Helicobacter Pylori Culture Rate and Antibiotic Resistance Patterns among patients with Dyspepsia at Moi Teaching and Referral Hospital, Eldoret, Kenya

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Helicobacter Pylori Culture Rate and Antibiotic Resistance Patterns among patients with Dyspepsia at Moi Teaching and Referral Hospital, Eldoret, Kenya

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is associated with upper gastrointestinal diseases including peptic ulcer disease, gastritis, gastric adenocarcinoma and mucosal associated lymphoid tissue lymphoma. *H. pylori* is a fastidious organism and thus difficult to culture especially after prolonged time between sample extraction and start of the culture. Triple therapy eradication regimens are available with little data on current antibiotic sensitivity patterns.
Objective: To determine the *H. pylori* culture rate and resistance patterns following 20 to 24 hour transportation in normal saline at Moi Teaching and Referral Hospital (MTRH).
Design: Cross-sectional descriptive study.
Methods: Participants aged 18 years and above referred for endoscopy due to dyspepsia were consecutively enrolled until the desired sample size was achieved. Participants underwent endoscopy during which biopsies were taken, two each from the gastric antrum and corpus. Rapid Urease Test (RUT) for *H. pylori* was done on one sample each from the antrum and corpus. For the samples that tested positive, their pair samples were put in normal saline and packed in ice in a cooler box and sent for *H. pylori* culture within 20 to 24 hours on brain heart infusion agar and subsequent antibiotic susceptibility testing.
Results: Between April 2014 and February 2015, 634 patients were screened of which 156 were enrolled to the study and subsequently underwent endoscopy, gastric biopsy and RUT. The enrolled participants had a median age of 41 (IQR: 28-58) years; and comprised of 64 (41%) males. The main indication for endoscopy was epigastric pains, seen in 151 (97%) of patients. Forty two (27%) of participants had previously received treatment for dyspepsia with either a proton pump inhibitor, histamine receptor type 2 blocker or anti *H. pylori* antibiotics. Eighty three (53%) had a positive RUT. Culture was done on 69 samples that reached the laboratory within 24 hours. *H. pylori* was isolated in 9 (13%) samples. All the 9 strains of *H. pylori* isolated were resistant to metronidazole. There was no resistance to clarithromycin.
Conclusion and recommendations: The culture rate of *H. pylori* following 20 to 24 hour delay was low. All the *H. pylori strains* isolated were resistant to metronidazole. Culture of *H. pylori* after 20-24 hour transportation in normal saline is not useful. A comparative study to determine the optimal transportation time and transport media is recommended. Clarithromycin based therapies without metronidazole is appropriate for *H. pylori* eradication regimens.

Key words: Helicobacter pylori, Culture, Antibiotic resistance, Resistance

Introduction

Helicobacter pylori (H. pylori) is a microaerophilic gram negative bacterium that colonizes the gastric mucosa. It's associated with development chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and Mucosa Associated Lymphoid Tissue (MALT) lymphoma (1-4). It is estimated that more than half of the world's population is infected with *H. pylori* (5).

Despite its unique role in the management of *H. pylori*, culture is not used routinely because of various factors: special conditions for transportation, urgency of specimen processing, expensive and complicated media, special incubation conditions and duration of culture (6). Regardless of these challenges culture is particularly useful because of the prospect of doing antibiotic susceptibility testing in patients who have used two courses of different antibiotic eradication regimes without cure (7).

Several factors affect *H. pylori* culture isolation rate: Recent use of antibiotic and proton pump inhibitors; prolonged time between specimen extraction and processing; choice of transport media; number and site of biopsies taken, provision of micro aerophilic environment for culture, duration of culture and use of selective media (8).

Samples have been processed after 24 hours of extraction without significant loss to diagnostic yield (9). The prospect of doing successful cultures following up to 24 hours delay from sample extraction provides an opportunity for centres unable to undertake cultures to transport samples for up to 24 hours to central laboratories where cultures can be undertaken.

Several transport media have been used for *Helicobacter pylori* with success. These include: Colombia blood agar, Brain Heart Infusion agar, brucella broth, cysteine albimi (10,11). Normal saline has been used successfully as a transport media without significantly affecting the isolation rate, providing a cheap transport media in resource poor settings (9). The choice of culture media also impacts on isolation rate of *H. pylori*. In a study that compared the culture media, the isolation rates were: Brain Heart Infusion Agar (96%), trypticase Soy agar (78%), Egg Yolk Agar (64%) and Colombia Blood Agar (32%) (12).

The main objective of this study was to determine the culture rate and antibiotic resistance patterns of *Helicobacter pylori* following 20-24 hour transportation time of specimens in normal saline among patients with dyspepsia at Moi Teaching and Referral Hospital. Secondary objective was to determine the current prevalence of *H. pylori* at MTRH.

Materials and methods

This was a cross-sectional descriptive study among patients with dyspepsia referred for upper gastrointestinal endoscopy at Moi Teaching and Referral Hospital, Uasin Gishu County, Kenya. Cultures were done at Pathologists Lancet Kenya Limited, a South African National Accreditation System (SANAS) accredited laboratory on 5th Avenue Office Suites, Upper Hill, Nairobi.

Consecutive sampling of patients who met the study criteria was done until the required minimum sample size of 126 was achieved for both prevalence and culture rate. Inclusion criteria included patients aged 18 years and above with symptoms of dyspepsia and not on PPI, H2R blockers or any antibiotic in the preceding two weeks before endoscopy. Failure to intubate the stomach or give consent resulted into exclusion. Informed written consent was obtained from all participants.

At endoscopy, 4 gastric mucosal forceps biopsies (2 from the antrum and 2 from the corpus) were obtained. Two (one each from the antrum and corpus) of the four gastric biopsies were immediately tested for active *H. pylori* infection using the rapid urease test (Esokit Hp Test). Patients whose rapid urease test turned positive within four hours had the other two gastric biopsies put in one milliliter of normal saline and transported overnight in a cooler box to Pathologists Lancet Kenya, Nairobi where the samples were cultured the following day at 9: 00am.

In the laboratory, *H. pylori* were cultured in selective Brain Heart Infusion Agar under microaerophilic conditions. Epsilometer (E) test strips were applied for clarithromycin, metronidazole, amoxicillin and tetracycline and incubated for a further 24-36 hours in non-selective culture media before the Minimum Inhibitory Concentrations (MICs) for each antibiotic was read.

MIC levels that were interpreted as sensitive were less than or equal to 0.25µg/ml for clarithromycin and amoxicillin, less than or equal to 2µg/ml for tetracycline and metronidazole. On the other hand MIC levels that were interpreted as resistant were equal or more than 1µg/ml for clarithromycin and amoxicillin, equal or more than 4µg/ml for tetracycline and equal or more than 8µg/ml for metronidazole. These MIC breakpoints specifically determined for *Helicobacter pylori* were based on Clinical Laboratory Standards Institute guidelines for clarithromycin and an updated appraisal for the rest of the antibiotics (13,14). MIC levels between susceptible and resistant break points for each antibiotic were regarded as intermediate. Data was analyzed using STATA version 13 special edition.

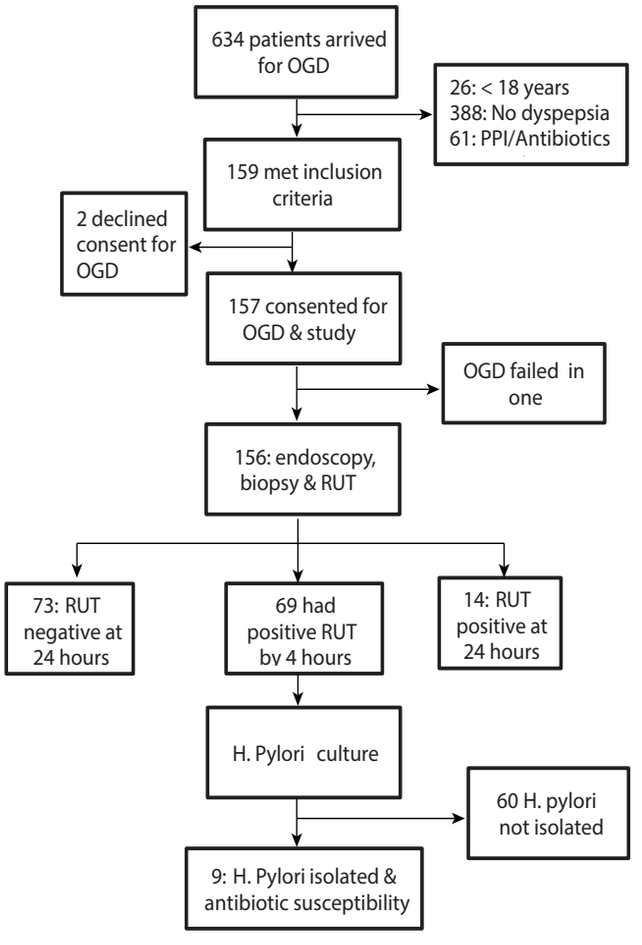
The study received partial funding from AstraZeneca and National Commission for Science Technology and Innovation (NACOSTI), but they played no role in the study design, execution, and data analysis and presentation of results.

This study was approved by Institutional Review and Ethics Committee (IREC), (Formal Approval Number: FAN: IREC 1048) and Moi Teaching and Referral Hospital management.

Results

Between April 2014 and February 2015, 634 patients presenting at the MTRH endoscopy unit for upper gastrointestinal endoscopy were screened of whom 156 were recruited into the study. The rest were excluded for various reasons as shown in Figure 1.

Figure 1: Enrolment schema



The 156 participants enrolled in the study were aged between 18 and 86 years with a median age of 41 (IQR: 28-58) years. Sixty four (41%) were male (Table 1).

Table 1: Demographic characteristics (n=156)

Characteristic	Frequency n (%)
Gender	
Male	64 (41%)
Female	92 (59%)
Age (years)	
18-24	25 (16%)
25-34	34 (22%)
35-44	32 (21%)
45-54	22 (14%)
55-64	20 (13%)
65-74	13 (8%)
>74	10 (6%)

Epigastric pain was the commonest symptom being reported by 151 (97%) of the participants followed by 37 (24%) who reported to have had postprandial fullness as the reason for OGD. Early satiety was not a common symptom of dyspepsia, being reported by only 18 (12%) of participants (Table 2).

Table 2: Clinical characteristics (n=156)

Characteristic	Frequency n (%)
Indications for endoscopy	
Epigastric pains	151 (97%)
Postprandial fullness	37 (24%)
Early satiety	18 (12%)
Dysphagia	4 (3%)
Previous treatment of upper GI disease	
Amoxicillin+Bismuth salt+PPI	2 (1.3%
Amoxicillin+clarithromycin+PPI	1(0.6%)
Amoxicillin+metronidazole+PPI	4 (2.7%)
Amoxicillin+PPI	1 (0.6%)
H2R blocker+PPI	1 (0.6%)
PPI	33 (21.1%)

Thirty three (21.1%) of participants had been treated previously with PPI while 7 had received standard *H. pylor*i eradication treatment (Table 2). The participants received these treatments on average 2.5 months (IQR 2-6) prior to presentation for current OGD and for a median treatment duration of 14 days.

Gastritis was the commonest endoscopic finding in the stomach occurring in 123 (79%) of the participants. Normal stomach was observed in 23 (15%) of the participants. Thirteen (8.3%) of patients had normal upper endoscopic findings. Other findings are as shown in Table 3.

Table 3: Gross endoscopic findings (n=156)

Finding	Frequency n (%)
Gastritis	123 (79%)
Duodenitis	30 (19%)
Oesophagitis	30 (19%)
Normal	13 (8.3%)
Duodenal ulcerations	9 (6%)
Gastric ulcerations	7 (4%)
Hiatus hernia	6 (4%)
Gastric atrophy	3 (2%)
Gastric outlet obstruction	2 (1.3%)
Oesophageal candidiasis	2 (1.3%)
Deformed pylorus	2 (1.3%)
Others	5 (3.2%)
Not done	3 (2%)

Eighty three (53%) of participants were positive for *H. pylori* on Rapid Urease Test (RUT). Patients who had postprandial fullness as the reason for endoscopy were more likely to be RUT positive as were patients who had duodenitis; p values 0.0449 and 0.0041 respectively (Table 4).

Table 4: Association between clinical characteristics and rapid urease test

Clinical characteristic	Frequency (n =156)	RUT positive (n=83)	RUT negative (n=73)	P-value
Epigastric pains	151 (97%)	80 (96.4%)	71 (97.3%)	1[f]
Postprandial fullness	37 (24%)	25 (30.1%)	12 (16.4%)	0.0449[c]
Early satiety	18 (12%)	11 (13.3%)	7 (9.6%)	0.4747[c]
Previous treatment	42 (26.9%)	23 (27.7%)	19 (26.0%)	0.8130[c]
Normal	13 (8.3%)	6 (7.2%)	7 (9.6%)	0.5946[c]
Oesophagitis	30 (19%)	12 (14.5%)	18 (24.7%)	0.1067[c]
Gastritis	123(79%)	67 (80.7%)	56 (76.7%)	0.5405[c]
Gastric ulcerations	7 (4%)	4 (4.8%)	3 (4.1%)	1[f]
Duodenitis	30 (19%)	23 (27.7%)	7 (9.6%)	0.0041[c]
Duodenal ulcerations	9 (6%)	6 (7.2%)	3 (4.1%)	0.5033[f]

[f] = Fischers exact [c] = Chi square test

Sixty nine samples that were positive for *H. pylori* within 4 hours on RUT were cultured. Culture yield was found in 9 (13%) of the samples.

Table 5: Association between clinical characteristics and culture rate

Clinical characteristic	Frequency (n =69)	Culture positive (n=9)	Culture negative (n=60)	P-value (Fischer exact test)
Epigastric pains	68 (98.6%)	9 (100%)	59 (98.3%)	1
Postprandial fullness	21 (30.4%)	1 (11.1%)	20 (33.3%)	0.2583
Early satiety	7 (10.1%)	2 (22.2%)	5 (8.3%)	0.2244
Previous treatment	20 (29.0%)	3 (33.3%)	17 (28.3%)	0.7120
Normal	4 (5.8%)	0 (0%)	4 (6.7%)	1
Oesophagitis	10 (14.4%)	2 (22.2%)	8 (13.3%)	0.6087
Gastritis	57 (82.6%)	9 (100%)	48 (80%)	0.3422
Gastric ulcerations	3 (4.3%)	0 (0%)	3 (33.3%)	1
Duodenitis	19 (27.5%)	4 (5.8%)	15 (25%)	0.2469
Duodenal Ulcerations	5 (7.2%)	0 (0%)	5 (8.3%)	1

There was no significant association between any patient characteristic (including demographics, patients' symptoms, endoscopic findings) and culture rate (Table 5).

There were no strains resistant to clarithromycin. Six (67%) samples were sensitive to amoxicillin while all the 9 strains were resistant to metronidazole. Two thirds of the strains were sensitive to tetracycline while a third were resistant (Table 6).

Table 6: Antibiotic resistance

Antibiotic	Sample size	Susceptibility level	n (%)
Clarithromycin		Sensitive	5 (56%)
	9	Intermediate	4 (44%)
		Resistant	0
Amoxicillin		Sensitive	6 (67%)
	9	Intermediate	1 (11%)
		Resistant	2 (22%)
Metronidazole		Sensitive	0
	9	Intermediate	0
		Resistant	9 (100%)
Tetracycline		Sensitive	6 (67%)
	9	Intermediate	0
		Resistant	3 (33%)

Discussion

Using the Rapid Urease Test (RUT), more than half (53.2%) of patients with dyspepsia undergoing endoscopy at MTRH were infected with *H. pylori*. Our findings were comparable to a previous study by Mwogi (15) in 2010 in the same setting that found a prevalence of 52.3% among adults patients undergoing endoscopy for dyspepsia, as well as another study by Kimang'a *et al* (10) study at Aga Khan University Hospital Nairobi in 2010 that found a prevalence of 54.8%. However, earlier Kenyan studies showed higher prevalence of *H. pylori* among patients with dyspepsia. Lule *et al* (16) in 1991 found a prevalence of 70% among dyspeptic patients. This indicates a general trend of decline of *H. pylori* prevalence among patients with dyspepsia. We attributed this improvement of socioeconomic status in Kenya as well as introduction of triple therapy eradication regimens in the country.

In our study we found *H. pylori* culture rate of 13% following a 24 hour transportation time of the samples to a central laboratory. Several factors could have contributed to the low culture rate observed in this study: first, 28% of the patients had previously been treated for dyspepsia with PPI, H2R blockers and/or antibiotics; second, patients who were not on any medications for up to only two weeks prior to enrolment as opposed to longer duration reducing the isolation rates due to coccoid forms the bacteria assume when exposed to acid suppression and antibiotics (17). The culture rate of 13% was much lower than several other studies. In a study by Veenendaal *et al* (9) in the Netherlands in 1993 in which culture was done after 24 hour delay as in this study, the culture rate was high at 84.6% while in another study by Hachem *et al* (12) in which culture was done 2 to 7 days after sample collection on BHIA as in our study the culture rate was 96%. However there are several differences in methodology between the two studies that could account for the disparity of culture rate with our study. First, while we excluded patients who were on antibiotics within the two weeks of presentation for OGD, Veenendaal *et al* (9) excluded patients who were on antibiotics within three months before presentation. Recent antibiotic and anti-gastric acid secretory drugs reduces yield of *H. pylori* cultures (18). Secondly, Veenendaal *et al* (9) used two antral biopsy specimens while we used one each from the antrum and corpus. This difference in specimen sampling could determine the difference in culture rate as most of the *H. pylori* is known to reside more in the gastric antrum than the corpus (8). Thirdly, our study used 1ml of normal saline as transport media while Veenendaal *et al* (9) used 0.2ml of normal saline. In Hachem *et al* (12) study, Cysteine Albimi media was used as transport media instead of normal saline. The larger volume in transport media in our study could have caused dilution of organisms resulting in low culture rate (19). Fourth, in Hachem *et al* (12) study, incubation was done up to 14 days while in our study culture was done for up to 7 days. Longer incubation periods have been shown to increase the isolation rate (8). Furthermore Veenendaal *et al* (9) study was done several years back (1993) before the widespread use *H. pylori* eradication regimes, which could have an effect on culture rate.

Lule *et al* (16) in a study done locally in Kenya found a culture rate of 70% in 1991, while Lwai-Lume *et al* (19) cultured 69% in 2004 and Kimang'a *et al* (10) isolated 92.3% in 2010. The major difference

between these studies and ours is that for all of them culture was done within 6 hours of sample collection which is expectedly supposed to give a better yield. Furthermore in Lwai-Lume *et al's* (19) study, patients on antibiotics, PPI and H2R blockers within 3 months before culture were excluded.

None of the *H. pylori* isolated in our study were resistant to clarithromycin. This finding is consistent with findings by Lwai-Lume *et al* (19) in 2004 that found only 6.4% of *H. pylori* were resistant and another study by Kimang'a *et al* (10) that found no clarithromycin resistant *H. pylori* among patients with dyspepsia at Aga Khan University Hospital Nairobi. These findings indicate that *H. pylori* in Kenya is still largely sensitive to clarithromycin.

The minority, 2 (22%), of isolated *H. pylori* were resistant to amoxicillin. This findings support previous studies that showed that *H. pylori* has not developed significant resistance to amoxicillin. Lwai-Lume *et al* (19) in 2004 found only 4.6% of *H. pylori* being resistant to amoxicillin while Kimang'a *et al* (10) in 2010 did not find any *H. pylori* strains resistant to amoxicillin. In these two studies, a higher MIC cut of 2mg/l was used to determine the level above which resistance was defined compared to our study that used the MIC cut off of 1mg/l as currently recommended by the Clinical Laboratory Standards Institute (CLSI) (13). The lower cut off in our study could account for a higher resistance in our study.

All *H. pylori* strains isolated in our study were resistant to metronidazole. This antibiotic is widely used for diarrhoeal and other conditions where it's often not indicated and this could explain the total resistance by *H. pylori* (20). Resistance of metronidazole is widespread with 10-50% resistance in developed countries and almost all strains in developing countries (21). Our findings on metronidazole resistance were similar to those reported by Lwai-Lume *et al* (19) in 2004 in which all *H. pylori* were resistant and another by Kimang'a *et al* (10) in 2010 in which 95.4% were resistant. However in another study by Sang *et al* (22) in 1991, no strains of *H. pylori* resistant to metronidazole were found. Sang *et al* (22) study was done more than two decades ago probably before widespread use of antibiotics, the use of which raises the incidence of antibiotic resistance (23).

Thirty three percent of *H. pylori* isolated were resistant to tetracycline. Our findings were higher than previous studies done locally in Kenya. Sang *et al* (22) in 1991 did not isolate any *H. pylori* resistant to tetracycline while Lwai-Lume *et al* (19) in 2004 found only 7.9% of *H. pylori* were resistant to tetracycline. These studies were done more than a decade ago and we postulate that since tetracycline was not part of *H. pylori* eradication regimes frequently used in Kenya, there was less resistance than when compared to our recent study. Our small sample size also has the possibility of exaggerating the proportions.

Study limitations

The culture isolation rates was too low to give a robust recommendation on recommendation for specific antibiotic for *H. pylori* eradication.

Conclusions and recommendations

Over half of the patients with dyspepsia undergoing OGD at MTRH are infected with *H. pylori*. The culture rate of *H. pylori* following 20 to 24-hour transportation time of samples to a central laboratory using normal saline as transport media is low. There were almost no resistant strains of *H. pylori* to clarithromycin while a few strains are resistant to amoxicillin and tetracycline. All *H. pylori* strains isolated were resistant to metronidazole.

We recommend patients with dyspepsia to be tested for *H. pylori* infection as advised by most guidelines. Culture of *H. pylori* after 20-24 hour transportation in normal saline is not useful. A comparative study to determine the optimal transportation time and transport media is recommended. Clarithromycin based therapies without metronidazole is appropriate for *H. pylori* eradication regimens although a larger study on sensitivity patterns is recommended to validate these findings.

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