Rapidity of diagnosis and management of H. Pylori in the endoscopy unit at Mater Dei Hospital

Daniela Zammit, Thelma Xerri, Pierre Ellul

Abstract

Introduction: H.pylori infection has been associated with various gastric pathologies and its prevalence varies between different countries. Furthermore, there is an increasing antibiotic resistance and the eradication rates have declined. There is clinical and administrative pressure as to provide the Rapid Urease Test (RUT) result as quickly as possible and ideally prior to discharge from the endoscopy unit.

Results: A total of 542 patients fulfilled the inclusion criteria. The patient`s mean age was 54.6 years and 52.4% were female.

The main clinical indications for an Oesophago-Gastro-Duodenoscopy (OGD) were dyspepsia (44.7%) and GORD (24.5%). The overall positivity rate was 15% of which 8.7% were early positive and 6.3% were late positive. Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013). There was no statistical significance between the H.pylori results and smoking (p= 0.6).

In this study, there was a variety of 10 different eradication regimes prescribed, the most popular being the use of a PPI 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (total of 27 cases) versus 14 days (23 cases).

Conclusion: This study demonstrates the importance of checking the RUT taken at endoscopy at 24 hours as this has given a 42% increase in the yield for H.pylori. It also demonstrates that various regimens are used in clinical practice. In view of the relatively low prevalence of H.pylori, especially amongst young patients, maybe it is prime time that treatment of H.pylori is specifically managed by culture and sensitivity to avoid worsening clarithromycin-resistance.

Keywords

Helicobacter pylori; triple therapy; OGD; Proton Pump Inhibitor; eradication regime.

Abbreviations:

- CLO: Campylobacter-like organism test
- CT scan: computerized tomography
- GI: Gastrointestinal
- GORD: Gastro-oesophageal Reflux Disease
- H.pylori: Helicobacter pylori

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- MALT: Mucosa-associated lymphoid tissue lymphoma
- OGD: oesophago-gastro-duodenoscopy
- PET scan: Positron Emission Tomography
- PPI: Proton Pump Inhibitor
- RUT: Rapid Urease Test

Introduction and Aims

Helicobacter pylori (H.pylori) is a gram-negative bacterium found in the stomach of more than 50% of the population worldwide.[1] It is linked to chronic gastritis, gastric and duodenal ulcers and stomach cancer.[2] Up to 85% of patients infected with H.pylori are asymptomatic;[3] therefore a 'test-and-treat' approach is adopted and is most effective in a population with a high prevalence of H.pylori infection (defined as a prevalence of more than 20%), especially in patients under the age of 50 years without any alarm symptoms.[4] There are various methods of testing; these can be divided into minimally-invasive (blood antibody test, stool antigen test or using the carbon urea breath test), and invasive (analysis of gastric biopsies through Rapid Urease Test (RUT test), histology and culture). None of the methods are 100% specific and sensitive. One of the most commonly used is the RUT test upon performing an oesophagogastroduodenoscopy (OGD).[5]

This gastric biopsy test is based on the activity of the H. pylori urease enzyme. This splits the urea test reagent to form ammonia. Ammonia, being alkaline, increases the pH. This is detected by a colour indicator. Tests that produce rapid reliable findings have been shown to reduce the overall cost of management of these patients by decreasing the need for telephone calls to be made to patients after 24 hours.

The standard first-line treatment option for H.pylori eradication is a 7-10 twice daily (b.d.) triple therapy of proton-pump inhibitor (PPI) together with amoxicillin and clarithromycin or metronidazole.[6] Unfortunately, such a regime is becoming increasingly ineffective worldwide due to clarithromycin resistance, with data showing that eradication rates have declined to less than 80% in both the United States and Europe.[7]

Several alternative regimes for eradication have been proposed, including the extension of the treatment duration to 10 or 14 days; using a different PPI; quadruple therapy with the use of bismuth with a PPI and two antibiotics; concomitant and sequential regimes; use of probiotics-supplemented triple therapy or using other antibiotics such as levofloxacin [8-11]. Despite such antibiotic regimens, a 100% eradication rate is rarely achieved. [13] The success of eradication therapy depends on patient compliance and bacterial factors such as antibiotic resistance.

Various studies have demonstrated different results on the correlation of smoking and prevalence of H.pylori infection. It is proposed that smoking is negatively associated with H.pylori infection due to an increase in gastric acidity following smoking,[9] whilst other studies showed a positive relationship in view of damage to gastric mucosal protection [10] and reduced efficacy of eradication therapy.[11-12] Others studies have demonstrated that there is no statistically significant difference in the rate of positive infections in relation to current or previous smoking status.[14] While most of the recent studies have concentrated on the choice and prescription of antibiotics there is minimal recent data on the timing of the interpretation of the RUT after an oesophago-gastro-duodenoscopy (OGD).

The primary aims of this study were:

1. To assess the diagnostic accuracy of the RUT by assessing it at 4 hours and 24 hours.
2. To determine whether there is a correlation between smoking and H.pylori infection.
3. To identify the different treatment regimes prescribed at our local hospital.

A secondary aim of the study was to determine the prevalence of positive H.pylori infections among patients undergoing an OGD..

Methodology

This was a prospective study performed between January 2016 and July 2016. Approval was obtained from the Malta University Research Ethics Committee. Ninety-five percent (95%) of the endoscopists who perform OGD's at Mater Dei Hospital agreed to participate. The following data was obtained and entered into the database: date of procedure; patient`s age; gender; clinical indication; RUT; treatment regime prescribed and smoking status. The exclusion criteria were: (1) patients had already been tested and/or treated for H.pylori (2) use of proton pump inhibitors in the 2 weeks prior to the test and (3) the use of antibiotics in the preceding 4 weeks.

The RUT used in each case by all endoscopists involved was the Kimberly-ClarK

CLOtest Rapid Urease Test. The test was defined as either negative, early positive or late positive.

The patients' OGD reports were checked on the same day of the procedure and the following day by two investigators. If the RUT test showed a colour change up to 4 hours after the procedure, it was marked as "early positive". If the RUT test demonstrated a positive test more than 4 hours later and within 24 hours, it was marked as "late positive".

Results

A total of 580 consecutive patients who performed an OGD at our centre were recruited. Thirty – eight (38) patients were excluded as 31 patients had been previously tested and/or treated for H. Pylori and another 7 patients did not have a CLO test taken during the OGD. From the 542 eligible patients, 52.4% were female (284 patients).

The minimum age was 15 and the maximum was 88. The patient`s mean age was 54.64 years (median age: 58 years; range 15 - 88 years). Figure 1 demonstrates the age distribution of the patients' cohort.

The main clinical indication was dyspepsia (44.7%). Other main indications were gastro-oesophageal reflux disease (GORD) (24.5%) and in the investigation of anaemia (10.1%). The other clinical indications are demonstrated in Table 1.

From the cohort, 85% of the RUTs were negative for H.pylori. The rest were positive and were classified into early positive (8.7%) and late positive (6.3%). Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013). Figure 2 demonstrates the percentage of positive RUT tests for every age group.

Figure 1: *Age distribution of patients who underwent OGD*
The minimum age was 15 and the maximum was 88. The patient`s mean age was 54.64 years (median age: 58 years; range 15 - 88 years).

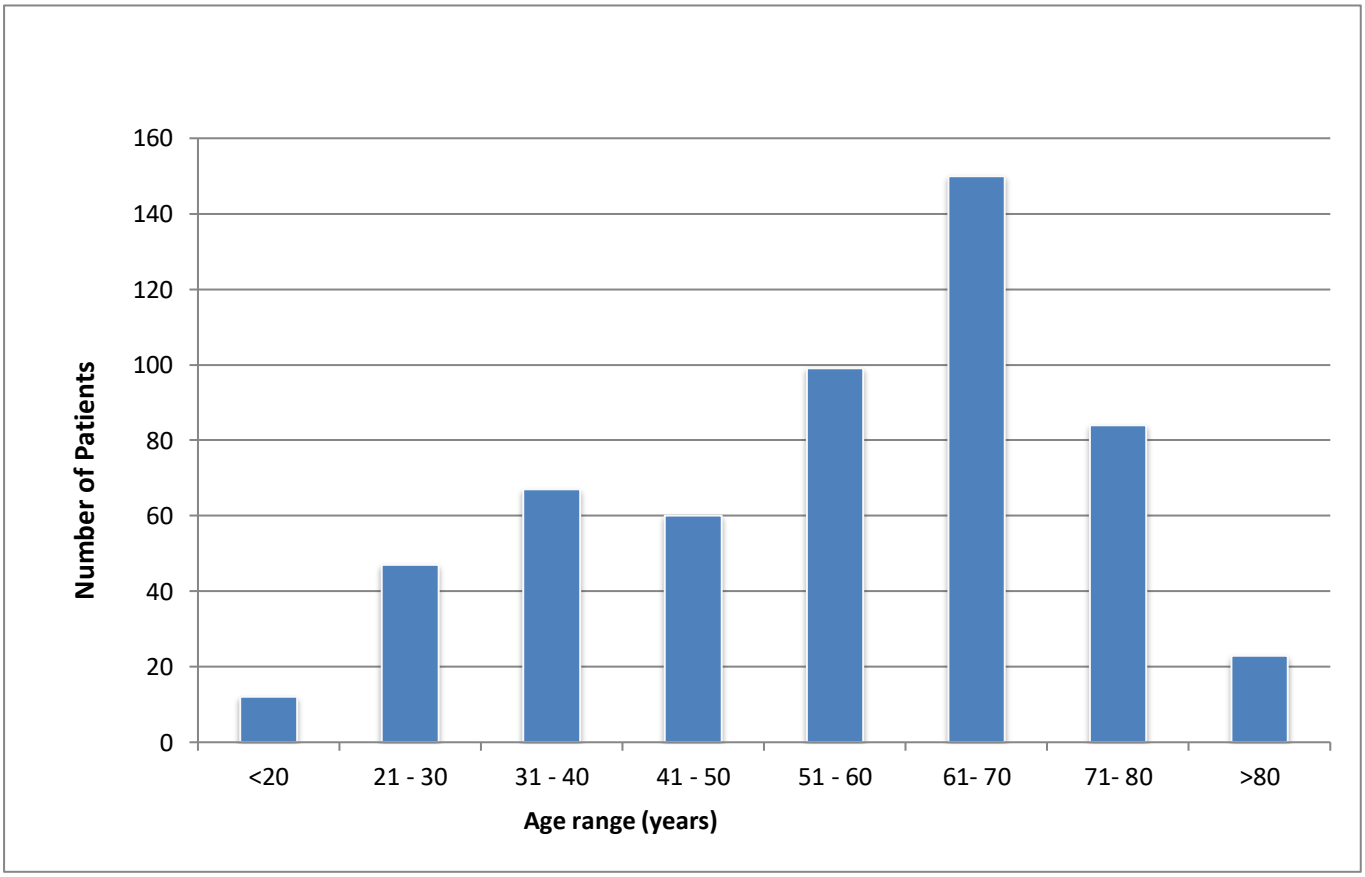


Table 1: *Clinical indication for OGD*

The main clinical indication was dyspepsia (44.7%). Other main indications were gastro-oesophageal reflux disease (GORD) (24.5%) and in the investigation of anaemia (10.1%).

Clinical Indication	Percentage (%)
Dyspepsia	44.7
GORD	24.5
Anaemia	10.1
Weight loss	2.2
Variceal Screening due to cirrhosis	2
Dysphagia	1.1
Not specified	3
Screening for upper GI cancer	6.5
Work-up for coeliac disease	2.2
Suspected upper GI bleeding	2
Gastric mass on CT scan and/or increased uptake on prior PET scan	1.7

Figure 2: *Percentage of Positive RUT in each age group*

From the cohort, 85% of the RUTs were negative for H.pylori. The rest were positive and were classified into early positive (8.7%) and late positive (6.3%). Analysis of patients' age with RUT positivity revealed that patients above the age of 60 years were more likely to have a positive result (p=0.013).

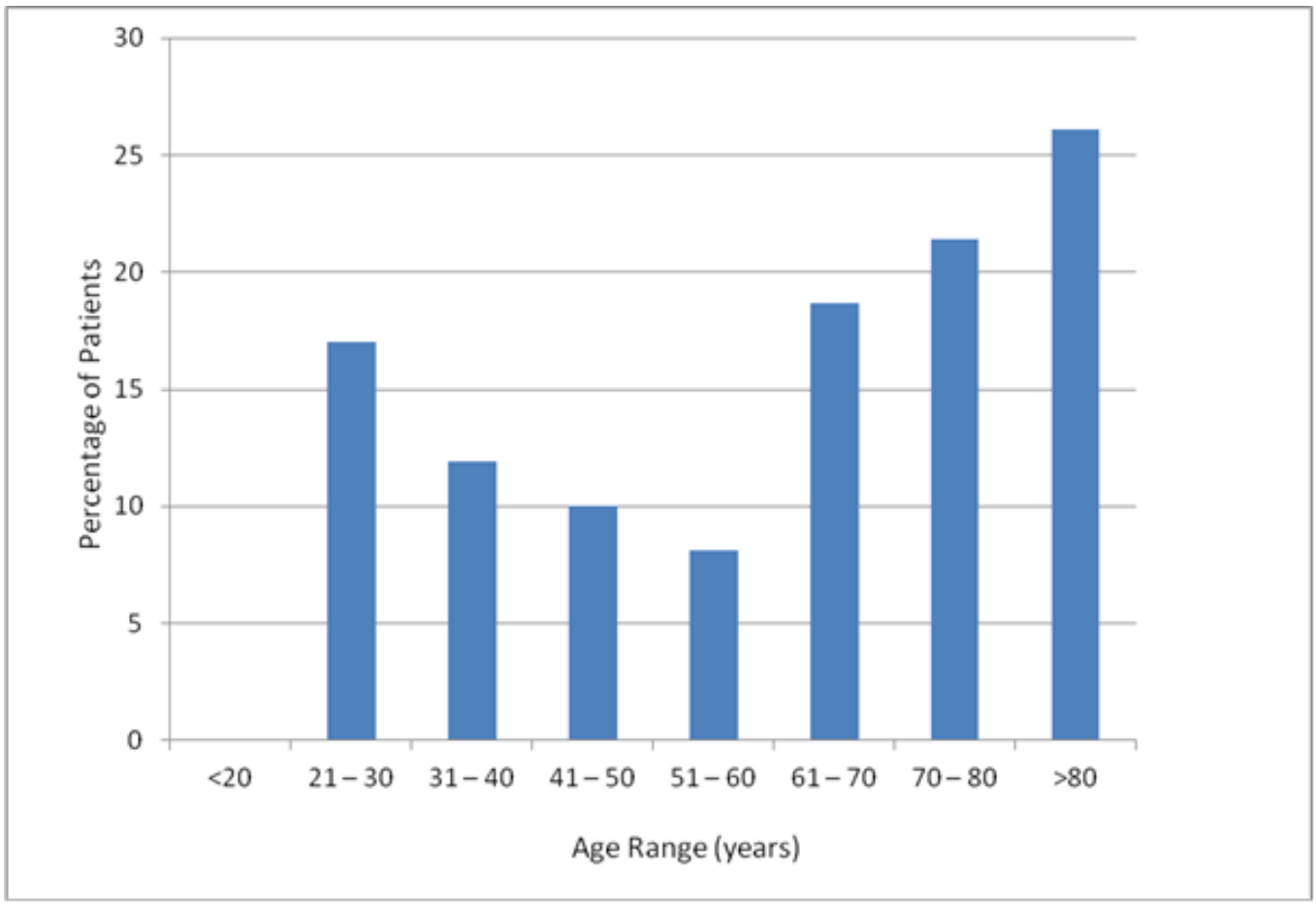
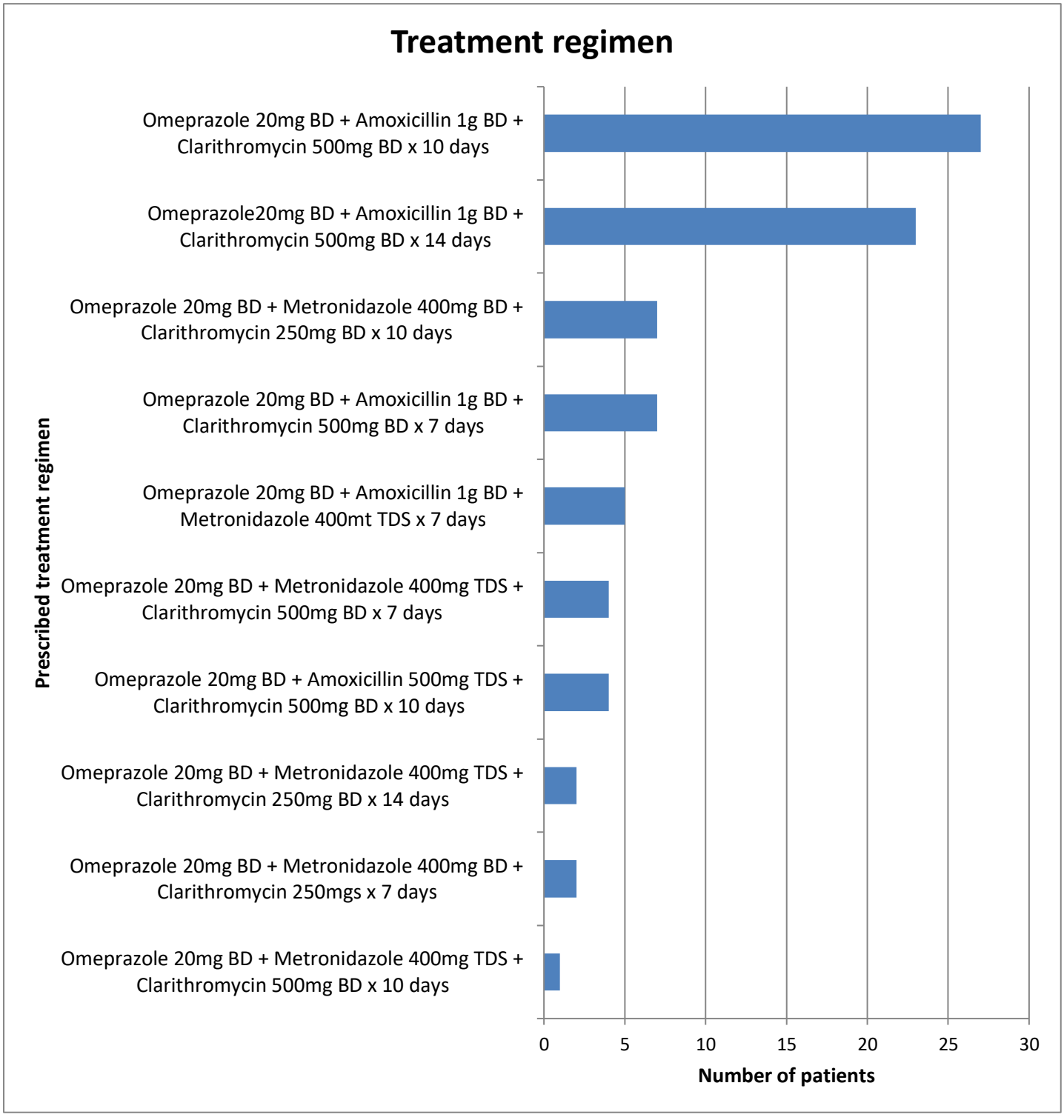


***Figure 3**: Treatment regimen prescribed to patients with a positive RUT*
The most commonly prescribed regimens were omeprazole 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (33%) and 14 days (28%). In the rest (39%), 10 different regimens were prescribed



From the patients with a negative RUT test, 25.4% were smokers. Similarly, from those with a positive result, 28.4% were smokers. There was no statistical significance between the H.pylori results and smoking (p=0.6).

The most commonly prescribed regimens were omeprazole 20mg BD + Amoxicillin 1g BD + Clarithromycin 500mg BD for 10 days (33%) and 14 days (28%). In the rest (39%), 10 different regimens were prescribed, as can be demonstrated in Figure 3.

Discussion

H. pylori infection is a cause of peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. RUTs are used widely throughout the world in endoscopy units to determine if patients are infected with H. pylori. The accuracy of these tests is important because a missed diagnosis of H. pylori infection can thus result in various pathologies.[15]

In the RUT, the gastric biopsy is put into a gel medium containing urea and a pH indicator. If present, the urease enzyme of H. pylori splits urea into ammonia and carbon dioxide. Ammonia alters the pH of the medium which then causes the colour change of the pH indicator. This process can take a variable amount of time and potentially there are various variables such as previous exposure to PPI`s, antibiotics and amount of urease that is produced by the bacterium.[16] The expectation from a clinical perspective and also administrative is to provide a quick and reliable result before the patient leaves the endoscopy unit in view of patient satisfaction and as to decrease the need for phone calls on the next day and other related paperwork.

The overall prevalence of 15% does not support the empirical treatment for H. Pylori amongst symptomatic patients within our population. There was a statistically significant difference in prevalence between patients below and above the age of 60 years (p=0.013). Furthermore, in patients under the age of 20 years, none of the patients had H. Pylori. One possible bias within the study group could have been that although patients were told to stop proton pump inhibitors 2 weeks prior to the OGD, they might not have done so and they might have consumed antibiotics in the preceding 4 weeks. This would have led to an under representation of H.pylori. Similarly, we only tested for H. pylori with one modality (the RUT) and did not compare the result with histology and/or culture as a reference standard. This could also have led to a lower incidence. However, previous studies have demonstrated that the RUT is 97% specific and 98% sensitive when compared to histology which was 100% specific and 91% sensitive[16] Furthermore, previous data from studies has demonstrated that overall positivity is 75% within 20 minutes, 85% are detected at 1 hour, 90% by 3 hours and 95% by 24 hours.[17] Data from our study contrasts significantly with this data as 42% of the RUT turned positive after 4 hours.

In view of this previous data and the costs involved, we did not check for H.pylori with other modalities. However, we assessed what really happens in the day-to-day clinical practice. It is important to note that there is limited recent analysis about the timing of the colour change for this RUT and most data is coming from the late 1980s. Thus, in view of increasing or changing antibiotic resistance patterns it might be prime time to review this, as analysis of the RUT at an early stage and not reviewing at 24 hours might lead to missing out on the diagnosis of H.pylori and thus not treating it.

Previous studies have demonstrated both positive and negative associations of smoking with H.pylori.[14] In this study there was no correlation between the presence of H.pylori and smoking. No H.pylori related malignancies were noted within this cohort.

Inconsistencies regarding the eradication regimes prescribed in the endoscopy unit are evident and depend on consultant preference and the junior doctors who prescribe the treatment after checking RUT. As culture with antibiotic sensitivities is not routinely performed when H.pylori infection is diagnosed, it is generally recommended that different antibiotics be given at higher doses for 14 days. [18] Our study concluded that only 28% of the positive RUT patients were prescribed such a regime.

Increased antibiotic resistance is a recognised problem affecting the overall success rate of eradication of H.pylori. To minimise the clinical impact of antimicrobial resistance and eradication failure, several studies recommend antimicrobial susceptibility testing prior to initiating treatment.[19-20] Ideally antibiotic choice should be based on culture and sensitivity of each H.pylori strain

cultured in the biopsy however this is not practiced at Mater Dei Hospital and the eradication therapy is chosen empirically.

The difficulties associated with performing culture and antibiotic sensitivity studies for H.pylori include both expense and the fastidiousness of the organism. Studies have shown that the use of a single antral biopsy for assessing efficacy of a particular treatment regimen may fail to detect resistant strains.[21] Thus resistance variability of H.pylori organisms at different gastric mucosal sites is a contributing factor to higher eradication rates and such antibiotic resistance would require multiple gastric biopsies from different sites.

Limitations to this study which may have affected the positivity rate of the RUT and thus the outcome of the study is that there is no recorded data of how many biopsies and from where they were taken and used for each RUT, although it is standard practice to take at least one sample from the antrum of the stomach.

Another possible limitation to the study is that there is no available follow up on successful eradication of H. Pylori though this was not one of the intended aims of the study as this is not routine practice at Mater Dei Hospital but the choice of the respective endoscopist.

Conclusion

This study demonstrates that various regimens are used in clinical practice. However, we have to note the increasing antibiotic resistance. Various eradications rates have been ascribed to different regimens. In view of the relatively low prevalence of H.pylori, especially amongst young patients, antimicrobial resistance studies of H.pylori should be actively considered as to have better guidance with regards to antibiotic prescription. Furthermore, the significant increase in positivity post- 4 hours necessitate that if the test is still negative at 4 hours, it has to be re-analysed at 24 hours.

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