



**Universitat de Girona**

FACULTY OF MEDICINE

**FINAL DEGREE PROJECT**

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**TARGETED vs. STANDARD TREATMENT AGAINST**  
*Helicobacter pylori*  
**Safety Assessment Clinical Trial**

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## TABLE OF CONTENTS

1. ABBREVIATIONS .....	3
2. ABSTRACT.....	4
3. BACKGROUND AND JUSTIFICATION.....	5
4. HYPOTHESIS .....	15
4.1. MAIN HIPOTHESIS .....	15
4.2. SECONDARY HIPOTHESIS.....	15
5. OBJECTIVES .....	15
5.1. MAIN OBJECTIVE .....	15
5.2. SECONDARY OBJECTIVE .....	15
6. METHODS.....	16
6.1. STUDY DESIGN.....	16
6.2. POPULATION .....	16
6.2.1. WITHDRAWAL CRITERIA.....	16
6.2.2. INCLUSION CRITERIA .....	17
6.2.3. EXCLUSION CRITERIA .....	17
6.3. SAMPLE SIZE.....	17
6.4. SAMPLE RECRUITMENT.....	18
6.5. STUDY STAFF .....	19
6.6. INTERVENTIONS .....	19
6.6.1. RANDOMIZATION .....	19
6.6.2. DEGREE OF BLINDING.....	20
6.7. VARIABLES.....	20
6.7.1. INDEPENDENT VARIABLE.....	20
6.7.2. DEPENDENT VARIABLE .....	20
6.7.3. COVARIATES .....	21
6.8. INDEPENDENT VARIABLE MEASUREMENTS .....	22
6.8.1. FIRST GROUP - EMPIRICAL TREATMENT.....	23
6.8.2. SECOND GROUP - TARGETED TREATMENT .....	24
6.9. DEPENDENT VARIABLES MEASUREMENTS .....	26
6.9.1. EVALUATION OF THE ADVERSE EVENTS (Assessment of Safety) .....	26
6.9.2. EVALUATION OF THE ERADICATION OF THE BACTERIA (Assessment of Efficacy) .....	29
6.9.3. EVALUATION OF THE CLARITHROMYCIN RESISTANCE .....	29
6.10. DATA COLLECTION .....	30

7. STATISTICAL ANALYSIS .....	31
7.1. MAIN OBJECTIVE ANALYSIS.....	31
7.2. SECONDARY OBJECTIVE ANALYSIS .....	32
8. ADVERSE EVENTS .....	32
8.1. AMOXICILLIN .....	32
8.2. CLARITHROMYCIN .....	33
8.3. LEVOFLOXACIN.....	34
8.4. ESOMEPRAZOLE .....	36
8.5. METRONIDAZOLE .....	37
8.6. BISMUTH SUBCITRATE .....	38
8.7. TETRACYCLINE .....	38
9. ETHICAL ASPECTS .....	40
10. STUDY LIMITATIONS .....	41
11. WORK PLAN .....	42
12. AVAILABLE MEANS TO CARRY OUT THE STUDY.....	43
13. BUDGET .....	44
14. REFERENCES.....	45
15. ANNEXES .....	48
15.1. EXPLANATION FOR THE PATIENT/ INFORMED CONSENT OF THE STUDY.....	48
15.2. INFORMED CONSENT OF THE ENDOSCOPY .....	52
15.3. INTERACTIONS AND CONTRAINDICATIONS OF DRUGS .....	54
15.3.1. AMOXICILLIN .....	54
15.3.2. CLARITHROMYCIN .....	54
15.3.3. LEVOFLOXACIN .....	55
15.3.4. ESOMEPRAZOLE .....	56
15.3.5. METRONIDAZOLE .....	56
15.3.6. BISMUTH SUBCITRATE.....	56
15.3.7. TETRACYCLINE .....	57
15.4. SURVEY.....	59
15.5. FLOWCHART MAIN VARIABLES MEASUREMENTS .....	61
15.6. TIMELINE .....	62

# 1. ABBREVIATIONS

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**AEMPS:** Agencia Española de Medicamentos y Productos Sanitarios.

**AF:** Alkaline phosphatase.

**ALT:** Alanine aminotransferase.

**AST:** Aspartate aminotransferase.

**BQT:** Bismuth quadruple therapy.

**Cag A:** Cytotoxin associated A antigen.

**<sup>13</sup>C:** Carbon 13.

**EMC:** Electronic Medicine Compendium.

**eCRF:** Electronic Case Report Form.

**GGT:** Gamma-glutamyl transpeptidase.

***Helicobacter pylori:*** *H. pylori*.

**HLA:** Human leukocyte antigen.

**HUDJT:** Hospital Universitari Dr. Josep Trueta.

**IL-8:** Interleukin-8.

**LTT:** Levofloxacin triple therapy.

**MALT:** Mucosa-associated lymphoid tissue.

**MedRA:** Medical Dictionary for Regulatory Activities.

**NDAID:** Non-steroidal anti-inflammatory drugs.

**PCR:** Polymerase chain reaction.

**PPI:** Proton pump inhibitor.

**ST:** Sequential therapy.

**STT:** Standard triple therapy.

**TNF:** Tumoral necrosis factor.

**Vac A:** Vacuolating cytotoxin A.

## 2. ABSTRACT

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*Helicobacter pylori* (*H. pylori*) is a gram negative bacteria that represents a considerable global burden in the world and is related to many gastrointestinal diseases (peptic ulcer, gastric MALT lymphoma or gastric cancer). Currently the triple standard therapy is less used as there is an increase of the clarithromycin resistance. Therefore patients have to receive several lines of treatment with the consequence of adverse events and the possibility to interrupt the treatment. This is why the main objective is to determine if making a culture and antibiogram to do a targeted treatment cause less adverse events with the same eradication than making an empirical treatment to eradicate *H. pylori*. The secondary objective is to determine the prevalence of resistance to clarithromycin in the province of Girona.

This is a multicentre clinical trial without blinding; patients are selected by non-probabilistic sampling, with a total sample of 868 patients randomized in two equal groups of 434 patients in each group. The study will last 2 years. The endpoints will be to evaluate the adverse events and eradication of each group of patients. Also it will be evaluated the resistance to clarithromycin.

**Key words:** *H. pylori*, targeted treatment, standard lines of treatment, adverse events, eradication, clarithromycin resistance and controlled clinical trial.

### 3. BACKGROUND AND JUSTIFICATION

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*Helicobacter pylori* is a gram negative spiral-shaped bacteria with prominent flagellums that allows it to penetrate in the thick mucous layer of the stomach, in order to proliferate where the pH is higher (1,2). As a protecting mechanism against the acid pH in the stomach, the bacteria has an urease positive activity (3). The urease is an enzyme that converts the urea in the gastric juice into alkaline ammonia and carbon dioxide (2), therefore *H. pylori* can survive in the acid atmosphere by creating a protective zone. As the bacteria colonizes the stomach mucosa, it creates an inflammatory reaction that causes cellular damage (1).

This infection affects approximately 50% of the world's population (4). However, the prevalence varies throughout the world, depending on the living conditions and status, as in the developing parts of the world may reach 80%, whereas the prevalence in the industrialized countries is about 20-50% (1,3,5). The prevalence of the *H. pylori* infection in Europe varies depending on the zone. In the Northern countries there is lower incidence of the infection than in the Southern and Eastern countries (6). In Spain, the infection rates range from 40% to 60%. And concretely in Girona, the prevalence was 56% of the population studied in a Primary Care Centre (the study was of 480 patients) (7).

The bacteria is acquired during the childhood (3), and the probability to have the infection is conditioned by low socioeconomic level, immigration and poor sanitary conditions (1), as the bacteria is transmitted fecal-oral, oro-oral or gastro-oral (6).

The infection of *H. pylori* is one of the main causes of gastroduodenal pathology (1) and represents a considerable global health burden. Nevertheless, most infected patients don't develop an illness due to this microorganism (3).

There are several factors that can make *H. pylori* ends up causing the disease to which is related to. One of those factors is the bacterial virulence, as some virulence markers of the bacteria like the cytotoxin associated A antigen (Cag A) are related to a high clinical response with inflammation of the gastric mucosa producing peptic ulcer disease and gastric carcinoma (1,3). Other virulence marker as vacuolating cytotoxin A (Vac A), that is present in all of the *H. pylori*'s strains, have allelic variants (s1a and s1b of the alleles s1 and s2, and alleles m1 and m2). The strains that contain s2m2 are associated with low or none cytotoxin. However, the alleles s1/m1 of the Vac A, together with Cag A, have high potential for the secretion of cytotoxic factors like alpha-TNF (tumoral necrosis factor) and IL-8 (interleukin-8), which are associated with peptic ulceration (1,3). Others factors that also must be taken into account are the age of the host, genetic susceptibility (like blood group, type of Lewis antigen or HLA type), environmental factors (like socioeconomical conditions, tobacco or diet), and immune response (8,9).

The bacteria colonize the human gastric mucosa and causes persistent immune response, that can be both cellular, with the infiltration of the mucosa by mononuclear and polinuclear cells, or humoral, with the formation of specific antibodies (1). This response can be produced by the bacterium's lipopolysaccharide, cytotoxins and urease activity (3).

The infection of *H. pylori* takes place in the antrum and corpus of the stomach. It produces a reduction on the somatostatine-producing D cells, which are cells that normally inhibits the liberation of gastrin, so, as a result, it will conduce to an increase of the production of the stomach acid, due to an increase of gastrin. Also it produces an increase of pH of the stomach because produces ammonia by the action of urease (10,11).

The predominance of the antral colonization, and its relation to an increase of gastric acid, can cause a surface gastritis that in some patients may remain stable or can progress to a

peptic ulceration in few years (8,9,12). Despite the fact that only a 10% - 20% of the infected patients will develop an ulcer during their lives, more that 80% of duodenal ulcers and more than 60% of gastric ulcers are associated with *H. Pylori* and, after *H. pylori* eradication, the ulcer heals (9).

Furthermore, the colonization of the bacteria is associated with active chronic gastritis or type B gastritis (1). As a consequence, some patients may later on develop a multifocal atrophic gastritis that can lead to an intestinal metaplasia which can finally cause a gastric cancer (1,9,11). Thus, it's known that *H. pylori* is one of the precursors of gastric cancer. Patients who are infected by *H. pylori* have between three and six times more risk to develop a gastric cancer than patients who are uninfected (11). Also, a 70% of patients with a gastric cancer are positive for *H. Pylori* (9). It is an important aspect because gastric cancer is the third cause of cancer death in the world as it represents almost three quarters of million deaths each year in the world population (11).

Moreover, *H. pylori's* infection is also associated with the gastric MALT (mucosa-associated lymphoid tissue) lymphoma. Concretely the Cag A protein of the bacteria is causally linked with this condition (4). Almost 90% of those patients are positive for the bacteria, and after its eradication most cases regress (9), thus the first line treatment in those patients is the eradication of *H. pylori* (4).

Therefore, *H. pylori* infection is related with two of the most important diseases in gastroenterology; the gastric cancer and the peptide ulcer disease, so it represents an important global burden on mortality, morbidity and health-care costs (3).



Aside from all the gastrointestinal diseases, an association between *H. pylori* and extra-digestive disorders as idiopathic thrombocytopenic purpura, vitamin B<sub>12</sub> deficiency and iron deficiency anaemia has been discovered (12).

In order to avoid all this pathologies, a careful investigation of the *H. pylori* infection must be performed. Current investigations are divided in the non-invasive techniques, and the invasive techniques, depending on the need of endoscopy (13). The different types of methods are illustrated in the table 1.

Table 1. Techniques used in the diagnosis for *Helicobacter pylori*.

	Sensibility	Specificity
<b>Non-invasive Techniques:</b>		
- <sup>13</sup> C Carbon urease breath test	90-96%	98-99%
- Venous serology	86-94%	78-95%
- Fecal antigens	89-92%	78-91%
<b>Invasive Techniques:</b>		
- Histology	93-96%	98-99%
- Culture of the biopsy	80-98%	100%
- The rapid urease test in the biopsy	88-95%	95-100%
- PCR (polymerase chain reaction)	100%	100%

*Adapted from; Helicobacter pylori: detección, tratamiento y valoración de la erradicación (13).*

The most used techniques are the <sup>13</sup>C urease breath tests (non-invasive), and the rapid urease test in the biopsy (invasive). Furthermore, the non-invasive one is generally used to verify the eradication of the *H. Pylori* after the treatment. It is carried out after six weeks from the end of the treatment (14).

Once the infection is detected, it is important to know when the infection needs to be treated or not. According to the *Spanish Consensus of the indications of treatment in the H. pylori infection* (15), the indications approved for the treatment of the bacteria are illustrated in the table 2.

Table 2. Indications for the treatment in *H. pylori*.

- Peptic ulcer,
- Non-investigated dyspepsia in patients < 50 years old without alarm signs or symptoms (with test and treat strategy),
- Functional dyspepsia,
- Patients with history of ulcer that have to be treated with NSAID during a large period,
- Low grade MALT lymphoma,
- Surgical resection of gastric cancer,
- First grade familiar of patients with gastric cancer,
- Gastric mucosa atrophy or intestinal metaplasia,
- Iron deficiency anaemia,
- Idiopathic thrombocytopenia purpure,
- Vitamin B<sub>12</sub> deficiency without an explicable cause,
- All patients with a positive diagnostic for *H. pylori*.

*Adapted from; III Spanish Consensus Conference on Helicobacter pylori infection (15).*

The most commonly used treatment in the *H. pylori* infection, for the last two decades, has been the standard triple therapy (STT); consisting on a proton pump inhibitor (PPI) and a combination of two antibiotics such amoxicillin (metronidazole if patients are allergic to penicillin) and clarithromycin (16). This STT is recommended if the resistance to clarithromycin is 20% or less (17). However, nowadays, because of the increase in prevalence of the clarithromycin resistance (16), a decrease of the eradications rates to less than 80% has been detected in several countries (14).

The resistance rates seem to be growing in the latest years, in Europe are about 11.1% and there is a wide difference between the north and the south of Europe (less than 10% and more than 20% of clarithromycin resistance respectively). Concretely in Spain, a study

carried out by *Molina-Infante, J. et al.* (18) founded that the clarithromycin resistance rate was nearly 20%.

So it is important to know the resistance rate in each country, as the prevalence of antibiotic resistance to *H. pylori* varies depending on the geography (19). It is relevant to focus the attention in Girona in order to evaluate if the resistance rates have increased and if it is convenient to change the first line of treatment in this region.

The antibiotic resistance can be primary or secondary depending on the innate resistance (primary) and the resistance acquired in the previously failed treatments with the same antibiotic (secondary) (20). The resistance to clarithromycin is due to mutations in three nucleotide positions which are A2143G, A2142G and A2142C in the peptidyl transferase loop of the gene 23S rRNA (19), which modifies the configuration of the ribosome and makes the drug unviable to *H. pylori* (21).

The resistance to clarithromycin is the main cause of treatment failure. However, there are other causes of, such as the compliance, type of strains, high bacterial load or high gastric acidity (12). The failure of the treatment implies the patient to be submitted to another line of treatment, with the consequence of the major risk to present adverse events and have a less quality of life.

Recently, *The European Maastricht IV / Florence Consensus Reports* dictated that the standard triple therapy isn't recommended anymore as an empirical use (12), suggesting to implant the empirical treatment in the population where clarithromycin resistance is below 20% and in the other cases make a culture and targeted treatment or use the new strategies treatment (16).

So, other strategies have been proposed in the first line of treatment, such as the sequential therapy (ST) that consists on administrating a proton pump inhibitor and amoxicillin during 5 days following by a PPI, clarithromycin and metronidazole for 5 days more. The ST can also last 14 days (14). In this study carried out by *Jyh-Ming Liou et al.* (14), this therapy seemed to be less affected to clarithromycin resistances than the STT, and also demonstrated that the efficacy of the eradication was higher in the ST (during 14 days) than the STT (during 14 days); as the results were eradication rate of 87.0% in the ST and eradication rate of 82.3% in the STT.

However it has been detected that the clarithromycin resistance affects in the efficacies on both treatments, and therefore it is needed to change the main antibiotic in those therapies (14). For this reason, the problem of being submitted to more than one type of treatment and to have the possibility to present adverse events it isn't solved.

The study carried out by *Jyh-Ming Liou et al.* (14) suggested that in patients who have failed the STT or ST, a substitution of the clarithromycin by levofloxacin was effective. Indeed, the second line treatment with levofloxacin triple therapy (LTT) is approved in Spain when there is a failure of the STT due to clarithromycin resistances (15).

Another potentially first line treatment is the bismuth quadruple therapy (BQT) (bismuth, tetracycline, PPI, metronidazole), which works independently to the resistance of clarithromycin and levofloxacin. Currently this therapy is approved to be the third line therapy for the *H. pylori* treatment in Spain, after the failure of the STT and LTT (15,16).

Despite the fact that there are lots of propositions to eradicate the *H. pylori* infection, none of them is the gold standard because the eradication rates vary depending on the antibiotic resistance. In Spain, the *III Spanish Consensus Conference on Helicobacter pylori Infection* established the guidelines for the *H. pylori* treatment that is illustrated in the table 3.

Table 3. Lines of treatment of the *H. pylori* infection.

LINE	MEDICATION	DOSE	ADMINISTRATION	DAYS
FIRST LINE	<b>Proton pump inhibitor:</b> ▪ Esomeprazole	40mg every 12 hours	Orally	During 10 days
	<b>Two antibiotics:</b> ▪ Clarithromycin	500mg every 12 hours	Orally	
	▪ Amoxicillin	1g every 12 hours	Orally	
SECOND LINE	<b>Proton pump inhibitor:</b> ▪ Esomeprazole	40mg every 12 hours	Orally	During 10 days
	<b>Two antibiotics:</b> ▪ Levofloxacin	500mg every 12 hours	Orally	
	▪ Amoxicillin	1g every 12 hours	Orally	
THIRD LINE	<b>Proton pump inhibitor:</b> ▪ Esomeprazole	40mg every 12 hours	Orally	During 10 days
	<b>Bismuth subcitrate</b>	120 mg every 6h	Orally	
	<b>Two antibiotics:</b> ▪ Tetracycline	500mg every 6 hours	Orally	
	▪ Metronidazole	500mg every 8 hours	Orally	

*Adapted from the III Spanish Consensus Conference on Helicobacter pylori Infection. (15).*

However, there is still a problem to solve about the eradication of the bacteria due to an increasing of clarithromycin resistance (the first line treatment). Thus, it is important to find out the correct line of treatment, otherwise patients may be submitted to lots of treatments and consequently to its adverse events that can lead to a minor quality of live and a poor adherence to the treatment. For this reason, as the empirical pharmacological treatments seems to don't work at the perfection, in this study we propose to do a culture – guided

treatment in one group of patients in order to compare the results in terms of adverse events against the group of patients that are treated by the empirical treatment.

Even though, in other bacterial infections, making a culture of the bacteria is a common step in their treatment, this is not the case of the *H. pylori* infection as the patient has to be submitted to an endoscopy (16). Nevertheless, if the patient has to be submitted to an endoscopy anyway, for an upper gastrointestinal disease related to *H. pylori*, it would be convenient to take biopsies to do the rapid urease test (clotest) and culture with antibiogram in order to determine the antibiotic resistance. Therefore, the patient could receive a targeted treatment depending on those results and avoid all the adverse events that can appear when performing several lines of treatment.

The *III Spanish Consensus Conference on Helicobacter pylori Infection* (15) suggests that in front of a failure of the second line of treatment, it should be convenient to realize a culture and targeted treatment, however emphasizing that its clinical utility have not been enough proved yet. Therefore it encourage to perform, in any specialized centres where there is the possibility to carry out an endoscopy, a culture-guided treatment. *Yuan Wemzhen et al.* (20) carried out a meta-analysis to compare the culture – guided triple therapy with the STT. They concluded that patients with STT had eradication rates of 75% versus the 90% of eradication rates achieved by the culture-guided therapy.

What reported above may justify the aim of the study which is to carry out the culture before the first line of treatment (in one of the patients' group) in order to avoid all the lines therapies and the adverse events. As the resistance to clarithromycin depends on the geographic region, it is also aimed of knowing the resistance rates in the province of Girona.

Therefore it will be done a culture-guided treatment to one group of patients in the study, and the empirical treatment in the other (STT-LTT-BQT), in order to detect the differences in adverse events in the two groups.

Despite the fact that in some studies (14,17) patients had no significant differences of adverse events between the groups of study, it is important to remark that patients in each group were treated only with one line of treatment. For instance *Malfetheiner P. et al. (17)*, carried out a study where patients have no significant differences of adverse events between the two groups of treatment which were 222 patients with STT and 216 with the BQT. However in the STT 51% of patients developed adverse events and in the BQT 47%. Although there were no significant differences, half of the patients developed adverse events for one round of treatment. Therefore, knowing that the prevalence of resistance to the first line of treatment have increased, several patients need to do more than one line of treatment, so the possibilities to increase the adverse events is also higher.

For this reason this study is aimed at verifying if making a tailored treatment based on a culture-guided treatment, causes less adverse events than implementing an empirical treatment, assuming that those patients will have to make more rounds of treatment due to the increase of the clarithromycin resistance in our setting.

## 4. HYPOTHESIS

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### 4.1. MAIN HIPOTHESIS

If we make a culture and targeted treatment in patients who have been diagnosed from *H. pylori* with a positive *clotest*, rather than giving them an empirical treatment, we will obtain less adverse events and better eradication rates.

### 4.2. SECONDARY HIPOTHESIS

The prevalence of resistance to clarithromycin in the province of Girona is in the range of 20%.

## 5. OBJECTIVES

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### 5.1. MAIN OBJECTIVE

To determine if making a culture and antibiogram to do a targeted treatment cause less appearance and severity of adverse events, with better eradication rates, than making an empirical treatment to eradicate *H. pylori*. It will be carried out in patients over eighteen years old submitted to a gastroendoscopy for any upper gastrointestinal symptom related to *H. pylori* and finally diagnosed from *H. pylori* by a positive *clotest*.

### 5.2. SECONDARY OBJECTIVE

Determine the prevalence of resistance to clarithromycin in the province of Girona, in patients over eighteen years old that have been submitted to an endoscopy for signs or symptoms related to *H. pylori* and their biopsies are submitted to a culture and antibiogram.



## 6. METHODS

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### 6.1. STUDY DESIGN

It will be a prospective, multicentre, without blinding, and randomized in a 1:1 ratio clinical trial. It is designed to evaluate the adverse events and eradication of empirical treatment and culture-guided treatment for *H. pylori* infection. The resistance to clarithromycin will be also evaluated.

### 6.2. POPULATION

This is a multicentre study. Its directed to patients over eighteen years old at the participant hospitals, that have to be submitted to an endoscopy and biopsies, for symptoms from the upper gastrointestinal tract, related or not to the symptoms and signs *H. pylori* can give.

#### 6.2.1. WITHDRAWAL CRITERIA

Patients can drop out the study; however, they have to communicate it to the responsible doctor. As it is a study on the adverse events according to the therapy, it is very important that any patient with serious adverse events or one that persists during several days, contact with the doctor prior to the decision to abandon the study. The study can stop if there is an incompliment of the law "*Ley del Medicamento*" or there is an incompliment of the ethical principles in the "*Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos*". Also, the patient will leave the study if becomes pregnant.

### 6.2.2. INCLUSION CRITERIA

- Patients over eighteen years old presenting one of the following symptoms and signs that have to be submitted to an endoscopy or are being under an endoscopy.
  - Symptoms: dyspepsia, heartburn, nausea, sense of fullness and abdominal swelling.
  - Signs (when during a gastroendoscopy is observed one of the following): chronic gastritis, peptic or duodenal ulcer and bleeding.
- Are self-sufficient or under a controlled environment in order to comply the treatment.
- Have signed the informed consent of the study and endoscopy (annex 15.1, 15.2).

### 6.2.3. EXCLUSION CRITERIA

- Have already been submitted to treatment against *H. pylori*.
- Used clarithromycin for the treatment of any other infection, especially pulmonary.
- During the last two months have ingested inhibitors of proton pump or any antibiotics.
- Have contraindications to the medication that is used in the study (annex 15.3).
- Assume medication that can produce interactions with the drugs used in the study (annex 15.3).
- Pregnant and breastfeeding women (annex 15.3).
- Aren't born in the province of Girona (developing countries have more prevalence of the infection) (1).
- Significant liver dysfunction.

## 6.3. SAMPLE SIZE

It will be performed using the GRANMO application. An alpha risk of 0.05 and a beta risk of 0.2 will be assumed. It will be a two side test. The group one and two will be formed by 434 patients each in order to achieve a related risk of 1,2 . It is assumed that the ratio between

the exposed and unexposed patients is 1, and the rate among unexposed patients is 51%. A drop-out rate of 10% is also estimated.

- **Multicentricity:** In order to achieve the whole sample of our study it is necessary to organize a multicentre study. The participant Hospitals will be the Hospital Universitari Dr. Josep Trueta (HUDJT) and three more which belong to the province of Girona, having a digestive endoscopy department and a laboratory for microbiological analysis. To establish the best communication we will name a director of the trial and an investigator doctor in each centre to supervise the study staff.

#### **6.4. SAMPLE RECRUITMENT**

A consecutive non-probability sampling will be used. The sample recruitment will be assessed at the HUDJT and the other participating hospitals. A total sample of 868 patients is needed. As in the HUDJT nearly sixty positive *clotest* each month are diagnosed, and taking into account that it's a multicentre study, it is estimated that the patient's recruitment will last 12 months. This method consists on selecting patients who meet the inclusion criteria when they are under a medical visit and are proposed to be submitted to an endoscopy to check their illness degree, or that during the performance of the endoscopy for any other illness they met the inclusion criteria (signs) for this study. Those patients will have been reported previously to the endoscopy and will have signed the informed consent.

The doctor will explain the patients in what the study consists of, so they can refuse or accept it. If they accept to participate in the study, they will have to sign the informed consent.

## 6.5. STUDY STAFF

- Laboratory technician: in charge to do the culture and antibiogram. A laboratory technician will operate in each of the participant hospitals for four hours a week during 18 months.
- Microbiologist Doctor: in charge to interpret the results of the culture and antibiogram and introduce them in the clinical trial database. There will be a microbiologist doctor in each of the participant hospitals for two hours a week during 18 months.
- Investigator Doctor: in charge to coordinate and guarantee the best quality of the study staff in each centre. He will also carry out the patient's recruitment and the data collection. Moreover, he will be coordinate with the Director of the study.
- Statistician: his participation is aimed at doing the statistical analysis of the collected data.
- Director of the study: is the coordinator of the participant hospitals in the study and will be in close contact with the investigator doctors of each centre.
- External supervisor: to control that the process is correctly performed. He will control the process every six months.

## 6.6. INTERVENTIONS

### 6.6.1. RANDOMIZATION

Patients will be randomized once they met the inclusion criteria, have signed the informed consent and have the result of a positive clotest of the gastric biopsy. The randomization will be carried out taking into account the influencing covariates in order to balance the artefacts they can produce. Patients will be randomly assigned at a 1:1 ratio between empirical treatment groups and culture-guided treatment group. The assignments will be

delivered inside an opaque envelope. An identification number to each patient will be assigned.

### **6.6.2. DEGREE OF BLINDING**

It will be a clinical trial without blinding. The patient will know if he/she is in the group of empirical treatment or in the group of the targeted treatment as the second one begins the treatment 10 days later. The doctor performing the randomization and data collection won't know which patients have to be submitted to an empirical treatment and which ones will be under the culture and targeted treatment.

## **6.7. VARIABLES**

### **6.7.1. INDEPENDENT VARIABLE**

The main independent variable is a qualitative nominal variable as it's related to the study of the differences between the empirical standard treatment of *H. pylori* and targeted treatment depending on the culture and the antibiogram.

The secondary independent variable is to perform the antibiogram in the patients submitted to a culture in order to determine the prevalence of resistance to clarithromycin.

### **6.7.2. DEPENDENT VARIABLE**

The main outcome variable is a qualitative nominal variable as is aimed at determining the adverse events of the medication used in the two groups of patients. The presence of adverse event will be evaluated as a qualitative nominal variable and the severity of the adverse events as a qualitative ordinal variable. The eradication of the bacteria as a qualitative nominal variable will be also evaluated.

The secondary outcome variable is to determine the prevalence of the resistances to clarithromycin in the group of patients that are submitted to the culture and antibiogram.

### 6.7.3. COVARIATES

- Age; it is a quantitative discrete variables and will be studied in years.
- Sex; it is a qualitative nominal variable and will be studied as man or woman.
- Socioeconomic status; it is a qualitative ordinal variables and will be evaluated using low, moderate and high socioeconomic status by asking the patient the kind of work (stable - temporal or hasn't any work).
- Treatment adherence: it is a qualitative nominal variable and will be evaluated by asking to the patient in the survey if he/she has followed the treatment (yes/no).
- Comorbidities;
  - Obesity; will be collected using the body mass index (BMI):
$$BMI = \frac{Weight (kg)}{(Height (m))^2}$$
It is a continuous quantitative variable. The weight will be collected with the patient without shoes and with a non-digital balance. The height will be collected also without shoes and will be measured in meters.
  - Smoking: it is a qualitative nominal variable and will be fixed in YES or NO.

The covariables sex, age and treatment adherence will be collected by the survey delivered to patients to fill it. By contrast, the socioeconomic status and the comorbidities will be collected by the doctor belonging to the study staff when he gives to the patient the prescription for the treatment.

## 6.8. INDEPENDENT VARIABLE MESUREMENTS

All patients in the study will be under an esophagogastroendoscopy carried out in the participating hospitals. The patient will have signed previously the informed consent of the test and the study. The endoscopy will be performed with a standard gastroscope (Olympus), and the endoscopy will deepen until the duodenum. All biopsies must be taken with a Boston biopsy clamp 2,8mm width. It would be appropriate to take biopsy in different places of the stomach in case of evident changes, apart from the biopsies that are required for the study.

All patients will be subjected to six biopsies, three of the antrum and three of the corpus of the stomach. From them, one biopsy of the antrum and one of the corpus will be used to perform the urease test (*clotest*) (9). This test can be executed directly with the biopsy obtained by the endoscopy and doesn't need any special procedures. It is only needed to put the biopsy in a *clotest* solution and wait for the result. The test will be positive if a change of colour from orange-yellow to pink is observed in the solution, which will indicate the presence of the enzymes' bacteria. The result can appear from one hour to 24 hours from the realization of the test. If it's positive during the time that the patient is in the controlling area after the endoscopy will be advised there, but if the *clotest* isn't positive during this time, the patient will be contacted by phone (collected in the informed consent of the study). Nonetheless all patients have to come to a medical visit in order to receive the prescription of the medication.

The other four biopsies will be saved in a pot with 0,5 ml of saline serum 0,8% (viable until six hours) and transported to the microbiological laboratory as quickly as possible. In case of a negative *clotest*, all the remaining biopsies will be dismissed.

When there is a positive result of the *clotest*, the randomization in the two groups will be performed.

#### **6.8.1. FIRST GROUP - EMPIRICAL TREATMENT**

They will receive the first line of treatment against *H. pylori* (15) which is the STT consisting on the combination of one PPI (esomeprazole 40mg every 12 hours) and two antibiotics (amoxicillin; 1g every 12 hours and clarithromycin; 500 mg every 12 hours) all taken orally and during ten days.

After six weeks of treatment they will be submitted to a urease breath test in order to evaluate the eradication of the bacteria. To perform that, the patient will go to the participant hospitals with 6 hours of fasting and ingest a solution (100mg) with urea isotopically marked with  $^{13}\text{C}$  (non - reactive); the breath is then collected 30 minutes later (a basal breath sample will be previously analysed). The test will be analysed in the laboratory of each participant hospital by means of the continuous flow / mass spectrometry technique. Results will be obtained by the relation of basal respiration and after the ingestion of 100 mg of  $^{13}\text{C}$ -urea.

If the urease breath test is positive it will be necessary to change to the second line treatment (15) which is LTT: PPI (esomeprazole 40 mg every 12 hours) and two antibiotics; amoxicillin (1g every 12 hours) and levofloxacin (500 mg every 12 hours) all taken orally and during 10 days. The patients will be subjected to another urease breath test after six weeks from this treatment in order to check again the eradication.

Furthermore, if a patient has another positive breath test he will have to receive the third line treatment (15) consisting on the BQT: Bismuth subcitrate 120 mg every 6 hours;



tetracycline 500 mg every 6 hours, PPI (esomeprazole 40 mg every 12 hours) and metronidazole 500 mg every 8 hours, all taken orally and during 10 days. Those patients will also come back after six weeks from the treatment for a further breath test. If the breath test is still positive, they will receive another endoscopy for a culture (according to the ordinary steps followed nowadays in the HUDJT).

### **6.8.2. SECOND GROUP - TARGETED TREATMENT**

The biopsies collected from patients of the second group will be submitted to culture and antibiogram, and depending on the results, a targeted treatment will be applied. The microbiological protocol of the HUDJT (22) will be followed for the specific culture and antibiogram to detect *H. pylori*.

#### **▪ CULTURE:**

In order to perform the culture and antibiogram the biopsies have to be placed in the sterile tub with 0.5 ml of 0, 8% saline serum (remains viable until 6 hours), and must be conserved in the refrigerator at 4°C while the sample is not processed (9,22). When the sample arrives to the laboratory a technician will first grind the content of the tub using a test tube and glass stirring rod, then he will place the fragments in a *Helicobacter plate* (PYL agar pylori Biomérieux). Prior to the inoculation, the plates should remain at room temperature, and 15 minutes before the inoculation it is recommended to put them in the oven at 37°C.

Alongside, in the case to dispose of a lot material, a part of the sample will be deposited in a glass microscopy slide and a Gram stain will be performed in order to observe under the optical microscopy if there is the presence of the gram negative bacillus.

The bacteria has to be incubated in plates of microaerophilia [obtained by AUXOMAT (AUX-65)] under a water saturated environment (35°C to 37°C) during 7 days. It is convenient to examine the cultures every 24h after the third day of incubation. The suspected colonies (clear grey, small and brilliant) will be identified by the fresh vision and by making a Gram staining to see de bacillus gram negative bacteria.

▪ **ANTIBIOGRAM:**

Once the microorganisms are isolated the antibiogram will be executed by using culture medium E-test (with an agar blood plate) and using the following antibiotics; amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin (22). The inoculum concentration for the antibiogram will be of  $10^7$ - $10^8$  UFC/ml equivalent to a pattern 2 of McFarland. The inoculation with microaerophilia will last 3 days at  $35 \pm 2^\circ\text{C}$  in a no selective medium. It is suggested to extend the incubation two more days if after three days no results have been observed (22).

Finally, depending on the results of the antibiogram, the patient will receive targeted treatment. If he is sensitive to clarithromycin, he will receive the first line treatment STT (as the first group) during 10 days. However, if the antibiogram indicates that the patient is resistant to clarithromycin he will receive the second line of treatment LTT (as explained in the first group) during 10 days (15).

After six weeks of the treatment, they will be submitted to the urease breath test. In this group of patient it is estimated that the culture-guided treatment is enough to succeed results. However, if the breath test is positive, the patient will have to follow the same steps as the group 1.

## 6.9. DEPENDENT VARIABLES MEASUREMENTS

### 6.9.1. EVALUATION OF THE ADVERSE EVENTS (Assessment of Safety)

#### ▪ DEFINITION

According to a protocol clinical trial, an adverse event is the appearance or worsening conditions of any sign, symptom or undesirable clinical state that may occur after the administration of the medication of the study.

#### ▪ PROCEDURES FOR RECORDING ADVERSE EVENTS

In order to evaluate the adverse events in the treatment of *H. pylori*, a survey will be delivered to the patient independently on which group of the study he belongs, in which the common adverse events arising from the medication taken may appear (there is an example of the survey in the annex 15.4).

The survey has been performed by using the datasheet of the medication used for the study (amoxicillin, esomeprazole, clarithromycin, levofloxacin, metronidazole, bismuth and tetracycline) available in the AEMPS (*Agencia Española de Medicamentos y Productos Sanitarios*) and the EMC (Electronic Medicine Compendium) which are explained in the section of adverse events (section 8). Considering the sample size of 868 patients, the frequency of intervals of  $<1/10$ ,  $<1/100$ ,  $\geq 1/100$ ,  $\geq 1/1000$  of the adverse events have been selected in order to consider the adverse events frequent and infrequent when related to the medication used in the study. The survey has been written in an understandable language for the patient.

If the study were finally carried out, it would be convenient to codify the adverse events in a homologated form like MedRA (Medical Dictionary for Regulatory Activities).

The survey will be delivered to both groups of patients:

- Group 1: the survey will be delivered once they receive the prescription of the treatment in the medical visit after the positive result of the *clotest*.
- Group 2: will receive the survey during the medical visit when there are the results of the antibiogram and can start to assume the targeted treatment.

All patients have to answer to the questions exposed during the days of the treatment at home, have to answer “YES” or “NO” to the questions that are exposed in the survey. Also they will have to record the duration of each adverse event (in days) and whether they needed treatment or not.

When the patient comes to the Hospital to perform the urease breath test, if the breath test result is positive, he will receive another exactly survey to fill it during the second treatment. Patients have to deliver the adverse events’ survey when they come to the medical visit for the results of the Breath test. It could be that some patients needed to complete more than one survey (up to three), thus is very important that patients deliver each filled survey in each medical visit. As patients have had to answer to “YES” or “NO”, if one patient has filled more than one survey it will be counted the numbers of YES and NO of the adverse events in totally.

▪ **CAUSALITY OF THE ADVERSE EVENT**

According to a protocol of clinical trial, the degree of certainty with which an adverse event is attributed to an alternative cause will be determined by how well the event can be understood in terms of: Known pharmacology of the studied drugs, clinically and / or plausible context supported by the temporal relationship or similar reaction previously observed with similar products.

Is in the medical visit for the results of the breath test, where the doctor will also report the causality by asking to the patient if the adverse event that have suffered is related to any illness that he/she has; if he/she has previously suffered this event or if the adverse event is related to the medication intake. If there isn't causality, the adverse event won't be taken into account. If there is causality, the adverse event will be considered a real adverse event.

▪ **SEVERITY OF ADVERSE EVENT**

It will be assessed by the investigator by asking the patient the intensity of the adverse event he suffered (mild, medium, severe, and serious). This information will be recorded as the following manner and analysed:

- **Mild:** transient adverse event that only require minimal treatment and doesn't interfere in the usual activities of daily living.
- **Moderate:** adverse event that is alleviated with additional specific therapeutic intervention (primary medical attention, or emergency service attention, complementary tests as blood test or imaging tests). Interferes with usual activities of daily living, but no significant or permanent risk of harm to the participant.
- **Severe:** adverse event that interrupts usual activities of daily living, causes significantly affects to clinical status and require intensive therapeutic intervention.
- **Serious:** an adverse event that causes the death or is life threatening.).

To avoid lacking of information, the doctor, with the previous consent of the patient, will access to his clinical history checking the existence of any further attentions. This values of the blood test will be considered as an adverse event: ALT (> 40 U/L), AST (>36 U/L), AF (>104 U/L), GGT (>50 U/L), Total bilirubin (> 1.2 mg/100ml), amylasemia (>205 U/L),

leukopenia (< 3800/mmc), thrombocytopenia (<130 million/mmc), eosinophilia (>6.0%), creatinine in blood (> 1.3 mg/100ml), and blood urea nitrogen (> 20 mg/dl).

### 6.9.2. EVALUATION OF THE ERADICATION OF THE BACTERIA (Assessment of Efficacy)

In order to evaluate the eradication of the bacteria in each group of patients it will be performed a breath test after six weeks of treatment. The results are obtained making an index between the basal breath values and the marked urea breath values. The presence of the bacteria will be annotated as YES (cured) or NO (no cured) depending on the results of the breath test. If the breath test is positive (index >3,5) it will be annotated as a NO and if the breath test is negative (index lower than 2,0) it will be annotated as YES. It is very important to evaluate the eradication in the first line treatment of the two groups in order to see if the culture guided treatment is really more effective that the empirical treatment.

### 6.9.3. EVALUATION OF THE CLARITHROMYCIN RESISTANCE

The secondary outcome variable is to determine the prevalence of the resistances to clarithromycin in the group of patients that are submitted to the culture and antibiogram. The results of the antibiogram will be expressed as minimum inhibitory concentration (MIC) of each antibiotic which are detailed in the table 4.

Table 4. Sensitivity and Resistance of Antibiotics

Antibiotic	E-test sensitivity	E-test: resistant
Amoxicillin	< 0,2 µg/ml	> 0,12 µg/ml
Clarithromycin	≤ 0,25 µg/ml	≥ 1 µg/ml
Metronidazole	≤ 8µg/ml	≥ 8 µg/ml
Tetracycline	≤ 1 µg/ml	≥ 2µg/ml
Levofloxacin	≤ 1 µg/ml	≥2 µg/ml

*Available in Protocol Laboratori Clínic ICS Girona. Hospital Univeristari Dr. Josep Trueta (22)*

Clarithromycin resistance is defined as a minimum inhibitory concentration (MIC) of  $1.00\mu\text{g/ml}$  or greater, intermediate resistance is defined as  $0.25\mu\text{g/ml}$  to less than  $1.00\mu\text{g/ml}$ , and sensitivity is defined as less than  $0.25\mu\text{g/ml}$ .

So when the antibiogram in those patients is assessed, the laboratory facultative will record the results of the clarithromycin resistance. Each antibiogram will be analyzed and the microbiologist doctor will have to write down the results in a data base consisting on two groups; the group of "YES" (which mean that are resistant to clarithromycin) and the group of "NO" (which means that aren't resistant to clarithromycin). Finally the results will be analyzed.

There is a flowchart in the annex 15.5 to better understand the circuit of the patients in the study measurements.

## **6.10. DATA COLLECTION**

Data will be collected from the database of the patients in the participating hospital of the study, who are introduced in a trial database. The information will be collected; during the trial entry and randomization, during the collection data of the surveys (presence of adverse events and severity), during the recollection of the covariables, during the evaluation of the eradication of the treatment, during the collection of the results of the antibiogram once it is confirmed the resistance to clarithromycin in the group two.

The main investigators of each participant hospital will send the obtained information to the main director of the study, then he will organize it to be analysed by the statistician. When a sample of 100 patients is achieved, a pilot plan will be performed with the obtained data

until then, in order to be sure that the survey, the staff and the methods are well designed. It will be also analysed how the organized circuits works.

## 7. STATISTICAL ANALYSIS

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### 7.1. MAIN OBJECTIVE ANALYSIS

In the main objective the variables are qualitative nominal, as we want to study the adverse events (YES/NO) and the eradication of the *Hr pylori* (YES/NO) after the *clotest* in the two groups of patients. The univariate analysis will be described in table of frequencies in order to analyse the distribution of the patients the categories (YES/NO) of each variable.

In the bivariate analysis, considering that the independent and dependant variables are qualitative nominal variables, two tables of contingence will be performed. The first one will be composed by the two groups of treatment (group 1 and group 2) and the occurrence of adverse events (YES/NO). The second one will be composed by the two groups of treatment (group 1 and group 2) and the eradication of the bacteria (YES/NO). Then will be analysed the proportions of the appearance of the variable in each group can be observed.

Once the table of contingence is performed we can compute the V of Crammer coefficient in order to determine the degree in which the dependent and independent variables are correlated. Afterwards, a Chi-square test will be used in order to verify if this obtained relation can be extrapolated.

Finally, despite the fact that the randomization of the clinical trial has been adjusted by the covariates, if there were some not contemplated covariates in the randomization, they



would be analysed using a regression logistic model (as the dependant variables are dichotomous variables) for the multivariate analysis.

Moreover, in the patients presenting adverse events, the severity of those adverse events will be analysed by classifying them in four categories as mild -1-, moderate -2-, severe -3- and serious -4-. As the severity is a qualitative ordinal variable, the results can be presented in a table of frequencies and be analysed in proportions, taking a confidence interval of 95%.

## **7.2. SECONDARY OBJECTIVE ANALYSIS**

The secondary objective, which is studying the resistance to clarithromycin, will be calculated by using the results obtained in the culture which are reported as “YES” or “NO” depending on if there is resistance or not. It will be analysed by calculating the proportion of resistances and a confidence interval of 95% will be established.

## **8. ADVERSE EVENTS**

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It is used the datasheet of the study medication of the AEMPS and the EMC. In order to determine the frequency of the adverse events it has been used: Very frequents ( $\geq 1/10$ ), Frequents ( $\geq 1/100 < 1/10$ ); infrequent ( $\geq 1/1000 < 1/100$ ); Rare ( $\geq 1/10000 < 1/1000$ ); Very rare ( $< 1/10000$ ) and unknown when cannot be estimated from the available data.

However in the study are only recorded the frequent and infrequent, due to the sample size of 868 patients.

### **8.1. AMOXICILLIN**

Obtained from the data sheet available in the AEMPS (23). The adverse events are infrequent and usually weak and transitory. Are the following ones:

- **Gastrointestinal:** Digestive intolerance as nauseas, slight and transient vomiting. Exceptionally mucocutaneous candidiasis, colitis (pseudomembranos-haemorrhagic).
- **Hypersensitivity:** Skin rashes, pruritus and urticarial. Exceptionally angioneurotic edema, anaphylaxis, serum sickness, multiform erythema, Stevens-Johnson syndrome, vasculitis, toxic epidermal necrolysis, bullous exfoliative dermatitis, interstitial nephritis.
- **Hepatic:** Moderate increasing of AST/ALT. Exceptionally hepatitis, cholestatic jaundice.
- **Hematologic:** Rarely cases of reversible leukopenia (severe neutropenia and agranulocytosis), reversible thrombocytopenia, and haemolytic anaemia. Exceptionally increase of clotting time and increase of prothrombin time.
- **Central nervous system:** Are exceptional and reversible; hyperreactivity, agitation, insomnia, confusion, behavioural changes and / or vertigo.
- **Oral candidiasis** (mouth or tongue).

## 8.2. CLARITHROMYCIN

Are obtained from the datasheet of AEMPS (24).

- **Nervous system:** frequents; headache, taste perversion, infrequent: convulsions, fainting and alteration of smell (usually along with altering flavour).
- **Ear and labyrinth:** Frequent: hearing loss (reversible with cessation of the treatment), tinnitus. Infrequent: vertigo.
- **Gastrointestinal:** Frequent: diarrheal, vomiting, nausea. Infrequent: pancreatitis, glossitis, stomatitis, abdominal pain, dyspepsia, tongue decolouration, teeth coloration (reversible with professional dental cleaning). Rare: oral candidiasis.
- **Hepatobiliary:** Infrequent: hepatic dysfunction (usually reversible), hepatitis and cholestasis (with/without jaundice), changes in tests of liver function. Rare: liver failure.

- **Skin/subcutaneous tissue:** Frequent: mild skin rashes. Infrequent: urticarial. Rare: Stevens – Johnson Syndrome, Toxic epidermal necrosis.
- **Immunologic:** Infrequent: allergic. Rare: anaphylaxis.
- **Psychiatric:** Infrequent: anxiety, insomnia, nightmares, confusion, and hallucination. Rare: disorientations, psychosis, depersonalization.
- **Blood and lymphatic:** Infrequent: leukopenia, Thrombocytopenia.
- **Metabolism–nutrition:** Rare: diminution of blood glucose levels sometimes associated with hypoglycemics or insulin.
- **Cardiac:** Rare: ventricular tachycardia, *torsades de pointes*, prolongation of QT interval.
- **Kidneys:** Rare: elevation of creatinine.
- **Musculoskeletal-connective tissue:** Unknown: Myalgia.

### 8.3. LEVOFLOXACIN

Are obtained from the datasheet of AEMPS (25).

- **Infections:** Infrequent: fungus and proliferation (*candida*) of other resident microorganisms.
- **Hematologic and lymphatic system:** Infrequent: leukopenia, eosinophilia. Rare: Thrombocytopenia, neutropenia. Unknown: Pancytopenia, haemolytic anaemia, agranulocytosis.
- **Immunologic system:** Infrequent: hypersensitivity, angioedema. Unknown: anaphylactic shock.
- **Metabolism and nutrition:** Infrequent: anorexia. Rare: Hypoglycaemia (especially in diabetic patients), Unknown: hyperglycaemia, hypoglycaemic coma.

- **Psychiatric:** Frequent: insomnia. Infrequent: anxiety, confusion, nervousness. Rare: Psychotic disorders, depression, abnormal sleep, agitation, nightmares. Unknown: Psychotic reactions with self-injury behaviour or suicide ideas.
- **Nervous system:** Frequent: headache, Dizziness. Infrequent: somnolence, tremor, dysgeusia. Rare: convulsions, paraesthesia. Unknown: Sensory or sensory motor peripheral neuropathy, including ageusia, parosmia including anosmia, dyskinesia, extrapyramidal disorder, syncope, benign intracranial hypertension.
- **Ocular:** Rare: Visual alterations (blurred vision). Unknown: transient loss of vision.
- **Ear and labyrinth:** Infrequent: vertigo. Rare: Tinnitus. Unknown: Audition loss and deficiency.
- **Cardiac:** Rare: tachycardia, palpitations. Unknown: ventricular arrhythmia, *torsades des pointes*, prolongation QT interval.
- **Vascular:** Frequent: phlebitis (only in the intravenous form). Rare: Hypotension.
- **Respiratory, thoracic and mediastinum:** Infrequent: dyspnoea. Unknown: Bronchospasm, Allergically pneumonitis.
- **Gastrointestinal:** Frequent: diarrheal, nausea, Vomiting. Infrequent: abdominal pain, dyspepsia, flatulence, constipation. Unknown: Haemorrhagic diarrhoea, that in case can indicate enterocolitis (including pseudomembranous).
- **Hepatobiliar:** Frequent: Increase of hepatic enzymes (ALT/AST, alkaline phosphatase, GGT). Infrequent: Increase of blood bilirubin. Unknown: Jaundice and severe hepatic injury (Hepatic insufficiency or fulminant acute insufficiency), Hepatitis.
- **Skin and subcutaneous:** Infrequent: exanthema, pruritus, urticarial, hyperhidrosis. Unknown: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiform, photosensitivity reaction, leukocytoclastic vasculitis, stomatitis.

- **Musculoskeletal and connective tissue:** Infrequent: arthralgia, myalgia. Rare: tendon disorders including tendinitis, muscular weakness. Unknown: rhabdomyolysis, Tendon rupture, ligament rupture, muscular rupture, arthritis.
- **Renal:** Infrequent: increase of blood creatinine. Rare: Acute renal insufficiency.
- **General disorders:** Infrequent: Asthenia. Rare: Pyrexia. Unknown: Pain (included thoracic, back and extremities).

#### 8.4. ESOMEPRAZOLE

Are obtained from the datasheet of AEMPS (26).

- **Blood and lymphatic system:** Rare: Leukopenia, thrombocytopenia. Very rare: Agranulocytosis, pancytopenia.
- **Immunologic system:** Rare: Hypersensitivity disorders (fever, angioedema, anaphylactic shock).
- **Metabolism and nutrition:** Infrequent: Peripheral edema. Rare: hyponatremia. Unknown: Hypomagnesaemia.
- **Psychiatric:** Infrequent: Insomnia. Rare: agitation, confusion, depression. Very rare: aggressively, hallucinations.
- **Central nervous system:** frequent: headache. Infrequent: dizziness, paraesthesia and somnolence. Rare: taste alteration.
- **Ocular:** Rare: blurred vision.
- **Ear and labyrinth:** Rare: vertigo.
- **Respiratory:** Rare: bronchospasm.

- **Gastrointestinal:** frequent: abdominal pain, constipation, diarrheal, flatulence, vomiting/nausea. Infrequent: mouth dryness. Rare: stomatitis, gastrointestinal candidiasis.
- **Hepatobiliar:** Infrequent: transaminase elevation. Rare: hepatitis with/without jaundice. Very: Hepatic insufficiency, encephalopathy in patient with existent hepatic disease.
- **Skin – subcutaneous tissue:** Infrequent: dermatitis, pruritus, eruption, urticarial. Very rare: multiform erythema, Steven-Johnson syndrome and toxic epidermic necrosis.
- **Musculoskeletal, bones and connective tissue:** Infrequent: Hip, wrist, spine fracture. Rare: arthralgia, myalgia. Very rare: muscular weakness.
- **Renal and urinary:** Very rare: interstitial nephritis.
- **Mama:** Very rare: Ginecomastia.
- **General disorders:** Rare: discomfort, increased sweating

## 8.5. METRONIDAZOLE

Are obtained from the datasheet of AEMPS (27).

- **Gastrointestinal:** Epigastria pain, nausea, vomiting diarrheal, oral mucositis, taste disorders, anorexia, and exceptionally and reversible a pancreatitis.
- **Hypersensitivity:** Rash, pruritus, urticarial, fever, angioedema, and exceptionally anaphylactic shock.
- **Central nervous system:** Sensorial peripheral neuropathy, headache, convulsion, vertigo, ataxia.
- **Psychiatric:** Confusion, hallucinations.
- **Vision:** Diplopia, myopia.

- **Haematological and lymphatic system:** Very rarely cases of agranulocytosis, neutropenia and thrombocytopenia.
- **Hepatobiliar:** very rarely reversible cases of alteration of hepatic profiles and colestatic hepatitis.

## 8.6. BISMUTH SUBCITRATE

The information is available in the EMC (28).

- **Gastrointestinal disorders:** Black tongue is common, Black stool is very common.

## 8.7. TETRACYCLINE

The information is available in the EMC (29).

- **Infections and infestations:** Frequency not known: overgrowth of resistant organisms (*Candida albicans*, in particular); this may cause glossitis, stomatitis, pseudomembranous colitis (*Clostridium difficile* overgrowth), enterocolitis (caused by resistant staphylococci), rectal and vaginal irritation, inflammatory lesions (with candida overgrowth) in the anus - genital regions.
- **Blood and lymphatic system disorders:** Rare: haemolytic anaemia, thrombocytopenia, neutropenia, eosinophilia, agranulocytosis, aplastic anaemia.
- **Immune system disorders:** Frequency not known: hypersensitivity reactions including Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis, urticaria, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus, fixed drug eruptions, exfoliative dermatitis.
- **Endocrine disorders:** Frequency not known: brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur.

- **Nervous system disorders:** Frequency not known: headache.
- **Eye disorders:** Frequency not known: visual disturbances, permanent visual loss.
- **Vascular disorders:** Frequency not known: bulging fontanelles in infants; benign intracranial hypertension in juveniles and adults. Presenting features were headache, dizziness, tinnitus and visual disturbances including blurring of vision, scotoma and diplopia. Treatment should cease if evidence of raised intracranial pressure develops.
- **Gastrointestinal disorders:** Rare: dysphagia, esophagitis and oesophageal ulceration (most of these patients took medication immediately before going to bed). Frequency not known: gastrointestinal irritations, nausea, abdominal discomfort, vomiting, diarrhoea, anorexia, pancreatitis, permanent tooth discolouration and enamel hypoplasia in children. Tooth discolouration has also been recorded in adults. If gastric irritation occurs, tablets should be taken with food.
- **Hepatobiliary disorders:** Rare: transient increases in liver function tests, hepatitis, jaundice, hepatic failure. Frequency not known: hepatotoxicity associated with fatty liver.
- **Skin and subcutaneous tissue disorders:** Frequency not known: erythematous and maculo-papular rashes, photosensitivity (Patients exposed to direct sunlight or ultraviolet light should be advised to discontinue treatment if any skin reaction occurs), pruritis, bullous dermatoses, skin discolouration.
- **Musculoskeletal, connective tissue and bone disorders:** Frequency not known: increased muscle weakness in patients with myasthenia gravis.
- **Renal and urinary disorders:** Rare: acute renal failure, nephritis. Frequency not known: raised serum urea, renal dysfunction, especially in patients with pre-existing renal impairment.



## 9. ETHICAL ASPECTS

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This clinical trial will be initiated only after receiving the approval by the IEC (Independent Ethic Committee). This study will be conducted with the fulfilment of the protocol, in accordance with Good Clinical Practice (GCP) and in conformity with the most recent version of the Declaration of Helsinki. This study must be submitted to the authorization of the Regulatory and Local Health Authorities in accordance with existing laws and regulations (*“Ley 29/2006, de 26 de Julio, de garantías y uso racional de los medicamentos y productos sanitarios”, and “Real Decreto: 223/2004 ensayo clínico de 6 de febrero”*).

Before the start of the study, the patient information sheet will be provided to the patients, and the Informed Consent will be signed by them (both the one of the study and the one of the endoscopy and biopsies). Patients will be informed on the aim, methods, anticipated benefits, and potential hazards of the study. Also will be explained to them that they are free to refuse and to withdraw from the study at any time without prejudice to future treatment. The endoscopy and the biopsies that are required for the study will be obtained in accordance with the *“Ley 14/2007, de 3 de Julio, de investigación biomédica, título II; investigaciones que implican procedimientos invasivos en seres humanos”*.

Personal patient data (personal identity and all personal medical information will be maintained in privacy), data collection and processing for the purposes of this study should be managed with precautions to ensure the confidentiality of those data, and in accordance with *“Ley Orgánica 15/1999, 13 Diciembre, Protección de Datos de Carácter Personal”*. The permission of the patient must be asked previously to the entry in his clinical history. Patients will not be identified by their names, but by their unique identification numbers. In

any presentation of the results of this study at meetings or in publications, the patient identities will remain confidential.

Information regarding compensation, insurance, and indemnity is addressed in the insurance policy.

An eCRF (electronic Case Report Form) will be used to record all patient data specified by this protocol. The eCRF must be completed, designated and trained by the study personnel.

Likewise it will be signed by doctor the responsible of the study.

## 10. STUDY LIMITATIONS

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### **Microbiological limitations:**

- *H. pylori* contains urease and it creates unfavourable condition for the cultivation of the bacteria (13).
- *H. pylori* is a labile bacteria, and it has to be transported to the microbiological laboratory as soon as possible.
- The quantity of the sample (biopsies) collected may be a limitation, because the more the sample amount, the more the possibility to grow the bacteria.
- The results obtained in the antibiogram are *in vitro*, not *in vivo*.

### **Patient's limitations:**

- Patients in the second group (targeted treatment) are treated later than the ones that are in the first group (first line of treatment directly).
- Patients who don't have treatment adherence can lead to misinterpretation of results.

- It is a clinical trial without blinding as the patients know in which group of treatment they belong. However it is the most ethical way to deal with the study.

### **Survey limitations:**

- To evaluate the adverse events non-validate survey is used. In order to obtain the less possible bias it will be contemplated the clinical history of the patient.
- It won't be ethical to make a blood test every two months in participant patients, so it will be evaluated by the clinical history and asking to the patient.
- It has not been possible to get a registration into the MEdRa dictionary in order to codify the adverse events in the study to make them homologated.

## **11. WORK PLAN**

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It will be performed in five phases (the timeline is in the annex 15.6):

- 1. Coordination phase (1 month):** As it is a multicentre study, before the study begins, all the study staff (study director, investigators doctors and the microbiologist staff (technician and the facultative) of each hospital) must have and kick off meeting in order to plan the methods and the timeline of the study.
- 2. Recruitment of patients (12 months):** This phase will take place in all participating hospitals and will be carried out by the investigators doctors of each hospital.
- 3. Data collection and processing data (15 months):** It will be assessed during the process of the recruitment of the patients and during their treatment. The results will be recorded as they are obtained. The data will be controlled periodically in order to avoid errors and control the evolution of the study. A pilot plan is also foreseen as soon as results of a sample of 100 patients are obtained in order to verify the performance of

the study. It will be done by the whole team of the study. The external supervisor will control the obtained information in the hospitals.

4. **Data analysis (3 months)**: It will be performed by the doctor investigators of each centre, the director of the study and the statistical consultant. All data obtained during the data collection will be analysed.
5. **Interpretation, publication and dissemination of results (6 months)**: it will be done by the investigators doctors and the director of the study. The interpretation and the elaboration will allow to present the study and to write scientific articles.

## **12. AVAILABLE MEANS TO CARRY OUT THE STUDY**

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As it is a multicentre study, the project will take place in the HUDJT and in the other three participant hospitals. Those centres will provide the majority of the means to perform the study. However the statistic and the tools for the culture and antibiogram will be paid for the study. In order to ensure the best communication with the participant hospitals, coordination meetings will be held quarterly (four meetings for year). Also it is needed to hire an external supervisor to control the process every six months.

## 13. BUDGET

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All the planned costs are exposed in the following table:

Table 5. Planned costs for the study.

	<b>CATEGORY</b>	<b>QUANTITY</b>	<b>TIME</b>	<b>COST (€)</b>
<b>PERSONAL</b>	Statistic	1	20 hours	700
	External supervisor	1	8 hours every 6 months	875
<b>SERVICES AND DISPOSABLE MATERIAL</b>	<b>MATERIAL</b>	<b>QUANTITY</b>	<b>PRICE</b>	<b>COST (€)</b>
	Latex gloves	20 boxes	5€	100€
	Pot of saline serum	500	0,10€	50€
	<i>H. pylori</i> antibiogram	500	15€	7500
	<i>H. pylori</i> specific Culture	500	12,98€	6490
	Surveys	1756	0,10 €	176
<b>INSURANCE POLICY</b>				20000
<b>DIETS COSTS</b>	<b>ACTIVITY</b>			<b>COST (€)</b>
	Coordination Meeting			687
	Congress (Reunión anual de la AEG, Madrid)			1000
<b>PUBLICATIONS</b>	BMC Gastroenterology (open Access)			1675
<b>TOTAL AMOUNT</b>				<b>39253</b>

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## 15. ANNEXES

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### 15.1. EXPLANATION FOR THE PATIENT/ INFORMED CONSENT OF THE STUDY

#### FULL INFORMATIU PEL PACIENT

#### TERÀPIA DIRIGIDA vs. TRIPLE TERÀPIA ESTÀNDARD EN EL TRACTAMENT DE L'*Helicobacter pylori*. Assaig Clínic d'Esdeveniments Adversos

Estudi multicèntric, randomitzat en dos grups; en relació amb el tractament de l'*Helicobacter pylori*, un grup es tractarà amb la triple teràpia estàndard i el segon grup se li realitzarà un tractament dirigit dependent dels resultats del cultiu.

Benvolgut pacient,

Està invitat a participar en un estudi de recerca que compara dos tractaments en pacients en els que se'ls hi ha diagnosticat el bacteri *Helicobacter pylori*. Es vol investigar quina de les dues teràpies (teràpia estàndard o tractament dirigit per cultiu) causa menys esdeveniments adversos amb la mateixa curació. Abans que vostè decideixi si participa o no a l'estudi, es important que llegeixi el full informatiu i, si té qualsevol dubte, pregunti al doctor que està al càrrec de l'estudi.

#### **Participació voluntària:**

Ha de saber que la seva participació en l'estudi es voluntària, i que pot dir que no, canviar de decisió o retirar el consentiment informat en el moment que ho consideri oportú. Sense que això alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament.

#### **Descripció de l'estudi:**

L'objectiu de l'estudi és comprovar si realitzar un cultiu i antibiograma (als pacients en els que se li ha diagnosticat el bacteri *Helicobacter pylori* mitjançant endoscòpia) i donar un tractament dirigit segons les resistències antibiòtiques, causa menys esdeveniments adversos que la triple teràpia estàndard, que consisteix en esomeprazol, amoxicil·lina i claritromicina.

L'estudi es realitzarà durant un període de 2 anys.

Grups de Tractament: Hi haurà dos grups de tractament, disposats aleatòriament un cop hagin acceptat participar en l'estudi i tinguin un "clotest" positiu.

- Grup 1: es tractaran amb la triple teràpia estàndard.
- Grup 2: se li cultivaran les biòpsies obtingudes i es realitzarà un antibiograma per tal de determinar a quin antibiòtic es sensible i poder-li donar un tractament dirigit.

Visites al centre de referència: Vostè haurà de tornar al centre hospitalari al cap de 2 mesos de realitzar el tractament que li ha tocat, per tal de realitzar la prova de l'alè (consisteix en ingerir un líquid marcat amb carboni 13 i bufar al cap de 30 minuts). Aquesta prova ens dirà si s'ha curat de la infecció. S'haurà de realitzar fins que surti negativa.

Com respondre l'enquesta: Cada cop que comenci un tractament se li facilitarà una enquesta en què seran avaluats els esdeveniments adversos que presenti. Vostè s'emportarà l'enquesta a casa i la omplirà durant la durada del tractament. Cada cop que es noti algun símptoma l'anotará a l'enquesta seguint el qüestionari. Si es nota algun símptoma que no està en forma de pregunta l'escriurà en l'apartat "d'altres". També haurà d'anotar la durada de l'esdeveniment advers.

Haurà de portar l'enquesta cada cop que vingui a recollir el resultat de la prova de l'alè. L'haurà de donar al metge que l'atengui i ell l'entregarà al doctor responsable de l'estudi del vostre centre.

**Interrupció de l'estudi:**

Pot deixar de participar en l'estudi quan vostè ho consideri oportú. Abans de fer-ho seria convenient que en parlés amb el doctor encarregat de l'estudi. El doctor responsable de l'estudi es Dr/a.....

Els motius de deixar l'estudi seran que; el pacient ho consideri oportú, tant per raons personals com mèdiques; el pacient pateixi esdeveniments adversos incompatibles amb la bona qualitat de vida, la pacient es quedi embarassada, no es compleixi amb la "*Ley del medicamento*" o amb els principis ètics del Reial Decret 223/2004.

**Beneficis:**

Esperem que la seva participació en l'estudi sigui beneficiosa. Esperem trobar la millor teràpia que causi els menors esdeveniments adversos als pacient fent d'entrada un cultiu per dirigir el tractament. No podem garantir que vostè no sofreixi esdeveniments adversos, però en un futur podem donar un tractament més dirigit als pacients i evitar que facin tantes tandes de tractament, i per tant, evitaríem l'exposició a molts medicaments i disminuiríem la possibilitat de tenir esdeveniments adversos.

**Riscos:**

Al ser un estudi que avalua els esdeveniments adversos es convenient que sàpiga quins esdeveniments adversos està sotmès a patir. Com que podria donar-se el cas que hagués de sotmetre's a les tres tandes d'antibiòtics, a continuació li posem la llista esdeveniments adversos que se li avaluaran. En cap cas vol dir que vostè els hagi de patir.

Esdeveniments adversos avaluats a l'enquesta facilitada als pacients: Mal de cap, mareig, insomni, malsons, somnolència, al·lucinacions, ansietat o nerviosisme, convulsió, confusió, desmai, vertigen, tremolors, pèrdua del gust, alteració olfacte, pèrdua d'audició, sorolls estranys fora de lo normal

(tinnitus), visió doble, pèrdua de la visió de lluny (miopia), pèrdua de la gana, dificultat per respirar, nàusees, vòmits, diarrea, febre, restrenyiment, color de la femta més fosca, dolor o cremor a la part alta de la panxa i/o sensació de plenitud, gasos, mal de panxa alt irradiat en forma de cinturó a l'esquena, coloració groguenca de la pell i/o dels ulls, erupcions cutànies ("sarpullido"), períodes d'al·lèrgia, urticària o picors a la pell, picors vaginals, taques blanques a la boca i picor de boca, sequedat de boca, inflamació de la llengua i/o geniva i/o llavis i/o gola, inflamació pell i mucosa dels llavis i/o ulls, decoloració de les dents, coloració negrosa de les dents, coloració negra de la llengua, augment de la sudoració, augment del cansament, acumulació de líquid a cames i/o turmells i/o peus, sensació de formigueig en alguna part del cos, dolor muscular i / o articular, descoordinació, fractura de canell, maluc o vertebral.

**Responsabilitat i assegurança:**

El promotor ha subscrit una pòlissa d'assegurança que cobreix, en els seus termes i condicions, la responsabilitat legal per danys ocasionats a les persones participants i derivats d'aquesta investigació, realitzada estrictament en conformitat tant amb el protocol científic com amb la legislació vigent.

**Confidencialitat:**

La informació mèdica i qualsevol informació obtinguda sobre vostè durant la durada de l'estudi es quedarà en confidencialitat segons la Llei Orgànica 15/1999 sobre Protecció de Dades Personals i el corresponent Reial decret 1720/2007.

Al ser un estudi que requereix proves invasives, les mostres del pacient seran destinades a experimentacions segons les condicions que requereix la llei 14/2007 de la investigació biomèdica.

**Compensació econòmica:**

La seva participació en l'estudi no li suposarà cap cost addicional.

**Consentiments informats:**

Vostè, en el cas de voler participar en l'estudi, haurà de firmar el consentiment informat de l'estudi, per tal de posar en manifest que coneix les condicions de l'estudi i les accepta. Es podrà agafar el temps necessari en pensar-s'ho i podrà parlar-ho amb qui cregui convenient.

També, al ser un estudi amb proves invasives, haurà de firmar el consentiment per realitzar-se l'endoscòpia i la presa de biòpsies amb el corresponent anàlisis amb test ràpid d'ureasa (clotest), cultiu i antibiograma.

## FORMULARI DE CONSENTIMENT INFORMAT

### TERÀPIA DIRIGIDA vs. TRIPLE TERÀPIA ESTANDARD EN EL TRACTAMENT DE

### *L'helicobacter pylori*. Assaig Clínic d'Esdeveniments Adversos

Estudi multicèntric, randomitzat en dos grups; en relació amb el tractament de *L'helicobacter pylori*, un grup es tractarà amb la triple teràpia estàndard i el segon grup se li realitzarà un tractament dirigit depenent dels resultats del cultiu.

Nom i cognoms del pacient: \_\_\_\_\_

Data de naixement: \_\_\_\_\_ Número de telèfon: \_\_\_\_\_

1. He llegit o m'han llegit el formulari informatiu sobre l'estudi. Estava escrit en un llenguatge entenedor per a mi.
2. He entès el que se'm demana de l'estudi.
3. He tingut temps per pensar que significa l'estudi per mi.
4. He parlat amb el doctor encarregat de l'estudi o el seu personal per tal de preguntar dubtes i entendre millor en què consisteix l'estudi.
5. He rebut suficient informació per entendre bé l'estudi.
6. He entès que puc abandonar l'estudi quan vulgui, tot i així haig d'informar al metge responsable.
7. Tinc consciència que el metge responsable de l'estudi es el Dr. /a..... i es a qui m'haig de referir en cas que tingui algun problema.
8. He entès que decideixi el que decideixi els meus drets legals no queden afectats.
9. He entès que puc tenir una còpia del consentiment informat i del formulari informatiu.
10. Voluntàriament, estic d'acord en participar en aquest estudi.

**Firma del pacient o representant legal:**

**Firma de l'investigador:**


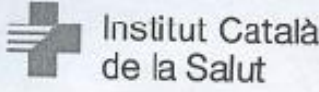
Nom: \_\_\_\_\_

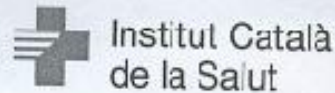
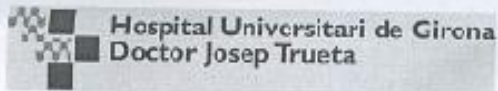
Nom: \_\_\_\_\_

Data de la signatura: \_\_\_\_\_

Data de la signatura: \_\_\_\_\_

## 15.2. INFORMED CONSENT OF THE ENDOSCOPY

															
<table border="0" style="width: 100%;"> <tr><td style="width: 40%;">Primer cognom</td><td>_____</td></tr> <tr><td>Segon cognom</td><td>_____</td></tr> <tr><td>Nom</td><td>_____</td></tr> <tr><td>Data de naixement</td><td>_____ Sexe</td></tr> <tr><td>NHC</td><td>_____ DNI</td></tr> <tr><td>CIP</td><td>_____</td></tr> <tr><td>Episodi origen</td><td>_____</td></tr> </table>		Primer cognom	_____	Segon cognom	_____	Nom	_____	Data de naixement	_____ Sexe	NHC	_____ DNI	CIP	_____	Episodi origen	_____
Primer cognom	_____														
Segon cognom	_____														
Nom	_____														
Data de naixement	_____ Sexe														
NHC	_____ DNI														
CIP	_____														
Episodi origen	_____														
<h3>Consentiment informat</h3>															
<table border="0" style="width: 100%;"> <tr> <td style="width: 50%;">Cognoms i nom de la persona responsable quan el pacient sigui menor o incapac de donar el seu consentiment</td> <td style="width: 20%;">DNI*</td> <td style="width: 30%;">Relació amb el/la pacient*</td> </tr> </table>		Cognoms i nom de la persona responsable quan el pacient sigui menor o incapac de donar el seu consentiment	DNI*	Relació amb el/la pacient*											
Cognoms i nom de la persona responsable quan el pacient sigui menor o incapac de donar el seu consentiment	DNI*	Relació amb el/la pacient*													
<h4>Nom del procediment</h4> <p>Esofagogastroscòpia</p>															
<h4>Descripció del procediment</h4> <p>L'endoscòpia digestiva alta (gastroscòpia) és un examen de la mucosa de l'esòfag, l'estómac i el duodé (primer bucell). Per a realitzar-la s'ha d'introduir a través de la boca una sonda òptica, llarga i flexible. Si és necessari en el curs de l'exploració, s'agafaran petites mostres del teixit (biòpsia), sense causar-li dolor, per analitzar-les amb un microscopi.</p> <p>Aquest procediment pot incloure: gastroscòpia diagnòstica, gastroscòpia terapèutica: esccerosi, polipectomia, dilatació, pròtesi, banderes elàstiques, gastrostomia endoscòpica.</p> <p>Aquesta exploració es realitza sota sedació moderada - profunda per endoscòpia digestiva diagnòstica o terapèutica.</p>															
<h4>Riscos generals</h4> <p>Qualsevol exploració, tractament o intervenció quirúrgica presenta uns riscos generals. El més greu és la possibilitat d'una parada cardíaca. Altres complicacions són les hemorràgies i les infeccions. En cas d'urgència vital, caldrà actuar sobre aquestes complicacions amb els mitjans oportuns per al bé del pacient, dels quals s'informarà (sempre que les circumstàncies ho permetin) el malalt o la persona que en sigui responsable.</p>															
<h4>Riscos específics d'aquest procediment</h4> <p>Gastroscòpia:</p> <ul style="list-style-type: none"> <li>Perforació</li> <li>Hemorràgia</li> <li>Infecció</li> <li>Gastroscopia diagnòstica 0,01-0,1 %</li> <li>Gastroscopia terapèutica 0,1-1%</li> </ul> <p>Sedació:</p> <ul style="list-style-type: none"> <li>Hipoxaturació d'oxigen - 0,43% (&lt;80%)</li> <li>Bradicàrdia - 0,2 %</li> <li>Broncoaspiracions - 0,03%</li> <li>Laringoespasme - 0,03%</li> <li>Convulsions - 0,035</li> <li>Trànsports neurogènics - 0,0002%</li> <li>Complicacions totals - 0,3%</li> </ul>															
Data impressió	16.10.2014	Hora impressió	10:22:00	Pàgina 1 de 2											



Primer cognom [redacted]  
Segon cognom [redacted]  
Nom [redacted]  
Data de naixement [redacted] Sexe [redacted]  
NHC [redacted] DNI [redacted]  
CIP [redacted]  
Episodi origen [redacted]

## Consentiment informat

### Riscs personalitzats

Atesa la meua situació clínica i les meves circumstàncies personals, els meus riscos, que m'han explicat i he entès perfectament, poden dur a alguna complicació durant el procediment.

Si així fos, dono el meu consentiment per què es modifiqui el procediment previst i es pugui resoldre el meu problema.

### Possibles alternatives

### Suggerències del malalt

### Autorització

He rebut la suficient informació verbal i/o escrita i he llegit el ful informatiu sobre l'exploració, sedació, tractament i/o intervenció quirúrgica que em realitzaran.

He pogut fer preguntes sobre aquest procediment.

Puc canviar d'opinió en qualsevol moment, abans de la realització del procediment, si així ho crec convenient.

He comprès la informació que m'ha estat donada, i per això conscientment autoritzo que es porti a terme el procediment.

Aquest consentiment es formula d'acord amb el que estableix la Llei 21/2000 de 29 de desembre publicada en el DOGC núm. 3303 de l'11 de gener de 2001.

Servei	Cognoms i nom del metge que informa	Número de col·legiat
GASTROENTEROLOGIA- AF	[redacted]	[redacted]

Signatura del/la pacient o responsable	Data	Signatura del metge que informa
--	------	---------------------------------

- Accepta
- No accepta

## 15.3. INTERACTIONS AND CONTRAINDICATIONS OF DRUGS

### 15.3.1. AMOXICILLIN

The information is adapted from the AEMPS (23).

**CONTRAINDICATIONS:** The only explicit contraindication is allergy to penicillin.

**INTERACTIONS:**

- It can't be associated with allopurinol as it can increase significantly the possibility of skin rash, especially in hiperuricemic patients.
- It can't be associated with bacteriostatic antibiotics (chloramphenicol, tetracycline, erythromycins or sulfamide) as those medications can antagonize its therapeutic action.
- Probenecib decrease the tubular secretion of penicillin leading to a prolongation of the serum concentration of amoxicillin.
- Amoxicillin can reduce the efficacy of the oral contraceptives.

### 15.3.2. CLARITHROMYCIN

All the information is adapted from the AEMPS (24).

**CONTRAINDICATIONS:**

- Hipersensitivity to clarithromycin or other macrolide antibiotic.
- It is contraindicated to administrate clarithromycin concomitant with cisparina, pomozida, terfenadina, disopiramida and quinidine,
- Don't administrate clarithromycin in patients with hypopotasemia (it causes a prolongation of the QT interval)
- Don't administrate in patients with severe hepatic insufficiency combined with renal insufficiency.
- Don't administrate in patients with congenital prolongation of QT interval.

**INTERACTIONS:** According to the AEMPS; "*Clarithromycin is a potent inhibitor of the isoenzyme 3A4 of cytochrome P450 (CYP 3<sup>a</sup>4), so it can increase the plasmatic levels of the medications that are metabolized by this pathway*" (24). Therefore, there are some precautions that we must take;

Medication that couldn't be used while treatment with Clarithromycin: Antiaritmics (Cisparina, Astemizol, Terfenadina, Pimodiza and quinidine, Ergotamine derivate (Ergotamine, dihidroegotamina).

Medication that should be used in precaution during the treatment with clarithromycin, which dose adjustment and close monitoring would be needed: Oral anticoagulants (warfarin), Inhibitors of HMG-CoA reductase (lovastatin, simvastatin); Antiepileptic drugs (phenytoin, carbamazepine, valproate), Immunosuppressive (cyclosporine, tacrolimus, sirolimus), Antineoplastic agents (vinca alkaloid as vinblastine). Benzodiazepines (alprazolam, midazolam, triazolam), Antifungals (fluconazole, itraconazole, ketoconazole), Antiretroviral (zidovulina), Colchicine, digoxin, eofilina, methylprednisolone, cilostazol, efavirenz, nevirapina, rifampicin, rifabutin, rifapentin, sildenafil, tadalafil, vardenafil, tolterodina, hipogluceciants or insulin,

Medication that increase the bioavailability of clarithromycin: Omeprazole, ritonavir, atazanavir, squinavir, verapamil.

### 15.3.3. LEVOFLOXACIN

All the information is adapted from the AEMPS (25).

**CONTRAINDICATIONS:** Hipersensitivity to levofloxacin, epilepsy, patients with antecedents of tendon pathologies related to fluoroquinolone, in children and teenager, during pregnancy and during breastfeeding (if it is in a perfusion solution).

#### **INTERACTIONS:**

##### Effects of other medications on levofloxacin:

- A decrease of the convulsive threshold may appear in patients that take concomitant levofloxacin and teofilina, fenbufeno or other NSAIDs.
- Probenecid and cimetidine have an effect statistically significant on the elimination of levofloxacin as those two medications can block the renal tubular secretion of levofloxacin.
- Iron salts, zinc salts, antacids that contain magnesium or alumina, didanosina; the absorption of Levofloxacin is decreased if there is a concomitant use of this medication.
- Sucralfate; reduction of the levofloxacin biodisponibility if it is administrated concomitant with sucralfate.

##### Effects of levofloxacin in other medications:

- There is an increase of 33% of the half-life of cyclosporine when it is administrated with levofloxacin.
- Antagonists of K Vitamine (warfarine); increase of the coagulation tests (PT/INR) and/or bleeding in patients treated with both medications.



- Medications that can increase the QT interval (class IA and III antiarrhythmic, tricyclic antidepressant, macrolides, antipsychotics)

#### 15.3.4. ESOMEPRAZOLE

All the information is adaptable from the data sheet of the drug in the AEM (26).

**CONTRAINDICATIONS:** Hypersensitivity, it can't be administered with nelfinavir.

#### **INTERACTIONS:**

Effects of esomeprazole on the pharmacokinetics of other drugs: Medication with an absorption pH dependant: it can reduce the absorption of itraconazol, Ketoconazole, digoxin.

Interaction with CYP 2C19 (esomeprazole inhibits this enzyme); It isn't recommended the administration of esomeprazole with atazanavir, nelfinavir. Diazepam, citalopram, imipramine, clomipramine, phenytoin.

#### 15.3.5. METRONIDAZOLE

The information is from the data sheet from the AEMPS (27).

**CONTRAINDICATIONS:** Hipersensitivity to imidazoles or to any component of metronidazole.

**INTERACTIONS:** it can produce an interaction with; disulfiram (adverse psychotic reactions have been notified when the patients receive disulfiram with metronidazole). Alcohol (it can't be used metronidazole with any alcohol drink or medication that contains alcohol). Oral anticoagulants; warfarin (it can produce a potentiation of the anticoagulant effect), lithium, creatinin, electrolytes (metronidazole can increase the plasmatic levels of those substances), cyclosporine (there is a risk of increasing of its plasmatic concentrations), phenytoin and phenobarbital (it produce an increase of the elimination of metronidazole), 5-fluoracile (there is an increase of its toxicity due to a decrease of its clearance).

#### 15.3.6. BISMUTH SUBCITRATE

The information is from the EMC (28).

**CONTRAINDICATIONS:** It should not be used by patients hypersensitive to Aspirin or other salicylates, by patients hypersensitive to any ingredient in its formulation, and by children under 16 years age.

**INTERACTIONS:** Bismuth contains salicylates, thus it should be used with caution if receiving drugs to thin the blood (anticoagulant therapy) or oral therapy for diabetes or treatment for gout. The use of Bismuth with tetracycline antibiotics can produce a decreasing of the bioavailability due to the interaction of aluminium magnesium silicate in the formulation.

### 15.3.7. TETRACYCLINE

The information is from the EMC (29)

**CONTRAINDICATIONS:** Known hypersensitivity to any of the tetracyclines or any of the other constituents in the formulation; Chronic renal/hepatic dysfunction; renal insufficiency, particularly if severe; Systemic lupus erythematosus; Children under 12 years; Pregnancy and breastfeeding women. Concomitant use of tetracyclines and Vitamin A or retinoids has reported cases of benign cranial hypertension, therefore concurrent use should be contraindicated.

#### **INTERACTIONS:**

- Absorption of tetracycline is impaired by the concomitant administration of iron, calcium, aluminium, magnesium, bismuth and zinc salts. Co-administration of these cations and tetracycline should be separated by two-three hours.
- Should be avoided taking tetracycline: antacids, bismuth containing ulcer-healing drugs, drugs such as quinapril tablets which magnesium carbonate and didanosine with calcium and magnesium excipients.
- Absorption of tetracycline is impaired by milk, and milk products.
- Patients who are treated with anticoagulant may require a downward adjustment of their anticoagulant dosage. Tetracycline may prolong the action of coumarin anticoagulants.
- Plasma-atovaquone concentration is reduced by tetracycline.
- Antidiarrhoeal preparations such as kaolin-pectin and bismuth subsalicylate difficult the absorption of tetracyclines.
- The coadministration of tetracyclines and diuretics aggravate nephrotoxicity.
- Avoid tetracycline in conjunction with penicillin as it may interfere with its bactericidal action.
- Should take caution with oral contraceptive and search for alternative contraceptive if there is necessary the concomitant administration as few cases of pregnancy or breakthrough bleeding have been attributed this concomitant use.
- Nephrotoxicity and death in some cases when tetracycline is combined with methoxyflurane.
- Tetracycline may increase the hypoglycaemic effects of insulin and sulphonylureas in patients with diabetes mellitus.

- The absorption of tetracycline may be reduced by the co- administration of sucralfate, therefore, separating administration should be considered.
- Tetracycline may produce an increase in serum lithium levels.
- Tetracycline may cause an increase in serum digoxin levels.
- Tetracycline may increase the risk of methotrexate toxicity. Monitoring of toxicity is necessary.
- Absorption of tetracycline is impaired by strontium ranelate (avoid concomitant use).
- Absorption of tetracycline may be reduced by colestipol and colestyramine.
- Increased risk of ergotism when tetracycline is given with ergotamine and methysergide.

## 15.4. SURVEY

### AVALUACIÓ DELS ESDEVENIMENTS ADVERSOS DEL TRACTAMENT PER *H. pylori*

Respongui l'enquesta fent una creu (  ) a la resposta que correspongui a la seva situació.

1. **Numero del pacient:** \_\_\_\_\_

2. **Edat:** \_\_\_\_\_

3. **Sexe:**

▪ Home

▪ Dona

4. **Ha seguit correctament les pautes de tractament?**

▪ Sí

▪ No

En el cas que la resposta sigui que no, especificar el motiu pel qual ha deixat el tractament:

\_\_\_\_\_

5. **Ha presentat algun dels següents símptomes o signes?**

SÍMPTOMA / SIGNE	NO	SÍ	En cas afirmatiu:	
			Durada	Ha requerit tractament?
Mal de cap				
Mareig				
Insomni				
Malsons				
Somnolència				
Al·lucinacions				
Ansietat / Nerviosisme				
Convulsió				
M'he sentit confús				
Desmai				
Vertigen				
Tremolors				
Pèrdua del gust				
Alteració olfacte				
Pèrdua d'audició				
Sorolls estranys fora de lo normal (tinnitus)				
Visió doble				
Pèrdua de la visió de lluny (miopia)				
Pèrdua de la gana				
Dificultat per respirar				
Nàusees				
Vòmits				

SÍMPTOMA /SIGNE	NO	SÍ	En cas afirmatiu:	
			Durada	Ha requerit tractament?
Diarrea				
Febre				
Restrenyiment				
Color de la femta més fosca				
Dolor o cremor a la part alta de la panxa i/o sensació de plenitud				
Gasos				
Mal de panxa alt irradiat en forma de cinturó a l'esquena				
Coloració groguenca de la pell i/o dels ulls				
Erupcions cutànies ("sarpullido")				
Períodes d'al·lèrgia				
urticària o picors a la pell				
Picors vaginals				
Taques blanques a la boca i picor de boca				
Sequedat de boca				
Inflamació de la llengua i/o geniva i/o llavis i/o gola.				
Inflamació pell i mucosa dels llavis i/o ulls				
Decoloració de les dents				
Coloració negra de les dents				
Coloració negra de la llengua				
Augment de la sudoració				
Augment del cansament				
Acumulació de líquid a cames i/o turmells i/o peus				
Sensació de formigueig en alguna part del cos				
Dolor muscular i / o articular				
M'he sentit descoordinat a l'hora de caminar o agafar objectes				
Fractura de canell				
Fractura de maluc				
Fractura de columna vertebral				

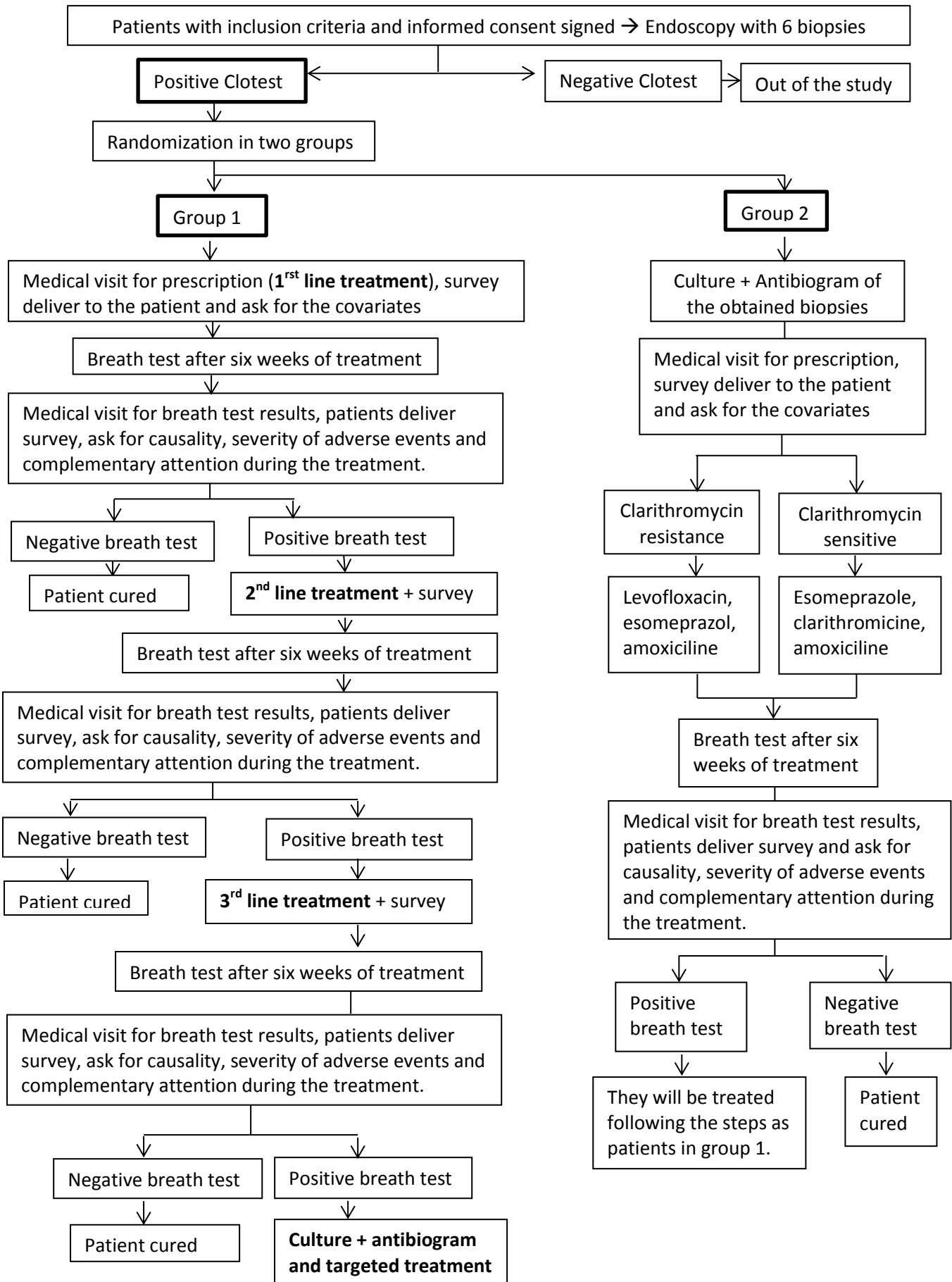
**6. Ha notat algun altre símptoma que no està especificat en la taula?**

- Sí
- No

En cas afirmatiu, especificar el que ha notat:

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### 15.5. FLOWCHART MAIN VARIABLES MEASUREMENTS



## 15.6. TIMELINE

AVTIVITY	JAN - FEB 2015	FEB - JUL 2015	AUG- JAN 2016	FEB- APRIL 2016	MAY- JUL 2016	AUG- OCT 2016	NOV- JAN 2016	STAFF
IEC pass								IEC personal
Coordination								All the staff
Patients recruitment								Investigator doctor
Collection and processing data								All the staff
Data analysis								Investigator doctor, study director and statistic
Interpretation, publication and dissemination of results								Investigator doctor and director of the study.