic symptoms underwent upper gastrointestinal endoscopy and biopsies for *H. pylori* culture. Despite the low sensitivity of cultures used then, it was surprising to find that up to 87.5% of patients with gastritis had *H. pylori* on culture. In a follow up study between 1993 and 1994 by Ogutu, et al (1998), to increase sensitivity, three different methods were used; culture, rapid urease test and histology. In the 120 patients sampled, all cases of peptic ulcer disease had evidence of *H. pylori* infection while dyspeptic patients with normal endoscopic mucosal findings had *H. pylori* in 80.5% of cases. On weighted average, the prevalence of *H. pylori* among patients undergoing upper gastrointestinal endoscopy then was 91%.[7]

With the increasing link between *H. pylori* infection and gastric inflammation and subsequent development of gastric ulcer, McFarlane, et al (2000) did a biopsy follow up study of a cohort of 51 *H. pylori* positive rural Kenyan patients over an average of 5.5 years. It was concluded that *H. pylori* gastritis with atrophy may provide a suitable

environment within the gastric mucosa for the development of gastric cancer but it is likely that other factors in the population determine further progress towards dysplasia and cancer.[33]

There were no studies on *H. pylori* that had been done in Eldoret and its environs prior to this study. A related study done by Ayuo, et al (1994) was based on a preliminary experience with upper gastrointestinal fibreoptic endoscopy in Eldoret. It was concluded that endoscopy was a safe procedure that should be made more available and that the pattern of peptic ulcer disease in Eldoret was similar to that in Nairobi.[34]

This study is an update on the previous study by Ogutu, et al which though published in 1998 was done among a cohort of patients in 1993 and 1994.[7]This is a study done almost 20 years ago. It is also appreciated that changes have occurred to improve the technology of detection of *H. pylori*. Recent data shows that rapid urease test is sufficient to be used as the gold standard for rapid diagnosis of *H. pylori*. Onders, et al (1997) in a study of accuracy and costs in the detection of *H. pylori* concluded that rapid urease test is the method of choice in those patients undergoing endoscopy in whom identification of the organism will change management.[35] This forms the basis of using rapid urease test as the sole method in this study.

CHAPTER THREE

METHODOLOGY

3.1 Study Design

This was a cross sectional study

3.2 Study Site

The study was carried out in the endoscopy unit, at the MTRH minor theatre, which is the second referral hospital in Kenya. In this theatre more than 500 endoscopies are done annually. In 2009 alone, 512 endoscopies were done, with more than 75% being upper gastrointestinal endoscopic examinations.[36] Upper gastrointestinal endoscopies are done on a daily basis from Monday to Friday, with all patients undergoing a standard preparation before the procedure. All endoscopic examinations are carried by either consultant gastroenterologists or endoscopic surgeon. The theatre is manned by nurses who have had training on endoscopic procedures and testing procedures for *H. pylori*.

3.3 Study Population

The study population comprised patients who had dyspepsia and had been referred for endoscopy at MTRH.

3.4 Sample Size

The sample size was calculated by substituting for n in the sample statistic Fischer's formula for prevalence studies. Thus;

$$n = \frac{Z^2_{\left(1-\frac{\propto}{2}\right)}.P(1-P)}{D^2}$$

Where n = sample size; Z = the z value corresponding to 95% confidence (1.96); α = significance level (5%); P = estimated prevalence; D = Precision

Using a precision of 5% and estimated prevalence of 91% (from a local study by Ogutu EO, et al)[7], a sample size of 126 patients was obtained.

3.5 Inclusion Criteria

1. Patients certifying Rome III criteria[1] for dyspepsia.
2. Informed written consent from patient or immediate relative or guardian.
3. Patients age is 18 years and above.

3.6 Exclusion Criteria

1. Patients with total obstructive esophageal lesions at endoscopy.
2. Use of any of the following drugs for at least two weeks prior to endoscopic examination: Proton pump inhibitors, H2 receptor blockers, bismuth salts, antibiotics or antifungal drugs.

3.7 Data Collection Procedure

Patients booked to undergo upper gastrointestinal endoscopy were given clear instructions on adequate preparation before endoscopy. They were advised to feed on a light diet on the day before endoscopy and to fast from midnight of the day of the procedure. Compliance was assessed before the procedure by a short history. Patients who were determined not to have complied were booked to undergo endoscopy at a later date and clearer instructions were given.

On arrival at the endoscopy unit, the ‘patient procedure request form’ was assessed by the principal investigator or the trained endoscopy nurse in the theatre. An informed consent for both endoscopy procedure and the *H. pylori* test was obtained by the researcher or the nurses from those patients with dyspepsia who had been referred for upper gastrointestinal endoscopy. Patients were informed of the additional procedure to be carried out for purposes of diagnosing *H. pylori*. They were informed of the possible benefits and risks of the procedure and an informed verbal and written consent was sort.

Once an informed written consent was obtained, the principal investigator or the endoscopy nurse administered a questionnaire and information on demographics, medication history and symptoms were collected. This information was filled in a form (appendix I).

At this stage patients were assessed to determine whether they met the inclusion and exclusion criteria. Patients meeting the inclusion criteria were then informed about the procedure. Any questions from the patients were answered and an informed consent was obtained. This was the point of recruitment into the study. Sequential sampling was done until the sample size of 126 was reached.

The endoscopy procedure was carried out by consultant gastroenterologist or consultant endoscopy. Visual findings were noted and a mucosal biopsy was obtained from two different sites for rapid urease test. The patient could still be excluded from the study based on endoscopic findings limiting *H. pylori* testing as is indicated in the exclusion criteria.

Mucosal tissues obtained were placed in two wells containing a buffer solution for rapid urease testing. Positive test was indicated by a color change from colorless to pink/red coloration. The test result was read at 30 minutes. If the result was negative, further color checks were made at 1 hour, 3 hour and 24 hour marks. After 24 hours, the result was read as negative.

Patients whose *H. pylori* test was positive had an additional note in the endoscopy report to the referring physician. *H. pylori* test results that turned positive after patient had left the endoscopy unit, was delivered to the patient or referring physician via the contact details left in the data entry form. This included the recommendation to start standard *H. pylori* treatment protocol. Those with negative tests had the result noted on the endoscopy note back to the referring physician.

All patients were informed of the results and appropriate counseling was done.

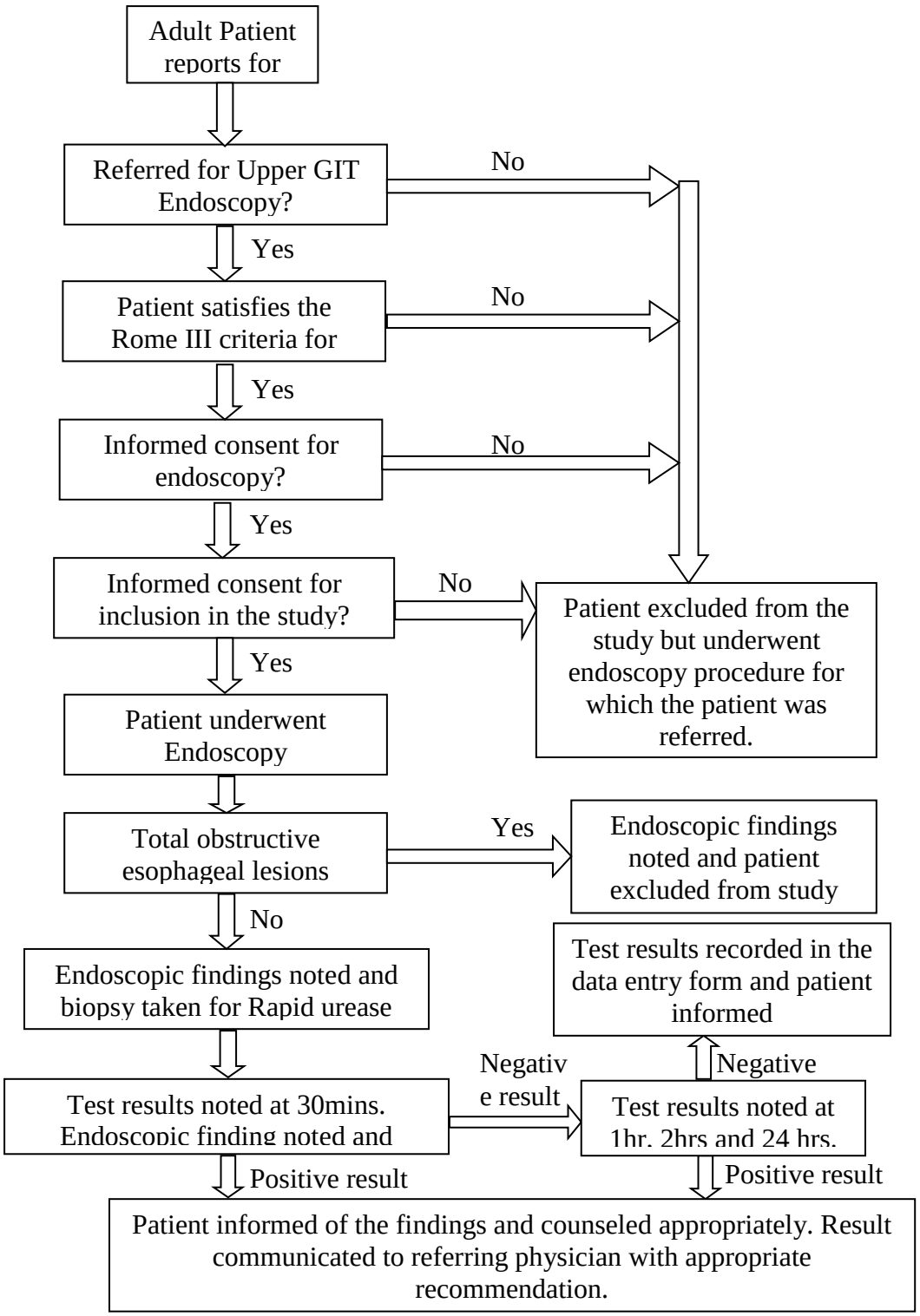

Figure 1 – Algorithm for the Study Procedure

3.8 Data management

Data was collected on a data entry form and later transferred to a computer database. Each data entry form had a unique identifier, which was the patient number. Data collected in the data entry form included the endoscopic findings and the result of the rapid urease test. Double entry was used while entering data on a computer to ensure accuracy.

3.9 Statistical analysis

The data was analyzed using SPSS version 17 and p-value of less than 0.05 was considered significant in all analyses. Frequency tables were generated for categorical variables in both *H. pylori* positive and *H. pylori* negative arms. Median and mean were used for continuous variables. The Chi-square test with goodness of fit was used to assess any association between variables among *H. pylori* positive and negative arms.

3.10 Ethical Considerations

Approval was sought from the IREC. Informed verbal and written consent was sought from all patients before the procedure. For the illiterate or blind patients, the researcher explained the contents of the consent form, and if the patient consents, a thumb print was used as an alternative to a written signature. Patients were informed about the outcome of results and counseled accordingly.

Costs for the rapid urease test kit and the writing material used to record results, as well as costs for contacting patients by telephone, post mail and email was paid for by the investigator. Patients were not given any inducements to participate in the study.

All patients participating in the study did so by free will and those who declined were not discriminated against. They underwent the endoscopy procedure for which they had been referred for as stipulated in the endoscopy procedure in the appendix.

The *H. pylori* testing procedure did not confer additional procedure risks other than those of endoscopy itself for which the patient was referred. *H. pylori* positive patients were recommended to be started on a standard treatment for its eradication. All patients were clearly informed of these risks before consenting for the procedure.

All information from the procedure was handled confidentially. Only patient codes were used in the data entry form and no reference to their names was made. The referring physician was informed of the results and the recommended way forward in the management of the patients.

CHAPTER FOUR

RESULTS

In total, 165 patients were screened for the study. Screening was done by sequential sampling until a sample of 126 was reached.

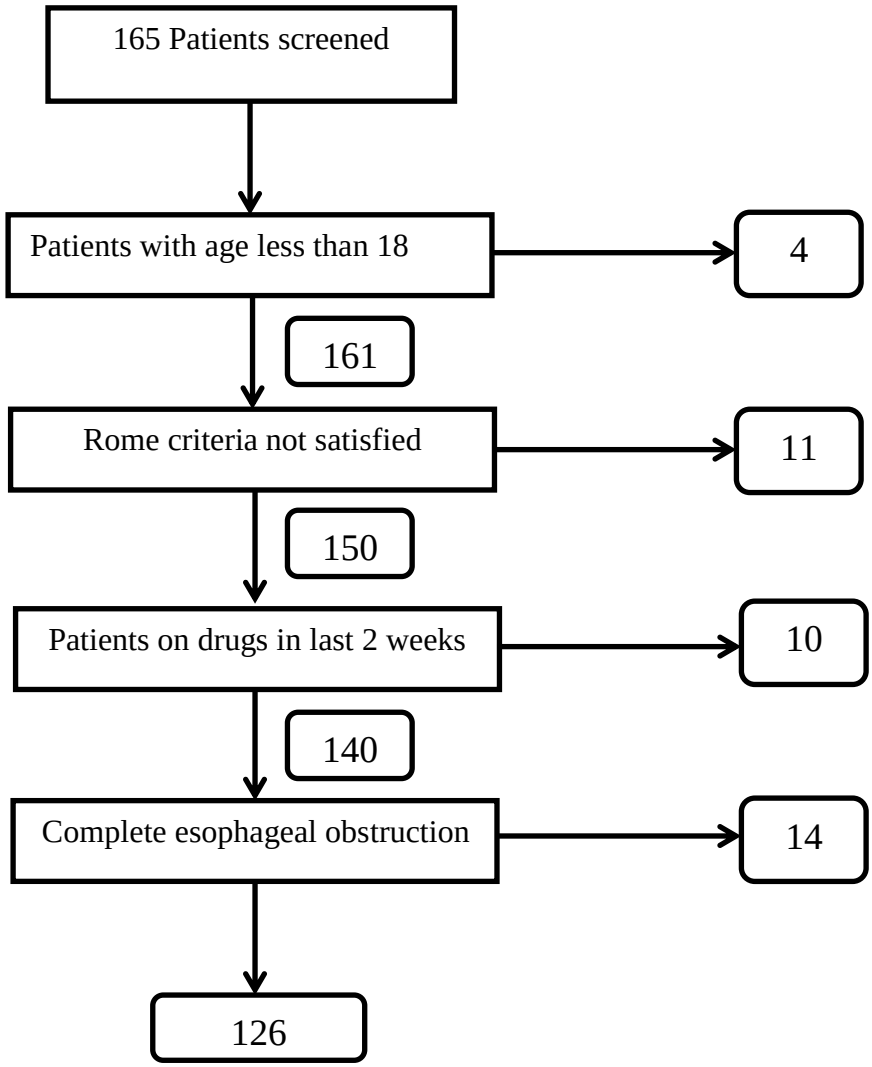

Figure 2: Recruitment Flow Diagram

Out of the 126 patients studied, 79% (100) were mainly from a rural environment; 52% (66) were males and 48% (60) were female.

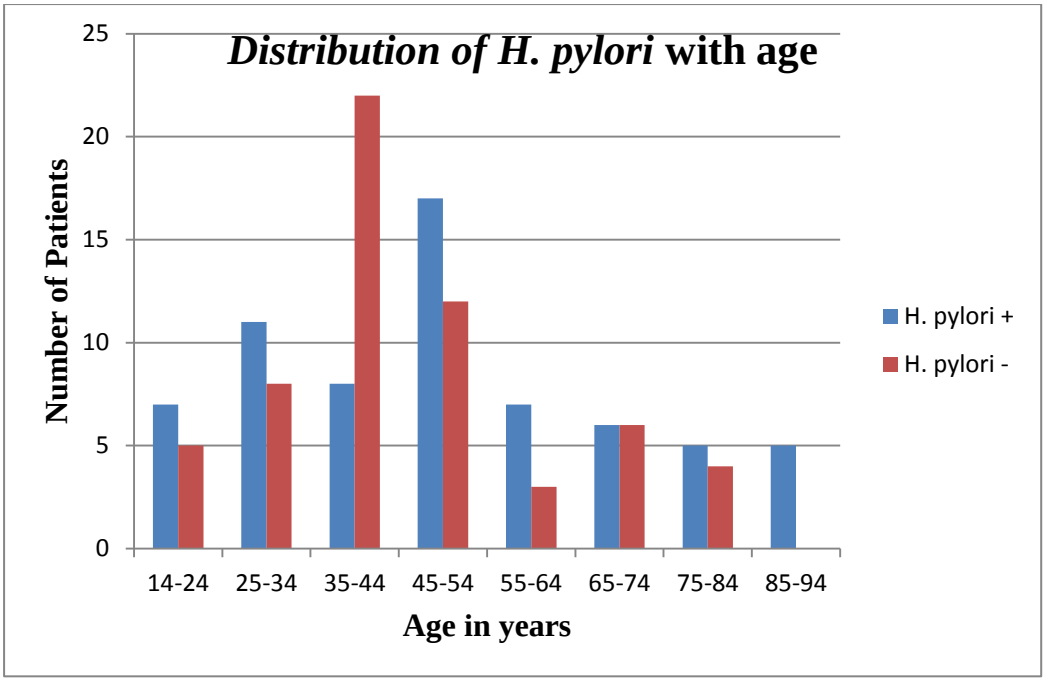

Figure 3: Age distribution among all patients recruited in the study

Majority of patients 61.9% (78) were between 25 and 54 years of age. Patients between 45 and 54 years of age were more likely to be *H. pylori* positive (58.6%) than in any other age strata. Patients between 35 and 44 years of age were more likely to be *H. pylori* negative (73.3%) compared to other age strata. The median age was 46 years. The mean age ± SD was 47.7±18.8.

There were 71.9% (23) patients above the age of 55 years who were *H. pylori* positive compared to 47.7% (50) of patients below the age of 55 years.

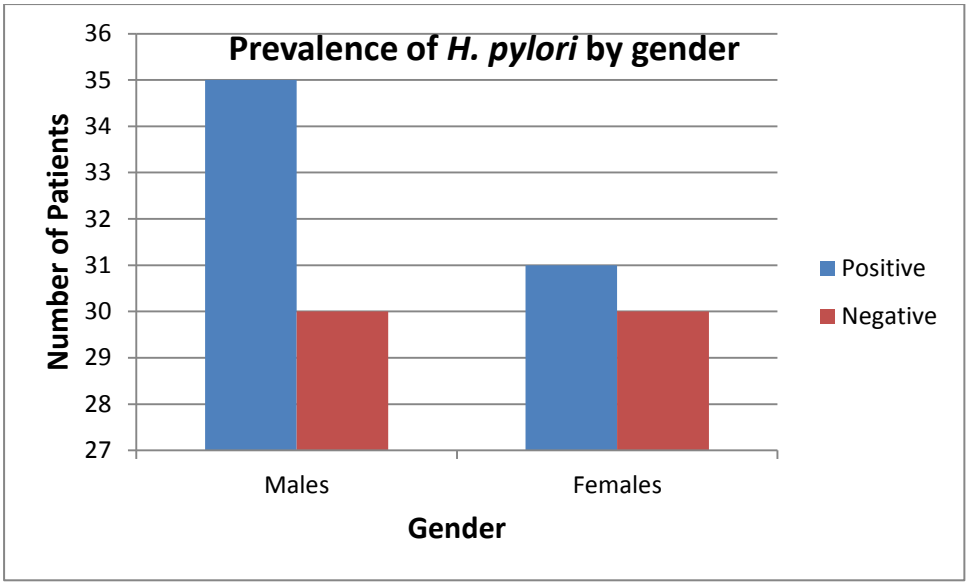

Figure 4: Prevalence among males and females

The majority of the patients studied were males comprising 51.6% (65) while 48.4% (61) were female. Overall, 53.8% (35) of males were *H. pylori* positive compared to 50.8% (31) of females

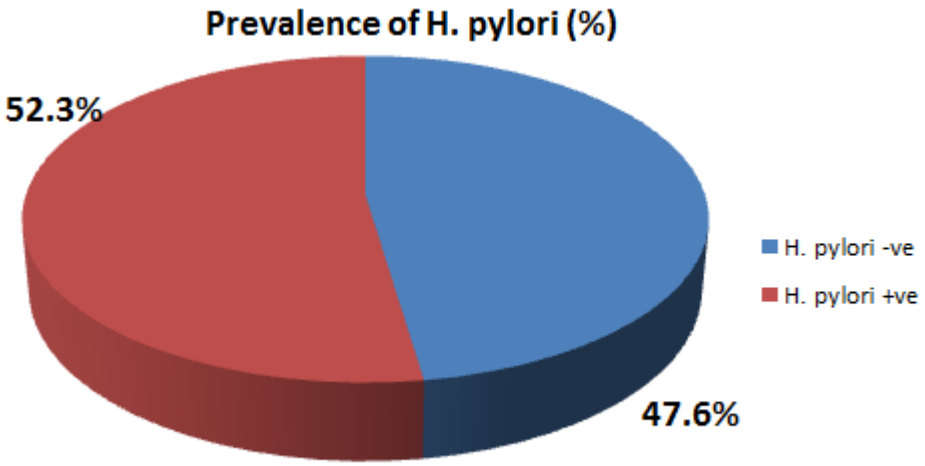

Figure 5: Prevalence of *H. pylori* in all patients recruited

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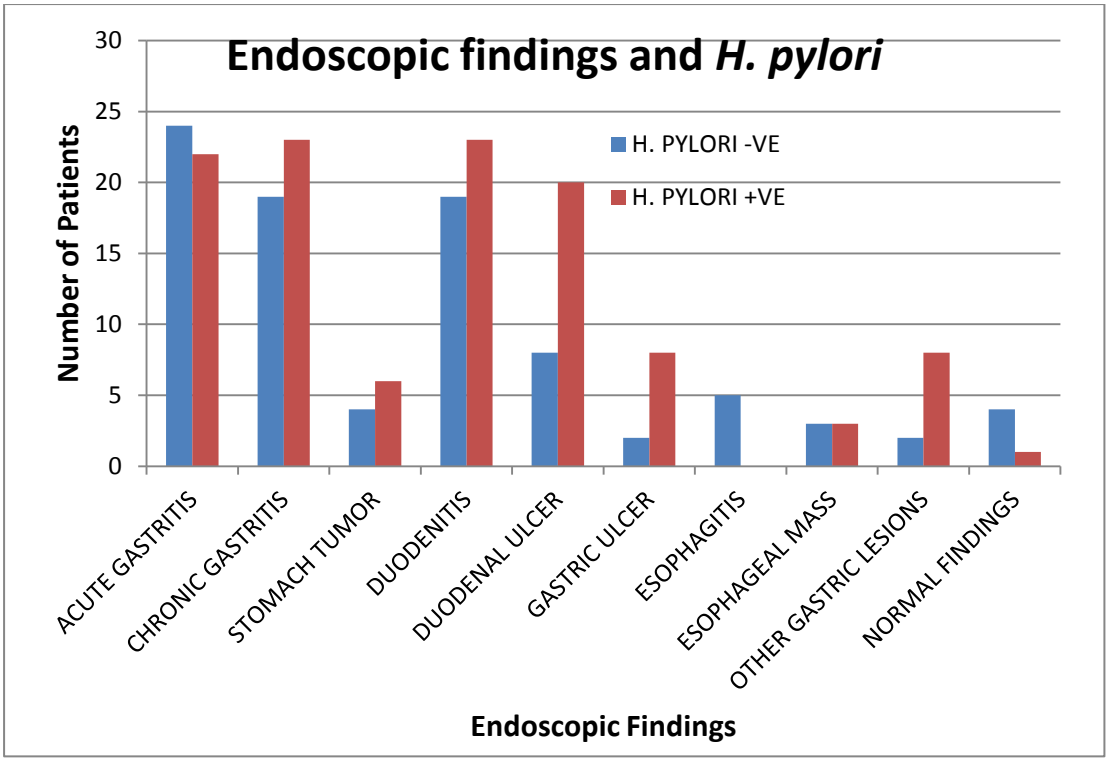

Figure 6: Relationship between endoscopic findings and *H. pylori* infection

These were visual findings during endoscopy. Abnormal findings were noted in 96% (121) of patients while only 4% (5) had normal endoscopic findings. The most frequent endoscopic finding was acute gastritis present in 36.5% (46) of patients, followed by chronic gastritis and duodenitis in 33.3% (42) of patients, and duodenal ulcers in 22.2% (28) of patients. There were 7.9% (10) of patients with gastric ulcers, gastric tumor and other gastric lesions. Other endoscopic findings included non-obstructive esophageal mass in 4.8% (6) of patients and esophagitis in 4% (5) of patients.

When duodenal ulcers and gastric ulcers are combined, 30.1% (38) of the patients had peptic ulcer disease, with 73.7% (28) of these patients being *H. pylori* positive.

Other gastric lesions included gastric outlet obstruction in 5.6% (7) of patients and Kaposi sarcoma lesions in 2.4% (3) of the patients.

Table 1: A tabular analysis of the relationship between endoscopy findings and *H. pylori* infection

	H. PYLORI +VE	*H. PYLORI* -VE	P VALUE
ACUTE GASTRITIS	22	24	0.768
CHRONIC GASTRITIS	23	19	0.537
STOMACH TUMOR	6	4	0.527
DUODENITIS	23	19	0.537
DUODENAL ULCER	**20**	**8**	**0.023**
GASTRIC ULCER	8	2	0.058
ESOPHAGITIS	0	5	0.025
ESOPHAGEAL MASS	3	3	1.000
OTHER GASTRIC LESIONS	8	2	0.058
NORMAL FINDINGS	1	4	0.180

All patients with esophagitis were *H. pylori* negative. Patients who had normal endoscopic findings had a strong association with being *H. pylori* negative. However, this association was not significant.

CHAPTER FIVE

DISCUSSION

In our study the prevalence of *H. pylori* among patients with dyspepsia referred for endoscopy was 52.3%. This compared well with a study by Kimang'a et al (2010) in Aga Khan Teaching Hospital, Nairobi which showed a prevalence of 54.8% in patients with dyspepsia[37]. An earlier study in KNH by Ogutu et al in 1993 found a higher prevalence of 81.7%[7].

This is a probable pointer that the prevalence of *H. pylori* among patients with dyspepsia has since reduced. A more probable explanation for this drop in prevalence is the fact that there has been an increase in awareness and use of drugs for *H. pylori* eradication in the recent past. There are also differences in patient demographics that could further explain this drop in prevalence. Patients from Ogutu et al[37] study were mainly from a low socioeconomic class compared with patients from Kimang'a et al[7] study who were mainly from high socioeconomic status despite same demographic region. Patients enrolled in our study were mainly from a rural setup but totally different demographic region compared with the other studies. Lifestyle changes could also have occurred in the period that could explain the drop in prevalence.

There was no statistical difference in prevalence of *H. pylori* between males and females in our study. Prevalence was 53.8% and 50.8% among males and females respectively. This is in keeping with the general knowledge that there is no gender predilection for *H. pylori*.

In our study, patients above the age of 55 years were more likely to be *H. pylori* positive (71.9% prevalence) compared to those below 55 (47.7% prevalence). This is expected given the high rates of acquisition by older populations compared with younger ones. Lule et al in 1991 found that the number of *H. pylori* isolated increased with age reaching a peak at 51 to 60 years[8]. This is in keeping with the knowledge that *H. pylori* infection is acquired in childhood and given the dropping prevalence with time, the elderly would be expected to bear the bigger burden of the disease.

Patients with peptic ulcer disease had a high *H. pylori* prevalence of 73.7% in our study. High prevalence of *H. pylori* among patients with peptic ulcer disease had also been demonstrated by Ogutu et al where all patients were *H. pylori* positive[7]. In a study by Wafula et al[38] in 2002, the prevalence among diabetics with peptic ulcer disease compared with those without peptic ulcer disease was statistically significant ($p = 0.021$). Other studies from outside Kenya have also shown this association.[5, 6, 39] Our study therefore is in keeping with the generally accepted principle of the positive association of *H. pylori* with peptic ulcer disease.

H. pylori was more prevalent in patients with duodenal ulcer compared to patients with normal endoscopic findings ($p<0.02$). This supports the overwhelming contribution of *H. pylori* to causation of duodenal ulcers. In the comparison study by Ogutu et al, the prevalence in duodenal ulcer patients was also significant compared to patients with normal endoscopic findings ($p<0.01$)[7]. However, an earlier study by Lule et al in 1991 had shown no statistical significance between the two groups with only 57% of patients with duodenal ulcers having *H. pylori* compared with 50% for

those with normal endoscopic findings[8]. In this study only *H. pylori* culture was used as a test and may have contributed to the low yield.

Although 8 (80%) of patients with gastric ulcers had *H. pylori* in our study, this was not statistically significant (p=0.058) although there was tendency to significance. Ogutu et al found a similar trend with a p value of 0.1[7]. This shows that although there is an association between *H. pylori* and gastric ulcers, the association is not as strong as it is in those patients with duodenal ulcers.

There was no association between the prevalence of *H. pylori* and gastritis (p=0.6). There was also no association between *H. pylori* and gastric tumors (p = 0.527). This study did not determine how many of the gastric tumors were gastric MALT lymphomas in which case an association could have been detected. Similarly, Ogutu et al found no association between *H. pylori* and gastric tumors[7]. In fact, in their study, majority of patients with gastric tumors were *H. pylori* negative (75%).

The reason for the low prevalence of *H. pylori* in patients with gastric malignancies also comes from the fact that malignancies develop long after *H. pylori* has been eradicated. There is also a tendency to biopsy necrotic tissue which has a low yield for *H. pylori*. A larger study powered to detect the difference may be necessary.

Majority of patients (96%) had abnormal endoscopic findings. The 2010 study by Kimang'a et al showed a similar trend with all patients having abnormal endoscopic findings[37]. The earlier study by Ogutu et al had surprisingly different results with normal looking mucosa the single most common finding[7]. The reason for this cannot

be easily identified but the use of different criteria to define dyspepsia may have contributed.

The single most common endoscopic finding in this study was gastritis present in 69.8% of patients. Kimang'a et al found similar findings with 60.9% having gastritis and forming the single most common finding[37]. Wafula et al found similar results among diabetics with 67.6% of those with dyspepsia having gastritis[38]. It can therefore be concluded from these current studies that the single most common endoscopic finding among patients with dyspepsia in Kenya is gastritis.

Endoscopic duodenitis was the second most common finding among patients with dyspepsia (33.3%). This was also the case by Ogutu et al[7] and Kimang'a et al[37]. The fact that duodenitis occur as the second most common finding after gastritis is not in itself surprising since the causative mechanisms in both aspects are similar. The concordance in results among the studies goes to show that despite the influence of inter-observer variability, endoscopic findings remain reliable.

Although peptic ulcer disease is a common finding in patients with *H. pylori*, it is not a universal finding in those patients with dyspepsia. It was the third most common finding in patients with dyspepsia accounting for 30.1% of cases. However, this single cohort of patients was the one with the highest *H. pylori* disease accounting for 73.7%. This is also the general finding in other studies done in Kenya.[7, 8, 37] Therefore peptic ulcer disease cannot be predicted from symptoms of dyspepsia and endoscopy is a necessity. However, once identified during endoscopy peptic ulcer disease has a high positive predictive value for presence of *H. pylori*.

Wafula et al found that diabetic patients had a lower prevalence of peptic ulcer disease compared with other populations[38]. The explanation for this is that diabetic patients with peptic ulcer disease may be missed out because of autonomic neuropathy and may not be evaluated for peptic ulcer disease. Our study did not study specific patient populations like diabetics.

Despite high prevalence of *H. pylori* in Kenya, complicated outcomes like gastric malignancies were low in our series present in only 7.9% of patients. The development of gastric malignancies after *H. pylori* infection is however time dependent. While our study may not have identified cases of malignancy, future causal relationship could not be ruled out. Kimang'a et al had similar findings with less than 1% of patients in that series having gastric cancer[37]. However of significance was that 60% of patients with malignancies in our study were *H. pylori* positive, though not statistically significant. In this regard, our study was not powered to detect an association between *H. pylori* and malignancies.

5.1 Limitations

There could have been a selection bias by selecting the sample of patients at the endoscopy unit. Patients who were referred for endoscopy but did not turn up may have been a special cohort with specific characteristics, e.g. from low socioeconomic profile.

In this study, patients who had positive *H. pylori* test were initiated on standard treatment but because of cost and time constraints, those patients were not followed

up to assess outcomes and response to treatment. This would have been important in assessing usefulness of *H. pylori* testing during endoscopy.

There are limitations of endoscopic findings conferred on the study because of user dependent nature of endoscopy. Visual findings at endoscopy were not corroborated. This could have led to over/under estimation of pathology. However, all endoscopies were done by experienced consultants to reduce this limitation.

We had a highly selective cohort of patients hence results cannot apply to the general population or any other specific population.

5.2 Conclusion

This study showed that slightly more than half of patients with dyspepsia were H. pylori positive. Gastritis remains the most common endoscopic finding among patients with dyspepsia. Only a third of patients with dyspepsia had peptic ulcer disease. However, these patients with peptic ulcer disease had a high likelihood of having *H. pylori* infection.

The older patients were more likely to have H. pylori infection when compared with the younger patients.

5.3 Recommendations

Given the surprisingly large number of *H. pylori* negative patients with dyspepsia, a study to find other causes of dyspepsia in our setup is recommended.

From this study, the prevalence of *H. pylori* among patients with dyspepsia is just above fifty percent. It is therefore recommended that there is need to have endoscopy and rapid urease test for *H. pylori* to ascertain diagnosis instead of treating all patients with dyspepsia for *H. pylori*.

The association of *H. pylori* and peptic ulcer disease is high and it is recommended that all patients with confirmed peptic ulcer disease can be treated for *H. pylori* infection in settings where there is no available method for testing for *H. pylori*.

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APPENDENCES

Appendix I – Data Entry Form

(To be filled by the investigator before endoscopy)

1. Patient Number ☐ Age ☐ Gender ☐

Telephone Number ☐ Address ☐

2. Has the patient been on any of the following medications for more than two (2) weeks in the last two (2) weeks? (Tick where appropriate)-From patient prescription notes or from patient.

Proton pump inhibitors ☐ H2 receptor blocker ☐ Antibiotics ☐

Antifungals ☐ Bismuth salts ☐ DON'T KNOW ☐

3. Which of the following symptoms does the patient have as the reason for referral for endoscopy? (Tick where appropriate)

☐ Epigastric pain (Upper abdominal pain)

☐ Post-prandial fullness (Upper abdominal fullness after eating)

☐ Dysphagia (Difficulty in swallowing)

☐ Early satiety (Feeling full earlier than expected after eating)

4. Endoscopic findings

Esophagus (Tick where appropriate and indicate level of lesion in centimeters)

Normal ☐ ☐ Erosions ☐ ☐ Ulcerations ☐ ☐ Growth ☐ ☐ Varices ☐ ☐

Others (Describe) _____

Stomach (Tick where appropriate and indicate the site after the tick)

Normal ☐ ☐ Erosions ☐ ☐ Ulcerations ☐ ☐ Growth ☐ ☐ Atrophy ☐ ☐

Others (Describe) _____

Duodenum (Tick where appropriate and indicate the site after the tick)

Normal ☐ ☐ Erosions ☐ ☐ Ulcerations ☐ ☐

Others (Describe) _____

5. Rapid urease test (2 biopsy specimens, one from prepyloric antrum and corpus)

Positive ☐ Negative ☐

Appendix II– Consent Form

Patient Number

I am DR SANG THOMAS MWOGI a student in the department of medicine, Moi University and I am carrying out a study to determine Helicobacter pylori infection among patients undergoing endoscopy at Moi Teaching and Referral Hospital. Helicobacter pylori is the organism which is known to cause peptic ulcer disease and infects the stomach and duodenum and could be responsible for your reason for referral to undergo endoscopy.

The study is not the endoscopy procedure that you have been referred to undergo. However it will take place during the endoscopy procedure. It involves a collection of your personal details like name, age and address and thereafter during endoscopy a small biopsy of your stomach lining will be taken and put into a testing solution, whose color change will inform us whether you have Helicobacter pylori or not. You will not be charged any additional fee for the test. You will be informed of the test results immediately after endoscopy and of any changes after 24 hours via the contact details you give us. There is the inconvenience that the endoscopy procedure will take longer and a small risk of stomach lining bleed during endoscopy.

You are free to withdraw from the study at any time before or after the procedure and your result from the study will be treated with confidence. Your withdrawing from the study does not interfere with you undergoing the endoscopy.

I agree to participate in the study,

NAME_____ SIGN_____
(Patient/Guardian)

WITNESS_____ SIGN_____
(Nurse/Doctor)

Appendix III – Rapid Urease Test Procedure

(Adopted from ESOKIT® Hp test)

Test Kit Contents

Each test kit consists of a twin well cartridge containing a substrate tablet in each well and an ampoule. The substrate tablet contains urea, phenol red and buffer salts in tablet form and an ampoule of buffer.

Principle of the test

If the urease enzyme of Helicobacter pylori is present in a biopsy specimen, the rise in pH associated with the hydrolysis of urea causes a change in color from yellow to pink/red.

Method

The cartridge lid is opened and each well filled with the buffer to a level marked on the well. All buffers are noted to ensure they are colorless before proceeding. If after addition of the buffer the reaction well in pink/red in color, the test kit is discarded. The lid is then closed and then agitated to dissolve the tablet in each well.

During endoscopy, a biopsy specimen, two to three millimeters in size, from the prepyloric antrum is added to well one. Another biopsy specimen of same size from the corpus is added to well two. Well two can be used as the negative control if no specimen is added. The lid is then closed immediately afterwards. On the label, the patients number, date and time the specimens were inserted are noted.

Pink/red coloration in the reaction wells indicates a positive reaction and therefore confirms the presence of Helicobacter pylori. Both wells do not have to give the same color change for it to be regarded as positive. Any color change to pink/red is regarded as positive. A positive result will be obtained within 30 minutes. If the result is negative after 30 minutes, further color checks are made at 1 hour, 3 hour and 24 hour marks. Color changes after 24 hours will be regarded as negative.

Test Specificity and Sensitivity

The rapid urease test has sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy as 98%, 100%, 100%, 98% and 99% respectively.[12]

False positive and negative results

False positive tests are unusual. However, false negative results can occur in patients with recent gastrointestinal bleeding or with the use of Proton pump inhibitors, H2 receptor antagonists, antibiotics, or bismuth-containing compounds. Obtaining tissue samples from the antrum and the fundus increases the sensitivity of the test.

Appendix IV – The Upper Gastrointestinal Endoscopy Procedure

Preparation

Patients are usually informed about the procedure and an informed consent obtained. Patients are usually advised not to feed from midnight of the day of the procedure, ensuring 8 hours diet free period.

The Procedure

Upper gastrointestinal endoscopy is usually performed on an outpatient basis unless the patient being referred is an inpatient. It is carried out at the MTRH endoscopy unit by consultant gastroenterologists or endoscopy surgeon. On arrival at the endoscopy unit, the patient is assessed for compliance with the preparation and whether the patient is fit to undergo the procedure.

The patient is positioned in the left lateral position; the throat is anesthetized by a spray or liquid 10% lidocaine. Intravenous sedation with diazepam 5-10mg is usually given to relax the patient, deaden the gag reflex and cause short-term amnesia. If it is a therapeutic procedure, intravenous propofol or fentanyl may be used. For some individuals who can relax on their own and whose gagging can be controlled, the exam is done without intravenous sedation.

The endoscope is then gently inserted into the upper esophagus. The patient can breathe easily throughout the exam. Other instruments can be passed through the endoscope to perform additional procedures if necessary. A polyp or tumor can be removed using a thin wire snare and electro cautery. Mucosal biopsy is taken using biopsy forceps. The exam takes from 15 to 30 minutes, after which the patient is taken to the recovery area. There is no pain with the procedure and patients seldom remember much about it.

Results

The results are then written on a standard endoscopy form indicating the findings throughout the upper gastrointestinal tract. Comments and recommendations are also indicated.

Side effects and Risks

A temporary, mild throat irritation sometimes occurs after the exam. Serious risks with upper GI endoscopy, however, are very uncommon. One such risk is excessive bleeding, especially with removal of a large polyp. In extremely rare instances, a perforation, or tear, in the esophagus or stomach wall can occur.

These complications may require hospitalization and, rarely, surgery. Quite uncommonly, a diagnostic error or oversight may occur since this is largely user dependent. Due to the mild sedation, the patient should not drive or operate machinery following the exam. For this reason, someone else should be available to drive the patient home.

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