SAFETY AND EFIDCACY OF A TEN DAY
HELIICOBACTER PYLORI ERADICATION REGIMEN
WITH RABEPRAZOLE, AMOXICILLIN AND
CLARITHROMYCIN

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LIST OF ABBREVIATIONS:

ATP: adenosine triphosphate
AUC: area under the curve
bid: twice a day
BSS: bismuth subsalicylate
cAMP: cyclic adenosine monophosphate
CBS: colloidal bismuth subcitrate
cpm: counts per minute
ELISA: Enzyme-linked immunosorbant assay
FDA: food and drug administration
GI: gastrointestinal
IFN: interferon
IgG: immunoglobulin G
ITT: intention-to-treat
LPS: lipopolysaccharide
MALT-lymphoma: mucosal associated lymphoid tissue lymphoma
MIC: minimum inhibitory concentration
NSAID: non steroidal anti-inflammatory drugs
OAC: omeprazole, amoxicillin, clarithromycin
PCR: polymerase chain reaction
PP: per protocol
PPI: proton pump inhibitor
qd: once daily/every day
qid: four times a day
RUT: rapid urease test
tid: three times a day

TNFα: tumor necrosis factor alpha
ACKNOWLEDGMENT

To our families
ABSTRACT

OBJECTIVE: We assessed the safety and efficacy of a 10-day twice daily rabeprazole-based triple therapy for *Helicobacter pylori* (*H. pylori*).

METHODS: *H. pylori* infected patients as confirmed by a rapid urease test were enrolled in an outpatient based open-label prospective trial. Symptomatic *H. pylori* infected patients were assigned to receive amoxicillin 1000 mg, clarithromycin 500 mg and rabeprazole 20 mg all twice daily for 10 days. No maintenance therapy was given during the follow up period. Patients were followed up during therapy by telephone calls to assess compliance and any occurrence of adverse effects. The efficacy endpoint was assessed by using the $^{14}$-C urea breath test (UBT). Occurrence of side effects was also evaluated.

RESULTS: A total of 104 patients were analyzed per intention-to-treat (ITT) and per-protocol (PP). Eradication rates of 87.5% (ITT) and 93.8% (PP) were obtained. Therapy was relatively well tolerated with minimal side effects.

CONCLUSION: Rabeprazole-based triple therapy is a suitable regimen for eradication of *H. pylori* infection.
Helicobacter pylori: An Overview

Before the first isolation and documentation of the organism, now known as *Helicobacter pylori*, it was assumed that the human stomach was a sterile environment because of the high levels of acid, which would exclude it as an ecologic niche for any organism. This bacterium was first introduced to the scientific community in 1982 by Marshall and Warren\(^1\), who described a campylobacter-like bacterium that was seen in large numbers in the gastric mucus of patients with chronic gastritis and duodenal ulcers. At that time the bacterium was identified as *Campylobacter pylori*.

Ongoing studies of the organism, particularly on the genetic level, resulted in its differentiation from the campylobacter genus and the introduction of a new one: *Helicobacter*. The organism is known as *Helicobacter pylori* (*Helico*: curved, *bacte*: staff, *pylori*: from pyloridis, reflective of its specific location and associated disease).

1.1 Microbiology

*Helicobacter pylori* (*H. pylori*) is a human pathogen adapted to live mainly in the gastric mucosa and areas of gastric metaplasia in the duodenum\(^2\). *H. pylori* is a Gram negative, spiral to curved, rod-shaped bacterium, approximately 0.5 \(\mu\)m in diameter and 3-5 \(\mu\)m long. It has 4-7 polar
sheathed flagella enabling free movement of the bacterium in gastric mucus viscous environments.

Figure 1: *Helicobacter pylori*.

*H. pylori* has also been found in nonhuman primates and cats, but it was not related to animal diseases.

1.2 **Prevalence and Epidemiology**

*H. pylori* is a worldwide pathogen; it affects the population of all five continents with varying infection rates among different geographical locations (Figure 2).
The prevalence of *H. pylori* infection has been found to be indirectly related to the socio-economic status of affected countries. In developing countries, 50-90% of the population is infected with the bacterium. Children usually rapidly acquire the infection between the ages of 2 and 8 years, and the majority are infected by adolescence (Figure 3).
Figure 3: *H. pylori* infection rates in developing countries. A lower socio-economic status is associated with a higher incidence of *H. pylori* infection and its fast acquisition at a younger age.  

However, in developed countries infection rates are much lower: 20% of the population younger than 40 years of age, and more than 50% of those above the age of 60 are infected. In younger children, *H. pylori* infection is uncommon (Figure 4).

Figure 4: *H. pylori* infection rates in developed countries.
Therefore, the higher the socioeconomic status, the lower is the prevalence of
*H. pylori* infection among the population. The main reasons for this are better
hygiene, less crowded households, better diagnostic and eradication
techniques that lead consequently to less contamination to the healthy and/or
younger population.

1.3 *Transmission*

The mode of transmission of *H. pylori* is still somehow controversial.

Four possible routes are postulated:

1.3.1 *Fecal-Oral Route:*

Even tough little data is available to support this hypothesis *H. pylori*
has been detected in contaminated waters, stools and dental plaques mainly
in developing countries\(^2,5\).

1.3.2 *Oral-Oral Route:*

The oral cavity has been proposed to be a reservoir for infections.
Studies have isolated *H. pylori* from oral specimens, particularly saliva and
dental plaques, although results of culture from these sources have been
mixed\(^6\). High prevalence of *H. pylori* infection was found in high density areas
with close personal contact as well as between spouses and family members.
The possibility of infection through kissing and oral-oral contamination is also
suggested.
Another possibility would be a direct contamination from esophageal reflux and vomiting, which occurs most frequently among young children\textsuperscript{7}. Neither oral nor fecal exposures have been established conclusively as a route of transmission since the organism is difficult to culture.

### 1.3.3 Iatrogenic Spread:

Infection can occur through contaminated gastrointestinal equipment which makes of endoscopy units high risk areas for the infection acquisition\textsuperscript{8}. However, this source can be eliminated by following proper equipment cleaning, decontamination procedures and universal precautions.

### 1.3.4 Animal Reservoir:

Although *H. pylori* was cultured from a colony of domestic cats, there is no evidence that this bacterium can transmitted from cats or other pets to humans\textsuperscript{5,10}.

### 1.4 Pathogenesis

The pathogenic effect of *H. pylori* starts once the bacterium enters the gastrointestinal (GI) tract and comes in contact with the gastric lumen. This induces an inflammatory response that will lead to the attraction of neutrophils (Figure 5-A) and the production of inflammatory mediators like TNF\textsubscript{α}, IFN and interleukins; all of which play an important role in the inflammatory process.
The inflammatory response can induce a number of changes in the gastric epithelium ultimately causing cell damage (Figure 5-B).

Figure 5: Three steps of *H. pylori* infection: Once *H. pylori* is in the stomach it causes the release of inflammatory mediators (A) which promote cell damage (B) and consequently lead to lymphoma and carcinoma (C) adapted from reference 11.
Chronic *H. pylori* infection can cause many disease states varying from a simple gastritis to carcinomas or lymphomas (Figure 5-C and Figure 6).

![Figure 6: Natural History of *H. pylori* infection](image)

1.5 **Virulence Factors**

Virulence factors of *H. pylori* are divided into two categories:

Colonization factors and factors that mediate tissue injury\(^{13}\).

1.5.1 **Colonization factors:**

The spiral shape of the bacterium and the presence of flagella allow its motility within the environment of the gastric fluid. When the bacterium reaches, adherence factors coated on the bacterium’s external surface allow its attachment to specific receptors on the gastric epithelial.
Once attached, *H. pylori* can produce large amounts of nitrogen metabolizing enzymes such as ureases which breaks down urea to ammonia and bicarbonate thus elevating gastric mucus pH and allowing the safe passage of *H. pylori* through the gastric acid layer to the protective mucus layer\(^4\). In addition, ammonia in itself is damaging to the epithelial cells of the gastric mucosa (Figure 7).

![Figure 7: Effect of *H. pylori* on urea](image)

### 1.5.2 Factors that mediate tissue injury:

*H. pylori* is able to secrete specific proteins like vacuolating cytotoxins (due to VacA gene) and other proteins like protease and lipase which further contribute to the mucus layer damage (Figure 8). Other virulence factors include the endotoxins -also known as lipopolysaccharides (LPS)- that stimulate the release of cytokines, interfere with the gastric epithelial cells and cause the loss of mucosal integrity.
Some *H. pylori* strains possess a cytotoxin-associated antigen -also known as CagA. These isolates cause more mucosal tissue injury than the strains that are devoid of this *cag* pathogenicity island because cagA is responsible for more prominent inflammatory tissue response by the host\textsuperscript{15}.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure8.png}
\caption{Virulence factors associated with *Helicobacter pylori*\textsuperscript{16}.}
\end{figure}

1.6 Diagnosis

A multitude of tests are available to determine whether a patient is infected with *Helicobacter pylori*. These different types of tests can be divided into 2 categories: Invasive tests which require an endoscopy and non-invasive tests which do not require endoscopic procedures\textsuperscript{17}.

1.6.1 Invasive Tests

Several tests fall into this category; they differ from each other by the way they positively identify *H. pylori* but they all have one common step: the need for endoscopy to obtain a biopsy specimen. Diagnosis of *H. pylori* is mainly done with invasive tests.
1.6.1.1 Histology:

Biopsies obtained from the gastric mucosa are sent the laboratory for pathological detection of motile *H. pylori*. Usually one biopsy specimen is not enough because the bacterium distribution in the stomach is not uniform and hence multiple biopsies should be taken in order to have a definite diagnosis and avoid false negative results. The most common histological stains used are the Warthin-Starry stain and the Giemsa stain. In to the visualization of *H. pylori*, histology is the only diagnostic test that provides information about the characteristics of the mucosal tissue.

![Histology images](image)

Figure 9: Normal lining of stomach as seen on histology (A) and an infected stomach lining (B)\textsuperscript{18}.

1.6.1.2 Culture:

Culturing a specimen obtained by endoscopy might be a definitive proof of infection; however obtaining *H. pylori* cultures is a sensitive and tedious procedure because the bacterium loses viability when exposed to the environment. In fact biopsies can be cultured up to 24 hours after being drawn if they are stored at 4°C, but they are stable for less than 6 hours if they are kept at room temperature (15°C).
1.6.1.3 Molecular biology techniques:

They are used to detect *H. pylori* in different specimen such as the gastric juice, dental plaques, feces and gastric biopsies. The most commonly used method is the polymerase chain reaction (PCR) that allows bacterium detection by amplification of a primer of the *H. pylori* genome. PCR offers minimal advantages over culture, histology and rapid urease tests if it is used to detect *H. pylori* from gastric biopsies. The PCR technique is primarily used to detect specific strains of *H. pylori* such as those that are *cagA* positive (type II) and those that are *cagA* negative (type I). *H. pylori* strains that are *cagA* positive are more virulent than those that are *cagA* negative. However, clinically; strain identification will not alter treatment approach. As PCR is an expensive technique, its usage is still limited to the research setting.

In the future, one possible clinical application of PCR would be to check for a point mutation in the *H. pylori* genome responsible for resistance to antibiotics to allow clinicians to achieve better cure rates.

1.6.1.4 Rapid Urease Test:

Rapid urease tests (RUT) are based on the urea breakdown to ammonia and carbon dioxide by the bacterium as described earlier (figure 7). For RUT, antral biopsies are the most common biopsies done. Several biopsy specimens are placed on the special disk at the back of the test and the disk is sealed. If urease (from *H. pylori*) is present in the samples biopsied then ammonia will be released and the color of the disk will change to pink (figure
10-B). If the color of the disk stays yellow and does not turn to a reddish/pinkish color after 24 hours then the patient is considered to be H. pylori negative (figure 10-A). This color change is due to the presence of phenol red, a pH indicator that is invisible at acidic pH and turns red once the pH of the medium becomes basic.

![Figure 10: Example of a negative rapid urease test (A) and a positive urease test (B).](image)

The results of RUT are seen within the first half hour after placing the biopsy sample on the test. A positive test after seconds of placing the sample asserts a colonization of the gastric mucosa by *H. pylori*. However, a yellow color after 30 minutes is not fully indicative of a negative test. Therefore we need to monitor the color change for 24 hours after the endoscopy procedure and if the color is still yellow at that time then we can assert that the specimen placed on the test contained no urease and hence no *H. pylori*.

Two main RUT advantages are cheap cost and rapid results. One possible disadvantage is the likelihood of false negative results in patients taking proton pump inhibitors (PPI). The urease test should be performed at least 4 weeks after discontinuation of the PPI.
ratio is recorded as zero in the mass spectrometer and any deviation from this ratio after the patient ingests the urea capsule is considered a positive finding. The urea breath test can be performed in children over the age of 7 but more studies are needed to validate its use in younger populations. The $^{14}$C-urea breath test was used to confirm eradication of *H. pylori* infection in our study population\textsuperscript{20}. The test was performed as follows:

The patients were requested to fast overnight and then had to give a control breath before drinking the $^{14}$C-labelled urea. The patient then had to exhale into a mouth piece that is connected through a tube to a scintillation counter vial that contains 20 ml of scintillation liquid, 0.5 mmol of hyamine dissolved in 2 ml of ethanol and a pH indicator thymolphthalein. This pH indicator has a blue color in basic media and it becomes colorless when the pH of the medium becomes acidic. Hence when the patient exhales into this solution the CO$_2$ liberated will acidify the solution and so the blue color will fade away and disappear (Figure 11).

![Diagram](image)

**Figure 11**: Diagram of the apparatus used for patients undergoing the $^{14}$C urea breath test\textsuperscript{19}. 
The patient was instructed to exhale one long breath until the solution becomes colorless. This vial was labeled background.

After that first exhalation, the patient was to drink a quantity of $^{14}\text{C}$-urea equivalent to 1.5 micro Curie (μC) mixed in 20 ml of water and wait for ten (10) minutes. During that time the patient's weight was recorded and he/she was not allowed to drink or eat anything.

After 10 minutes, the patient had to take a deep breath and exhale into the scintillation counter vial just like the first exhalation. This vial was labeled patient.

A third vial that contained 1.5 μC of labeled-urea was labeled as standard. Once the three vials were obtained 10 ml of scintillation fluid were further added to each one of them and they were placed in the scintillation counter.

The values obtained from the scintillation counter along with the weight of the patient were plugged into the equation shown below and a ratio was obtained.

\[
\frac{\text{Patient (cpm)} \times \text{weight (Kg)}}{\text{standard (cpm)} \times 2}
\]

A ratio that yields a value >1.5 meant that the patient was \textit{H. pylori} infected and a value below 1.5 meant that the patient was \textit{H. pylori} negative$^{19}$.

\[1.6.2.2 \quad \textbf{Stool Antigen Detection:}\]

This is an enzymatic immunoassay (EIA) test that checks for the presence of \textit{H. pylori} antigen in the feces. Stool antigen detection testing kits are available and this method of diagnosis and detection of \textit{H. pylori} infection is rapidly gaining importance in the medical field.
1.6.2.3 Serology:

Serology tests that detect anti-\textit{H. pylori} IgG antibodies in the serum of patients were the first non invasive technique used to assess possible \textit{H. pylori} infections. Currently the solid phase assay is the most commonly used technique as it is the case with the enzyme-linked immunosorbant assay (ELISA) test. Just like the stool antigen detection test, ELISA checks for the presence of anti- \textit{H. pylori} antibodies in the blood. If the antibodies are present, a colored spot appears on the assay (Figure 12).

![Image of ELISA test](image)

1. Antibodies (Y) to the bacterium (★) are bound to wells of a microtiter plate.

2. Add the patient sample suspected of containing the bacterium or its antigens and wash the wells with buffer.

3. Add the anti-\textit{H. pylori} antibody containing conjugated enzyme.

4. Wash with buffer.

5. Add substrate for enzyme and measure amount of colored product.

\textit{Figure 12: Method of ELISA testing}^{21}. 
1.6.3 Conclusion:

At present there is no single invasive or non-invasive test that is a gold standard for the diagnosis or confirmation of *H. pylori* eradication. The choice of the test to be used depends on the clinical setting and preference of the clinician. Most of the times two tests are performed to confirm the diagnosis; the choice is usually based on the sensitivity and specificity of each test (Table 2).

**Table 2:** Sensitivity and specificity of diagnostic tests\(^ {22}\).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity (%)</th>
<th>+Predictive Value</th>
<th>-Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>93.1</td>
<td>99.0</td>
<td>99.4</td>
<td>88.7</td>
</tr>
<tr>
<td>RUT</td>
<td>89.6</td>
<td>100.0</td>
<td>100.0</td>
<td>84.1</td>
</tr>
<tr>
<td>Non-invasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UBT</td>
<td>90.2</td>
<td>95.8</td>
<td>97.5</td>
<td>84.3</td>
</tr>
<tr>
<td>Salivary Antibody</td>
<td>89.0</td>
<td>94.0</td>
<td>89.0</td>
<td>94.0</td>
</tr>
<tr>
<td>Stool Antigen</td>
<td>94</td>
<td>91</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>IgG</td>
<td>91.3</td>
<td>91.6</td>
<td>95.2</td>
<td>85.3</td>
</tr>
</tbody>
</table>

1.7 Who should get treated?

There is still no consensus on which *H. pylori* positive patients should be treated. A rough guideline has been set up by the European *Helicobacter pylori* Study Group: it divides patients according to disease state and either recommends or advises that such patients be treated with an *H. pylori* eradication therapy\(^ {23}\) (Table 3).
**Table 3:** Maastricht guidelines for the treatment *H. pylori* infected patients.

<table>
<thead>
<tr>
<th>Indications for which treatment is strongly recommended</th>
<th>Indications for which treatment is advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Duodenal or gastric ulcer (active or not, including complicated peptic ulcer disease)</td>
<td>- Functional dyspepsia</td>
</tr>
<tr>
<td>- MALT lymphoma</td>
<td>- Gastroesophageal reflux disease (in patients requiring long-term profound acid suppression)</td>
</tr>
<tr>
<td>- Atrophic Gastritis</td>
<td>- Use of NSAIDs</td>
</tr>
<tr>
<td>- Recent resection of gastric cancer</td>
<td></td>
</tr>
<tr>
<td>- First-degree relative of patient with gastric cancer</td>
<td></td>
</tr>
<tr>
<td>- Desire of the patient (after full consultation with the physician)</td>
<td></td>
</tr>
</tbody>
</table>

Despite the guidelines stated above, an ethical question comes to mind when a patient has tested positive for *H. pylori*. *H. pylori* is considered to be a major risk factor if not a cause of some types of cancer such as mucosal associated lymphoid tissue (MALT) lymphoma and gastric cancer. In fact *H. pylori* is considered to increase the relative risk of gastric cancer by a factor of six24. Should we eradicate this organism from the patient because he/she is at risk of developing cancer in the future?
2.1 General Overview

All currently available proton pump inhibitors are substituted benzimidazoles, they only differ by substitution to the pyridine or benzimidazole moieties. To date, there are 5 proton pump inhibitors available on the Lebanese and international market: Omeprazole (Losec®, Astra Zeneca), Lansoprazole (Lanzol®, Hoechst Marion Roussel), Pantoprazole (Inipomp®, Synthelabo), Rabeprazole (Pariet®, Janssen-Cilag) and Esomeprazole (Nexium®, Astra Zeneca).

Figure 13: Structure of proton pump inhibitors.
2.2 Mode of Action

Proton pump inhibitors (PPI) undergo activation by protonation to a sulphenamide form. This activated moiety binds covalently to the cysteine residue of the alpha-subunit of the H⁺,K⁺-ATPase pump (proton pump) which irreversibly inhibits the activity of the gastric proton pump (Figure 14) thus increasing the intragastric pH and reduces the volume of gastric juices consequently delaying gastric emptying.²⁵

![Diagram of proton pump and inhibitors](image)

Figure 14: Site of Action of proton pump inhibitors. cAMP: cyclic adenosine monophosphate. ATP: Adenosine triphosphate.²⁶

Most PPI have a pKa of <4 and so they accumulate in the gastric areas with lower pH. It is in these areas that they get protonated and become active.

In addition to inhibiting the gastric proton pump, PPIs have antibacterial effects against *H. pylori* itself and thus they aid the antibiotics in eradicating the microorganism from the stomach. In fact each proton pump inhibitor has been
attributed a minimum inhibitory concentration (MIC) for *H. pylori* eradication\textsuperscript{27, 28} (Table 4).

<table>
<thead>
<tr>
<th></th>
<th>MIC(_90) ((\mu)g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>25</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>6.25</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>25</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>100</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 4:** Minimum inhibitory concentrations of proton pump inhibitors.

### 2.3 Contraindications

Patients who have had a hypersensitivity reaction to any substituted benzimidazole cannot take proton pump inhibitors. Also there is a cross sensitivity between all proton pump inhibitors, so patients who are allergic to one PPI should not be rechallenged with another agent of this family\textsuperscript{29}.

### 2.4 Side Effects

The major known adverse effects of proton pump inhibitors affect the gastrointestinal system and the central nervous system.

#### 2.4.1 Gastrointestinal Side Effects:

Diarrhea, nausea, vomiting, constipation, abdominal pain and flatulence were among the most commonly reposted side effects. Other GI adverse events included: dysphagia, anorexia, irritable colon.
2.4.2 Central Nervous System Side Effects:

Headache and dizziness were the most common side effects, headache being the most prevalent side effect with rabeprazole\(^30\).

2.4.3 Miscellaneous Side Effects:

Gynecomastia, skin inflammation, dry mouth, dry skin, cough\(^31,32\).

Many other less common side effects have been reported with PPIs, they are summarized in the table below.

**Table 5:** Side effects associated with proton pump inhibitors.

<table>
<thead>
<tr>
<th>Reversible peripheral edema</th>
<th>Increased serum gastrin levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fulminant hepatitis</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Mild inflammation of the gastric antrum</td>
<td></td>
</tr>
</tbody>
</table>

2.5 **Drug Interactions**

PPIs do not as -a class per say- exhibit any drug/drug interactions. Interactions of proton pump inhibitors can be divided into two categories: 1) CYP 450 dependent interactions, and 2) pH dependent interactions\(^33\).

2.5.1 CYP 450 Dependent Interactions:

Each agent taken individually possesses different effects on concurrently administered drugs.

Omeprazole reduces the plasma clearance of diazepam by up to 54%. But since diazepam has a wide therapeutic index, the clinical effect of this interaction is minimal\(^34\). Also, at a minimum dose of 40 mg per day, omeprazole increases the
elimination $t_{1/2}$ of phenytoin and decreases its clearance by 15-20%$^{35}$. Since phenytoin has a narrow therapeutic index, its plasma levels should be closely monitored$^{34}$.

Being a CYP 450 inhibitor, lansoprazole increases the clearance of theophylline by $\sim$10%$^{36}$. It may also decrease the effectiveness of oral contraceptives$^{37}$.

As for esomeprazole, like omeprazole; it decreases the clearance of diazepam by $\sim$45% but this effect is also not clinically significant$^{38}$.

To date, there have been no reports of interactions with either rabeprazole or pantoprazole (Table 6).

<table>
<thead>
<tr>
<th></th>
<th>Rabeprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Lansoprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP 450 dependent metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Warfarin</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Theophylline</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>pH-dependent absorption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### 2.5.2 pH Dependent Interactions:

Since PPIs decrease gastric acid secretion, they increase gastric acid pH hence altering the rate or extent of the absorption of some drugs especially acidic drugs which require an acidic environment to be absorbed. In order for acidic drugs to be absorbed, they should be present in the stomach in an non-ionized form. An increase in the pH of the stomach will cause such drugs to be in an ionized form and hence the extent of their absorption will be altered. Subsequently the administration of
PPIs has increased the absorption of digoxin (a basic molecule) and decreased that of ketoconazole (an acidic molecule)\textsuperscript{34}.

### 2.6 Pharmacokinetics of Proton Pump Inhibitors

Proton pump inhibitors have different pharmacokinetic parameters. Their bioavailabilities vary from as low as 35% with omeprazole to as high as 90% with esomeprazole. PPIs are highly bound to plasma proteins and have a pKa of 3 to 4 with the exception of rabeprazole that has a pKa of 5.0. PPIs have a short elimination half life of about one hour, but their duration of action is much longer because they bind covalently to the proton pump\textsuperscript{37} (Table 7).

Food decreases the bioavailability of lansoprazole by up to 50% and delays the absorption of pantoprazole by up to 2 hours.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Lansoprazole</th>
<th>Rabeprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) ((\mu)g/ml)</td>
<td>0.08-8</td>
<td>1.1-3.3</td>
<td>0.6-1.2</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{max}}) (hr)</td>
<td>1-3</td>
<td>2-4</td>
<td>1.3-2.2</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>(t_{1/2}) (hr)</td>
<td>0.6-1</td>
<td>0.9-1.9</td>
<td>0.9-1.6</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>35-68%</td>
<td>77%</td>
<td>80%</td>
<td>52%</td>
<td>90%</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>95</td>
<td>98</td>
<td>97-99</td>
<td>95-98</td>
<td>97</td>
</tr>
<tr>
<td>pKa</td>
<td>4.0</td>
<td>3.8</td>
<td>3.9</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Cl (L hr/kg)</td>
<td>0.45</td>
<td>0.08-0.13</td>
<td>0.2-0.28</td>
<td>0.50</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7: Pharmacokinetic parameters of proton pump inhibitors\textsuperscript{38, 39}.

**2.7 Patient information:**

When dispensing any proton pump inhibitor to a patient, he/she should be counseled on the following: The medication should be administered before meals and the patient should swallow the tablet/capsule whole without chewing or crushing it. In
the event that the proton pump inhibitor is a capsule and that the patient has difficulty swallowing, the content of the capsule can be mixed with cool soft apple juice and then swallowed immediately without chewing\textsuperscript{31, 32, 40}.

2.8 Brief Overview about Rabeprazole

2.8.1 Mechanism of Action of Rabeprazole:

The mode of action of rabeprazole is similar to that of the other PPIs but it differs from other agents by its higher pk\(a\) (pk\(a\)=5). This higher pk\(a\) allows for rabeprazole to be protonated to the active sulphenamide form over a wider pH range, hence activation will occur faster and hypothetically, patients will be relieved faster than with other PPIs. In fact, a study done on porcine gastric vesicles showed that rabeprazole fully inhibited the proton pump much faster than other agents in its class\textsuperscript{41} (Table 8).

<table>
<thead>
<tr>
<th>Activation time (min)</th>
<th>Rabeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>At pH 1.2</td>
<td>1.3</td>
<td>2.0</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>At pH 5.1</td>
<td>7.2</td>
<td>90</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>% inhibition of the H+/K+/ATPase pump</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 10 min</td>
<td>100%</td>
<td>66%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>At 45 min</td>
<td>100%</td>
<td>100%</td>
<td>83%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Hence, rabeprazole will be more suitable in patients who suffer from hypochlorhydria or those who have a gastric pH close to 5.
2.8.2 Dosage in Renal Failure:

Dosage adjustments of rabeprazole are not required in patients who suffer from renal failure\textsuperscript{42}.

2.8.3 Dosage in Hepatic Insufficiency:

The elimination of rabeprazole was decreased in patients with mild to moderate hepatic impairment and the area under the curve (AUC) - from 0 to 24 hours - was increased by 100\%. However, accumulation of the drug did not occur suggesting no need for dosage adjustments in this category of patients\textsuperscript{43}.

The pharmacokinetics of rabeprazole in severe hepatic insufficiency have not been studied, so caution should be exerted when using this drug in patients with severe hepatic impairment.
Helicobacter pylori Eradication Regimen

In order to discuss the many studies that have dealt with *H. pylori* eradication, it is important to define what is considered a successful study and what is meant by the term eradication.

An *H. pylori* eradication study is considered successful if the eradication yielded by the treatment regimen is above 80%. Hence any study that provides a success rate of less than 80% means that it is not clinically warranted to use such treatment regimen for *H. pylori* eradication.

Eradication is defined as successful if the urea breath test or histology fail to demonstrate *H. pylori* infection a minimum of 6 weeks after discontinuation of the study medication or 4 weeks after discontinuation of the proton pump inhibitor.

To date there are nine different regimen approved by the food and drug administration (FDA) for the eradication of *H. pylori* (table 9), however numerous studies have been conducted using different antibiotics, proton pump inhibitors and varying lengths of therapy. Since the literature on different *H. pylori* eradication regimen is very extensive, we will try to briefly summarize the trials that have been addressed in most meta-analyses on this subject.
Table 9: FDA approved treatment options for *H. pylori* eradication\(^ {12} \). bid: twice a day, qd: once a day, qid: four times a day, tid: three times a day.

<table>
<thead>
<tr>
<th>Double therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 40 mg qd, plus clarithromycin 500 mg tid for 2 weeks, then omeprazole 20 mg qd for 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole 30 mg bid, plus amoxicillin 1 g tid for 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Ranitidine bismuth citrate 400 mg bid, plus clarithromycin 500 mg tid for 2 weeks; then ranitidine bismuth citrate 400 mg bid for 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Ranitidine bismuth citrate 400 mg bid, plus clarithromycin 500 mg bid for 2 weeks; then ranitidine bismuth citrate 400 mg bid for 2 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triple therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20 mg bid, plus clarithromycin 500 mg bid, plus amoxicillin 1 g bid for 10 days</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole 30 mg bid, plus clarithromycin 50 mg bid, plus amoxicillin 1 g bid for 10 days</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole 30 mg bid, plus clarithromycin 50 mg tid, plus amoxicillin 1 g bid for 10 days</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole 40 mg qd, plus clarithromycin 500 mg bid, plus amoxicillin 1 g bid for 10 days</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quadruple therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth subsalicylate 525 mg qid, plus tetracycline 500 mg qid, plus metronidazole 250 mg qid for 2 weeks, plus any H(_2)-receptor antagonist or PPI for 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

3.1 Single Therapy

The use of single therapies has shown very little efficacy in the eradication of *H. pylori* infections. Efficacy rates ranging from as low as 20% with amoxicillin to as high as 40-60% with clarithromycin were reported\(^ {48} \). Many agents have been used as monotherapy for *H. pylori* eradication some of them were shown to be effective
whereas others -like azithromycin and tetracycline- have yielded disappointing results\textsuperscript{49}. Since \textit{H. pylori} does not develop resistance to amoxicillin, it would be logical to think that monotherapy with this antibiotic would provide good clinical response. However it was shown that amoxicillin by itself achieves less than a 20\% eradication rate of \textit{H. pylori}\textsuperscript{60}.

Finally, bismuth salts have been tried as monotherapy however because of the issue of frequent dosing (every 2 hours), these agents have not yielded astonishing results: there was a huge problem of patient non compliance with the treatment drug.

In summary, single agent therapies should not be used for the treatment of \textit{H. pylori} infected patients as they do not achieve eradication rates above 80\%.

3.2 \textbf{Double Therapy}

Many different dual therapy combinations have been tried for \textit{H. pylori} eradication; most of them involve a PPI, an H\textsubscript{2} receptor antagonist or a bismuth-containing compound plus an antibiotic.

It has been shown that colloidal bismuth subcitrate (CBS) along with amoxicillin yields eradication rates ranging from 33\% to 70\% depending on the dose and frequency of administration of the two agents. Because of a low eradication rate, bismuth along with a single antibiotic is not considered an adequate \textit{H. pylori} eradication technique.

On the other hand, the combination of clarithromycin and ranitidine bismuth citrate (RBC) is FDA approved and has yielded success rates of about 80\%\textsuperscript{12}.

A meta-analysis performed by Chiba \textit{et al.} suggested that the eradication rate of the combination omeprazole/amoxicillin irrespective of the dose given and the duration of therapy was in the range of 60\%\textsuperscript{51}. But studies done in Germany with omeprazole and
at least 2 g of amoxicillin per day suggest eradication rates as high as 80-85%; however, these results were not duplicated in similar trials.\textsuperscript{52}

Clarithromycin and omeprazole or lansoprazole have also been studied. Studies suggest eradication rates of 83% when clarithromycin 500 mg tid for 2 weeks and omeprazole 40 mg qd for 4 weeks are given for \textit{H. pylori} eradication.\textsuperscript{53} But again, when trying to duplicate these results, US studies yielded a disappointing 64% eradication.\textsuperscript{54}

A summary of some double therapy eradication regimen is provided in table 10.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|c|c|c|}
\hline
\textbf{Author} & \textbf{PPI} & \textbf{Antibiotics} & \textbf{N} & \textbf{Duration of therapy (days)} & \textbf{Eradication Rates %} \\
\hline
Di Caro \textit{et al.}\textsuperscript{55} & R: 20 mg bid & L: 500 mg qd & 20 & 10 & 65 \\
Stack \textit{et al.}\textsuperscript{56} & R: 20 mg bid & C: 500 mg bid & 9 & 7 & 63 \\
Miyoshi \textit{et al.}\textsuperscript{57} & R: 10 mg bid & A: 500 mg tid & 101 & 14 & 62 \\
Uehihara \textit{et al.}\textsuperscript{58} & R: 20 mg bid & A: 2g bid & 111 & 14 & 79 \\
Peterson \textit{et al.}\textsuperscript{59} & - & RBC: 400 mg bid C: 500 mg tid & 205 & 28 & 82 \\
\hline
\end{tabular}
\caption{Dual therapy for \textit{Helicobacter pylori} eradication. A: amoxicillin, C: clarithromycin, L: levofloxacin, R: rabeprazole, RBC: ranitidine bismuth citrate.}
\end{table}

3.3 \textit{Triple Therapy}

Triple therapies combining a proton pump inhibitor and two antibiotics are the standard treatment for \textit{H. pylori} infection today.

There is a big controversy regarding length of the triple therapy, currently the United States favor treatments of 10 to 14 days but many European trials have used shorter
regimen varying from 3 to 7 days. Since there is yet no answer to this question, a
different approach has been used to identify the optimal length of therapy: cost
effectiveness analyses have been performed and it is suggested that the 7 day
therapies are the most cost effective strategy\(^80\).

Besides the classical proton pump inhibitor plus 2 antibiotic triple therapies,
A summary of some studies involving PPI-based triple therapies is displayed in Table
11.

**Table 11:** Triple therapy for *H. pylori* eradication. A: amoxicillin, C: clarithromycin, O:
Omeprazole, R: rabeprazole.

<table>
<thead>
<tr>
<th>Author</th>
<th>PPI</th>
<th>Antibiotics</th>
<th>N=</th>
<th>Duration of therapy (days)</th>
<th>Eradication Rates %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgopoulos <em>et al.</em>(^61)</td>
<td>O: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>80</td>
<td>10</td>
<td>88.8 88.8</td>
</tr>
<tr>
<td>Isomoto <em>et al.</em>(^62)</td>
<td>R: 10mg bid</td>
<td>A: 750g bid C: 400mg bid</td>
<td>70</td>
<td>5</td>
<td>66 70</td>
</tr>
<tr>
<td>Laine <em>et al.</em>(^63)</td>
<td>O: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>50</td>
<td>10</td>
<td>90 91</td>
</tr>
<tr>
<td>Luth <em>et al.</em>(^64)</td>
<td>R: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>20</td>
<td>4</td>
<td>90 90</td>
</tr>
<tr>
<td>Miwa <em>et al.</em>(^65)</td>
<td>R: 10 mg bid</td>
<td>A: 500 mg bid C: 200 mg bid</td>
<td>100</td>
<td>7</td>
<td>87 89.7</td>
</tr>
<tr>
<td>Wong <em>et al.</em>(^66)</td>
<td>R: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>58</td>
<td>3</td>
<td>72 72</td>
</tr>
<tr>
<td>Wong <em>et al.</em>(^56)</td>
<td>R: 10 mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>58</td>
<td>7</td>
<td>88 91</td>
</tr>
</tbody>
</table>

To date there are no published data on *H. pylori* eradication with 10-day double dose
triple therapy with rabeprazole, amoxicillin and clarithromycin.
3.4 Quadruple Therapy

This regimen has the highest cure rate but it is also the most complicated one with the highest number of pills per day. Patients receiving quadruple therapy also experience many side effects.

The combination of four different agents for eradication of *H. pylori* has been used in two different ways: as primary therapy or as a second line therapy when triple therapy fails to eradicate the organism - mainly due to resistance.

Quadruple therapy consisting mainly of metronidazole, tetracycline omeprazole and bismuth subcitrate; has been given to patients for 7 days as a as a first-line combination for *H. pylori* infections. The eradication rates recorded 2.5 months after the end of therapy were in the order of 90.2% ITT and 95.7% PP. However we cannot assert that this therapy is better than triple therapy, head to head trials comparing both regimen are needed.

Many studies on quadruple therapy for patients with persistent *H. pylori* infection following triple therapy failure were performed. However there is neither a "miracle cocktail", nor an optimal duration of therapy for this indication. The most commonly prescribed antibiotics are metronidazole and tetracycline. In the United States, the extension on such treatments for 2 weeks is the preferred approach.

A study performed by Georgopoulos *et al.* consisted of administering two different quadruple regimens to patients who had failed traditional OAC triple therapy. A total of 46 patients received omeprazole 20 mg bid, bismuth 120 mg qid, metronidazole 500 mg bid and tetracycline 500 mg qid for 7 days. Results of this therapy yielded 83.7% by ITT and 89.1% by PP analysis. Shifting from tetracycline to clarithromycin 500 mg bid yielded eradication rates of 58.7% by ITT and 64.3% by PP analysis. These rates were lower than that obtained with tetracycline perhaps
because the patient was colonized with *H. pylori* strains that were resistant to clarithromycin—which is a possible reason to explain the failure of the triple therapy in the first place.

However the gold standard of quadruple therapy—which is FDA approved—is to give the following medication for 14 days: Metronidazole 500 mg tid, tetracycline 500 mg qid, bismuth subsalicylate 525 mg qid and a proton pump inhibitor.

The major side effects of quadruple therapy are fatigue, taste disturbance and metallic taste, loose stools and diarrhea, epigastric pain, nausea, vomiting, bloating and asthenia.

A summary of some studies involving quadruple regimen is displayed in Table 12.

---


<table>
<thead>
<tr>
<th>Author</th>
<th>PPI</th>
<th>Antibiotics</th>
<th>N=</th>
<th>Duration of therapy (days)</th>
<th>Eradication Rates %</th>
<th>ITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvet <em>et al.</em></td>
<td>O: 20 mg bid</td>
<td>B: 120 mg tid M: 500 mg tid T: 500 mg tid</td>
<td>115</td>
<td>7</td>
<td>90.2</td>
<td>95.7</td>
<td></td>
</tr>
<tr>
<td>Georgopoulos <em>et al.</em></td>
<td>O: 20 mg bid</td>
<td>B: 120 mg qid M: 500 mg bid T: 500 mg qid</td>
<td>46</td>
<td>7</td>
<td>83.7</td>
<td>89.1</td>
<td></td>
</tr>
<tr>
<td>Georgopoulos <em>et al.</em></td>
<td>O: 20 mg bid</td>
<td>B: 120 mg qid M: 500 mg bid C: 500 mg qid</td>
<td>42</td>
<td>7</td>
<td>58.7</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td>Borody <em>et al.</em></td>
<td>O: 20 mg bid</td>
<td>CBS: 108 mg qid T: 250 mg qid M: 200 mg qid</td>
<td>125</td>
<td>12</td>
<td>97.6</td>
<td>97.6</td>
<td></td>
</tr>
<tr>
<td>Graham <em>et al.</em></td>
<td>O: 20 mg qd</td>
<td>BSS: 525 mg qid M: 500 mg qid T: 500 mg qid</td>
<td>26</td>
<td>14</td>
<td>92.3</td>
<td>92.3</td>
<td></td>
</tr>
</tbody>
</table>
4 Future Trends and Vaccination

4.1 Future Trends

Many questions remain uncertainly answered regarding *Helicobacter pylori*, and well-designed clinical trials are still needed to target many issues:

1. The exact mechanism by which *H. pylori* is acquired is still somewhat controversial.

2. Studies targeting the pediatric population concerning mechanism of transmission and consequences of the infection in childhood.

3. Studies assessing the impact of *H. pylori* eradication in progression and regression of atrophic gastritis and gastric adenoma. Even though studies are suggesting that early gastric MALT-Lymphomas can go into complete histological and endoscopic remission after eradication of *Helicobacter pylori*.

4. Direct comparative trials of drug regimens are needed, and new therapies should be tested against FDA approved regimens.

5. Emphasis should be placed on prevention and treatment vaccination strategies that may be the key to control *H. pylori* infection worldwide. Therefore, vaccine development should have the highest research priority.

6. Finding the ideal time and age range when the vaccine should be administered.
4.2 Vaccination

The increasing interest in the development of vaccination methods against *Helicobacter pylori* is due to many factors:

- Despite all new advances in diagnostic and therapeutic modalities regarding *H. pylori* identification and treatment, still more than 50% of the worldwide population is infected with the bacteria, which includes all the direct and indirect costs and complications of such a high incidence of the disease.

- Current therapies, even though more than 85% successful, are associated with many problems that can affect eradication rate. First, most treatment regimens require the ingestion of multiple agents several times a day which might lead to decreased compliance, and they are associated with many potentially bothersome side-effects (i.e., nausea, diarrhea, abdominal pain, colitis...). Moreover, *H. pylori* eradication therapies are expensive, especially in developing countries where the infection is endemic, added that the widespread treatment of *H. pylori* could result in the development of antibiotic resistant strains. Furthermore, it is important to mention that *H. pylori* cure does not protect from subsequent infection that is relatively rare but possible. Finally, pharmaceutical therapies do not address the particular need of non symptomatic individuals who are at risk of developing gastric adenocarcinoma caused in part by *H. pylori* infection.

Two types of vaccines are potentially possible (Table 13):

1) Prophylactic vaccine
2) Therapeutic vaccine, which eliminates an existing infection and secures long-lasting immunity.

**Table 13:** Approaches to the development of an *H. pylori* vaccine.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live attenuated</td>
<td>&quot;Complete&quot; immunity</td>
<td>Wild strains do not lead to clearance or immunity</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficult to grow</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-resistance to human antigens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety concerns</td>
<td></td>
</tr>
<tr>
<td>Recombinant live vectors (altered bacteria or viruses that express <em>H. pylori</em> antigens)</td>
<td>Adjuvant possibly not needed</td>
<td>Anti-vector immunity</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Simplify vaccine administration</td>
<td>? Poor immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Recombinant urease</td>
<td>Urease is an important immunologic target</td>
<td>Requires adjuvant multiple-dose schedule</td>
<td>Phase 1/II trials</td>
</tr>
<tr>
<td></td>
<td>in natural resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acid stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Little antigenic variation between strains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other subunit antigens</td>
<td>—</td>
<td>As yet poorly characterized</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be difficult to produce at scale</td>
<td></td>
</tr>
</tbody>
</table>

Studying the *H. pylori* vaccine has now been facilitated by the development of several animal models that have allowed for the safety and efficacy of vaccination against *H. pylori* to be determined.

Animal studies on prophylactic and therapeutic vaccines where encouraging, but human studies did not yet show a success in *H. pylori* vaccination, however, a trend towards improving vaccines formulations and safer delivery system may promise encouraging results.
Trials are also conducted to determine the optimal route of administration of the investigational vaccine. Many studies showed that the oral route is the preferred one, but alternative routes like rectal or intranasal vaccination were also proposed\textsuperscript{73}. Recently, systemic immunizations are considered, and intraperitoneal or subcutaneous injections of antigen are also under investigation.
5 Safety and Efficacy of a Ten Day
Helicobacter pylori Eradication Regimen with
Rabeprazole, Amoxicillin and Clarithromycin

5.1 Introduction

It is widely accepted that most peptic ulcers are associated with H. pylori infections leading to chronic gastritis\textsuperscript{74}. Furthermore, strong evidence suggests its association with adenocarcinoma of the stomach and MALT- lymphoma\textsuperscript{75}. The eradication of this organism leads to enhanced ulcer healing and reduces the chance of ulcer recurrences. Usual eradication regimens consist of a combination of antibiotics and anti-secretory agents. Many of these eradicating therapies require that the patients ingest a large number of pills at very frequent intervals over a period of at least 7 days, making compliance and tolerability difficult\textsuperscript{76}. In addition, antibiotic resistance is an emerging problem and has to be taken into account when choosing a regimen\textsuperscript{77}. Also, the selection of the acid reducing agent plays an important role in the extent of eradication efficacy\textsuperscript{76,78}. The optimal duration of treatment is still unknown. Most European studies favor therapies of 7 days or less, whereas most US-based studies favor longer duration mainly 10 to 14 days\textsuperscript{76}. To date, there are no reports on double dose ten day triple therapy with rabeprazole, amoxicillin and clarithromycin. The purpose of this study is to investigate the efficacy and safety of a 10 day rabeprazole-based triple therapy for H. pylori eradication in the Lebanese population.
5.2 Material and Methods

The study was conducted at the endoscopy unit of the American University of Beirut Medical Center (AUB-MC) from January to September 2002. Oral informed consent was obtained from all the patients before being enrolled in the study.

5.2.1 Study design

All outpatients with dyspepsia referred for outpatient and having a positive rapid urease assay (CLO test®, Ballard medical products, Draper, Utah, USA or Pronto Dry®, Medical Instruments Corp, Brignais, France) and/or a positive histology for H. pylori infection, were enrolled in this open label prospective study. Exclusion criteria were the following: Children under the age of 18; patients with esophageal, gastric, or definitive acid-lowering surgery; pyloric stenosis; gastric cancer; gastric diseases such as hypersecretory syndromes; liver diseases and end stage renal failure, treatment with therapeutic doses of antireflux medications or regular treatment with nonsteroidal anti-inflammatory (NSAID) drugs (within 2 weeks of enrollment), a past history of poor compliance to medications; allergy to rabeprazole, amoxicillin or clarithromycin; previous H. pylori eradication therapy, pregnancy or lactation and finally travel during time enrolled in study. We excluded patients who traveled during the time enrolled in the study because they were unable to return for the follow up test. NSAID and other PPI use were not allowed during the time of the study. Enrolled patients were interviewed and counseled regarding appropriate medication use to ensure better compliance. Phone calls evaluated compliance and potential side effects. After a minimum of four weeks following completion of therapy, patients underwent a ¹⁴C-urea breath test (UBT) in order to evaluate for eradication of H.
*pylori*. This four-week period between treatment and UBT testing is used to eliminate false negative results whereby *H. pylori* may not be detected due to suppression of growth rather than successful eradication. Patients were instructed to discontinue any PPI therapy a minimum of two weeks prior to UBT testing. Patients who had a compelling indication for the endoscopy (grade C/D esophagitis or deep ulcers) repeated the endoscopy.

### 5.2.2 Endoscopy:

Endoscopy was performed with a forwarding viewing videoscope and antral biopsies were taken. The specimen was subjected to a rapid urease test (RUT) or was sent to the lab for microscopic viewing (histology). A negative RUT was defined as the absence of color change after 24 hours. The rapid urease test has a sensitivity of $\sim 89.6\%$ and a specificity of $\sim 99\%$ to detect *H. pylori* infections whereas histology has a sensitivity of $93.1\%$ and a specificity of $\sim 99\%$.

### 5.2.3 Protocol:

The medications were dispensed in pill boxes to avoid any errors in compliance. Instructions on how to take the medication was attached at the back of each box. Each box was filled with the following: rabeprazole (Pariet®, 20 mg tablets, Janssen-Cilag), 20mg bid, clarithromycin (Klacid®, 250 mg tablets Abbott, Italy) 500 mg bid, amoxicillin (Amoximex®, 1000mg tablets, Cimex, Switzerland) 1 g bid for 10 days. Patients were instructed to take the rabeprazole tablet 30 minutes before eating; the two antibiotics were to be taken with meals.
If the patient still complained of dyspeptic symptoms, then rabeprazole 20 mg daily was given for 4 weeks. Eradication was defined as successful if urea breath test or histology failed to demonstrate *H. pylori* infection a minimum of 6 weeks after discontinuation of the study medication or 2 weeks after discontinuation of the proton pump inhibitor.

### 5.2.4 Urea Breath Test:

A Carbon 14 Urea Breath Test (UBT) was performed a minimum of 6 weeks after the end of therapy or 2 weeks after discontinuation of the proton pump inhibitor to document eradication of infection. A urea breath test value below the cut off value of 1.5 was considered a negative UBT meaning that eradication was successful.\(^{81}\)

### 5.2.5 Follow Up:

Recruited patients were followed up by phone calls on days 3, 7 and 10 of therapy and after 6 weeks to check for compliance and for the occurrence of side effects. A reminder phone call was done to schedule the urea breath test, time at which patients were asked about the occurrence of dyspeptic symptoms. If the patients did not return for the UBT or histology they would be contacted by phone. If they refused to come back, they were questioned over the phone about occurrence of dyspeptic symptoms and were excluded from the per protocol analysis.
5.2.6 Study Endpoints:

Endpoints of the study included an efficacy endpoint which checked for eradication rate per $^{14}C$ UBT at 6 weeks post treatment, and a safety endpoint which checked for the occurrence of side effects.

5.2.7 Statistical Analysis:

The endpoints were analyzed using intention-to-treat analysis (ITT) and per-protocol analysis (PP). Per-protocol analysis included those patients who had consumed at least 80% of the study medications (~6 days). Intention-to-treat analysis included those patients who took all of the study medication had completed follow up and had undergone the last endoscopy or urea breath test to confirm eradication.

5.3 Results

5.3.1 Patients:

During the specified study period, 104 patients were identified of which 52 were males and 52 were females with a mean age of 51.6±16.5 years (Table 14). The tables below summarize the patient characteristics at entry as well as the cause of their dyspepsia.
**Table 14:** Patient demographics. RUT: rapid urease test.

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>104</td>
</tr>
<tr>
<td>Female/Male</td>
<td>52 (50)</td>
</tr>
<tr>
<td>Male</td>
<td>52 (50)</td>
</tr>
<tr>
<td>Mean Age ± SD (years)</td>
<td>51.59 ±16.49</td>
</tr>
<tr>
<td>Age Range</td>
<td>16-88</td>
</tr>
<tr>
<td>RUT Positive</td>
<td>75</td>
</tr>
<tr>
<td>Histology Positive</td>
<td>38</td>
</tr>
<tr>
<td>Smoker</td>
<td>35 (33.6)</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>24 (23.1)</td>
</tr>
</tbody>
</table>

**Table 15:** Patient characteristics. Note that some patients might have more than one pathology at the same time.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers Gastric/Duodenal</td>
<td>9/26</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>34</td>
</tr>
<tr>
<td>Grade A</td>
<td>20</td>
</tr>
<tr>
<td>Grade B</td>
<td>6</td>
</tr>
<tr>
<td>Grade C</td>
<td>4</td>
</tr>
<tr>
<td>Grade D</td>
<td>1</td>
</tr>
<tr>
<td>Not Specified</td>
<td>3</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>13</td>
</tr>
<tr>
<td>Gastritis</td>
<td>65</td>
</tr>
</tbody>
</table>

No patient withdrew due to adverse effects. All patients completed therapy; seven patients were excluded from the final per protocol analysis (Table 16).
Table 16: Reasons for exclusion from final analysis.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled Subjects</td>
<td>104</td>
</tr>
<tr>
<td>Drop-outs</td>
<td></td>
</tr>
<tr>
<td>- Non Compliant</td>
<td>2</td>
</tr>
<tr>
<td>- Trial Drug not finished</td>
<td>2</td>
</tr>
<tr>
<td>- Lost to follow-up</td>
<td>3</td>
</tr>
<tr>
<td>Completed Study</td>
<td>97</td>
</tr>
</tbody>
</table>

104 patients enrolled

7 patients excluded

97 completed study

89 UBT

- 5 UBT positive
- 84 UBT negative

8 Pathology

1 Pathology positive

7 Pathology negative

Figure 15: Algorithm of Study. UBT: Urea Breath Test.

5.3.2 Efficacy endpoint:

*H. pylori* was eradicated in 91 out of 97 patients per protocol 93.8% and in 91 out of 104 patients yielding an intention to treat eradication rate of 87.5%
5.3.3 Safety endpoint:

All patients finished the prescribed therapy, although some of them reported mild to moderate side effects. The most common of which would be a bitter taste attributed to the study drug clarithromycin. Other reported side effects were fatigue, diarrhea and abdominal cramps (Table 17).

**Table 17:** Side effects reported during therapy.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter Taste</td>
<td>25 (24.0)</td>
</tr>
<tr>
<td>Fatigue/Somnolence</td>
<td>13 (12.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (8.6)</td>
</tr>
<tr>
<td>Abdominal Pain/Cramps</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2.9)</td>
</tr>
</tbody>
</table>
5.4 Discussion

Current standards for eradication are mainly based on the use of triple therapy which consists of 1 PPI and 2 antibiotics (mainly amoxicillin, clarithromycin, or metronidazole). Triple therapies combining a proton pump inhibitor and two antibiotics are the standard treatment for *H. pylori* infection today.

There is a big controversy regarding length of the triple therapy, currently the United States favor treatments of 10 to 14 days but many European trials have used shorter regimen varying from 3 to 7 days 

<table>
<thead>
<tr>
<th>Author</th>
<th>PPI</th>
<th>Antibiotics</th>
<th>N=</th>
<th>Duration of therapy (days)</th>
<th>Eradication Rates %</th>
<th>ITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgopoulos et al.</td>
<td>O: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>80</td>
<td>10</td>
<td>88.8</td>
<td>88.8</td>
<td></td>
</tr>
<tr>
<td>Isomoto et al.</td>
<td>R: 10mg bid</td>
<td>A: 750g bid C: 400mg bid</td>
<td>70</td>
<td>5</td>
<td>66</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Laine et al.</td>
<td>O: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>50</td>
<td>10</td>
<td>90</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Luth et al.</td>
<td>R: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>20</td>
<td>4</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Miwa et al.</td>
<td>R: 10 mg bid</td>
<td>A: 500 mg tid C: 200 mg bid</td>
<td>100</td>
<td>7</td>
<td>87</td>
<td>89.7</td>
<td></td>
</tr>
<tr>
<td>Wong et al.</td>
<td>R: 20mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>58</td>
<td>3</td>
<td>72</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Wong et al.</td>
<td>R: 10 mg bid</td>
<td>A: 1g bid C: 500mg bid</td>
<td>58</td>
<td>7</td>
<td>88</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

*Table 18: Triple therapy for *H. pylori* eradication. A: amoxicillin, C: clarithromycin, O: omeprazole, R: rabeprazole.*

Rabeprazole is a highly potent, long acting inhibitor of gastric acid secretions and has a more rapid onset of action than other PPIs available on the market. It has a higher pka than other PPIs (rabeprazole pka=5 versus pka ranging from 3 to 4 for the other agents) allowing it to be protonated to the active sulphenamide form over a wider pH
range, hence activation will occur faster and patients will be relieved faster than with other PPIs\(^{68}\). To date, there are no reports on 10 day rabeprazole triple therapy for \textit{H. pylori} eradication.

Possible limitations of the study could be that it was an uncontrolled open label trial, where patients were followed up by phone calls and the side effects reported were patient subjective thus opening the door for interpatient variability. Strict follow-up in the study design might have improved compliance.

### 5.5 Cost Analysis

The total cost of the rabeprazole-based therapy (rabeprazole+ amoxicillin+ clarithromycin) provided sums up to 174,200LL. Switching from an omeprazole-based therapy to a rabeprazole-based therapy results in a 20% cost reduction. On the other hand, the rabeprazole therapy was more expensive than a pantoprazole therapy (Table 19).

**Table 19:** Comparative cost with different proton pump inhibitors. PPI: Proton Pump Inhibitor.

<table>
<thead>
<tr>
<th>PPI</th>
<th>Cost (LL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabeprazole (Pariet(^{®}))</td>
<td>174,200</td>
</tr>
<tr>
<td>Omeprazole (Gastrimut(^{®}))</td>
<td>155,170</td>
</tr>
<tr>
<td>Omeprazole (Losec(^{®}))</td>
<td>217,048</td>
</tr>
<tr>
<td>Lansoprazole (Lanzor(^{®}))</td>
<td>194,192</td>
</tr>
<tr>
<td>Pantoprazole (Inipomp(^{®}))</td>
<td>95,364</td>
</tr>
</tbody>
</table>
Recommendations

Rabeprazole 20 mg bid, amoxicillin 1g bid and clarithromycin 500mg bid for 10
days is a safe and effective regimen for eradication of \textit{Helicobacter pylori} infection.
It provides a 93.8\% efficacy rate and minimal adverse effects.
Appendix A: Patient Instructions

The following is a copy of the instructions attached to the back of the pill boxes handed to each individual patient:

- **Amoximex® 1g**
  تناول الحبة البيضاء مع الاكل صباحا و مساء

- **Pariet® 20 mg**
  تناول الحبة الصغيرة نصف ساعة قبل الاكل صباحا و مساء

- **Klacid® 250 mg**
  تناول الحبタン الصفر اوتان مع الاكل صباحا و مساء
Appendix B: Patient Questionnaire and follow-up sheet
AMERICAN UNIVERSITY OF BEIRUT-MEDICAL CENTER
INTERNAL MEDICINE DPT, GASTRO-ENTEROLOGY DIVISION

Name:                      Date: 
Age:                      Sex: 
Weight:                   Height: 
Cell Phone:               Home Phone:

Chief Complaint & Brief History of Present illness: (specify Severity & Duration)

Diagnosis: (Specify site of disease)

Tests used for Diagnosis: (Circle test used)
  - Clo Test
  - Pathology

Social History:
  - Smoker   Y   N
  - Alcohol  Y   N
  - Married: Y   N
  - Possible present or near future pregnancy or lactation: Y   N
  - Work occupation:

Past Medical History:
  - Renal diseases Y   N
  - Liver diseases Y   N
  - Surgeries: Y   N (Exclude if esophageal, gastric or acid-lowering surgery)
  - Allergies Y   N
  - Arthritis Y   N
  - Infections Y   N
  - Active Cancer: Y   N
  - Previous H. pylori eradication therapy: Y   N
  - OTHERS:
Past Medication History:

- NSAIDs

- Anti-ulcer/reflux meds: (If Yes Specify):
  Last dose taken:
  (Exclude or Delay tx if taken for > 5 days within 1 week prior to enrollment)

- Antibiotics:
  Last dose taken:
  (Exclude or Delay tx if taken within 1 month prior to enrollment)

- OTHERS:

Past compliance:  POOR    GOOD    VERY GOOD    Unknown
Follow-up Data Sheet

Date of Start of Therapy:

Call 1:
Date:
Compliance:

<table>
<thead>
<tr>
<th>Side effects</th>
<th></th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Onset</td>
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<td>Duration</td>
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<tr>
<td>Frequency</td>
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<tr>
<td>Intensity</td>
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<tr>
<td>Action Taken</td>
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</tr>
<tr>
<td>Outcome</td>
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</tbody>
</table>

Other Pertinent info:

Call 2:
Date:
Compliance:

<table>
<thead>
<tr>
<th>Side effects</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Onset</td>
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<td></td>
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<tr>
<td>Duration</td>
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<td></td>
</tr>
<tr>
<td>Frequency</td>
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<td></td>
</tr>
<tr>
<td>Intensity</td>
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<td></td>
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<tr>
<td>Action Taken</td>
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<td></td>
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<tr>
<td>Outcome</td>
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</tbody>
</table>

Other Pertinent info:
Date of End of Therapy:

Call 3 (End of Therapy):
Date:
Compliance:

<table>
<thead>
<tr>
<th>Side effects</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
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<tr>
<td>Duration</td>
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<td></td>
</tr>
<tr>
<td>Frequency</td>
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</tr>
<tr>
<td>Intensity</td>
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<tr>
<td>Action Taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
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</tr>
</tbody>
</table>

Other Pertinent info:

Did patient take any PPI post-therapy:    Y  N
If Yes, Specify Type of PPI, Dose and Duration of intake:

Expected Date of UBT:

Actual Date of UBT:

UBT Value:

Result:
REFERENCES


